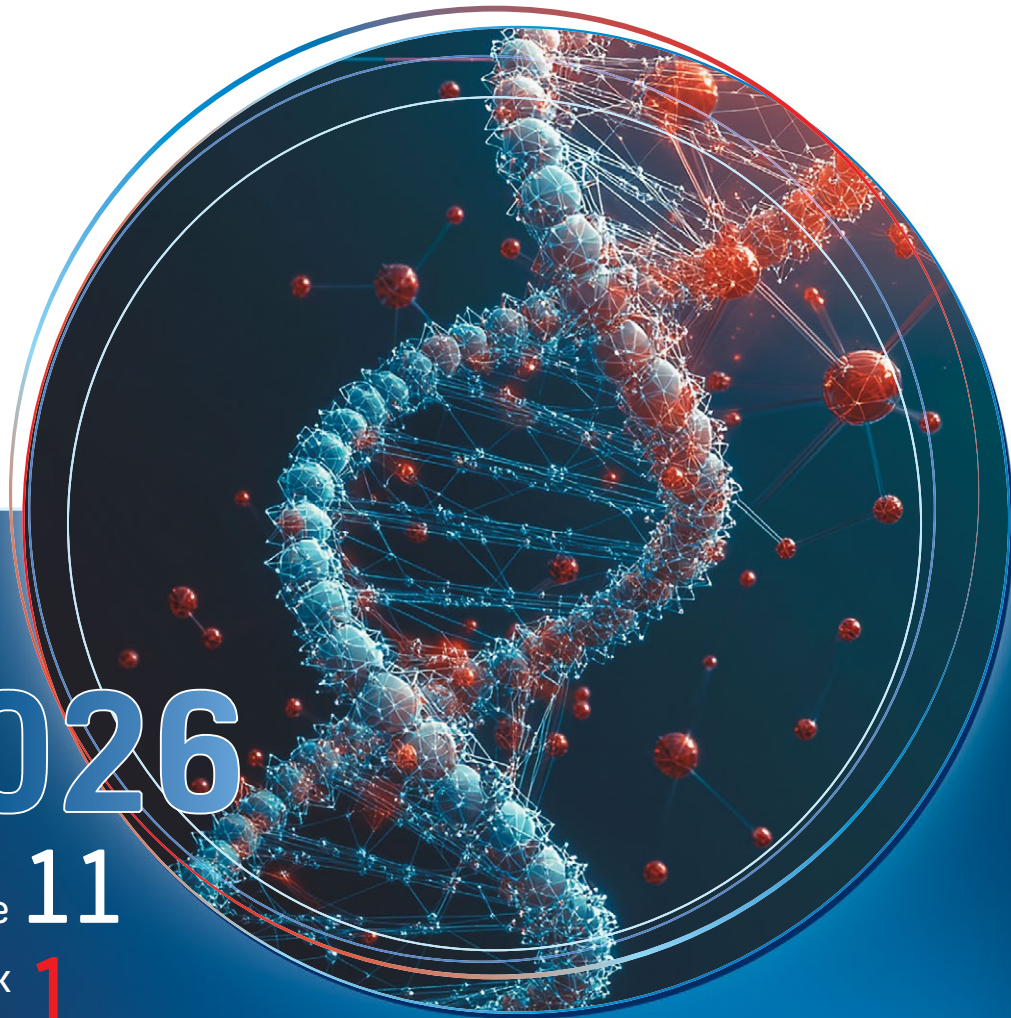


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Early prediction of acute myocardial infarction in patients with new coronavirus infection and acute coronary syndrome

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Abstract

Background. Considering the wide prevalence of COVID-19 (SARS-CoV-2) worldwide and in the Russian Federation, high frequency of its mutations and non-persistent post-infection and post-vaccination immunity, the epidemic potential of COVID-19 persists. The experience of the pandemic demonstrated high mortality among individuals with coronavirus and ACS (acute coronary syndrome), specifically, from myocardial infarction (MI).

Aim: to create a multifactorial model for prediction of myocardial infarction using laboratory and instrumental data of progression of COVID-19 in ACS patients.

Material and methods. The open prospective non-randomized study included 104 patients with ACS due to severe COVID-19 hospitalized in 2022. To solve the problem of early prediction of MI among patients, observation groups were formed: Group 1 (n=35), patients with unstable angina and Group 2 (n=69) with MI. All patients underwent round-the-clock monitoring of vital functions using a dynamic bedside monitor. Laboratory parameters (general clinical and biochemical), cytokine levels (1b, 2, 4, 6, 10, interleukins, γ interferon, tumor necrosis factor α) and instrumental parameters (CT of chest organs, EchoCG) were studied. Scores were calculated using the SOFA (Sepsis-related Organ Failure) and SAPS II (Simplified Acute Physiology Score) scales. Statistical data processing was performed in the SPSS 25.0 software suite. Mathematical

modeling was performed using multidimensional logistic regression. An analysis of the characteristic curves (ROC curves) in the predicted probability of developing MI in the multidimensional model was performed. The results were considered statistically significant at $p < 0.05$. Based on the data obtained, a multidimensional logistic regression model was constructed with step-by-step inclusion or exclusion of predictors using the Wald algorithm.

Results. The prognostic model included SAPS II scores, cytokines (γ interferon, TNF α), and CT scans. The analysis revealed that the developed mathematical model for assessing the risk of MI in patients with ACS on the background of severe COVID-19, created by the method of multidimensional logistic regression based on cytokine profile, lung CT and SAPS II scale, has a sensitivity of 98.6% and a specificity of 85.7%.

Conclusion. Early predictors of MI development have been established in COVID-19 patients with ACS: the degree of lung damage according to CT data, the number of points on the SAPS II scale, levels of interferon and tumor necrosis factor, on the basis of which a mathematical model has been built that allows predicting MI in patients with severe COVID-19.

Keywords: COVID-19, myocardial infarction, cytokines, model, prediction.
Conflict of interest: nothing to disclose.

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Возможности прогнозирования развития инфаркта миокарда у больных новой коронавирусной инфекцией с острым коронарным синдромом

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Аннотация

Обоснование. В связи с широким распространением вируса SARS-CoV-2 в мире и в России, его постоянными мутациями, а также нестойким поствакцинальным и постинфекционным иммунитетом у населения, в настоящее время сохраняется эпидемический потенциал новой коронавирусной инфекции (COVID-19). Опыт пандемии продемонстрировал высокую летальность среди больных COVID-19 с острым коронарным синдромом (ОКС), в частности, от инфаркта миокарда (ИМ).

Цель: на основании лабораторно-инструментальных особенностей течения COVID-19 у больных с ОКС разработать модель прогнозирования развития ИМ у данной категории больных.

Материал и методы. В открытое проспективное нерандомизированное исследование были включены 104 пациента с ОКС на фоне тяжелого течения COVID-19, госпитализированных в 2022 году. Для решения задачи прогнозирования ИМ среди пациентов были сформированы группы наблюдения: группа 1 (n=35) – пациенты с нестабильной стенокардией (НС) и группа 2 (n=69) – с ИМ. Всем пациентам проводился круглосуточный мониторинг витальных функций с помощью прикроватного монитора в динамике. Исследовались лабораторные (общеклинические, биохимические) показатели, уровень цитокинов (интерлейкины: 1b, 2, 4, 6, 10, интерферон γ , фактор некроза опухоли α); инструментальные (КТ

органов грудной клетки, ЭхоКГ); рассчитывали баллы по шкалам SOFA (Sepsis-related Organ Failure) и SAPS II (Simplified Acute Physiology Score). Статистическая обработка данных выполнена в среде пакета SPSS 25.0. Выполняли математическое моделирование с помощью многомерной логистической регрессии. Проводили анализ характеристических кривых (ROC-кривых) в предсказанной в многомерной модели вероятности развития ИМ. Результаты считали статистически значимыми при $p < 0,05$. По полученным данным была построена многомерная модель методом логистической регрессии с пошаговым включением или исключением предикторов по алгоритму Вальда.

Результаты. В прогностическую модель вошли баллы по шкале SAPS II, цитокины (интерферон гамма, фактор некроза опухоли альфа) и степень поражения легких по данным компьютерной томографии. В ходе прове-

денного анализа установлено, что разработанная математическая модель оценки риска развития ИМ у больных с ОКС на фоне тяжелой формы COVID-19, созданная методом многомерной логистической регрессии, обладает чувствительностью 98,6% и специфичностью 85,7%.

Выводы. Установлены ранние предикторы развития ИМ у пациентов с ОКС на фоне COVID-19: степень поражения легких по данным КТ, количество баллов по шкале SAPS II, уровни цитокинов (интерферона и фактора некроза опухоли). На основании данных предикторов разработана математическая модель, позволяющая прогнозировать ИМ на фоне тяжелой формы COVID-19.

Ключевые слова: COVID-19, инфаркт миокарда, цитокины, модель, прогнозирование.

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COVID-19 – новая коронавирусная инфекция; ОКС – острый коронарный синдром; НС – нестабильная стенокардия; ИМ – инфаркт миокарда; СРБ – С-реактивный белок; КФК – креатинфосфокиназа; ИЛ – интерлейкин; ФНО- α – фактор некроза опухоли- α ; SOFA – Sepsis-related Organ Failure; SAPS II – Simplified Acute Physiology Score.

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INTRODUCTION

Due to the wide prevalence of the SARS-CoV-2 virus worldwide and in Russia, its continued mutations and the unstable post-vaccination and post-infection immunity among the population, the epidemic potential of the new coronavirus infection (COVID-19) still persists. The experience of the pandemic showed a high level of lethality (up to 40%) from cardiovascular complications among COVID-19 patients [1]. N.R. Smilowitz et al. (2020) report that a third of patients hospitalized with COVID-19, already had signs of myocardial damage as early as on admission; follow-ups showed that the share of such patients reached 47%, which resulted in a quadruple increase of intra-hospital mortality, from 9.7% to 39.1% [2]. A 3.3-fold increase of mortality in the event of an acute coronary syndrome (ACS) in COVID-19 patients is reported by Turkish researchers T. Çınar et al. (2022) [3]. Currently, a number of direct and indirect mechanisms are studied by which SARS-CoV-2 influences the development of cardiovascular complications: from tissue penetration to induction of a massive systemic inflammatory reaction [4]. Cytokine-mediated myocardial damage, as the leading cause of cardiac damage under COVID-19, is reported in a study of American authors [5]. SARS-CoV-2 disrupts the interaction of the angiotensin converting enzyme 2 (ACE2), renin-aldosterone and kinin-kallikrein systems that balance the inflammation, cell proliferation and platelet aggregation resulting in the hemostasis disorder and myocardial damage [6]. The work of Russian researchers shows a multi-component mechanism of ischemia/infarction of the myocardium under COVID-19 that includes the dysfunction of the renin-angiotensin-aldosterone system, hyperinflammation and 'cytokine storm', endothelial dysfunction and coagulopathy, hypoxemia and hypoxia [1]. The clinical diagnostics of the

ACS against the background of an acute infectious disease may be complicated: pains in the chest, respiratory and cardiovascular failure are characteristic both for a severe form of COVID-19 and for ACS including unstable angina (UA) and myocardial infarction (MI). According to cardiologists' recommendations, diagnostics of the ACS shall include ECG and blood serum troponin test; however, some authors point out that the test is not always specific, especially in the event of an acute infectious disease [7, 8]. Therefore, the search for laboratory indicators and data of instrumental analysis of the predictors to predict MI, that would be available in practical healthcare, still remains a vital question.

AIM

To create a model for prediction of myocardial infarction using laboratory and instrumental data of progression of COVID-19 in ACS patients.

MATERIAL AND METHODS

The open prospective non-randomized study included 104 patients with ACS on the background of severe progression of COVID-19 (predominantly, Omicron strain), hospitalized throughout the year 2022. The diagnosis of COVID-19 and ACS, their verification, and patient treatment was performed according to the effective provisional methodological recommendations "Prevention, diagnostics and treatment of the new coronavirus infection (COVID-19)" and clinical recommendations of the Society of Cardiology¹.

Inclusion criteria: men and women aged 50 to 80 years with severe form of COVID-19 combined with ACS who received no glucocorticosteroids and anticoagulants on the pre-hospitalization stage, availability of a signed informed consent.

¹ Provisional methodological recommendations "Prevention, diagnostics and treatment of the new coronavirus infection (COVID-19)", version 16, 2022; Clinical recommendations "Acute coronary syndrome without ST segment elevation of the cardiogram" 2020; Clinical recommendations "Acute coronary syndrome with ST segment elevation of the cardiogram" 2020.

Predictors	Group I, UA (n=35) Me (Q1; Q3)	Group II, MI (n=69) Me (Q1; Q3)	p-value
Age	63.00 (54.00; 68.00)	64.00 (54.50; 76.50)	0.121
CT of lung involvement, %	40.00 (35.00; 45.00)	45.00 (40.00; 60.00)	<0.001
SAPS II score	16.00 (15.00; 18.00)	24.00 (21.00; 25.50)	<0.001
SOFA score	16.00 (14.00; 17.00)	16.00 (14.00; 18.00)	0.462
Thickness of the pericardium cavity, mm	5.00 (2.00; 7.00)	5.00 (3.00; 7.00)	0.912
Systolic pressure in the PA (mm Hg)	49.90 (35.00; 54.60)	51.60 (46.00; 58.50)	0.118
Pulmonary acceleration time, ms	61.00 (45.00; 80.00)	47.00 (36.00; 69.00)	0.004
Banded neutrophils, %	2.00 (1.00; 4.00)	8.00 (6.00; 10.00)	<0.001
Segmentonuclear neutrophils, %	55.00 (49.00; 70.00)	72.00 (64.55; 78.50)	<0.001
Lymphocytes, %	30.00 (19.00; 36.00)	11.40 (7.80; 20.00)	<0.001
Platelets, 10 ⁹ /L	322.00 (224.00; 416.00)	175.00 (126.00; 234.00)	<0.001
Total protein, g/L	63.80 (59.40; 69.90)	54.10 (48.95; 61.35)	<0.001
C-reactive protein, mg/L	76.00 (35.20; 129.70)	157.80 (110.95; 252.00)	<0.001
CPK, U/L	1179.00 (765.00; 1504.00)	2088.00 (1974.50; 2394.50)	<0.001

Table 1. Characteristics of potential predictors (instrumental and laboratory) of MI in ACS patients with severe COVID-19

Таблица 1. Характеристика потенциальных предикторов (инструментальных и лабораторных) ИМ у пациентов с ОКС на фоне тяжелой формы COVID-19

Exclusion criteria: patients with severe and terminal concomitant pathologies, oncological, autoimmune and allergic diseases, patients with co-infections (viral hepatitis, type B, C, and HIV infection), mental disorders, pregnancy, refusal from examination. To address the task of IM prediction among COVID-19 patients admitted for hospitalization, two groups were formed according to ACS progression type: Group I (n=35), patients with unstable angina, and Group II (n=69), patients with myocardial infarction.

All patients underwent 24-hour monitoring of vital functions using the bedside monitor Nihon Kohden PVM-2703 (Japan) taking the electrocardiogram (ECG), heart rate (HR), arterial blood pressure (BP), respiratory rate (RR), saturation (SpO₂), body temperature (T^o). The ECG was registered daily on the "Aksion EC3TC-3/6-04" (Russian Federation). Transthoracic echocardiography (EchoCG) was taken for each patient at least twice using the portable ultrasonic examination device GE HealthCare LOGIQ E, manufactured by General Electric (USA). Scores were calculated using the SOFA (Sepsis-related Organ Failure) and SAPS II (Simplified Acute Physiology Score) scales. Computed tomography (CT) of the chest organs was performed on the CT scanner GE Revolution EVO (Russian Federation). Laboratory tests were performed on the hematological (Mindray BC-6800, China) and biochemical (Roche Cobas c 311, Switzerland) analyzers, the cytokine tests (interleukins (IL): 1b, 2, 4, 6, 10, interferon γ (IFN- γ), tumor necrosis factor α (TNF- α) were tested using diagnostic kits (R and D Diagnostics Inc., USA) with the sensitivity of 1 pg/mL.

Statistic processing of data was performed in the SPSS 25.0 suite (IBM Corporation, Armonk, New York, USA, License No.5725-A54). Normality of distribution was assessed using the Shapiro-Wilk test. Descriptive statistics are presented as median and quartiles: Me (Q1; Q3). The Mann-Whitney U test was used for group comparisons. Multivariate logistic regression modeling was performed. Receiver operating characteristic (ROC) curve analysis was conducted using the probability of MI development predicted by the multivariate model. Results were considered statistically significant at $p < 0.05$.

Predictors	Group I, UA (n=35) Me (Q1; Q3)	Group II, MI (n=69) Me (Q1; Q3)	p-value
IL-1b, pg/mL	8.51 (8.25; 8.92)	9.17 (8.58; 9.74)	<0.001
IL-2, pg/mL	0.05 (0.04; 0.08)	0.08 (0.05; 0.11)	0.019
IL-4, pg/mL	10.91 (10.63; 11.23)	10.31 (9.79; 10.77)	<0.001
IL-10, pg/mL	86.60 (84.22; 89.68)	84.44 (81.72; 87.16)	0.003
IFN- γ , pg/mL	9.75 (9.36; 11.41)	8.88 (8.32; 9.56)	<0.001
TNF- α , pg/mL	22.21 (21.46; 23.92)	23.69 (21.56; 25.53)	0.026
IL-6, pg/mL	14.90 (13.90; 15.50)	15.84 (15.05; 16.53)	<0.001

Table 2. Characteristics of potential predictors (cytokine profile) of MI in ACS patients with severe COVID-19

Таблица 2. Характеристика потенциальных предикторов (цитокиновый профиль) ИМ у пациентов с ОКС на фоне тяжелой формы COVID-19

RESULTS

The average age of patients with the severe form of COVID-19 and ACS was 63.00 (54.25; 72.75) years, there were 56.7% women. The patients were admitted in the end of the first or beginning of the second week of the disease (days of admission in the comparison groups: 9.00 (7.00–11.00) and 9.00 (7.00–12.00), respectively, $p=0.369$). The groups were comparable in sex and age, duration of the disease and structure of concomitant pathology. The level of blood saturation with oxygen on admission was from 78.00% to 99.00%, the median values between the groups did not differ statistically (95.00% in patients of Group I and 94.00%, in Group II, $p=0.178$). More than 70 laboratory and instrumental indicators were analyzed in patients with ACS against the background of severe COVID-19; the most significant of them follow in **Tables 1 and 2**.

Using the obtained data, the risk of MI was evaluated using logistic regression method. On the first stage, univariate models were constructed, when each equation forcibly included only one risk factor (predictor). Using the results of these models, exponential coefficients of regression were derived interpreted as odds ratio (OR) and their 95% confidence intervals (95% CI) (**Table 3**). As expected, the indicators that had no differences in paired comparisons, turned out to be statistically insignificant

Indicator	OR [95% CI]	p-value
Age	1.02 (0.99–1.05)	0.260
CT lung involvement, %	1.07 (1.02–1.11)	0.002
SAPS II score	3.62 (2.01–6.49)	<0.001
SOFA score	1.06 (0.88–1.28)	0.559
Thickness of the pericardium cavity, mm	0.99 (0.84–1.17)	0.929
Systolic pressure in the PA (mm Hg)	1.03 (0.99–1.06)	0.155
Pulmonary acceleration time, ms	0.97 (0.96–0.99)	0.005
Banded neutrophils, %	1.80 (1.45–2.24)	<0.001
Segmentonuclear neutrophils, %	1.11 (1.06–1.17)	<0.001
Lymphocytes, %	0.88 (0.83–0.93)	<0.001
Platelets, 10 ⁹ /L	0.99 (0.98–0.99)	<0.001
Total protein, g/L	0.88 (0.82–0.93)	<0.001
C-reactive protein, mg/L	1.02 (1.01–1.03)	<0.001
CPK, U/L	1.00 (1.00–1.01)	<0.001
IL-1b, pg/mL	3.71 (1.79–7.67)	<0.001
IL-2, pg/mL	5.31 (1.42–19.89)	0.013
IL-4, pg/mL	0.33 (0.16–0.67)	0.002
IL-10, pg/mL	0.83 (0.73–0.94)	0.002
IFN-γ, pg/mL	0.36 (0.22–0.57)	<0.001
TNF-α, pg/mL	1.33 (1.06–1.68)	0.014
IL-6, pg/mL	1.95 (1.33–2.85)	0.001

Table 3. Assessment of MI risk in ACS patients with severe COVID-19 by univariate logistic regression: combination of models

Таблица 3. Оценка риска ИМ у больных с ОКС на фоне тяжелой формы COVID-19 методом одномерной логистической регрессии: совокупность моделей

predictors in the equations. The majority of studied laboratory and instrumental indicators manifested as risk factors with OR above one (1). Elevated values of the following indicators are associated with poor prognosis: lung involvement as seen on CT, SAPS II score, percentage of banded and segmentonuclear neutrophil leukocytes, concentration of the C-reactive protein, IL-1b, IL-2, TNF-α, IL-6 and activity of CPK in the blood serum. Indeed, all of these signs are markers of severity of COVID-19 progression. Conversely, the lower pulmonary acceleration time and lower concentrations of total protein, IL-4, IL-10, IFN-γ are associated with more favorable prognosis: the OR of these indicators is below one (1).

Then, different variants of multivariate models were constructed by the logistic regression method with step-by-step inclusion of predictors using the Wald algorithm. The models differed not only in their construction approach but also in their initial sets of potential predictors. The issue is that many of these predictors are closely interrelated and

therefore cannot be simultaneously selected by a stepwise algorithm for inclusion in the regression equation. Thus, the SAPS II severity scale is statistically significantly interrelated with all of the studied cytokines (correlation coefficients from 0.3 to 0.6 in absolute values). Thus, the inclusion of SAPS II score in the number of potential predictors ‘displaced’ the other risk factors from the equation, that were included in the prognostic model in the univariate or multivariate version without this severity scale. Some of the prognostic indicators were included in all constructed mathematical models, and some varied from one variant to another. In this paper, we make an example of the model with the best analytical characteristics (**Table 4**). Thus, the area under the ROC curve (AUC) was 0.99 ± 0.01, and Youden’s index at a threshold probability of 0.22 was 0.84. These results indicate that the constructed model has excellent discriminatory performance.

According to the constructed multivariate logistic regression, the probability of MI development in patients with COVID-19 with ACS can be calculated using the following equation:

$$p = 1 / (1 + e^{-(1,71X1 + 0,16X2 - 1,10X3 + 0,77X4 - 45,99)}),$$

where e – base of natural logarithms (rounded to 2.72); X1 – SAPS II score; X2 – CT lung involvement percentage; X3 – concentration of gamma-interferon in the blood serum in pg/mL; X4 – concentration of the tumor necrosis factor alpha in the blood serum in pg/mL.

The SAPS II scale turned out to be the most powerful prognostic factor of MI with the odds ratio (OR)=5.52 (95% CI: 1.86–16.42) (p=0.002). The second most influential predictor was the CT lung involvement degree with OR=1.17 (95% CI: 1.00–1.36) (p=0.045). TNF-α and IFN-γ, while keeping their roles of the risk factor and protective factor, turned out statistically insignificant (p=0.083 and p=0.056). Nevertheless, such levels of significance (more than 0.05, less than 0.10) in the exploratory mathematical models are viable, in the opinion of some authors. The decrease of their prognostic capacity is accounted for by the interrelation with two more powerful predictors, which turn out to be sufficient for the predicted variant of the ACS, viz. the myocardial infarction. The model had high predictive accuracy. The sensitivity, with the threshold probability of 0.22, was 98.6%, and the specificity was 85.7%.

At the next stage, this model was validated on a test dataset. The test set comprised 30 patients with COVID-19 who presented with ACS, which subsequently resolved as

Predictors in the model	Regression coefficient b	SE b	Wald’s statistics	OR (95% CI)	p-value
SAPS II score	1.71	0.56	9.45	5.52 (1.86–16.42)	0.002
CT lung involvement, %	0.16	0.08	4.00	1.17 (1.00–1.36)	0.045
TNF-α, pg/mL	-1.10	0.58	3.66	0.33 (0.11–1.03)	0.056
IFN-γ, pg/mL	0.77	0.44	3.01	2.16 (0.91–5.14)	0.083
Constant	-45.99	19.12	5.79	–	0.016

Table 4. Assessment of MI risk in ACS patients with severe COVID-19 by multivariate logistic regression using cytokine profile, lung CT and SAPS II score

Таблица 4. Оценка риска ИМ у больных с ОКС на фоне тяжелой формы COVID-19 методом многомерной логистической регрессии по цитокиновому профилю, КТ легких и шкале SAPS II

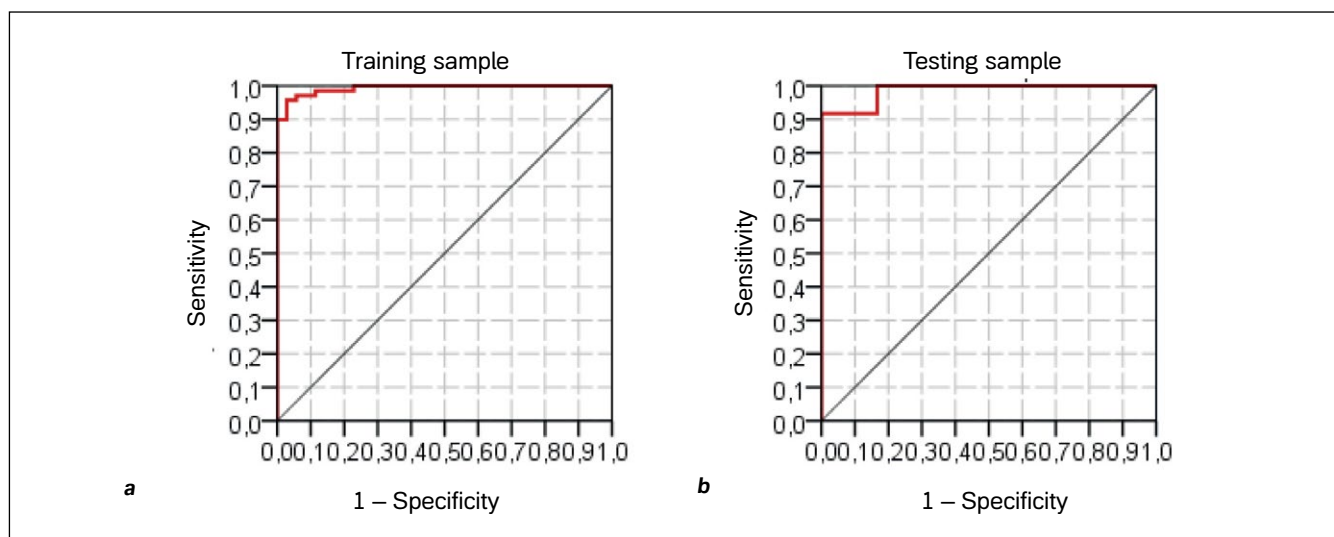


Figure 1. ROC curves of MI risk prediction in ACS patients with severe COVID-19 by multivariate logistic regression models: a – training sample, b – testing sample.

Рисунок 1. ROC-кривые прогнозирования риска ИМ у пациентов с ОКС на фоне COVID-19 по многомерным моделям логистической регрессии: а – по обучающей выборке, б – по тестовой выборке.

UA in 6 individuals and MI in 24. These patients were not included in the construction of the mathematical model described above. For all of them, the probability of MI risk was calculated using the regression coefficients obtained from the training dataset.

At the next stage, for patients in the main (training) and testing samples the ROC-curves were plotted (**Fig. 1**). The area under the ROC-curve for the testing sample was 0.98 ± 0.02 , and the Youden's index was 0.79.

The areas under the curve of these models are shown in **Table 5**.

DISCUSSION

As of today, the available literature describes individual models predicting ACS in COVID-19, despite the significant contribution of this complication in the overall mortality under the new coronavirus infection. Thus, M. Rashid et al. (2021) used the analysis of 517 cases of COVID-19 with ACS to report high in-hospital mortality (24.2%) in this group of patients and note its increase to 41.9% within 30 days after recovery from COVID-19 [9]. According to I.I. Serebrennikov et al. (2023), the cumulative mortality (60 days) in the COVID-19 with the ACS cohort was 48.3% [8]. There are several foreign and Russian studies

Tested model	AUC	SE AUC	p	95% CI
MI model: testing sample	0.99	0.01	<0.001	0.98–1.00
Testing of the MI model on the testing sample	0.98	0.02	<0.001	0.95–1.00

Notes: AUC – area under curve, SE AUC – standard error of AUC, p – statistic significance of difference from a useless classifier.

Примечания: AUC – area under curve – площадь под графиком, SE AUC – standard error of AUC – стандартная ошибка AUC, p – статистическая значимость отличия от бесполезного классификатора.

Table 5. Area under curve of the prediction model of MI risk assessment in ACS patients with severe COVID-19

Таблица 5. Площадь под ROC-кривой прогностической модели оценки риска ИМ у пациентов с ОКС на фоне COVID-19

focusing on predictors of adverse outcomes of ACS under COVID-19: level of ceramides (in the analysis of the metabolome profile), complex of 8 parameters (age, atrial fibrillation status, severe and extremely grave progression of the SARS-CoV-2 infection, acute kidney injury, chronic kidney failure of stage 2 and above, levels of ferritin, albumen, glucose), that predict the risk of a lethal outcome in the ACS but not its variant [10, 11]. In multicenter cohort studies performed in China and Iran, in the acute period of COVID-19 with the development of ACS, a correlation was identified between the calcification of coronary arteries, blood calcium level, and adverse outcome (in-hospital death) [12, 13]. The retrospective study of N.R. Smilowitz et al. (2020) demonstrated a close correlation between the degree and the duration of increase of cardiac troponin in COVID-19 patients with subsequent critical progression of ACS and lethal outcome [2]. There are individual Russian studies focusing on the outcome of ACS in the post-COVID period. There is a multivariate regression model of adverse outcomes of ACS in patients in the post-COVID period with the following predictors: chronic heart failure, presence of soluble fms-like tyrosine kinase-1, hypokinesia zones on EchoCG, carrier status of the TT/AA genotype of the rs2285666 genetic marker of the ACE2 gene. The sensitivity of the model is 93.5%, specificity, 21.8%, accuracy, 76.6% [14, 15]. We could not find in the available literature a model that would have predicted the variant of ACS development with high accuracy and specificity using predictors available in practical healthcare at the peak of the COVID-19 disease. Undoubtedly, such a model is needed to prevent development of negative scenarios of the acute coronary syndrome.

CONCLUSION

The proposed mathematical model allows for prediction of myocardial infarction in patients with a severe form of COVID-19 with a sensitivity of 98.6% and specificity of 85.7%. This provides not only practical but also scientific value, since the group of independent predictors includes not only the known factors determining the severity of the main disease, but also the two cytokines characterizing the immune response to the infection. ■

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. A.V. Lunina: scientific data collection, systematization and analysis, writing of the manuscript. D.Yu. Konstantinov, L.L. Popova: study concept, detailed manuscript editing and revision. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	Участие авторов. А.В. Лунина – сбор и обработка научного материала, написание текста; Д.Ю. Константинов, Л.Л. Попова – разработка концепции исследования, редактирование текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
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Some indicators of glycome in various forms of multiple sclerosis

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Abstract

Aim: identification of protein glycosylation features in various clinical forms of multiple sclerosis.

Material and methods. We studied the indicators of glycome, viz. interleukin-6 (IL-6) and P-selectin glycoprotein (SELP) in 135 patients with various forms of multiple sclerosis (MS): relapsing-remitting MS (RMS) - 71, secondary progressive MS (SPMS) - 49, primary progressive MS (PPMS) - 15 patients. An ELISA Multiscan FC analyzer was used at 450 nm using appropriate diagnostic kits. Statistical processing was performed using the Mann - Whitney criterion. Multiple comparisons of groups of different MS course were performed using the Kruskal - Wallis test. Correlation analysis was performed based on Spearman's rank correlation coefficient. Statistical reliability of conclusions was determined at the 5% level of significance.

Results. This study attempted to identify the relationship between IL-6 and SELP levels and MS shape, duration, and severity, revealing only a significant association of SELP with disease duration for RMS. There were no data on the relationship of these indicators with the age and sex of patients.

Conclusions. The studies carried out show a certain specificity of changes in glycosylation of proteins in multiple sclerosis, which makes it possible to use them as markers for diagnosing various forms of multiple sclerosis and similar diseases. Despite the fact that the study showed a significant association only in SELP and only with the duration of the disease in relapsing-remitting MS, it is possible to obtain additional results with an increase in the number of patients included in the study, as well as with the inclusion of other glycome parameters in the study.

Keywords: multiple sclerosis, variants of course, protein glycosylation indices.
Conflict of interest: nothing to disclose.

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Некоторые показатели гликома при различных формах течения рассеянного склероза

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Аннотация

Цель: выявить особенности гликозилирования белков при различных клинических формах рассеянного склероза.

Материал и методы. Изучены показатели гликома – интерлейкин-6 (IL-6) и гликопротеин P-селектин (SELP) у 135 больных с такими формами течения рассеянного склероза (РС), как ремиттирующий РС (РРС) – 71 больной, вторично-прогрессирующий РС (ВПРС) – 49 пациентов, первично-прогрессирующий РС (ППРС) – 15 пациентов. Использован ИФА-анализатор Multiscan FC при длине волны 450 нм с применением соответствующих диагностических наборов. Статистическая обработка проводилась с использованием критерия Манна – Уитни. Множественные сравнения групп различного течения РС проводились с помощью критерия Краскела – Уоллиса. Анализ корреляции выполнен на основе коэффициента ранговой корреляции Спирмена. Статистическая достоверность выводов определялась на 5% уровне значимости.

Результаты. В настоящем исследовании была предпринята попытка выявления зависимости уровня IL-6 и SELP от формы, длительности

течения и тяжести РС, что выявило только значимую связь SELP с длительностью течения заболевания для РРС. Данных о связи этих показателей с возрастом и полом пациентов получено не было.

Выводы. Показана определенная специфичность изменений гликозилирования белков при рассеянном склерозе, что позволяет использовать их в качестве маркеров для диагностики различных форм рассеянного склероза и сходных с ним заболеваний. Хотя в проведенном исследовании была выявлена значимая связь только у SELP и только с длительностью заболевания при ремиттирующей форме РС, не исключена возможность получения дополнительных результатов при увеличении количества включенных в исследование пациентов, а также при включении в исследование других показателей гликома.

Ключевые слова: рассеянный склероз, варианты течения, показатели гликозилирования белков.

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Список сокращений

PC – рассеянный склероз; PPC – ремиттирующий рассеянный склероз; ВПРС – вторично-прогрессирующий РС; ППРС – первично-прогрессирующий РС; EDSS – Expand Disability Status Scale – расширенная шкала оценки инвалидности; ИФА – иммуноферментный анализатор; нм – нанометр; нг – нанограмм; пг – пикограмм; IgG – иммуноглобулин G; SELP – гликопротеин P-селектина; sRAGE – молекулы гликации; ПИТРС – препараты, изменяющие течение рассеянного склероза; ЦСЖ – цереброспинальная жидкость.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that affects people of younger age leading an active working life. The disease is steadily progressive, results in an inevitable disability and, often, has a poor prognosis. The specific course of the disease depends largely on the clinical type of MS: a clinically or radiologically isolated syndrome with relapsing-remitting, secondary progressive, or primary progressive course [1, 2]. Each type of course of MS has its own specifics and regularities, as well as indications for prescription of MS disease-modifying therapy (DMT). Therefore, establishing criteria for specific disease courses to optimize diagnosis, predict the further progression of MS, and prescribe adequate DMTs tailored to the disease form represents a crucial and relevant clinical objective [3, 4]. Much interest lies in the comparative characteristics of progression of various forms of MS, their transformation based on objective parameters, and the role of predictors of different forms of the disease that determine the its specific course [5–7].

The human glycome comprises the entirety of sugars within the organism – both free and those incorporated into more complex molecules. It consists of glycoproteins and glycolipids. In its complexity, glycome exceeds the proteome in diversity due to the even greater structural variation of its constituent carbohydrates, and its complexity is further amplified by the extensive interactions of carbohydrates with each other and with proteins [8]. According to J.D. Marth, glycans are natural biological modifiers that typically do not simply “turn on or off” physiological processes but rather modulate cellular behavior in response to external stimuli [9]. In the pathogenesis of a number of diseases, disorders of protein glycosylation play a leading or a decisive role. Disorders of protein glycosylation concern a number of medical aspects, which complicates the identification and diagnostics of protein glycosylation disorders [10, 11].

Studies of glycome alterations in MS are a new and prospective approach in the diagnostic of the disease. Existing research shows that glycoproteins in MS patients differ from those in healthy individuals and from those observed in other neurological conditions, i.e. there are specific alterations of glycome in MS. It is very important that glycome alterations correlate with the age and sex of patients, with the clinical form of the disease, and the degree of disablement on EDSS, which may be instrumental in early diagnostics of MS, identification of the type of the disease and prediction of its course [12].

AIM

Identification of protein glycosylation features in various clinical forms of multiple sclerosis.

MATERIAL AND METHODS

Some parameters of glycome were studied in 135 patients with MS, among which 71 patients had the relapsing-remitting form (RMS), 49 patients, secondary progressive (SPMS), and 15, primary progressive form of MS (PPMS). It is to be noted that the number of studied patients in the groups approximately matches the distribution of clinical forms of the disease in the population of MS patients. The duration of disease in the studies patients varied from 1 to 31 years. All patients were followed up in the MS Center of the V.D. Seredavin Samara Regional Clinical Hospital. The diagnosis of MS was verified using McDonald criteria (2017).

The study was performed in two stages.

The preliminary study included assays from 90 patients of interleukin-6 (IL-6), P-selectin glycoprotein (SELP), SIGLEC-9 immunoglobulin, glycation molecules (sRAGE) on the Multiskan ELISA reader at 450 μm wavelength using the following test kits: Interleukin-6-IFA-BEST (Vector-Best), ELISA Kit for Receptor Advanced Glycation Endproducts (Cloud-Clone Corp.), ELISA Kit for P-selectin (Cloud-Clone Corp.), ELISA Kit for Sialic Acid Binding Ig Like Lectin 9 (Cloud-Clone Corp.). Among patients, there were 35 men (38.9%) and 55 women (61.1%). The patients' age was between 18 and 74 years. The comparison group included 30 healthy individuals of similar age and sex.

On the second stage, Interleukin-6 (IL-6) and P-selectin glycoprotein (SELP) values were studied in a group of 135 patients that included 90 patients of the previous stage of the study. Among the patients there were 84 women (62.2%) and 51 men (37.8%). The median age was 41 (33; 50) years.

Statistic processing of data was performed in IBM SPSS Statistics 26.0. Quantitative variables were assessed for normality of distribution using either the Shapiro–Wilk test or the Kolmogorov–Smirnov test with Lilliefors correction, depending on the expected frequency count. Since the quantitative data either followed a non-normal distribution or represented ordinal variables, comparisons between the two independent groups (patients with MS and individuals without demyelinating diseases) were performed using the Mann–Whitney U test. Non-parametric data are presented as median (Me) with lower and upper quartiles (Q1; Q3). Multiple comparisons between groups with different MS

disease courses were conducted using the Kruskal–Wallis test. Correlation analysis was performed using Spearman's rank correlation coefficient. Statistical significance of the findings was determined at the 5% significance level.

The weighted arithmetic mean for the investigated glycome parameters was calculated using the following formula:

$$\bar{x} = \frac{\sum x_i f_i}{\sum f_i}$$

A weighted mean is an average that accounts for the weight (importance) of each element within a dataset. It is used when sample elements have different significance, such as when combining results from samples of varying sizes, or when the contribution of each element needs to be factored in proportionally to its importance.

RESULTS

From the products of glycosylation, the most interest was on part of SELP serum. The numbers in the studied group (patients with MS regardless of the course of disease, n = 88) vary from 29.49 to 173.54 ng/mL with an average (weighted average) value of 67.994, while the indicators in the control group (individuals without demyelinating and inflammatory diseases, n = 30) vary between 27.432 to 125.314 ng/mL, the average value being 57.734 ng/mL.

Serum IL-6 quantification levels in patients with MS (n = 90) demonstrated considerable variability, from 0.00 to 104.93 pg/mL, the average being 3.884. In the control group (n = 30), the IL-6 levels vary from 0.258 to 4.0115 pg/mL, the average being 1.611 pg/mL.

When analyzing the marker levels by groups depending on the course of multiple sclerosis, the following results were obtained:

RMS (n = 50):

SELP (n = 48): min. 29.49; max. 122.21 ng/mL, avg. 68.981 ng/mL.

IL-6 (n = 50): min. 0.00; max. 109.93 pg/mL, avg. 4.335 pg/mL.

PPMS (n = 5):

SELP: min. 30.92, max. 62.89 ng/mL, avg. 44.52 ng/mL.

IL-6: min. 0.00; max. 0.01 pg/mL, avg. 0.002 pg/mL.

SPMS (n = 35)

SELP: min. 30.48; max. 173.54 ng/mL, avg. 69.995 ng/mL.

IL-6: min. 0.00; max. 56.14 pg/mL, avg. 3.794 pg/mL.

The levels of sRAGE and SIGLEC-9 were also analyzed. Study group: sRAGE (n = 90) min.: 0.00; max.: 0.05 ng/mL, weighted avg.: 0.001, mean square deviation: 0.00667. SIGLEC-9 (n = 90) min.: 0.00; max.: 0.29 ng/mL, weighted avg.: 0.0216, mean square deviation: 0.0577. Control group: sRAGE (n = 30) min.: 0.00; max.: 0.638 ng/mL, weighted avg.: 0.0615. SIGLEC-9 (n = 30) min.: 0.00; max.: 0.1647 ng/mL, weighted avg.: 0.0216, mean square deviation: 0.0577.

Following the results of the preliminary analysis of laboratory findings, it was decided to study the IL-6 and SELP levels. They demonstrated the most informative value and variability both as compared to the control group in a greater number of patients and within the analysis of groups with different courses of MS. At the same time, the sRAGE and SIGLEC-9 levels demonstrated low absolute values within the studied group and showed no significant differences from the control group.

The second stage involved analysis of the levels of blood serum IL-6 and SELP in 135 patients with different courses of MS (RMS: 71, SPMS: 49, PPMS: 15) and 30 healthy individuals from the comparison group. The glycome levels of IL-6 and SELP were compared in the two groups using the Mann – Whitney test. The level of IL-6 in MS patients was 0.47 (0; 1.91) pg/mL, in the comparison group: 0.745 (0.495; 1.05) pg/mL, without a statistically significant difference (p = 0.178). The SELP glycome level in the study group was 53.02 (35.84; 78.32) ng/mL, in the comparison group: 47.665 (40.34; 66.245) ng/mL, also without a statistically significant difference (p = 0.899).

In all of the studies groups including different courses of the MS disease, the glycome levels were analyzed using the Kruskal–Wallis test. No statistically significant differences were found in the assessment of IL-6 (p = 0.752) and SELP (p = 0.655).

The correlation between the glycome levels of IL-6 and SELP and the duration of the MS disease is shown in **Table 1**. In RMS patients, Spearman's rank correlation was used to establish a statistically significant direct correlation between the duration of the disease and the SELP level (p = 0.278 with 95% CI: 0.039-0.489; p = 0.019).

The correlation between the glycome levels of IL-6 and SELP from the degree of disability on EDSS (Expanded Disability Status Scale) was tested using the Spearman's rank correlation. The correlation was statistically insignificant. The data is shown in **Table 2** (rank correlation).

MS course	SPMS (n = 49)		RMS (n = 71)		PPMS (n = 15)	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
IL-6	- 0.130	0.373	- 0.021	0.863	0.185	0.510
SELP	0.230	0.112	0.278	0.019	0.315	0.252

Table 1. IL-6 and SELP by MS duration

Таблица 1. Показатели IL-6 и SELP в зависимости от длительности течения РС

MS course	SPMS (n = 49)		RMS (n = 71)		PPMS (n = 15)	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
IL-6	0.086	0.556	- 0.011	0.930	0.229	0.412
SELP	- 0.155	0.289	- 0.016	0.891	0.302	0.274

Table 2. IL-6 and SELP by EDSS

Таблица 2. Показатели IL-6 и SELP в зависимости от значений шкалы инвалидизации EDSS

Thus, only the significant correlation between the SELP level and the duration of the MS disease for RMS was established.

DISCUSSION

According to A. Cvetko et al. (2020), immunoglobulins G were most notable for their fucosylated nucleus and abundance of structure with a high content of mannose. In the plasma proteins, they noted an increase in the complexity of glycans: the number of highly branched structures was increasing that carried multiple residues of galactose and sialic acid. Some N-glycans and IgG showed good sensitivity and specificity, based on which the correlation of probability of MS from the level of N-glycans and IgG in the plasma was derived [12].

Peng Peng Ip et al. (2021) used 49 glycoproteins of the serum to calculate the levels of 286 glycopeptides and compared them in groups of patients with RMS (n = 45) and opticomyelitis spectrum diseases (n = 23), as well as in 6 healthy individuals. In these groups, differences were found in site-specific N-glycans in the structures involved in the inflammatory process that were seen as potential markers for differential diagnosis of MS and opticomyelitis spectrum diseases [13].

P. Dojesak et al. (2022) studied the N-glycome in the blood serum of female patients with MS and compared it with the control group. In the MS group, higher levels of sialylation, galactolysis and mannose were found [14].

M. Wuhrer et al. (2015) studied protein glycosylation in 48 pairs of cerebrospinal fluid and blood serum of 27 patients with different forms of MS and of 21 healthy individuals or patients with other nervous system diseases. The study concluded that glycosylation of IgG1 was different in the cerebrospinal fluid and in the blood serum both in the MS group and in the control group. In the case of MS, glycosylation was elevated in the fluid but not in the serum. The most changes of fucosylation of GlcNAc were seen 2-3 months after exacerbation of MS,

and glycosylation of IgG1 correlated with the synthesis of intrathecal IgG and with the cytolysis in the cerebrospinal fluid [15].

The correlation for age and sex of MS patients was identified by quantitative and qualitative methods using the residual sugars that were more manifested in the cerebrospinal fluid than in the blood serum. J. Decker et al. (2016) showed that galactosylation of IgG in the fluid depends on the age and sex: higher levels were seen in men and in patients aged 25–50. The decrease of galactosylated IgG correlates with the progression of MS and increase of disability scores on the EDSS, and is accompanied by an increased intrathecal synthesis of IgG [16].

In this study, we made an attempt to identify the dependence of the IL-6 and SELP levels from the course, duration of the disease and severity of MS, and found out only the significant correlation between the SELP and the duration of disease for RMS. No data was found between the correlation of these indicators with the age and sex of patients.

CONCLUSION

The completed studies show some specificity in the changes of glycosylation of proteins in multiple sclerosis, which allows for the use of these values as markers for diagnostics of various forms of MS and similar diseases.

Despite the fact that this study succeeded only in establishing the significant correlation only for SELP and only for the duration of disease for the relapsing-remitting multiple sclerosis, additional results may be obtained if more patients or if other glycome levels are included in the study. Considering the multiformity of the proteome and variety of its modifications in various media of the body (blood serum and plasma, cerebrospinal fluid), and the diversity of approaches towards its study (numerous quantitative and qualitative biochemical methods), the further search for markers and predictors of MS progression seems promising. ■

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical expertise: minutes No. 255 of the meeting of the Committee on Bioethics at SamSMU dated October 26, 2022.	Этическая экспертиза: протокол №255 заседания комитета по биоэтике при СамГМУ от 26 октября 2022 г.
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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Elizarov M.A.: formulation of the idea and goal of the study, literature search, writing of the text. Poverennova I.E.: verification of the results of reproduction, scientific supervision of the project. Lakhov A.S.: software development, development of research algorithms, evaluation of the results. Zolotov M.O.: development of methods, laboratory control of the study. Persteneva N.P.: statistical and theoretical data analysis. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	Участие авторов. Elizarov M.A. – формулировка идеи и цели исследования, литературный поиск, написание текста. Пoverennova I.E. – проверка результатов воспроизведения, научное руководство проектом. Лaхов A.C. – создание программного обеспечения, разработка алгоритмов исследования, оценка результатов. Золотов M.O. – разработка методов, лабораторный контроль проведения исследования. Перстенева Н.П. – статистический и теоретический анализ данных. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
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Scientific-medical educational cluster as a tool for addressing strategic objectives in public health and healthcare organization at the regional level

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Abstract

The current stage of technological evolution in healthcare is characterized by the synergy of biomedical sciences and digital technologies, shaping a new paradigm of evidence-based medicine. Generative artificial intelligence (GenAI), with its potential to process heterogeneous data and generate predictive models, is a key driver for the personalization of medical services. This study conducted a multi-level analysis of the institutional and technological aspects of developing a scientific and medical cluster. A scientific-medical educational cluster (SMEC) represents a promising organizational and economic model aimed at consolidating the resources of science, education, practical healthcare, and business to achieve strategic public health goals.

Aim: to study modern approaches to the development of scientific-medical educational clusters as a tool for addressing strategic objectives of public health and healthcare organization on the regional level.

Material and methods. The study utilized a systems approach, a content analysis method for research data on the issue, and an analytical method for assessing the effectiveness of the cluster model in the context of Russian regions.

Results. Key systemic limitations were identified: fragmented management, shortage of personnel and management competencies, and insufficient focus of scientific research on public health priorities. The challenges of forming scientific and medical educational clusters in the current context and ways to address them were identified.

Conclusion. Organization of scientific-medical clusters is a key factor in the development of an innovative healthcare ecosystem, ensuring the integration of academic science, educational institutions, the business sector, and government regulation. Key factors for the success of scientific and medical educational clusters in the region include the leading role of the healthcare authority in coordinating all cluster participants; focus on public health priorities determined based on epidemiological analysis and monitoring data; integration of educational programs in artificial intelligence management and healthcare economics into cluster activities to train personnel capable of working in an interdisciplinary environment; investments in innovations with achievable medical, demographic and economic indicators.

Keywords: scientific-medical cluster, healthcare management.

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Научно-медицинский образовательный кластер как инструмент решения стратегических задач в области охраны общественного здоровья и организации здравоохранения в регионе

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Аннотация

Современный этап технологической эволюции в здравоохранении характеризуется синергией медико-биологических наук и цифровых технологий, формирующей новую парадигму доказательной медицины. Генеративный искусственный интеллект (генИИ), обладающий потенциалом обработки гетерогенных данных и генерации предиктивных моделей, выступает ключевым драйвером персонализации медицинских услуг. В рамках данного исследования проведен многоуровневый анализ институциональных и технологических аспектов формирования научно-медицинского кластера. Научно-медицинский образовательный кластер (НМОК) представляет собой перспективную организационно-экономическую модель, направленную на консолидацию ресурсов науки, образования, практического здравоохранения и бизнеса для достижения стратегических целей в области общественного здоровья.

Цель: изучить современные подходы к формированию научно-медицинских образовательных кластеров как инструмента решения стратегических задач в области охраны общественного здоровья и организации здравоохранения в регионе.

Материал и методы. В исследовании применены системный подход, метод контент-анализа данных научных исследований по проблеме, аналитический метод для оценки эффективности кластерной модели в условиях российских регионов.

Результаты. Выявлены ключевые системные ограничения: фрагментарность управления, дефицит кадров, управленческих компетенций и недостаточная ориентация научных разработок на приоритеты общественного здоровья. Определены проблемы формирования научно-медицинских образовательных кластеров в современных условиях и путей их решения.

Заключение. Формирование научно-медицинских кластеров выступает ключевым фактором развития инновационной экосистемы здравоохранения, обеспечивающей интеграцию академической науки, образовательных институтов, предпринимательского сектора и государственного регулирования. Ключевыми условиями успешности НМОК в регионе являются такие показатели, как лидирующая роль органа управления здравоохранением в координации всех участников кластера; ориентация на приоритеты общественного здоровья, определяемые на основе эпидемиологического анализа и данных мониторингов; интеграция образовательных программ в сферу управления искусственным интеллектом и экономики здравоохранения в деятельность кластера для подготовки кадров, способных работать в междисциплинарной среде; инвестиции в инновации с достигаемыми медико-демографическими и экономическими показателями.

Ключевые слова: научно-медицинский кластер, управление здравоохранением.

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Список сокращений

НМОК – научно-медицинский образовательный кластер;

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INTRODUCTION

Modern technology plays a key role in the development and enhancement of competitive capacity of countries on the international arena. The Russian Federation independently shapes the technological policy by continuously improving its effort in the sphere of science and innovation, by controlling the critically important technology ensuring their stability

and independent development. It is worthwhile analyzing the country's internal approaches to identify the priorities of development in the sphere of technology via integration of science, education and technology [1, 2].

Medicine is one of the dynamically developing areas of science and practice. Innovative approaches towards diagnostics, treatment and prevention of diseases necessitate

continuous updating of knowledge and technology. At the same time, successful implementation of scientific ideas is impossible without the joint effort of scientists, doctors, entrepreneurs and state structures. Development of modern medicine calls for a comprehensive approach comprising close cooperation between the scientific, medical, educational, commercial and state public institutions. In the context of the global technological race, formation of scientific medical clusters becomes a strategic priority to ensure competitive capacity of the nation [3, 4].

According to the "Triple Helix" theory of H. Etzkowitz (2017), an innovative ecosystem emerges at the intersection of interests of three stakeholders: the academic institutions, the business and the state; each of them having its specific features. However, they all are interconnected and are indispensable for the national sovereignty. At present, the Triple Helix model gains more importance in the light of implementation of "Healthcare" and "Science" national projects, both focusing on the development of critical technologies [5].

The scientific, educational and technological components in the sphere of healthcare promote the formation of a specific scientific and technological environment, the scientific and medical educational cluster (SMEC). Studies show that the medical industry has a multiplicative effect: every Ruble invested in the healthcare generates up to three Rubles of added value via creation of jobs, development of related industries improvement of quality of human capital. At the same time, some researchers note an imbalance between the scientific potential and commercialization of research: only 12% of medical patents are implemented in clinical practice [6, 7].

The formation of the SMEC is an effective tool to achieve sustainable growth and improved competitive capacity of regions. This opportunity allows for integration of resources and competences of all stakeholders by creating conditions to scale scientific achievements and implementation of advanced technologies in the daily medical practice [8, 9].

Development of artificial intelligence (AI) technologies has transformed approaches to the interaction between the doctor and the patient making remote follow-up, automated data processing and creation of new decision-making support tools possible. The major contribution of AI lies in its capacity of processing heterogeneous medical data creating substantially new possibilities to customize medical assistance. The rapid development of AI and the specifics of management in the medical sphere necessitate AI product developers and medical institutions to cooperate within the cluster in order to focus on specific areas of medicine and to select those AI products that meet their business model, have potential for further commercialization and can be smoothly and organically implemented in the regional healthcare systems. It is obvious therefore that some of the most important characteristics of a modern SMEC include its digital infrastructure [10–12].

■ AIM

To study modern approaches to the development of scientific-medical educational clusters as a tool for addressing strategic objectives of public health and healthcare organization on the regional level.

■ MATERIAL AND METHODS

The materials were scientific publications on the country's SMEC over the past ten years.

The study utilized a content analysis and generalized the literature data to assess the potential effect of clustering on the key indicators of people's health and efficiency of resource use considering the results of analysis of opinions on the work of scientific and medical educational clusters from heads of medical organizations, representatives of executive authorities and profile departments in regional healthcare structures.

The analytical method was used to study the successful practices of integration of structural components of science, education and medicine into clusters, specifically, the project "Smart platform of cardiovascular pathology diagnostics" (Oryol), that allowed for appraisal of the effect for the healthcare system, viz. reduction of diagnostic time and reduction of load on X-ray specialists, and results of the "MedBioTech" acceleration program.

The system analysis and the method of organizational modeling was used for the structural and functional characteristics of the cluster, its participants, and for the identification of methods of solving the problems related to scientific and medical clusters from the perspective of healthcare management in the regions.

■ RESULTS

In the course of the study, the modern SMEC was defined as a system of related organizations and institutions united with a single goal of promoting medical innovations and improvement of efficiency of provision of medical services [3].

The major components of the cluster are institutions of higher medical and pharmaceutical education, research institutes and laboratories, clinical hospitals and specialized medical organizations, pharmaceutical and medical device manufacturing companies, and state structures regulating the industry and supporting the financing programs [8, 13].

The advantages of SMEC organization include improved performance and reduced cost of research, improved availability of high-quality medical services for the population, stimulation of technological progress and development of new approaches towards disease diagnostics and treatment, improvement of regional economic activity by increase of number of jobs and amount of tax revenue.

In the modern conditions, medical clusters also have some fundamental specific features related to additional sources of external financing, lack of fixed linkage to geographical location of stakeholders, importance of implementation of modern information and computer technologies, as well as different approaches to administration of emergency and planned medical intervention [14].

Cluster approach in the knowledge-based economy became one of the driving forces in the strategies of social and economic development of Russia, which lead to state that the cluster approach is actively used in education [15].

At the same time, there are some barriers that preclude active formation of a full-scale scientific and medical cluster: insufficient coordination of actions between representatives of

Strengths	Weaknesses
Availability of scientific research projects with patents in the sphere of biotechnologies. Support of state digital programs.	Low investment activity (below 5% of the gross regional product). Outflow of young specialists (approx. 12% over five years).
Opportunities	Threats
Participation in federal grants (national projects). Partnership with JSC "Aviaavtomatika" (transfer of technology).	Competition with Moscow clusters. Sanctions restricting equipment export.

Table 1. SWOT analysis of the medical cluster potential in the Oryol region

Таблица 1. SWOT-анализ потенциала медицинского кластера Орловской области

different structures; limited financial resources to implement ambitious projects; insufficient motivation of commercial companies to invest in long-term projects; low level of public awareness of the existing initiatives and prospects of cluster development [16, 17].

We performed a SWOT-analysis of the potential of the medical cluster and considered its strengths, weaknesses, opportunities and threats using the example of the Oryol Region (**Table 1**) [18].

The SWOT-analysis of the potential of the Oryol Region revealed that the key threats are not just the sanctions but rather the internal organizational barriers, namely low investment activity, outflow of workforce and weak coordination of efforts.

It is worthwhile mentioning some economic effects of clusterization. Implementation of an AI diagnostic platform in 12 medical institutions of the region (2022-2023) resulted in reduced time of processing of CT scans by 40%; reduced expenditure on repeated examinations by 18 million Rubles per year; increased patient satisfaction up to 89% in 2023 (vs. 67% in 2021). According to the forecast of the cluster multiplicative effect, by the year 2030, additional 1200 jobs will be created and the tax revenue will increase by 2.3 billion Rubles.

Organization of scientific and medical clusters is an important element of innovative development of the Oryol Region, but this process involves some administrative obstacles and institutional complications.

DISCUSSION

Organization of the scientific and medical cluster is a vital factor of innovative development of the region. Thanks to the consolidated effort of all stakeholders, it is possible to achieve a qualitatively new level of provision of medical services, enhancement of investment attractiveness of the region and strengthening of positions of Russian manufacturers of drugs and medical equipment. Successful implementation of these tasks will necessitate energetic interaction between all stakeholders of the process, and consistent implementation of proposals and recommendations.

Having analyzed the existing experience, we identified some challenges in the organization of scientific and medical educational clusters and methods of their resolution (**Table 2**).

To address these challenges, it is necessary to create effective mechanisms of interaction between all participants of the process. These mechanisms include the following components: organization of a coordination council for regular discussions of issues of interaction and development of a reconciled strategy; financial support, i.e. raising of grants and focused financing to implement significant projects; informational openness, or transparency in the questions of resource distribution and promotion of successful practices; preparation of workforce reserve – development of special training and internship programs for aspiring specialists; use of AI technologies that improve training outcomes by creating a personalized, immersive and interactive environment and support clinical

Challenge	Core	Methods of resolution
High initial expenditure	Deployment of SMEC infrastructure requires substantial financial investment. Construction of laboratories, medical institutions, procurement of equipment and modern jobs require investment of capital. Without state support and raising of private investment, such projects render economically unviable.	Public-private partnership (PPP), raising of grants and subsidies from federal and regional authorities, use of tax incentives and preferences for investors.
Underqualified workforce	Scientific and medical centers require highly qualified specialists including doctors, researchers and engineers. Understaffing in Russian regions is a serious problem related to low standard of living, lack of social conditions and low salaries.	Creation of attractive working conditions, increased salaries, development of educational programs to train specialists in the local higher educational institutions, relocation and adaptation programs for new employees.
Limited access to financing of scientific research	Financing of scientific projects largely depends on state grants and contracts that are distributed in a centralized fashion. Regional scientific institutions face limited access to such resources, especially in the conditions of competition with large federal scientific centers.	Forming of a regional scientific policy aimed to support local initiatives, development of mechanisms of targeted financing of prospective areas of science and medicine.
Underdeveloped technological chains	Successful performance of SMECs required close links between the science, education and industry. Lack of established technological chains complicates implementation of research achievements into practice and decreases competitive capacity of products and services.	Development of cooperation between universities, research institutions and industry, support of startups and innovative companies, organization of specialized technoparks and business incubators.
Problems of interaction between business and science	Private investors and entrepreneurs are often under-informed about the prospects of cooperation with the scientific community. Low level of trust and lack of experience of management of joint projects also preclude effective interaction.	Organization of conferences, workshops and forums focusing on making contacts between the science and the business; organization of special agencies and foundations assisting development of mutually beneficial relations.

Table 2. Ways to solve problems related to scientific-medical clusters

Таблица 2. Пути решения проблем, связанных с научно-медицинскими кластерами

decision-making and sharpening of practical skills [19]; raising private investment by initiating partnership with large companies ready to invest funds in science-intensive projects.

The potential for consolidating the resources of the region in the field of medical education to subsequently create globally competitive medical products should incorporate the aforementioned competency synergies. Analysis of the conducted research on this topic also leads to the conclusion that integrating all elements of the regional SMEC will enable the selection of priority training vectors for specialists, based on an assessment of the current needs of the constituent entity of the Russian Federation [20].

CONCLUSION

Organization of scientific and medical clusters is a key factor of development of an innovative healthcare system that integrates the academic science, educational institutions, private sector and state regulation. Organization of SMEC under governance and with direct involvement of healthcare

stakeholders is a strategic tool to enhance the efficiency of the system of public health and to improve its performance indicators. The cluster model enables a shift from the disparate efforts of individual institutions to targeted, coordinated activities focused on the ultimate outcome: improvement of public health.

Key conditions for the success of a regional scientific and medical education cluster include such indicators such: the leading role of the public health authority in coordinating all cluster participants; focus on public health priorities determined through epidemiological analysis and monitoring data; the integration of educational programs in AI management and health economics into the cluster activities to train personnel capable of working in an interdisciplinary environment; and investments in innovations with achievable medical-demographic and economic indicators.

A prospective area of further research is the development of a system of performance indicators of the SMEC integrated with criteria of evaluation of work of administrators of health authorities and medical institutions. ■

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Sociological analysis of medical and preventive care needs among students of a Russian multidisciplinary university

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Abstract

Aim: to identify students' needs for medical and preventive care, identify barriers to access to medical services, and assess readiness to implement the integrated University of Health model using the example of the RUDN University.

Material and methods. A sociological survey was conducted by interviewing 682 students (489 Russian, 193 foreigners) aged 17-35 years, divided into different courses, faculties and areas of study. An author's questionnaire of 60 questions was used with the inclusion of a validated EQ-5D-5L questionnaire to assess the quality of life.

Results. The majority of students (73.2%) rated their health as good and excellent. However, a significant number of students noted difficulties with mental and emotional health. Anxiety states were noted in 44.7% of students, the average value on the EQ-5D-5L health scale was 70.8 ± 15.2 points out of 100. Limited physical activity is observed in 39.3% of students, insufficient

sleep is typical for 49.8% of respondents. 89.4% of students are aware of the presence of the university Clinical Diagnostic Center, while only 52.8% applied there. The main barriers to access are organizational (long waiting 20.1%, inconvenient time 15.0%). 69.6% of students are positive about the idea of the integrated "University of Health" model and 67.7% are ready to actively use the services offered.

Conclusion. The study confirms the need to develop an integrated model of medical and preventive care. The high readiness of students for the concept of the "University of Health" creates conditions for the successful implementation of this model in the practice of a multidisciplinary university.

Keywords: medical and preventive care, accessibility of medical care, academic medical cluster, University of health.

Conflict of interest: nothing to disclose.

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Социологический анализ потребностей студентов российского многопрофильного университета в медико-профилактической помощи

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Аннотация

Цель: выявить потребности студентов в медико-профилактической помощи, определить барьеры доступа к медицинским услугам и оценить готовность к внедрению интегрированной модели «Университет здоровья» на примере РУДН им. Патриса Лумумбы.

Материал и методы. Проведено социологическое исследование методом анкетирования 682 студентов (489 российских, 193 иностранных) в возрасте 17–35 лет, распределенных по разным курсам, факультетам и направлениям подготовки. Использована авторская анкета из 60 вопросов с включением валидированного опросника EQ-5D-5L для оценки качества жизни.

Результаты. Большинство студентов (73,2%) оценили свое здоровье как хорошее и отличное. Однако значительное число обучающихся отметили сложности с психоэмоциональным здоровьем. Тревожные состояния отмечены у 44,7% студентов, среднее значение по шкале здоровья EQ-5D-5L составило $70,8 \pm 15,2$ балла из 100. Ограниченная физическая активность наблюдается у 39,3% студентов, недостаточный

сон характерен для 49,8% опрошенных. 89,4% студентов осведомлены о наличии Клинико-диагностического центра университета, однако обращались туда только 52,8%. Основными барьерами доступа являются организационные (длительное ожидание 20,1%, неудобное время 15,0%). 69,6% студентов положительно относятся к идее интегрированной модели «Университет здоровья» и 67,7% готовы активно использовать предлагаемые услуги.

Заключение. Исследование подтверждает необходимость развития интегрированной модели медико-профилактической помощи. Высокая готовность студентов к концепции «Университет здоровья» создает условия для успешной реализации этой модели в практике многопрофильного университета.

Ключевые слова: медико-профилактическая помощь, доступность медицинской помощи, академический медицинский кластер, университет здоровья.

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■ INTRODUCTION

Students are a special social group experiencing a critical period of formation of fundamental habits and stereotypes that shape their health for their entire life. Entering a university comes with a marked stress of the adaptive potential of the organism and exposes it to many risk factors that often surpass the adaptive capacity [1–3]. Preservation of students' health is one of priority tasks of the education and the healthcare systems of the Russian Federation.

Scientific research performed in Russian higher education institutions shows that over 50% of students have health disorders. Studies of the Research Institute of Hygiene and Health Protection of Children and Adolescents show that in the past two decades prevalence of functional disorders among young people has increased significantly. Intensive academic activity, psycho-emotional stress, unhealthy living, lack of physical activity, sleeping and food pattern disorders contribute to development of various diseases and functional disorders [4–6].

The problem of psycho-emotional condition of students is especially urgent. According to the research performed in 2024 by the scientists of Moscow City Pedagogical University, the most common psychological problem of students is high anxiety identified in 46% respondents, while 32% of the students experience difficulties in the identification of life goals and require psychological support [7].

Modern healthcare research confirms a direct correlation between the health of the students and their academic performance. Thus, unfavorable physical condition may significantly reduce academic efficiency precluding achievement of educational goals and might result in academic expulsion. Support of students' health becomes not just a medical but rather pedagogical task of utmost importance [8, 9].

At the same time, the present-day system of medical assistance to students in the Russian universities is often fragmented and insufficiently integrated. Primary healthcare, prevention activities, sanatorium and resort treatment and rehabilitation often function as separate weakly connected components. This results in an inefficient use of resources and precludes full satisfaction of students' needs in a comprehensive medical and preventive care [10, 11].

Considering the above, more and more attention is paid to the development of the Health Promoting University concept recommended by the WHO. It comprises a comprehensive integrated approach towards improvement of health of all members of the university community including students and faculty by bringing together the effort of the medical services, academic units, administration and social services. The integrated model provides a coordinated provision of medical care, prevention care, healthy living promotion programs and psychological support in the unified organizational system [12–14].

The Patrice Lumumba Peoples' Friendship University of Russia (RUDN) is a multidisciplinary university, the alma mater for students from 152 countries of the globe. On the one hand, this creates additional opportunities for

the cultural enrichment of the students; on the other hand, it forms specific challenges in supporting their health including language barriers, adaptation complications, differences in the cultural approaches to health and perception of medical services [15, 16].

The RUDN had a Clinical Diagnostic Center (CDC), healthcare center and several other medical divisions including the university clinical hospital. Despite these resources, the integral model of medical and preventive care to students that would unite these components in an effective manner has yet to be created. At the moment, the academic medical cluster is formed that would have to assume responsibility and respond to all the healthcare needs of the students and the faculty.

■ AIM

To identify students' needs for medical and preventive care, identify barriers to access to medical services, and assess readiness to implement the integrated University of Health model using the example of the RUDN University.

■ MATERIAL AND METHODS

This study is a descriptive cross-sectional sociological study planned and performed with the generally accepted standards of social-hygienic monitoring. The choice of this design is accounted for by the need to obtain a cross-sectional concept of prevalence of various health metrics, student behavior and needs in medical and preventive care at certain moments. The main tool to obtain information was sociological surveys implemented by questionnaires. It enabled an outreach to a representative sample, collection of systematized data from the general aggregate, collection of systematized data across a wide range of questions on the health status, behavioral risk factors, lifestyle, availability and use of medical services, as well as of attitude towards innovative integrated models of medical care.

The study was performed at the Patrice Lumumba Peoples' Friendship University of Russia. The data were collected for four weeks in September 2025. This period allowed minimizing of the impact of seasonal fluctuations of health condition and avoiding periods of maximum academic load, that could have adversely influenced the quality and the completeness of responses. The questionnaire was made in the Russian language and later professionally translated into the English language to ensure its accessibility for foreign citizens without a proper command of Russian.

The general population of the study were full-time students from their first to sixth year taking master's, resident's and postgraduate courses. It was divided into five majors (medical, engineering-technical, humanitarian, scientific and economic), which ensured high heterogeneity across educational profiles.

Inclusion criteria: students of at least 17 years of age, capable of reading and filling out the questionnaire in the Russian or English language, providing a written informed consent to participate in the study.

Exclusion criteria: students not enrolled in full-time courses, students on academic leave, providing responses

not to all questions, students demonstrating obvious signs of careless, random or deliberately incorrect responses to questions in the questionnaire (e.g., identical responses to all questions or logically incompatible combinations of responses).

The sample size was calculated in compliance with principles of mathematical statistics in order to provide sufficient power of the study. The calculation included the following parameters: confidence interval 95% ($\alpha = 0.05$), statistical accuracy of the study 80% ($1-\beta = 0.80$), allowed error of sampling $\pm 4\%$, which is standard for sociological surveys of this scale, and the tentative share of the feature in the general sample of $p = 0.5$ (the maximum conservative evaluation providing the maximum required sample volume). The application of the calculation formula enabled the calculation of the minimally required number of 600 respondents. As the result of the study, the total number of respondents was 682 people, which exceeded the minimally required amount and provided an adequate power for all planned analyses.

The participants of the study were selected by stratified random sampling. This approach ensured a proportionate representation of all significant subgroups of the general total and prevented a systematic shift of results. The general total was stratified by three major features: 1) year of study, since the students of different years may have significantly differing needs in medical and preventive care depending on their adaptation to the university; 2) faculty or major, considering that students from the medical major have a higher awareness of health care; 3) citizenship (Russian or foreign), considering potential differences in cultural aspects.

Within each stratum, the respondents were selected by simple random sampling using pseudo-random number generation algorithm (a function of SPSS Statistics 26.0). The size of each stratum in the sample was proportionate to the size of the respective stratum in the general total of the RUDN, which ensured that the final sampling was representative.

At the outset of the study, invitations were sent to 780 students selected under the above mentioned procedure of the stratified random sampling. Consent for participation was obtained from 722 students (92.6% of all invited individuals). Later, 710 students returned their completed questionnaires (91.0% of invited individuals). Following the data quality control (checking of completeness of questionnaire fill-out, logical consistency of responses and lack of signs of careless completion), the final analysis included 682 students or 87.3% of the initial number of invited individuals and 96.1% of individuals who returned their questionnaires. The high percentage of responses shows good motivation of the students to participate in the study and good quality of research procedures.

In order to collect the data, the authors developed a complex structured questionnaire. It was based on consultations with experts in the sphere of healthcare and student medicine, and on a tentative pilot test on a sample of 50 students not included in the main study.

The questionnaire consisted of 60 questions organized in nine logically connected sections. Section 1 contained

10 questions to collect social-demographic and social-economic characteristics of respondents. Section 2 had 10 question on self-assessment of health and on behavioral risk factors. Section 3 had 8 questions on social determinants of health. Section 4 had 13 questions on the use of medical services including awareness of the RUDN CDC. Section 5 had 6 questions to study awareness of the concept of the University of Health integrated model concept. Section 6 had 5 questions on the needs of students in prevention services. Section 7 was a set of questions of the WHO validated EQ-5D-5L questionnaire including five dimensions of quality of life (mobility, self-care, regular activities, pain/discomfort, anxiety/depression). Section 8 had 2 questions on the students' informational needs. Section 9 had 3 open questions to allow students formulate proposals to improve medical care, remarks, and provide additional comments.

Statistical processing of data was performed in the SPSS Statistics v. 26.0 (IBM, USA) with additional R ver. 4.0 for specialized analytics, and in Microsoft Excel 2019 for data preparation and visualization. The level of statistical significance for all tests was set at $p < 0.05$.

■ RESULTS

The sample demonstrated high representativeness in the main social and demographic parameters and adequately reflected the structure of the student population of the university. The gender distribution showed a slightly higher percentage of women ($n=367$, 53.8%) over men ($n=315$, 46.2%), which matches the general trend in the Russian higher education. In terms of age, the most numerous group comprised students aged 20–22 ($n=265$, 38.9%), which is logically explained by the distribution across years of study. In terms of citizenship, the sample included a majority of Russian ($n=489$, 71.7%) over foreign citizens ($n=193$, 28.3%), which reflects the distribution in the student community of the RUDN. In their majors of study, the students represented the medical (26.7%, $n=182$), humanitarian (24.6%, $n=168$), engineering and technical (23.8%, $n=162$), scientific (19.9%, $n=136$) and economic (5.0%, $n=34$) majors. The detailed distribution of the sample across all social and demographic features is shown in **Table 1**.

The analysis of self-assessment of health revealed a positive perception of the health condition by students. The majority of students estimated their health as good (308 students, 45.2%) or excellent (191 students, 28.0%), making a total of 73.2% of the sample with a positive self-assessment of health (95% CI: 69.7–76.5%). At the same time, a substantial part of students (183 students, 26.8%) indicated presence of health problems and estimated their health as satisfactory (136 students, 19.9%), bad (38 students, 5.6%), or very bad (9 students, 1.3%).

The level of physical activity of the students was lower than expected. The majority of students ($n=268$, 39.3%) had a low level of physical activity practicing sports less than twice a week or not practicing sports at all. The distribution of activity levels was as follows: 2-3 times a week for 237 students (34.8%), 4-5 times a week for 136 students (19.9%), daily, for 41 students (6.0%), once a

Feature	N	%	95% CI	Feature	N	%	95% CI
Sex				Citizenship			
Women	367	53.8	50.0–57.5	Russian	489	71.7	68.2–75.0
Men	315	46.2	42.5–50.0	Foreign	193	28.3	25.0–31.8
Age, years				Study major			
17–19	122	17.9	15.1–20.9	Medical	182	26.7	23.5–30.1
20–22	265	38.9	35.2–42.7	Humanitarian	168	24.6	21.6–27.9
23–25	187	27.4	24.1–30.9	Engineering and technical	162	23.8	20.9–27.0
26–35	108	15.8	13.2–18.8	Scientific	136	19.9	17.1–23.1
Year of study				Economic	34	5.0	3.5–6.9
Year 1	122	17.9	15.1–20.9				
Year 2	163	23.9	21.0–27.1				
Year 3	156	22.9	19.9–26.1				
Year 4	102	15.0	12.5–17.8				
Master's course	139	20.4	17.6–23.5				

Notes: CI – confidence interval (95%), n – absolute number, % – relative frequency

Примечания: ДИ – доверительный интервал (95%), n – абсолютное количество, % – относительная частота.

Table 1. Socio-demographic characteristics of the sample (N=682)

Таблица 1. Социально-демографические характеристики выборки (N=682)

week for 102 students (15.0%), less than once a week for 68 students (10.0%), no sports activities for 102 students (15.0%). Only 196 individuals (28.7%) had a high level of physical activity (4-5 time a week or more), which shows the necessity of promotion of physical activities among student youth.

Students' nutrition, assessed by frequency of consumption of fruit and vegetables, showed insufficient consumption by the majority of population. Only 136 students (19.9%) consumed fruit and vegetables daily, 171 students (25.1%), 5-6 days a week, 171 students (25.1%), 3-4 days a week, 136 students (19.9%), 1-2 days a week, and 68 students (10.0%) never consumed fruit and vegetables. Generally, only 45.0% (n=307) students consumed fruit and vegetables more than three days per week, which necessitates improvement of nutrition habits among the student population.

The duration of sleep for students is a significant problem. The average duration of sleep was 6.9 ± 1.8 hours, while the WHO recommendation is 7–9 hours for adult young individuals. Almost half of the students (n=340, 49.8%, 95% CI: 46.0–53.6%) slept less than the recommended number of hours. Thus, 56 students (8.2%) slept less than 5 hours, 130 students (19.1%) slept for 5-6 hours, 173 students (25.4%) students slept for 6-7 hours. Two hundred students (29.3%) had adequate hours of sleep (7-8 hours), 102 students (15.0%) students slept for 8-9 hours, and 41 students (6.0%) slept for more than 9 hours. Thus, chronic sleep debt is a widely spread problem among the student population of the RUDN. It correlates with high levels of stress and may significantly affect the quality of life.

The levels of stress related to academic activity was quite high. 286 students experienced stress often or very often (42.0%), 239 students experienced stress sometimes (35.0%), seldom, 102 students (14.9%), never, 55 students (8.1%). Thus, the absolute majority of students (77.0%) experienced some or other degree of academic stress, and 42.0% experienced it often or always.

The analysis of socioeconomic factors affecting the health of students revealed considerable differences

in the material circumstances of living. Good material status of families was reported by 238 students (34.9%), average, by 307 students (45.0%), difficult, by 102 students (15.0%), and very hard, by 35 students (5.1%). It is to be noted that the influence of financial difficulties on their health was admitted by 165 students (24.2%), showing a direct correlation between the economic factors and perception of health status. This fact emphasizes the importance of accounting for socioeconomic determinants in the development of health improvement programs for students.

Availability of time to rest and recreate is a critical factor for health maintenance. 136 students (19.9%) responded often having the time to rest, 273 students (40.0%), sometimes, 205 students (30.1%) rarely, and 68 students (10.0%), almost never. Thus, 40.1% students had limited time to rest, which correlates with a high level of stress and creates prerequisites for the development of psycho-emotional problems.

Access to sports facilities in the universities was assessed as available and actively used by 82 students (12.0%); 273 students (40.0%) students responded "access to sports facilities is available, but I use them rarely"; 136 students (19.9%) responded "access to sports facilities is available, but not convenient for me"; 136 students (19.9%) reported limited availability of sports facilities, and 41 students (6.0%) reported "no access to sports facilities". Despite the availability of sports and recreation facilities at the university, the same are underutilized by the students. This may reflect organizational complications and low motivation of the students.

The use of services of the RUDN Clinical Diagnostic Center by students reveals a considerable gap between the awareness and the reality. The awareness of the availability of the CDC was high: 205 students (30.1%) knew about the CDC and sought care, 273 students (40.0%) knew about it but did not seek care in it, 136 students (19.9%) heard about it, and only 68 students (10.0%) were not aware of its existence. Thus, 89.4% (610 students, 95% CI: 87.0–91.5%) of students were aware of the existence

of the CDC at the university to some extent; at the same time, this high degree of awareness did not convert into the respective use of services for the majority of student population.

The actual use of CDC services by the students within the past year showed the following distribution. Thus, 82 students (12.0%) appealed to the CDC several times (over 5 times per year); a few (2–5) times, 137 students (20.1%); once, 123 students (18.0%). In total, 360 students (52.8%, 95% CI: 49.0–56.6%) appealed to the CDC at least once within the past year. At the same time, 171 students (25.1%) never appealed to the CDC but wanted to, and 169 students (24.8%) never appealed to the CDC and had no wish to do so. In other words, half of the students (322 individuals, 47.2%) did not use CDC services within the studied period, despite their availability, which relates to main outcomes of the access difficulty analysis.

Among the students who did appeal to the CDC (n=360), the quality of services was assessed as follows. 71 students (19.7%) evaluated them as excellent, 145 students (40.3%) as good, 90 students (25.0%) as satisfactory, and 36 students (10.0%), as bad. Thus, 60.0% students (216 individuals), already using the CDC services, assessed them positively (excellent or good), which shows a rather high level of satisfaction among students who actually appealed to the CDC and implies that the major problem lies not in the quality of services but in their availability.

The analysis of barriers precluding students' access to medical services revealed a distinct structure shown in **Fig. 1**. Organizational barriers were the most significant (65.1% from all mentioned obstacles), including the long wait for admission (20.1%), inconvenient working hours of the CDC (15.0%), remote location (12.0%), complicated appointment system (10.0%), insufficient information (8.1%). Medical barriers (38.3%) included a limited range of services (15.0%), insufficient number of profile specialists (10.0%), lack of psychological services (8.1%), low quality of services (5.3%). Financial barriers (16.0%) were expressed in a lesser degree: the high cost of services was mentioned by 68 students (10.0%), lack of insurance by 41 students (6.0%). Psychological barriers (20.1%) included shyness or fear of appealing to the CDC (8.1%), language barrier, for foreigners (7.0%), lack of trust to medical services (5.0%). Thus, the obtained data indicates the priority task of removing the organizational barriers in the development of the systems of medical care for students.

The correlation between the students' citizenship and the use of CDC services, shown in **Fig. 2**, revealed statistically significant differences. Russian students appealed to the CDC in 55.8% of the cases (273 students), while the foreign students did so in 45.6% of the cases (88 students, $p=0.048$). This difference may stem from language barriers and from the differences in the cultural perception of medical services and their availability.

The sanatorium and rehabilitation facility of the RUDN is used even less than the CDC. 55 students (8.1%) applied there more than once; 82 students (12.0%), only once; 136 students (19.9%) never applied there but would like

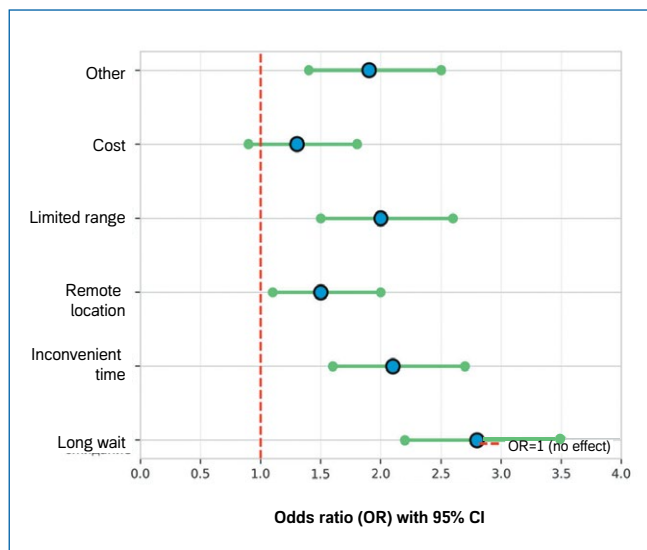


Figure 1. Barriers to access to medical services.

Рисунок 1. Барьеры доступа к медицинским услугам.

to; 171 students (25.1%) were not aware of its existence; and 238 students (34.9%) never applied there and had no wish to do so. Thus, 60.0% of students either did not know about the existence of the sanatorium and rehabilitation facility or never used its services, which points at a critical need of raising awareness of this important resource.

A comprehensive analysis of students' quality of life using the EQ-5D-5L questionnaire revealed significant differences in the distribution of problems across individual components. The use of the questionnaire provided an objective assessment independent of the subjective health self-assessment identified earlier.

The analysis of components showed a most favorable situation in the "Self-care" component, where 546 students (80.1%) had no problems, and 136 students (19.9%) had problems of various degrees of manifestation. "Mobility" was problematic for 205 students (30.0%), while 477 students (70.0%) experienced no limitations. "Habitual activities" were limited for 238 students (34.9%), while 444 students (65.1%) experienced no such limitations. The greatest problems were identified in the following components: "Pain/Discomfort" (273 students, 40.0% with problems), especially in the "Anxiety/Depression" component (305 students, 44.7% with problems, 95% CI: 41.0–48.5%). Thus, psychoemotional problems were the most prevalent among students, which aligns with the previously identified high stress levels and warrants serious attention in the development of health promotion programs.

The visual analog scale (VAS) of the EQ-5D-5L questionnaire showed an average score of 70.8 ± 15.2 points out of 100 (95% CI: 69.6–72.0), with a median of 72 points (interquartile range 60–82). The distribution of students in their evaluations was as follows. The score of 90–100 points (excellent) was given by 82 students (12.0%); 70–89 points (good) by 308 students (45.2%); 50–69 points (satisfactory) by 205 students (30.1%); 30–49 points (bad) by 68 students (10.0%); below 30 points (very bad) by 19 students (2.8%). Thus, the average

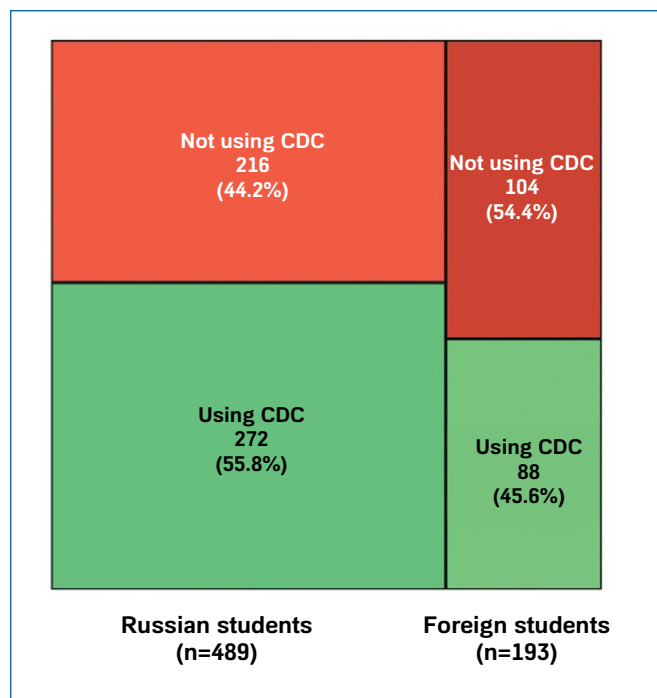


Figure 2. Use of CDC services, by citizenship.
Рисунок 2. Использование услуг КДЦ по гражданству.

quality of life as per VAS was 70.8, showing a necessity of focused intervention to improve the outcomes, especially considering the fact that only 57.2% students assessed their health as good or excellent (**Fig. 3**).

Ideal health (understood as complete lack of problems in all five components of the EQ-5D-5L) was reported only by 76 students (11.1% of the sample, 95% CI: 8.9–13.6%), which indicates a high prevalence of some health problems or other among the student population. This result considerably differs from the high percentage of students (73.2%) giving a positive self-assessment of physical health that was identified earlier, which might reflect both an underestimation of existing problems by respondents and a difference between the physical and psycho-emotional components of health.

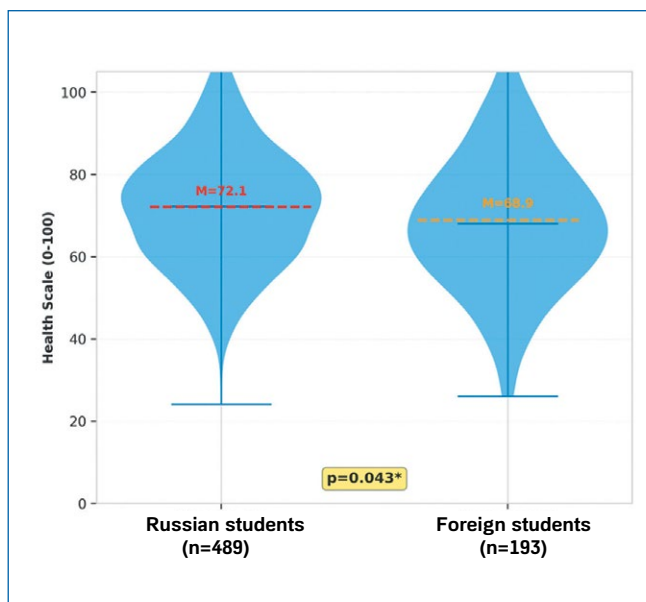


Figure 3. Distribution of quality of life indicators (EQ-5D-5L VAS).
Рисунок 3. Распределение показателей качества жизни (EQ-5D-5L VAS).

The comparative analysis of the results of the EQ-5D-5L questionnaire between the subgroups of students found some statistically significant differences (**Table 2**). The average score on the Health Scale for Russian students was 72.1±14.8 points and 68.9±15.9 points for foreign students, showing a statistically significant but clinically mild deterioration of quality of life on part of foreign students. No statistically significant differences were found between men and women (M=71.6±15.5 vs. 70.1±15.0, t=1.00, p=0.231). Students with a history of chronic diseases had significantly lower scores of quality of life (M=62.3±16.2) as compared to the students without chronic conditions (M=74.2±14.1, t=7.12, p <0.001), demonstrating a strong impact of somatic pathology on the psychosocial well-being. The students who appealed to the CDC for assistance had higher scores of quality of life (M=73.4±14.5) versus those who did not appeal there

Metric	Russian students (n=489)	Foreign students (n=193)	P	With chronic diseases (n=137)	Without chronic diseases (n=545)	t	P
Health Scale (VAS), M±SD, points	72.1±14.8	68.9±15.9	0.043*	62.3±16.2	74.2±14.1	7.12	<0.001***
Anxiety / depression, n (%)	208 (42.5)	97 (50.3)	0.067	80 (58.4)	225 (41.1)	χ²=11.52	0.001**
Appealed to the CDC, n (%)	273 (55.8)	88 (45.6)	0.048*	98 (71.5)	265 (48.6)	χ²=16.45	<0.001***
Sleep debt (<7 hrs), n (%)	231 (47.2)	107 (55.4)	0.034*	75 (54.7)	263 (48.4)	χ²=1.89	0.156
High level of stress, n (%)	196 (40.1)	89 (46.1)	0.122	69 (50.4)	217 (39.8)	χ²=5.04	0.024*
Smoking (any), n (%)	110 (22.5)	52 (26.9)	0.211	38 (27.7)	125 (22.9)	χ²=1.37	0.234
Low physical activity (<2 times per week), n (%)	184 (37.6)	84 (43.5)	0.145	60 (43.8)	208 (38.2)	χ²=1.36	0.234
Ready for the University of Health, n (%)	342 (69.9)	121 (62.7)	0.056	96 (70.1)	371 (68.1)	χ²=0.23	0.634

Notes: M – mean value; SD – standard deviation; t – Student’s t-test. Significance level: * p <0.05; ** p <0.01; *** p <0.001. Chronical conditions: history of diagnosed chronic diseases. CDC – RUDN Clinical Diagnostic Center.

Примечания: M – среднее значение; SD – стандартное отклонение; t – t-критерий Стьюдента. Уровень значимости: * p <0,05; ** p <0,01; *** p <0,001. Хрон. болезни – наличие диагностированных хронических заболеваний. КДЦ – клиничко-диагностический центр РУДН.

Table 2. Comparative analysis of EQ-5D-5L indicators between subgroups of students

Таблица 2. Сравнительный анализ показателей EQ-5D-5L между подгруппами студентов

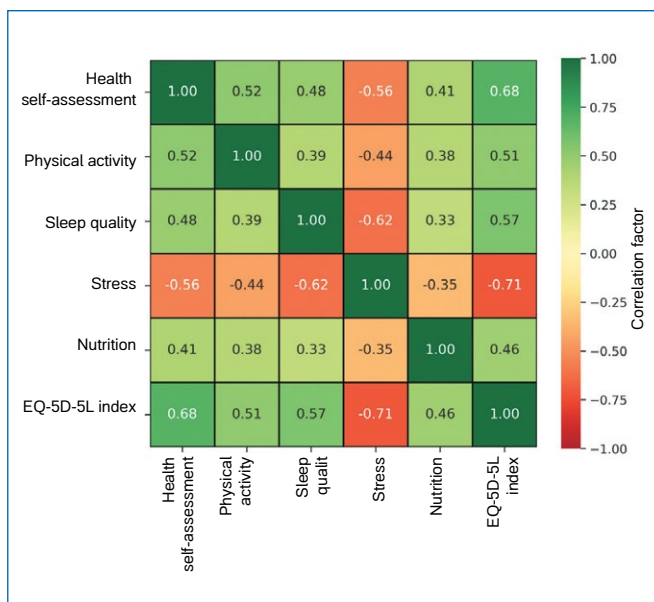


Figure 4. Correlation matrix of student health factors (n=682).
Рисунок 4. Корреляционная матрица факторов здоровья студентов (n=682).

($M=68.1 \pm 15.7$, $t=3.56$, $p=0.012$), which may indicate a positive effect of the medical assistance received and a healthy behavioral choice of students ready to seek assistance in medical institutions.

The correlation analysis (**Fig. 4**) found statistically significant correlations between health components. The strongest reverse correlations were identified between the stress level and the quality of life score ($r = -0.708$, 95% CI: $-0.744 - -0.669$, $p < 0.001$), emphasizing the critical importance of psycho-emotional well-being. The strong positive correlation was found between the self-assessment of health and the Health Scale score ($r = 0.682$, 95% CI: $0.639-0.722$, $p < 0.001$).

The quality of sleep showed strong negative correlations with stress levels ($r = -0.624$, $p < 0.001$), which confirms the known mechanisms of mutual effect of these factors. Physical activity showed a moderate positive correlation with the quality of life ($r = 0.518$, $p < 0.001$) (**Fig. 5**), indicating a proven positive effect of active lifestyle.

The students' awareness of the concept of the integrated medical cluster "University of Health" showed the following distribution. The concept was known to and understood by 123 students (18.0%); 239 students (35.0%) heard about it; 185 students never heard about it (27.1%); 135 students (19.8%) first learned about it within the study. Thus, 53.0% were to some extent aware of the concept of the "University of health", while 47.0% either were not aware of it or heard about it for the first time. This result indicates a necessity of raising the students' awareness of the possibilities of an integrated approach towards medical care.

The understanding of the concept of the "University of Health" by students was diverse and incomplete. Integrated medical services, as the core of the concept, were properly identified by 238 students (34.9%), promotion of healthy lifestyle was seen in the concept by 171 students (25.1%), expansion of sport possibilities by

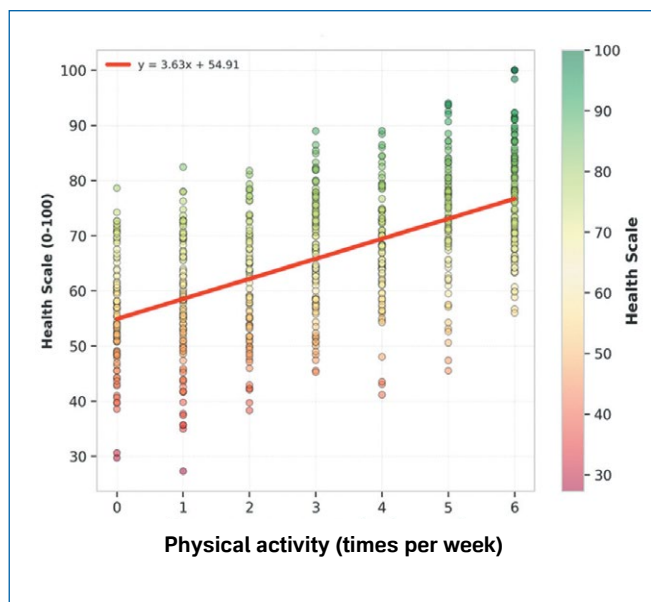


Figure 5. Correlation of physical activity and quality of life, $p < 0.001$.
Рисунок 5. Корреляция физической активности и качества жизни, $p < 0.001$.

82 students (12.0%), improvement of food habits, by 55 students (8.1%), combination of different approaches, by 82 students (12.0%), and 55 students were not aware of the concept (8.1%). Thus, only 34.9% of the students had a clear understanding of the integrated and systemic nature of the model, which shows the necessity of educational activities to improve the understanding of the concept.

The students' attitude towards the idea of integrated medical care within the concept of the "University of Health" was generally positive: 191 students (28.0%) expressed a highly positive attitude; 284 students (41.6%), a positive attitude; 137 students (20.1%) had a neutral attitude; negative attitude was expressed by 55 students (8.1%), and highly negative, by 15 students (2.2%). In total, 475 students (69.6%, 95% CI: $66.0-73.0\%$) had a positive attitude towards the idea of the "University of health", which shows a high potential of the implementation of this model into the practice of the university.

The students' readiness to use the services of the integrated model was even higher than the positive attitude towards the idea. 218 students (31.9%) were definitely ready to use such services; 244 students (35.8%) were rather ready to use the services; 150 students (22.0%) were neutral about using the services; 55 students (8.1%) were rather not ready to use the services, and 15 students (2.2%) were definitely not ready to use the services. Thus, 462 students (67.7%, 95% CI: $64.0-71.2\%$) expressed their readiness to actively use the services of the proposed integrated model, which shows the high demand and significant potential for the successful implementation of this project at RUDN.

Analysis of students' interest in various types of preventive services revealed differentiated needs. The greatest interest was shown in mental health screening (205 students, 30.1%), which logically correlates with the previously identified high prevalence of psycho-emotional problems and stress levels. Clinical examination interested

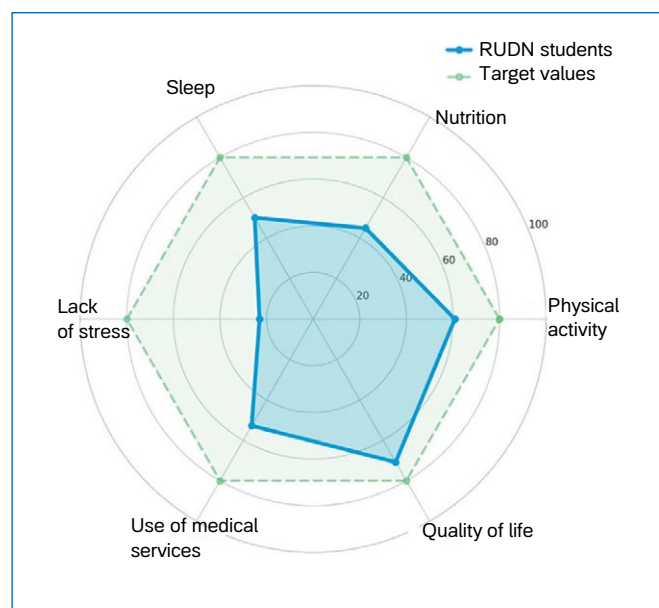


Figure 6. Students' health profile (% or points).
Рисунок 6. Профиль здоровья студентов (% или баллы).

171 students (25.1%); vaccination interested 136 students (19.9%); dental preventive care, 123 students (18.0%); sports medicine interested 102 students (15.0%). Less popular, yet still significant, were other types of prevention (gynecological, urological, nutritional care; prevention of dermatological, orthopedic, and gastrointestinal conditions), with interest ranging from 6% to 15%.

DISCUSSION

The present study revealed a complex picture in which high rates of subjective well-being among students coexist with significant objective psycho-emotional problems, insufficient physical activity, and unhealthy lifestyle patterns (**Fig. 6**).

An interesting observation was the paradoxical difference between the students' self-assessment of their health (73.2% students assessed their health as good or excellent) and the results of an objective measurement of quality of life using the EQ-5D-5L questionnaire (average score on the Health Scale 70.8 ± 15.2 points, only 11.1% with ideal health). This discrepancy may be accounted for by several factors. First, the students, being young people, are prone to perceive their health condition from the standpoint of the lack of serious somatic diseases while underestimating psycho-emotional problems, especially prevalent in the student community. Second, the adaptation to the stressful educational environment may result in the normalization of high levels of stress and psycho-emotional tension as a 'normal' condition, which is reflected in the positive self-assessment. Third, students may be under-informed as to the components of quality of life that go beyond physical health.

The most significant outcome of the study is the high prevalence of psycho-emotional problems among students. According to EQ-5D-5L, 44.7% of students had problems with anxiety and depression, which increases the incidence of problems with mobility (30.0%) or pain (40.0%). This finding aligns with the growing number of

studies demonstrating an increasing prevalence of psychic disorders including depression and anxiety disorders among students of higher educational institutions worldwide (**Fig. 6**).

The link between the high level of academic stress (77.0% of students experience some or other degree of stress, 42.0% experience is often or constantly) and psycho-emotional problems is confirmed by the significant negative correlation between the stress level and the Health Scale score ($r = -0.708, p < 0.001$). The educational process in the higher educational institution contains many stress-inducing factors, including the highly intensive academic program, necessity of achieving high academic results, financial difficulties, uncertainty with respect to the future career and adaptation to the new social environment (especially for foreign students). Moreover, the chronic lack of sleep, a common problem for almost half of respondents (49.8% students reported sleeping less than 7 hours), is a well-known aggravating factor for psycho-emotional problems and burnout syndrome.

These findings indicate an urgent need for the development of specialized psycho-emotional support for students, including access to psychological counseling, stress management programs, and interventions aimed at improving sleep quality. It is to be noted that psycho-emotional support was identified by 30.1% of students as the most interesting type of preventive care, indicating a growing awareness of this issue among the students themselves.

One of the most important correlations in the area of use of medical services was the paradox of high awareness of the CDC (89.4% respondents knew of its existence) versus relatively low of actual use (52.8% respondents appealed there within the year). Logistic regression analysis demonstrated that student awareness of the "University of Health" concept was the most significant predictor of readiness to use integrated services (OR = 3.44, 95% CI: 2.12–5.58, $p < 0.001$). However, for awareness of the CDC, this effect was less distinct, suggesting a difference between knowledge of the service's existence and understanding of its value, as well as the formation of the habit of seeking care.

Analysis of access barriers revealed that organizational barriers dominate among the reasons for not using services (65.1%), including long waiting times for appointments (20.1%), inconvenient working hours (15.0%), and remote location (12.0%). Financial barriers (16.0% of all mentioned) were less significant than might have been expected, reflecting the presence of the mandatory health insurance system and the relatively well-off financial situation of the majority of RUDN students. However, 24.2% of students indicated that financial difficulties affect their health, pointing to a discrepancy between objective access (insurance coverage) and subjective perception of financial barriers.

Another interesting point is the difference in the CDC service use by Russian (55.8%) and foreign (45.6%, $p = 0.048$) students that may reflect both the language barriers and cultural differences in the perception and use of medical services. The results indicate a necessity

of a specialized approach towards integration of foreign students into the system of medical care.

The study found a very high level of students' awareness of the necessity of an integrated approach to health. Thus, 69.6% students perceived the idea of the "University of Health" positively, and 67.7% expressed their readiness to use the proposed services. These results are considerably higher than expected and show that the RUDN student community is open to innovative models of medical care.

Logistic regression analysis revealed several interesting patterns in predictors of readiness for an integrated model. In addition to awareness of the concept (OR = 3.44), female gender was associated with increased readiness (OR = 1.25, p = 0.046), while foreign citizenship was associated with lower readiness (OR = 0.73, p = 0.018). The presence of chronic diseases, as expected, was a strong predictor of readiness (OR = 2.44, p < 0.001), reflecting the objective need for comprehensive care. Interestingly, each additional year of study correlated with a slight increase in readiness (OR = 1.09, p = 0.048), suggesting that senior students have greater experience interacting with the university healthcare system.

CONCLUSION

The results of this study have important practical consequences for the design of programs of health improvement for students and for the implementation of the "University of Health" innovative model at the RUDN. The obtained data show priority areas of development and form a reliable foundation for the planning of activities to improve the system of medical assistance to students.

Psycho-emotional support is to be regarded as the priority in the development of programs of health improvement for students. The implementation of evidence-based stress management programs is recommended, including elements of cognitive-behavioral therapy, relaxation techniques, and other methods with proven effectiveness for maintaining mental health. RUDN operates its own psychological service; however, it may become more in demand in the near future.

Overcoming organizational barriers while accessing medical services is one of the most perspective areas to introduce changes. The introduction of a modern electronic appointment scheduling system is recommended, enabling

students to book appointments at their convenience. Additionally, it is advised to extend the operating hours of the CDC to accommodate students' diverse class schedules, along with the active development of remote consultations via videoconferencing. The latter is particularly relevant in the post-pandemic context and given the growing popularity of telemedicine among young people.

Integrating health promotion programs with the core educational process appears to be a strategically important step for achieving maximum coverage and effectiveness of preventive care. It is recommended to incorporate health-preserving elements into the mandatory components of curricula across all faculties. This should include not only traditional physical education but also a modern approach to health literacy, encompassing an understanding of health components, risk factors, disease prevention methods and principles of a healthy lifestyle.

Preventive activities and educational initiatives may take place during classes as short informational sections, interactive tasks and discussions. Integration of health-preservation elements into courses of humanitarian and social sciences is an especially effective approach: it is possible to discuss the social determinants of health, effect of lifestyle on well-being and psychological aspects of health. It is also recommended to develop facultative and elective courses dedicated to various aspects of health (e.g., psycho-emotional well-being, physical activity, healthy eating) that would attract motivated students and enable them study these questions in depth.

The high level of demand for the integrated model "University of Health" revealed in the study, combined with the students' clear need in psycho-emotional support, preventive medicine and comprehensive healthcare gives RUDN a unique opportunity to lead the way in the development and implementation of innovative approaches to preservation of students' health. Successful implementation of this model may become an example for Russian and foreign universities.

The results of the study show that with some specific conditions present it is possible to create an independent healthcare system that would readily respond to needs of young people and assist improvement of quality of life of students, which in its turn may have a positive effect on the quality of education and training of aspiring specialists. ■

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Consent for publication. All study participants signed a written informed consent form.	Согласие на публикацию. Все участники исследования подписывали добровольное информированное согласие.
Study funding. The study was the author's initiative without external funding.	Источник финансирования. Исследование выполнено по инициативе автора без привлечения финансирования.
Conflict of interest. The author declares that there are no obvious or potential conflicts of interest associated with the content of this article.	Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Statement of originality. No previously published material (text, images, or data) was used in this work.	Оригинальность. При создании настоящей работы автор не использовал ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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Diagnostic value of blood biomarkers for the diagnosis of lung cancer

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Abstract

Aim: to evaluate the diagnostic value of 20 biomarkers in lung cancer and to determine their informative value for potential use in clinical practice.

Material and methods. The study included 85 patients with non-small cell lung cancer (NSCLC) and 190 healthy volunteers. Biomarker levels were measured using modern immunological and biochemical methods. Statistical analysis included the Mann–Whitney U test, and diagnostic performance was assessed by the area under the receiver operating characteristic curve (AUC). For markers showing an inverse association, an additional ROC analysis was performed with inversion of the outcome variable. Optimal biomarker cut-off values were determined using the Youden's index.

Results. Patients with NSCLC demonstrated statistically significant changes in the concentrations of most of the studied biomarkers after strict Bonferroni correction. Increased levels of CEA, CA 125, HE4, B2M,

high-sensitivity C-reactive protein (hsCRP), D-dimer, CYFRA 21-1, and LRG-1 were observed, along with decreased levels of ApoA1, ApoA2, TTR, ApoA4, RANTES, and VEGFR1. The highest AUC values were shown by HE4 (0.903), ApoA2 (0.860), CYFRA 21-1 (0.836), ApoA1 (0.795), D-dimer (0.793), TTR (0.790), ApoA4 (0.784), B2M (0.765), and LRG-1 (0.757).

Conclusion. Certain blood biomarkers demonstrate high AUC values, indicating their potential utility for the diagnosis of NSCLC. The combined use of multiple biomarkers may improve the effectiveness of minimally invasive lung cancer diagnostics, which warrants further investigation. Validation of these findings in multicenter studies is required.

Keywords: lung cancer, diagnosis, biomarkers, HE4, CYFRA 21-1.

Conflict of interest: nothing to disclose.

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Диагностическая ценность биомаркеров крови для диагностики рака легкого

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Аннотация

Цель: оценить диагностическую ценность 20 биомаркеров при раке легкого и определить их информативность для возможного использования в клинической практике.

Материал и методы. В исследование были включены 85 пациентов с немелкоклеточным раком легкого (НМРЛ) и 190 здоровых добровольцев. Уровни биомаркеров определялись современными иммунологическими и биохимическими методами. Статистическая обработка включала U-критерий Манна – Уитни, а диагностическая ценность оценивалась по площади под ROC-кривой (AUC). Для оценки информативности маркеров с обратной ассоциацией проведен дополнительный ROC-анализ с инверсией переменной состояния. Определены пороговые значения биомаркеров с использованием индекса Юдена.

Результаты. У пациентов с НМРЛ отмечены статистически значимые изменения концентраций большинства исследованных биомаркеров с учетом строгой поправки Бонферрони: повышение уровней CEA, CA

125, HE4, B2M, вчСРБ, D-димер, CYFRA 21-1, LRG-1, а также снижение ApoA1, ApoA2, TTR, ApoA4, RANTES и VEGFR1. Наибольшие значения площади под кривой показали HE4 (0,903), ApoA2 (0,86), CYFRA 21-1 (0,836), ApoA1 (0,795), D-димер (0,793), TTR (0,79), ApoA4 (0,784), B2M (0,765), LRG1 (0,757).

Выводы. Отдельные биомаркеры крови демонстрируют высокие значения площади под кривой, что указывает на потенциал их применения с целью диагностики НМРЛ. Комплексное использование биомаркеров может повысить эффективность малоинвазивной диагностики рака легкого, что требует дальнейшего исследования. Для подтверждения полученных данных требуется валидация в многоцентровых исследованиях.

Ключевые слова: рак легкого, диагностика, биомаркеры, HE4, CYFRA 21-1.

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НМРЛ – немелкоклеточный рак легкого; НДКТ – низкодозная компьютерная томография.

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INTRODUCTION

Lung cancer remains one of the most important problems of modern oncology. According to the Global Cancer Observatory (GCO) project of the World Health Organization, in 2022, lung cancer was the leader in morbidity (2,480,675 new cases) and mortality from cancer (1,817,469 lethal outcomes) [1]. From the biological standpoint, lung cancer is characterized by a variety of morphological types, and the non-small cells lung cancer (NSCLC) accounts for approx. 85% of all cases of the disease [2].

In the Russian Federation, the situation is further aggravated by the fact that 42.2% of the patients are diagnosed at advanced stages, which makes the prognosis considerably poorer [3]. The 5-year overall survival (OS) median varies from 68.4% at stage I to 5.8% at stage IV of the disease [4]; therefore, the development of new affordable methods of early diagnostics of lung cancer still has high clinical significance.

The only method of early identification of lung cancer with a proven efficiency is the low-dose computed tomography (LDCT) in high-risk groups. The NLST study showed that the annual LDCT screening among high-risk groups decreases mortality from lung cancer by approx. 20% [5]. Based on these data, LDCT screening is implemented in some countries [1]. In Russia, only the pilot projects are underway, and the national lung cancer screening has not been implemented so far. The LDCT method has serious limitations: it involves only the smokers and provides a very high level of false-positive results (above 90% of identified foci, according to NLST data, were benign); besides, multiple irradiation poses extra risk [1, 5]. Therefore, the search for other non-invasive diagnostic methods supplementing the screening and identifying tumors at early stages is highly important.

One of prospective areas of study is the use of tumor biomarkers identified in the blood test. The tumor produces fragments of DNA, RNA, proteins, and exosomes into the bloodstream, i.e. products that may serve as indicators of a malign tumor and that may be viewed as potential biomarkers [6, 7].

In the context of studying the biomarkers to diagnose lung cancer, especially interesting are the biomarkers of different groups depending on their biological function and chemical origin. In the context of lung cancer diagnostics, tumor-associated including carcino-fetal antigens were studied; inflammation and immune response markers, or

chemokines; metabolism markers and apolipoproteins; coagulation and angiogenesis markers [8].

Thus, the problem of late diagnostic of lung cancer and the lack of a simple screening test necessitate further study of the role of blood biomarkers in the NSCLC diagnostics. The search for reliable non-invasive markers capable of diagnosing the tumor at an early stage will potentially improve treatment outcomes and decrease the disease mortality.

MATERIAL AND METHODS

Patients, taking of samples, measurements of biomarkers

The study included 85 patients with histologically confirmed non-small cells lung cancer and 190 healthy individuals. Men accounted for 63.5% (54) patients in the study group, and 52.1% (99) in the control group. The median age of patients in the study group was 62.14 years, and 48.86 years in the control group.

Levels of 20 biomarkers were measured including the following: apolipoproteins A1, A2, A4, B (ApoA1, ApoA2, ApoA4, ApoB), alpha fetoprotein (AFP), beta-2-microglobulin (B2M), carbohydrate antigen 19-9 (CA 19-9), cancer antigens 15-3 and 125 (CA 15-3, CA 125), carcinoembryonal antigen (CEA), cytokeratin fragments 19 (CYFRA 21-1), epididymis protein 4 (HE4), highly-sensitive human C-reactive protein (hsCRP), D-dimer, total prostate-specific antigen (tPSA), soluble form of vascular cell adhesion molecule 1 (sVCAM 1), transthyretin (TTR), regulator of activity of normal T-lymphocyte expression and secretion (RANTES), vascular endothelium growth factor receptor 1 (VEGFR-1), leucine-rich α -2 glycoprotein 1 (LRG-1). The analysis of tPSA was only performed among men (the tables provide metrics for the male subgroup). The levels of ApoA4, RANTES, VEGFR-1 and LRG-1 were not altered in 10 patients die to lack of solutes of interest at the moment of serum analysis.

The levels of AFP, CA 15-3, CA 19-9, CA 125, HE4, CEA, CYFRA 21-1 and tPSA were measured by electrochemiluminescence assay on the Cobas e411 analyzer (Roche Diagnostics, Germany); levels of hsCRP, ApoA1, ApoA4, ApoB, TTR were measured on the Advia 1800 analyzer (Siemens Healthcare, Germany) by immunoturbidimetric technique; levels of sVCAM-1, RANTES, VEGFR-1 and LRG-1 were identified by enzyme-linked immunosorbent assay (ELISA) (QuantikineR kits, R&D systems, US) using a Biochrom

Anthos 2020 microplate reader (Biochrom, UK); B2M and D-dimer were measured by chemiluminescent immunoassay on the Immulite 2000 analyzer (Siemens Medical Solutions, USA); and the ApoA2 level was measured using the fermentative colorimetric method (Randox laboratories, UK).

The study was approved by the local ethical committee of the Sechenov First Moscow State Medical University. All patients provided an informed consent for the participation in the study.

Statistical processing of data

The statistical processing was performed after formalization and conversion of the obtained data into electronic spreadsheets by various methods of the SPSS Statistics v. 23.0 software suite (IBM, USA).

The distribution of the main analyzed variables was determined using the Kolmogorov–Smirnov test and deviated from normality; therefore, nonparametric statistical methods were employed. For descriptive statistics of quantitative variables, the median and interquartile range or the mean and standard deviation were used. Comparisons between categories of independent quantitative variables were performed using the Mann–Whitney U test. Differences were considered statistically significant at a p-value <0.05. Qualitative (categorical) indicators are presented as absolute and relative frequencies (n, %).

On the next stage of the study, to assess the diagnostic significance of each of the biomarkers, the analysis of Receiver Operating Characteristic was performed (ROC analysis). The binary variable “presence of lung cancer” (1 – disease, 0 – control group) was used as the state variable. For each biomarker, a receiver operating characteristic curve was plotted, and the area under the curve (AUC), standard error, statistical significance level (p-value), and 95% confidence interval were calculated. Depending on the direction of the association between the marker and the diagnosis, higher or lower biomarker values were used as predictive markers during ROC analysis.

The analysis was performed in the SPSS Statistics using its ROC Curve Analysis built-in function. The interpretation of the diagnostic value of the AUC was performed in compliance with the following criteria: AUC < 0.6 – low diagnostic value, 0.6–0.75 – moderate value, 0.75–0.9 – high value, > 0.9 – very high value. In order to assess the optimal threshold value of biomarkers, the Youden’s index was used.

RESULTS

Characteristics of the studies sample

The study included 275 patients, of which 85 were the NSCLC group (study group), and 190 were healthy individuals (control group). In the entire cohort, men prevailed (n=153; 55.6%) over women (n=122; 44.4%).

The clinical and demographic characteristics of the studies population are shown in **Tables 1** and **2**. The control group included 91 women aged from 41 to 68 years and 99 men aged from 40 to 64 years. The NSCLC group included 31 women aged from 42 to 80 and 54 men aged from 36 to 78 years. The median age of the control group

Metric	Category	Value
T-status:	T1	24 (28.2%)
	T2	42 (49.4%)
	T3	9 (10.6%)
	T4	5 (5.9%)
	Tx	5 (5.9%)
N-status:	N0	39 (45.9%)
	N1	5 (5.9%)
	N2	8 (9.4%)
	Nx	33 (38.8%)
M-status:	M0	61 (71.8%)
	M1	6 (7.1%)
	Mx	18 (21.2%)

Table 1. Clinical characteristics of patients in the study group (NSCLC)

Таблица 1. Клинические характеристики пациентов исследуемой группы (НМРЛ)

was 48.86 [95% CI 47.97–47.94] years, the average age in the study group was 62.14 [95% CI 60.07–64.21] years.

The analysis of clinical characteristics of the study group showed the following distribution in the T-status: T1 in 24 (28.2%), T2 in 42 (49.4%), T3 in 9 (10.6%), T4 in 5 (5.9%) patients. In 5 (5.9%) patients, the T-status was not specified (Tx).

Distribution in the N-status: lack of metastases in regional lymph nodes (N0) was seen in 39 (45.9%) patients, N1 in 5 (5.9%), N2 in 8 (9.4%), while in 33 (38.8%) patients the N-status was not specified (Nx).

Distribution in the M-status: lack of remote metastases (M0) was diagnosed in 61 (71.8%) patients, the presence of metastases (M1) in 6 (7.1%), while in 18 (21.2%) cases the M-status was not specified (Mx).

Because of the retrospective character of the analysis the possibility of specifying clinical data of the patients was limited, therefore, the “x” code in the TNM status was used to identify the non-specified status of the T, N and M.

Diagnostic value of isolated biomarkers

On the first stage of the analysis, median concentrations were identified between the groups (NSCLC vs. control). The significance of differences was assessed using the Mann – Whitney non-parametric test for two independent samples, which was accounted for by the distribution of indicators different from normal. The obtained data is shown in **Table 3**.

Comparative analysis of biomarker concentrations revealed statistically significant differences between the study and control groups for the majority of the investigated

Metric	Control group	Lung cancer	p-value
Sex:			0.103
Female	91 (47.9%)	31 (36.5%)	
Male	99 (52.1%)	54 (63.5%)	
Age, years			<0.001
Median, (Q1-Q3)	47 (45–53)	63 (56–68)	

Table 2. Demographic characteristics (sex, age) of the study sample
Таблица 2. Демографические характеристики (пол, возраст) исследуемой выборки

Indicator	Unit	Control group	NSCLC group	p-value
AFP	IU/mL	2.40 [1.60; 3.40]	2.02 [1.50; 3.00]	0.131
CEA	ng/mL	1.60 [1.00; 2.40]	2.95 [1.40; 5.50]	<0.001*
CA 19-9	IU/mL	4.75 [3.00; 8.00]	6.50 [3.92; 12.43]	0.012
CA 125	IU/mL	8.70 [6.70; 12.80]	16.50 [9.75; 25.04]	<0.001*
HE4	pmol/L	48.45 [42.50; 57.70]	95.60 [71.70; 125.10]	<0.001*
tPSA	ng/mL	0.880 [0.620; 1.230]	0.937 [0.570; 2.010]	0.247
CA 15-3	IU/mL	14.75 [10.80; 18.60]	17.71 [12.50; 24.90]	0.001
B2M	ng/mL	1441.00 [1297.00; 1637.00]	1801.00 [1526.00; 2233.00]	<0.001*
hsCRP	mg/L	0.00 [0.00; 2.00]	3.00 [1.00; 11.00]	<0.001*
D-dimer	ng/mL	83.50 [57.50; 140.00]	210.00 [123.00; 340.00]	<0.001*
CYFRA 21-1	ng/mL	1.26 [1.00; 1.64]	2.52 [1.62; 3.76]	<0.001*
ApoA1	g/L	1.57 [1.42; 1.76]	1.29 [1.09; 1.49]	<0.001*
ApoA2	g/L	0.289 [0.266; 0.321]	0.218 [0.181; 0.249]	<0.001*
ApoB	g/L	1.01 [0.86; 1.18]	0.93 [0.79; 1.12]	0.016
TTR	mg/dL	26.00 [22.00; 29.00]	19.00 [15.00; 24.00]	<0.001*
sVCAM-1	ng/mL	640.00 [565.00; 743.00]	683.00 [567.00; 897.00]	0.031
ApoA4	g/L	71.00 [56.40; 79.90]	44.15 [29.05; 64.00]	<0.001*
RANTES	pg/mL	51853.00 [40784.00; 68671.00]	44249.50 [22911.50; 62450.50]	0.001*
VEGFR1	pg/mL	121.00 [107.00; 135.00]	94.50 [78.50; 143.00]	<0.001*
LRG-1	pg/mL	52902.00 [39539.00; 68016.00]	74278.50 [61214.00; 103649.00]	<0.001*

Notes: * – statistically significant differences after correction for multiple comparisons.

Примечания: * – статистически значимые различия после выполнения поправки на множественные сравнения.

Table 3. Biomarker values in the studied groups (median, [Q1;Q3])

Таблица 3. Значения биомаркеров в исследуемых группах (медиана, [Q1;Q3])

parameters. No statistically significant differences were found for AFP ($p = 0.131$) or tPSA ($p = 0.247$).

The study included an analysis of over 20 biomarkers, which increases the possibility of type I error due to multiple comparisons. Under the strict Bonferroni correction (significance threshold $p < 0.0025$), statistical significance was maintained for the majority of biomarkers, including HE4, D-dimer, CYFRA 21-1, CA 125, β 2-microglobulin, hs-CRP, ApoA1, ApoA2, ApoA4, TTR, LRG-1, and VEGFR1. In contrast, differences for CA 19-9 ($p = 0.012$), CA 15-3 ($p = 0.001$ at borderline), ApoB ($p = 0.016$), and sVCAM-1 ($p = 0.031$) no longer reached the level of statistical significance.

Patients with NSCLC demonstrated significantly higher levels of (2.95 vs. 1.6 ng/mL), CA 125 (16.5 vs. 8.7 IU/mL), HE4 (95.6 vs. 48.45 pmol/L), hsCRP (3 vs. 0 mg/L), D-dimer (210.00 vs. 83.5 ng/mL), CYFRA 21-1 (2.52 vs. 1.26 ng/mL), and LRG-1 (74278.5 vs. 52902.00 pg/mL). Some indicators, conversely, demonstrated lower values in the patients of the control group versus control group, including the ApoA2 (0.226 vs. 0.296 g/L), ApoB (0.96 vs. 1.03 g/L), TTR (19.09 vs. 25.81 mg/dL) and ApoA4 (46.98 vs. 68.71 g/L).

Next stage involved the ROC-analysis (Table 4) that revealed significant differences in the diagnostic value of the studied biomarkers.

The highest diagnostic indicators were seen in HE4, CYFRA 21-1, ApoA1, D-dimer, TTR, ApoA4, B2M and LRG-1. This might point at the potential of use of these biomarkers in order to diagnose the NSCLC. Moderate predictive value was seen in CA 125, hsCRP, CEA, VEGFR1, RANTES and CA 15-3.

To determine the optimal threshold concentrations of biomarkers for most effectively differentiating patients with NSCLC from control group individuals, Youden's index was used. The optimal thresholds, sensitivity (Se),

specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and test accuracy are presented in **Table 4**. For most biomarkers, diagnostic relevance was observed when the concentration exceeded the threshold; for ApoA1, ApoA2, ApoA4, TTR and VEGFR1, a decrease in the level was associated with the presence of the disease.

DISCUSSION

In the recent years, various minimally invasive approaches to early diagnostics of NSCLC based on the analysis of blood biomarkers received much attention. Hundreds of candidates are described in the literature, from tumor markers (CEA, CYFRA 21-1, CA 125 etc.) to genetic markers (circulating tumor DNA, mRNA, exosomes), biochemical and proteomic indicators. The results of our study match the literature data with respect to CYFRA 21-1, CA 125, D-dimer and HE4 as the most informative biomarkers for the lung cancer diagnostics. It is to be noted that the majority of lipid proteins (ApoA1, ApoA2, ApoA4, ApoB, TTR) and the RANTES, B2M, LRG-1 and VEGFR1 molecules have not been hitherto analyzed in key publications on biomedicine as markers for lung cancer diagnostics. High levels of AUC for ApoA2, LRG-1, B2M, ApoA1 and TTR in the early identification of lung cancer for such metrics as sensitivity and specificity demonstrated in our study open new opportunities to decode molecular mechanisms of tumor progression of lung cancer and may facilitate development of new diagnostic approaches.

Increased levels of CEA, CYFRA 21-1 and CA 125 in the NSCLC group match the findings of earlier studies of M. Li et al. (2015) [9]. The marker CA 19-9, specific for the gastrointestinal tract tumors, may still be produced by bronchial glands and is moderately increased in approx. one third of patients with NSCLC. Meanwhile, T. Kodama

Biomarker	AUC	95% CI	Threshold value	Direction of correlation	Sensitivity, Se	specificity, Sp	PPV	NPV	Accuracy	p-value
HE4	0.903	0.857–0.948	68.445	≥	0.835	0.879	0.755	0.923	0.866	< 0.001
ApoA2	0.86	0.807–0.914	0.235	≤	0.718	0.968	0.910	0.885	0.891	< 0.001
CYFRA 21-1	0.836	0.780–0.893	2.24	≥	0.612	0.937	0.813	0.844	0.836	< 0.001
ApoA1	0.795	0.733–0.857	1.395	≤	0.694	0.805	0.615	0.855	0.771	< 0.001
D-dimer	0.793	0.731–0.855	116.5	≥	0.8	0.679	0.527	0.884	0.716	< 0.001
TTR	0.79	0.727–0.852	20.5	≤	0.576	0.863	0.653	0.82	0.775	< 0.001
ApoA4	0.784	0.717–0.850	45.95	≤	0.553	0.899	0.689	0.833	0.8	< 0.001
B2M	0.765	0.700–0.830	1594	≥	0.682	0.732	0.532	0.837	0.716	< 0.001
LRG-1	0.757	0.688–0.826	56105	>	0.842	0.593	0.454	0.903	0.664	< 0.001
CA 125	0.749	0.683–0.816	14.5	≥	0.576	0.832	0.605	0.814	0.753	< 0.001
hsCRP	0.735	0.667–0.802	2.105	≥	0.576	0.853	0.636	0.818	0.767	< 0.001
CEA	0.671	0.599–0.742	2.925	≥	0.506	0.842	0.589	0.792	0.738	0.039
VEGFR1	0.658	0.582–0.733	98	≤	0.553	0.873	0.636	0.829	0.781	< 0.001
RANTES	0.628	0.551–0.704	29274	≤	0.368	0.915	0.636	0.783	0.759	0.001
CA 15-3	0.623	0.549–0.696	19.725	≥	0.424	0.811	0.5	0.759	0.691	0.01
CA 19-9	0.595	0.521–0.669	5.7	≥	0.576	0.616	0.402	0.765	0.604	0.02
ApoB	0.591	0.516–0.665	0.975	≤	0.624	0.553	0.384	0.766	0.575	0.007
sVCAM-1	0.581	0.507–0.656	808.5	≥	0.4	0.878	0.597	0.765	0.73	0.006
tPSA	0.557	0.460–0.653	1.59	≥	0.389	0.859	0.6	0.72	0.693	0.337
AFP	0.557	0.483–0.631	2.58	≤	0.682	0.489	0.374	0.775	0.549	0.087

Table 4. ROC analysis of biomarkers indicating direction of association, optimal cutoff value, and diagnostic characteristics

Таблица 4. ROC-анализ биомаркеров с указанием направления связи, оптимального порогового значения и диагностическими характеристиками

et al. (2007) note that the increased level of CA 19-9 is seen in approx. 40% of patients with non-malignant lung diseases such as idiopathic interstitial pneumonia, collagen-associated pulmonary fibrosis, diffuse panbronchiolitis and bronchoectases [10]. The values of sensitivity (57.6%) and specificity (61.6%) of this biomarker identified in our study align with literature data.

In our study, the marker HE4 (human epididymis secretory protein 4) was one of the most perspective biomarkers to diagnose NSCLC with sensitivity and specificity values of 83.5 and 87.9, respectively. These data align with findings of Y He et al. (2019), according to which the values of sensitivity and specificity of this biomarker for the diagnostics of NSCLC are 73% and 86%, respectively. The same study also notes that in NSCLC patients the concentrations of HE4 are statistically significantly higher than in healthy individuals, and the increase of HE4 is registered in early stages and does not depend on the size of the tumor [11].

NSCLC patients demonstrate activation of systemic inflammation and coagulation. According to J. Torrecilla et al. (2014), the highly sensitive C-reactive protein (hsCRP) is several times higher in NSCLC patients (in our study, the median hsCRP is 3 mg/L vs. 0 mg/L in healthy individuals, $p < 0.001$). CRP is an acute-phase protein whose synthesis is stimulated by proinflammatory cytokines (IL-6) in response to the presence of the tumor. The increase of its level points at an active inflammatory process; for example, it is known that $CRP > 40$ mg/L is associated with the presence of metastases in NSCLC [12]. Another important biomarker is the D-dimer, a product of fibrin proteolysis. In the event of lung cancer, its levels are often elevated due to tumor-induced hypercoagulation. In our study, in the NSCLC group the median level of the D-dimer was 210 ng/mL vs. 83.5 ng/mL in the control group ($p < 0.001$). The elevated

level of the D-dimer is characteristic of malignant tumors and reflects activation of coagulation and fibrinolysis. According to N. De Pooter et al. (2021), the basal levels of D-dimer increase over age, and the especially high levels in elderly NSCLC patients are to be interpreted with allowances for age [13]. Nevertheless, the high levels of D-dimer in NSCLC correlate with advanced stages of the disease and act as an independent poor prognosis factor [14]. Thus, the CRP and the D-dimer are not specific of lung cancer but indicate the severity of the disease and the systemic processes.

Statistically significant results were found for the biomarkers from the acute phase protein group and for apolipoproteins. We found that in the event of NSCLC, levels of some transport proteins and blood apolipoproteins decrease. For example, the levels of transthyretin (TTR, prealbumin), the transport protein of thyroxin and retinol, was significantly lower in lung cancer patients than in healthy individuals (19.0 vs. 26.0 mg/dL, $p < 0.001$). The decrease of TTR may reflect the nutritive status: deficient prealbumin is often seen in some oncological diseases due to inflammation-induced malnutrition [15]. Among patients in the NSCLC group, apolipoprotein levels were reduced: ApoA1, ApoA2, ApoA4 and ApoB. According to R. Xu et al. (2023), in the event of NSCLC, reduction of ApoA1 and ApoA2 are seen with simultaneous increase of ApoB in comparison with the control group, which partially aligns with our findings [16].

Changes of levels of some cytokines and vascular factors are also noteworthy. The level of sVCAM-1 was elevated in the NSCLC group (median 683 vs. 640 ng/mL, $p=0.031$). Among cytokines, most interesting is the RANTES chemokine (CCL5). In our study, the RANTES level was lower among patients with NSCLC than in the group of healthy volunteers (median 44249 vs. 51853 pg/mL, $p=0.001$). CCL5 (RANTES) is a

proinflammatory cytokine attracting lymphocytes; the decrease of its systemic level in lung cancer may reflect exhaustion of the immune system or binding of CCL5 in the tissues by tumor microenvironment. Some studies report an ambiguous role of CCL5: on the one hand, the high level of RANTES was found in some tumors and related to their progression, on the other hand, in some localizations (e.g., breast cancer) paradoxically high concentrations of RANTES in the blood are associated with a more favorable prognosis, likely due to an active anti-tumor immune response [17]. Data on systemic CCL5 for lung cancer are limited; it can be supposed that a decrease of the circulating RANTES reflects its absorption by tumor and stromal cells in the lungs and the immunosuppressive action related to it. Another important factor of angiogenesis in cancer is the VEGF and its receptors. We measured the levels of VEGFR1 (sFlt-1) and found a mild but reliable increase of this receptor in NSCLC patients (94.5 vs. 121 pg/mL, $p < 0.001$). The sVEGFR1 is an endogenous inhibitor of angiogenesis binding the excessive VEGF-A; its growth may reflect a compensatory reaction to the excessive production of VEGF by the tumor. In general, the increase of sVCAM-1, CRP, D-dimer and the decrease of RANTES may indicate a presence of a systemic inflammation, activation of the endothelium and alteration of the immune regulation in NSCLC.

The comprehensive analysis of the literature and our own data enabled the identification of both known and potentially novel biomarkers with high diagnostic potential for lung cancer diagnosis. Existing scientific evidence and our findings indicate the possibility of improving the diagnostic accuracy of NSCLC by developing panels comprising a combination of biomarkers. This approach requires validation in multicenter studies involving larger patient cohorts.

Another key result of our study was the quantitative determination of optimal cut-off values of 20 studies biomarkers to diagnose the NSCLC using the Youden's index. This finding comprises an important scientific contribution: before, many publications and meta-analyses did not provide cut-off values or varied greatly, which complicated comparison of results of different studies and their clinical applications. Thus, in the meta-analysis of

Y. He et al. (2019) studying the diagnostic value of HE4 to diagnose lung cancer, the cut-off values varies from 32.45 to 150 pmol/L [11]. The wide scattering of cut-off values may complicate reproducibility of results and interpretation of scientific data.

The cut-off values proposed by us allow for alignment and standardization of the approach towards NSCLC diagnostics. The specific cut-off values identified with the aid of the Youden's index, may serve as the single basis for screening and differential diagnostics. This reduces the variance of diagnostic characteristics between different centers and studies, improved result reproducibility and simplifies integration of biomarker screening data into clinical practice. In this way, unification of cut-off values of markers simplifies their use in the event of suspected NSCLC and facilitates standardization of diagnostic algorithms.

Limitations of study. Our study was a single-center study characterized with an age imbalance between the groups, which might affect the level of specific biomarkers, especially inflammatory and metabolic ones. Besides, the results were not checked against an external cohort, which decreases the possibility of their generalization and necessitates validation versus independent populations. Besides, we assessed the biomarkers using the ROC-analysis, without construction of combined models that could have potentially increased diagnostic accuracy. These factors must be taken into account in the interpretation of data and in the planning of future multi-center studies utilizing multi-marker panels.

■ **CONCLUSION**

The greatest AUC values we demonstrated by the following biomarkers: HE4 (0.903), ApoA2 (0.86), CYFRA 21-1 (0.836), ApoA1 (0.795), D-dimer (0.793), TTR (0.79), ApoA4 (0.784), B2M (0.765) and LRG1 (0.757). The combination of the identified changes indicates systemic reactions associated with oncological diseases, emphasizing the significant role of these proteins in the pathogenesis of lung cancer. The obtained data point to the potential for developing multi-marker panels based on the identified biomarkers for NSCLC diagnosis. Validation on independent samples in multicenter studies is required to confirm the findings. ■

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
<p>Ethics approval. The study was approved by the Local Ethics Committee of the First Moscow State Medical University named after I.M. Sechenov (№ 16-21 from 16.09.2021).</p>	<p>Этическая экспертиза. Исследование было одобрено локальным этическим комитетом Первого Московского государственного медицинского университета имени И.М. Сеченова (№ 16-21 от 16.09.2021 г.).</p>
<p>Consent for publication. All patients signed a written informed consent form.</p>	<p>Согласие на публикацию. Все пациенты подписывали добровольное информированное согласие.</p>
<p>Study funding. The study was the authors' initiative without external funding.</p>	<p>Источник финансирования. Работа выполнена по инициативе авторов без привлечения финансирования.</p>
<p>Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.</p>	<p>Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.</p>
<p>Contribution of individual authors. Zhilenkova A.V.: study design and concept, statistical analysis, writing of the manuscript. Voronova V.M.: study design and concept, statistical analysis. Orlova E.V., Istranov A.L., Sekacheva M.I.: review and editing. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.</p>	<p>Участие авторов. Жиленкова А.В. – разработка концепции и дизайна исследования, проведение статистического анализа, написание текста. Воронова В.М. – разработка концепции и дизайна исследования, проведение статистического анализа. Орлова Е.В., Истранов А.Л., Секачева М.И. – рецензирование и редактирование. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.</p>

Statement of originality. No previously published material (text, images, or data) was used in this work.	Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
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Selective intra-arterial chemotherapy for locally advanced inoperable head and neck cancer: an analysis of long-term survival in an open prospective study

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Abstract

Patients with locally advanced inoperable head and neck cancer (HNC) have an unfavorable prognosis and a rapid fatal outcome with standard systemic chemotherapy and/or radiation therapy. The median overall survival(s) with traditional treatment does not exceed 12-16 months.

Aim: to evaluate the long-term survival of patients and the effectiveness of selective intra-arterial chemotherapy (IAC) in locally advanced inoperable HNC.

Material and methods. An open prospective study included 56 patients with locally advanced inoperable HNC (stage IVA-IVB) who received selective IAC using high doses of Cisplatin and other chemotherapy drugs selectively injected into the arteries feeding the tumor. The studied patients were stratified by tumor location (oropharynx, tongue, floor of the oral cavity, and other locations), the presence of lymphatic metastases, and concomitant pathology. The primary endpoint was an analysis of overall survival in the medium follow-up term (mean follow-up 39 months, range 10-221 months). The secondary endpoints were the tumor response to treatment, the safety of the procedure, and the quality of life.

The initial cohort (n=56) was characterized by such indicators as age 59.8 ± 9.8 years (41-81), men 84.8% (n=47), women 15.2% (n=9). The main risk factors included smoking (69.7%, n=39), hypertension (93.9%, n=52), type 2 diabetes mellitus (90.9%, n=51), and atherosclerosis of the brachiocephalic arteries (54.5%, n=30). The average comorbidity was 3.1 ± 0.7 risk factors per patient, reflecting the age and severity of the population. The localization of the primary tumor is represented by the oropharynx (24.2%), tongue

(21.2%), bottom of the oral cavity (15.2%), and other localizations (39.4%). The presence of metastases to regional lymph nodes was detected in 51.5% of patients (n=28). The majority of patients (90.9%, n=51) received one SHIFT procedure, the minority (9.1%, n=5) received two or three procedures.

Results. Of the 56 initially enrolled patients, 33 patients are alive at the time of writing (end of 2025) (58.9%, 95% CI: 44.7–72.6). This is a significantly higher value compared to the expected survival rate with standard treatment, in which this indicator does not exceed 15-20% after 24-39 months. The average tumor response to treatment was 7.9 ± 5.4 according to the surrogate effect index (range: 3.2–31.9). The incidence of complications was low (12.1%, n=4), and included mucosal edema (n=1), hyper-salivation (n=1), contrast leakage into neighboring structures (n=1), scratching, and a feeling of lack of air (n=1). No deaths directly related to the WATCH procedure were recorded.

Conclusion. Selective intra-arterial chemotherapy is an effective and safe treatment method for patients with locally advanced inoperable head and neck cancer, significantly improving long-term survival and quality of life compared to standard treatment. The results of the study confirm the need to introduce this method as a standard approach in the treatment of inoperable forms of HNC in specialized institutions.

Keywords: head and neck cancer, selective intra-arterial chemotherapy, survival, Cisplatin, locally advanced cancer, inoperable cancer.

Conflict of interest: nothing to disclose.

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Селективная внутриартериальная химиотерапия при местно-распространенном неоперабельном раке головы и шеи: анализ долгосрочной выживаемости в открытом проспективном исследовании

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Аннотация

Пациенты с местно-распространенным неоперабельным раком головы и шеи (РГШ) характеризуются неблагоприятным прогнозом и быстрым летальным исходом при стандартной системной химиотерапии и/или лучевой терапии. Медиана общей выживаемости при традиционном лечении не превышает 12–16 месяцев.

Цель: оценка долгосрочной выживаемости пациентов и эффективности селективной внутриартериальной химиотерапии (ВАХТ) при местно-распространенном неоперабельном РГШ.

Материал и методы. В открытое проспективное исследование были включены 56 пациентов с местно-распространенным неоперабельным РГШ (стадия IVA–IVB), которые получали селективную ВАХТ с использованием высоких доз Цисплатина и других химиопрепаратов с избирательным введением в артерии, питающие опухоль. Исследуемые пациенты были стратифицированы по локализации опухоли (ротоглотка, язык, дно полости рта, другие локализации), наличию лимфатических метастазов и сопутствующей патологии. Первичной конечной точкой был анализ общей выживаемости в среднесрочной перспективе (среднее наблюдение 39 месяцев, диапазон 10–221 месяц) наблюдения. Вторичными конечными точками стали ответ опухоли на лечение, безопасность процедуры, качество жизни.

Исходная когорта (n=56) характеризовалась такими показателями, как возраст 59,8 ± 9,8 года (41–81), мужчины 84,8% (n=47), женщины 15,2% (n=9). Основные факторы риска включали курение (69,7%, n=39), артериальную гипертензию (93,9%, n=52), сахарный диабет 2 типа (90,9%, n=51), атеросклероз брахиоцефальных артерий (54,5%, n=30). Средняя коморбидность составила 3,1±0,7 фактора риска на пациента, что отражало возраст и тяжесть популяции. Локализация первичной опухоли

представлена ротоглоткой (24,2%), языком (21,2%), дном полости рта (16,1%), другими локализациями (39,4%). Наличие метастазов в регионарные лимфатические узлы выявлено у 51,5% пациентов (n=28). Большинство пациентов (90,9%, n=51) получило одну процедуру ВАХТ, меньшинство (9,1%, n=5) получило две или три процедуры.

Результаты. Из 56 исходно включенных пациентов на момент написания статьи (конец 2025 года) живы 33 пациента (58,9%, 95% ДИ: 44,7–72,6). Это составляет существенно более высокое значение по сравнению с ожидаемой выживаемостью при стандартном лечении, при котором этот показатель не превышает 15–20% через 24–39 месяцев. Средний ответ опухоли на лечение составил 7,9±5,4 по суррогатному показателю эффекта (диапазон: 3,2–31,9). Частота осложнений была низкой (12,1%, n=4), включала отек слизистой (n=1), гиперсаливацию (n=1), затекание контраста в соседние структуры (n=1), першение и чувство нехватки воздуха (n=1). Ни одного летального исхода, непосредственно связанного с процедурой ВАХТ, зафиксировано не было.

Заключение. Селективная внутриартериальная химиотерапия является эффективным и безопасным методом лечения для пациентов с местно-распространенным неоперабельным раком головы и шеи, существенно улучшающим долгосрочную выживаемость и качество жизни по сравнению со стандартным лечением. Результаты исследования подтверждают необходимость внедрения этого метода как стандартного подхода в лечении неоперабельных форм РГШ в специализированных учреждениях.

Ключевые слова: рак головы и шеи, селективная внутриартериальная химиотерапия, выживаемость, Цисплатин, локально-распространенный рак, неоперабельный рак.

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Список сокращений

РГШ – рак головы и шеи; ХЛТП – химиолучевая терапия;

ВАХТ – внутриартериальная химиотерапия.

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INTRODUCTION

Head and neck cancer remains one of the most complex problems in today's oncology. Every year, over 600,000 new cases of squamous cell head and neck cancer (HNC) are registered worldwide. At the moment of being diagnosed, over 40% of patients have locally advanced (TNM stage III–IV). The majority of these patients are inoperable since the tumor process has invaded into vital structures (internal carotid artery, base of the skull, vertebral column, orbital cavity), which severely restricts therapeutic possibilities [1–3].

The standard approach towards treatment of the locally advanced inoperable HNC includes radiotherapy

(doses of 60–70 Gy) to ensure local control, systemic chemotherapy (Cisplatin, 5-Fluorouracil, Docetaxel) to suppress systemic progression, and combined treatment, or concurrent chemoradiotherapy (CRT).

However, the results of such approaches are most often unsatisfactory. The median of overall survival in the standard concurrent CRT is not over 12–16 months, and 5-year survival varies in the range of 15–40% depending on the tumor localization, stage, and the patient's overall condition. For patients with stage 4B/4C (most prevalent in the group of inoperable patients) the prognosis is even poorer: the median of overall survival is 3–9 months, and one-year survival is below 20% [4–6].

Chemotherapy is associated with high toxicity that significantly reduces the quality of life of patients. The patients develop such complications as grade 3 – 4 hematologic toxicity (in 40–60% patients), mucositis necessitating parenteral feeding (in 30–40%), xerostomia, impairments of hearing and speech function (often as remote effects), and mortality related to treatment (2–5%).

At the same time, surgical intervention in the case of locally advanced HNC is often not possible from a technical perspective and/or may result in a critical loss of function and quality of life (loss of voice, chewing, swallowing, deformation of physique) [7–9].

AN alternative approach that became widely spread in Japan and that is being implemented in other countries involves selective intra-arterial infusion of high doses of drugs directly into the tumor-feeding arteries (IAC). The advantages of this approach are the high concentrations of drugs in the tumor (10–100-fold increase vs. systemic delivery), minimal systemic toxicity (caused by fast metabolism of the drugs in the liver and by local neutralization), preservation of the function (possibility of organ-saving approach without radical surgery) and improved prognosis (some studies show results approaching those of radical surgery) [10–11].

Notwithstanding the notable outcomes, the IAC method is less common in Russia. This is related to the need of special equipment (angiograph), the need to train specialists in the field of imaging and interventional vascular surgery, lack of sufficient publications in the Russian language providing data on long-term survival.

This study intends to demonstrate our own experience of using selective IAC in inoperable HNC with an analysis of long-term survival.

■ MATERIAL AND METHODS

Study design and patient selection

The open prospective cohort study was performed in 2020–2021 on the clinical site of the Peoples' Friendship University of Russia by the same surgical team.

Inclusion criteria: the study enrolled 56 consecutive patients with a confirmed diagnosis of squamous cell carcinoma of the head and neck, locally advanced disease (stage IVA–IVB), inoperable status defined as the impossibility to perform radical tumor resection without critical damage to vital structures (internal carotid artery, skull base, spine, orbit), absence of distant metastases (M0), age ≥ 18 years, and ECOG performance status of 0–2.

Exclusion criteria: presence of distant metastases; metastatic disease from other organs; pregnancy and lactation, history of intolerance to Cisplatin; creatinine clearance < 60 mL/min; thrombocytopenia $< 50 \times 10^9/L$.

Assessed parameters: tumor response (assessed via a CT-based surrogate efficacy endpoint); complications of IAC (immediate and delayed); current patient status (alive/deceased); follow-up duration.

Statistical processing of data was performed in the Statistica 12.0 software suite. The distribution of quantitative data was tested for normality using the Shapiro–Wilk test. For normally distributed data, parametric tests were applied (Student's t-test

for independent samples); results are presented as arithmetic mean and standard deviation ($M \pm SD$). Qualitative variables are presented as absolute values and percentages [n (%)]. The 95% confidence interval for proportions was calculated using the Wilson method. Differences were considered statistically significant at a p-value < 0.05 . Survival analysis was performed using the Kaplan–Meier method with estimation of the median follow-up period.

Selective IAC was administered under local anesthesia by highly qualified endovascular surgeons (experience of 5+ years) in specialized angiography laboratories. Before the procedure, complex visualization of the primary tumor and of the regional vascular architectonics by three-dimensional angiography and magnetic resonance imaging was performed. This allowed for a precise identification of the arterial features of tumor blood supply, identification of variant anatomy of the vascular pool and to plan an optimal approach. Based on the results of the preoperative planning, selective catheterization of arteries feeding the primary tumor was performed.

Depending on the tumor location, the external carotid artery, lingual artery, facial artery, maxillary artery or their branches were cannulated. Ensuring optimal catheterization selectivity was critically important to minimize systemic toxicity and to maximize local accumulation of the drug in the tumor. In the next stage, super-selective microcatheterization was performed by implanting a microcatheter directly in the arterial branched directly feeding the tumor tissue. This ensured the maximum selectivity of the infusion providing concentrated delivery of the drug to the lesion focus while minimizing the drug contact with the surrounding healthy tissues.

Infusion of high doses of Cisplatin (usually, 100–150 mg per each catheterized arterial territory) was administered via microcatheters with simultaneous intravenous infusion of sodium thiosulfate. Sodium thiosulfate had the critical role of a neutralizing agent quickly inactivating the Cisplatin in the systemic bloodstream and drastically lowering the risk of development of nephrotoxicity, ototoxicity and other systemic adverse effects traditionally observed in parenteral administration of Cisplatin.

The drug infusion was performed in conditions of a temporary controlled blood flow reduction in the catheterized artery by moderate increase of the arterial blood pressure and decrease of the linear blood flow velocity. This created a local hypoxic micro-environment in the tumor: according to contemporary concepts, it potentiates the cytotoxic effect of the drug in a substantial manner by accelerating apoptosis of the tumor cells and increasing their sensitivity to the effect of Cisplatin. Besides, the decrease of the local blood flow slows down the drug dilution in the tumor tissue thereby assisting its prolonged effect on the tumor cells.

Throughout the procedure, distribution of the contrast and the drug in the arterial system and in the tumor were radiologically controlled. The use of digital subtraction angiography allowed for a real-time assessment of the blood flow, exclusion of incidental flow of the contrast to

Category	Parameter	Initial cohort (n=56)	Patients alive at the time of follow-up (n=33, 58.9%)	Deceased patients (n=23, 41.1%)
		n (%) or M±SD	n (%) or M±SD	n (%) or M±SD
Demography	Age, years	59.8 ± 9.8 (41–81)	60.1 ± 9.5	59.2 ± 10.3
	Men	47 (83.9%)	28 (84.8%)	18 (78.3%)
	Women	9 (16.1%)	5 (15.2%)	4 (17.4%)
Harmful habits	Smoking	38 (69.6%)	23 (69.7%)	15 (65.2%)
	Alcohol abuse	28 (50.0%)	16 (48.5%)	12 (52.2%)
Cardiovascular comorbidity	Arterial hypertension	52 (92.9%)	31 (93.9%)	21 (91.3%)
	Type 2 diabetes mellitus	51 (91.1%)	30 (90.9%)	21 (91.3%)
	BCA atherosclerosis	30 (53.6%)	18 (54.5%)	12 (52.2%)
	Avg. comorbidity (factors per patient)	3.1 ± 0.7	3.1 ± 0.7	3.1 ± 0.7
Tumor characteristics	Primary tumor localization:			
	Oropharyngeal cavity	13 (23.2%)	8 (24.2%)	5 (21.7%)
	Tongue	12 (21.4%)	7 (21.2%)	5 (21.7%)
	Floor of the mouth	9 (16.1%)	5 (15.2%)	4 (17.4%)
	Other localization*	22 (39.3%)	13 (39.4%)	9 (39.1%)
	Lymph node involvement (N-status):			
	N+ (with metastases)	28 (50.0%)	17 (51.5%)	11 (47.8%)
	N0 (without metastases)	28 (50.0%)	16 (48.5%)	12 (52.2%)

Notes. Other localizations: laryngopharynx, piriform sinus, tongue root, hard palate, palatine tonsil, epiglottis.

Примечания. Другие локализации – гортаноглотка, грушевидный синус, корень языка, твердое небо, небная миндалина, надгортанник.

Table 1. Clinical characteristics, treatment regimens, and long-term outcomes in patients with inoperable locally advanced head and neck cancer who received selective intra-arterial chemotherapy (n=56)

Таблица 1. Клиническая характеристика, схемы лечения и долгосрочные результаты у пациентов с неоперабельным локально-распространенным раком головы и шеи, получивших селективную внутриартериальную химиотерапию (n=56)

adjoining arterial branches and checking the adequacy of infusion to the target area.

After the infusion, the microcatheter and the standard catheter were gradually retrieved with control angiography to visualize the vascular patency, lack of thrombosis, dissection of the wall or other angiographic complications. Once homeostasis was achieved in the place of arterial puncture and bleeding was controlled, the patients were transferred to an intensive follow-up ward.

Throughout the follow-up period after the procedure, intensive parenteral hydration with saline solutions was administered to prevent acute kidney damage, and highly potent anti-nauseants were prescribed (antagonists of 5-hydroxy-triptamine-3 and corticosteroids) to prevent nausea and vomiting; in case of necessity, additional nephroprotective agents were used.

RESULTS

Characteristics of the initial and the studies cohort

The study included 56 patients with inoperable locally advanced head and neck cancer (IVA–IVB). The initial cohort was characterized with a prevalence of men (83.9%, n=46) over women (16.1%, n=9) at the median age of 59.8 ± 9.8 years (in the range of 41–81 years). Harmful habits were seen often, 69.6% of the patients were smokers (n=38), and half of patients (50.0%) had a history of alcohol abuse (n=28).

Cardiovascular comorbidity was extremely high, which reflected the age and the severity of condition of the population. Arterial hypertension was seen in 92.9% patients (n=52), type 2 diabetes mellitus in 91.1% (n=51), atherosclerosis of brachiocephalic arteries in 53.6% (n=30). The average cumulative comorbidity burden was 3.1 ± 0.7 factors per patient. The primary localization of the

tumor varied between such locations as the oropharyngeal cavity (23.2%, n=13), tongue (21.4%, n=12), floor of the mouth (16.1%, n=9), pyriform sinus, laryngeal pharynx, epiglottis and other locations (39.3%, n=22). Half of the patients (50.0%, n=28) had regional lymphatic metastases (N+), the remaining half (50.0%, n=28) had no lymphatic involvement (N0) (**Table 1**).

Treatment results

Selective IAC was administered using three major schemes. The DC scheme (Docetaxel + Cisplatin) was used in 39.3% patients (n=22), CF (Cisplatin + 5-Fluoruracil) in 33.9% (n=19), DCF (Docetaxel + Cisplatin + 5-Fluoruracil) in 26.8% patients (n=15). The absolute majority of the patients (90.9%, n=30) underwent one procedure of selective IAC, while the rest of the patients underwent two (3.0%, n=1) or three procedures (6.1%, n=2) (**Table 2**).

At the time of analysis, after the median 39 months of the follow-up (range of 10–221 months) 33 patients from the initial cohort were alive (58.9%, 95% confidence interval: 44.7–72.6), and 23 patients were deceased (41.1%). It is of critical importance that the initial characteristics of the living and the deceased patients were practically identical which eliminated the selection bias in the analysis of results. Among the living patients, the tumor response was 7.9 ± 5.4 (range: 3.2–31.9), and the optimal result (score ≥10) was attained in 36.4% patients (n=12). The complications of the selective IAC were seen infrequently, in 12.1% patients (n=4), and all complications were minor (Grade 1–2): swollen mucosa (n=1), hypersalivation (n=1), contrast influx (n=1), one undefined complication (n=1). The mortality related directly to the procedure was 0%.

The flow of 56 patients (**Fig. 1**) with inoperable head and neck cancer (stage IVA–IVB) over three schemes

Chemotherapy scheme	Parameter	Initial cohort (n=56)	Patients alive at the time of follow-up (n=33, 58.9%)	Deceased patients (n=23, 41.1%)
	DC (Docetaxel + Cisplatin)	22 (39.3%)	12 (36.4%)	9 (39.1%)
	CF (Cisplatin + 5-Fluoruracil)	19 (33.9%)	11 (33.3%)	7 (30.4%)
	DCF (Docetaxel + Cisplatin + 5-Fluoruracil)	15 (26.8%)	8 (24.2%)	7 (30.4%)
IAC characteristics	Number of procedures:			
	One procedure	–	30 (90.9%)	–
	Two procedures	–	1 (3.0%)	–
	Three procedures	–	2 (6.1%)	–
Treatment response and safety	Tumor response (M±SD)	–	7.9 ± 5.4	–
	Range (min.–max.)	–	3.2–31.9	–
	Optimal response (score ≥10)	–	12 (36.4%)	–
Procedure-related complications		–	4 (12.1%)	–
	Swollen mucosa (Grade 1)	–	1 (3.03%)	–
	Hypersalivation (Grade 1)	–	1 (3.03%)	–
	Contrast influx (Grade 1)	–	1 (3.03%)	–
	Irritation and sensation of lack of air	–	1 (3.03%)	–
	Procedure-related mortality	–	0 (0%)	–
Long-term outcomes	Total number of patients	56 (100%)	33 (58.9%)	23 (41.1%)
	Follow-up median, months (range)	–	39 (10–221)	–
	Overall three-year survival	–	58.9% (95% CI: 44.7–72.6)	–

Notes. DC = Docetaxel + Cisplatin (122 mg Cisplatin per arterial area + Docetaxel 75 mg/m²). CF = Cisplatin + 5-Fluorouracil (100-150 mg Cisplatin intravenously delivered to the artery + 500 mg/m² 5-FU intravenously). DCF = Docetaxel + Cisplatin + 5-Fluorouracil (triple scheme for extremely common tumors). Tumor response rate - radiographic assessment of tumor regression (higher values indicate a better response).

Примечания. DC = Доцетаксел + Цисплатин (122 мг Цисплатина на артериальную территорию + Доцетаксел 75 мг/м²). CF = Цисплатин + 5-Фторурацил (100–150 мг Цисплатина в/в доставка в артерию + 500 мг/м² 5-ФУ в/в). DCF = Доцетаксел + Цисплатин + 5-Фторурацил (тройная схема для крайне распространенных опухолей). Показатель ответа опухоли – радиографическая оценка регрессии опухоли (более высокие значения указывают на лучший ответ).

Table 2. Treatment regimens and long-term outcomes in patients with inoperable locally advanced head and neck cancer who received selective intra-arterial chemotherapy (n=56)

Таблица 2. Схемы лечения и долгосрочные результаты у пациентов с неоперабельным локально-распространенным раком головы и шеи, получивших селективную внутриартериальную химиотерапию (n=56)

of selective IAC (DC – Docetaxel + Cisplatin, CF – Cisplatin + 5-Fluoruracil, DCF – Docetaxel + Cisplatin + 5-Fluoruracil) shows, by final outcomes, a similar 58.9% survival regardless of the chosen chemotherapy scheme (n=33 living, n=23 deceased at the moment of analysis).

In our study (**Fig. 2**), the patients with locally advanced inoperable head and neck cancer who underwent IAC by 39th month (median follow-up term) had a survival of 58.9%. The curve is mild (blue line), with no drastic falls, which shows a long-term control of the disease. The second curve reflects literature data (median of 12–16 months, 3-year survival of ~20%). It demonstrated fast decline of survival, the median (intersection of 50%) is reached at the 14th month. In this way, the IAC method takes patients from the 1-year median survival to a group of long-livers.

DISCUSSION

The bubble chart (**Fig. 3**) shows a paradoxical discrepancy between the extremely high comorbidity of patients and the achieved long-term survival. The X-axis shows the number of cumulative risk factors (arterial hypertension, type 2 diabetes mellitus, atherosclerosis,

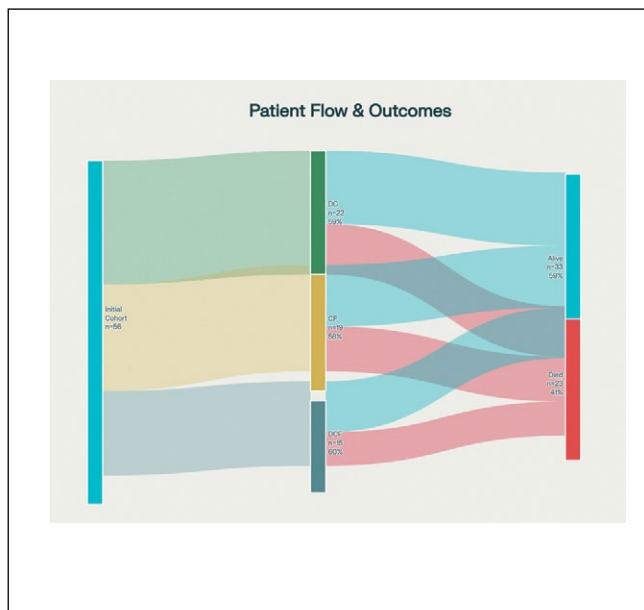


Figure 1. Flow diagram of included patients in selective intra-arterial chemotherapy for inoperable head and neck cancer.

Рисунок 1. Диаграмма потока включенных пациентов при селективной внутриартериальной химиотерапии неоперабельного рака головы и шеи.

Treatment method	3-year OS	Median OS	Sample size	Comorbidity
This study (IAC)	58.9%	39 months	56 (100% inoperable)	3.1 ± 0.7 (extreme)
Standard CRT	18–35%	12–16 months	Varied	Normal
Systemic CT only	10–15%	6–12 months	Varied	Selected (low risk)
RADPLAT (D. Yoshida)	78%	60+ months	102 (some operable)	Normal
Aigner et al. (DC only)	65%	NR	97	Not reported
Palliative care	<5%	3–9 months	Varied	High

Table 3. Comparison of the results obtained with other studies and treatment options
Таблица 3. Сравнение полученных результатов с другими исследованиями и вариантами лечения

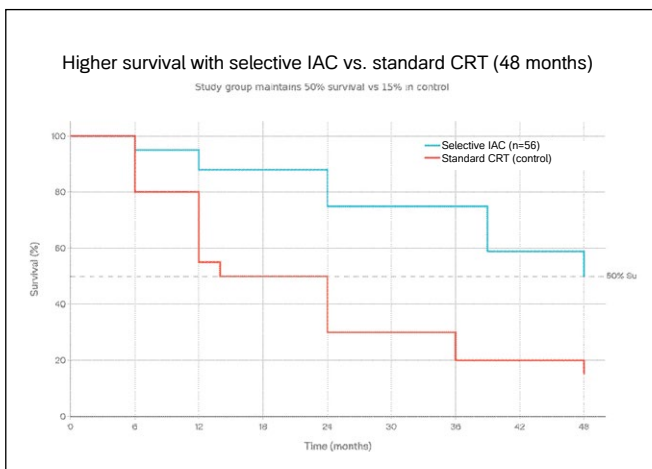


Figure 2. Kaplan - Meier curve plot for patients with completed IAC.
Рисунок 2. График кривых Каплана – Майера у пациентов с выполненным ВАХТ.

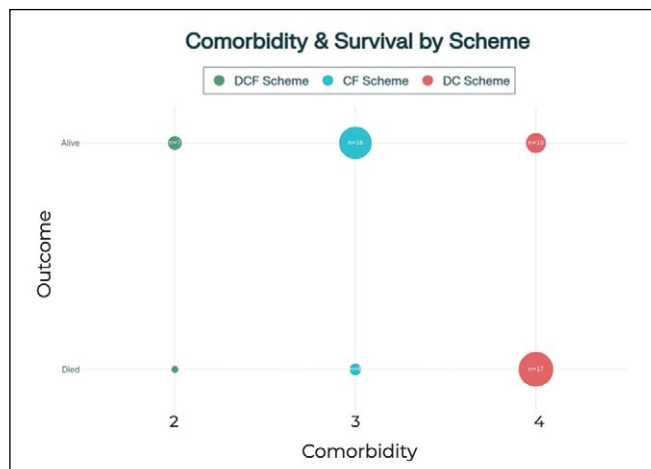


Figure 3. The relationship between cumulative cardiovascular comorbidity and long-term survival with selective intra-arterial chemotherapy.

Рисунок 3. Взаимосвязь между кумулятивной кардиоваскулярной коморбидностью и долгосрочной выживаемостью при селективной внутриартериальной химиотерапии.

smoking; range of 2–4 factors). The Y-axis shows the outcome (alive vs. deceased). The size of the bubble matches the number of patients in each category. Even though 92.9% were hypertensive, 91.1% diabetics, and 53.6% had atherosclerosis (average comorbidity 3.1 ± 0.7), 58.9% reached long-term survival. This shows that selective IAC is a safe and effective method for high-risk patients who would have not qualified for systemic chemotherapy.

Comparison against other methods

The survival of 58.9% in our study demonstrates clinical advantages of selective IAC versus published results of alternative methods. According to Cochrane Systematic Review on treatment of inoperable cancer of the head and neck, concurrent chemoradiotherapy yields 3-year overall survival in the range of 18–35%, whereas systemic palliative chemotherapy restricts to 10–15% (OS median of 6–12 months). In the cohorts receiving only the palliative treatment, 3-year survival does not exceed 5%. The results of our study are between the reference method of super-selective intra-arterial chemoradiotherapy (RADPLAT, 78% according to D. Yoshida, 2023) and other published series of selective IAC. Thus, K.R. Aigner et al. (2019) analyzed 97 patients and reported 65% 3-year survival in selective intra-arterial

chemotherapy without radiological treatment, and M.S. Olshansky et al. (2020) showed in a retrospective study that selective IAC is 88% more efficient than the systemic chemotherapy in the OS median criterion (325 days vs. 173 days, p<0.01) [12–15].

CONCLUSION

Selective IAC is an effective and safe method of treatment of inoperable head and neck cancer that yields significantly better results than the traditional approaches. The achieved 58.9% long-term survival is a considerable improvement as compared to expected survival in standard treatment. The method features an especially favorable safety profile (12.1% minor complications, zero procedure-related mortality), preservation of function and possibility of delivery to high-risk patients. The results comply with international standards and show the potential of combined approaches. Selective IAC should be regarded as a standard treatment approach in specialized institutions that have the required equipment and experience. Further randomized studies are needed to optimize protocols of combined treatment (IAC + radiotherapy ± systemic chemotherapy) and to identify prognostic factors. ■

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Algorithm for surgical treatment of patients with metastatic colorectal cancer complicated by intestinal obstruction

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Abstract

Aim: to develop an algorithm for selecting the optimal surgical intervention for patients with metastatic colorectal cancer complicated by obstructive intestinal obstruction.

Material and methods. The study is based on an analysis of the treatment outcomes of 202 patients with metastatic colorectal cancer complicated by obstructive intestinal obstruction. The patients were divided into two groups. Group 1 included 119 patients who underwent primary tumor removal as the first stage. Group 2 included 83 patients who underwent only symptomatic drainage surgery to relieve intestinal obstruction.

Results. The one-year mortality rate was 37 patients (31.1%) in Group 1 and 51 (61.4%) in Group 2. Multivariate analysis identified predictors influencing the

one-year mortality rate: the number of internal organs affected by metastases, albumin/globulin ratio, Krebs index, MCV index, and the planned targeted therapy regimen.

Conclusion. Based on this analysis, a step-by-step decision-making algorithm was developed to determine the indications for primary tumor removal, and a computer program was created to calculate the one-year mortality risk in patients with metastatic colorectal cancer.

Keywords: metastatic colorectal cancer, intestinal obstruction, adverse events of chemotherapy, palliative surgery, cytoreductive surgery – R2 resection.

Conflict of interest: nothing to disclose.

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Алгоритм хирургического лечения больных метастатическим колоректальным раком, осложненным кишечной непроходимостью

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Аннотация

Цель: разработать алгоритм, позволяющий выбрать оптимальный объем хирургического вмешательства больным метастатическим колоректальным раком, осложненным обтурационной кишечной непроходимостью.

Материал и методы. Исследование основано на анализе результатов лечения 202 пациентов метастатическим колоректальным раком, осложненным обтурационной кишечной непроходимостью, которые были разделены на две группы. В первую группу вошли 119 пациентов, которым первым этапом выполнено удаление первичного опухолевого очага. Вторую группу составили 83 пациента, которым выполнена только дренирующая симптоматическая операция, направленная на ликвидацию кишечной непроходимости.

Результаты. Показатель одногодичной летальности в первой группе составила 37 человек (31,1%), а во второй группе – 51 (61,4%) пациент.

Многофакторный анализ выявил предикторы, влияющие на показатель одногодичной летальности: количество внутренних органов, пораженных метастазами, альбумин/глобулиновый коэффициент, лейкоцитарный индекс Кребса, индекс MCV, схема предстоящей таргетной терапии.

Заключение. Разработан этапный алгоритм принятия решения, позволяющий определить показания к удалению первичной опухоли, и создана программа ЭВМ для расчета риска одногодичной летальности больных метастатическим колоректальным раком.

Ключевые слова: метастатический колоректальный рак, кишечная непроходимость, нежелательные явления химиотерапии, паллиативная операция, циторедуктивная операция – R2 резекция.

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Список сокращений

КРР – колоректальный рак; МКРР – метастатический колоректальный рак;

ХТ – химиотерапия; ТТ – таргетная терапия; КН – кишечная непроходимость.

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INTRODUCTION

The colorectal cancer (CRC) ranks third in morbidity and mortality in the world and in the Russian Federation [1, 2]. In the Samara Region, the morbidity and mortality rates correlate with the overall indicators of the Russian Federation [3]. The high rate of mortality from this pathology stems from a large number of neglected diseases. In the international practice, the incidence of the primary metastatic CRC is within 17–32%. From the data of V.A. Aliev and A.D. Kaprin it follows, that despite the active implementation of screening programs and gradual decrease of morbidity rate in the Russia Federation, the primary metastatic CRC (mCRC) is identified in 20–30% cases, which has a statistically significant poorer outcome [4, 5].

According to the clinical recommendations of the AOR, RUSSCO, NCCN, the primary method of mCRC treatment is chemotherapy (CT) combined with targeted therapy (TT), and the surgical stage of treatment is only auxiliary and preparatory for the systemic therapy. The complications developing on various stages of treatment result in extension of the term of the start of therapy and necessitate reduction of dosages of administered drugs, increase of intervals between cycles, or require cancellation of therapy, which aggravates the remote outcomes. About 45% of patients die within the first year after being diagnosed [6].

One of the most frequent complications is the intestinal obstruction (IO) [7]. Prior to administration of CT and TT, patients with IO require surgical treatment to rectify the existing complications on the first stage. This poses the question as to the volume of surgical intervention: formation of a colostomy or performance of a debulking operation to remove the primary tumor site.

AIM

To analyze outcomes of complex treatment of patients with metastatic colorectal cancer and develop an algorithm for selecting the optimal surgical intervention for this category of patients.

MATERIAL AND METHODS

Based on the experience of treatment of patients with mCRC complicated by IO, a study was performed at the Samara Regional Clinical Oncology Dispensary that included 202 patients.

Inclusion criteria: patients with mCRC complicated by obturation intestinal obstruction in the stage of compensation or subcompensation; histological type of tumor: adenocarcinoma; debulking operation to remove the primary lesion or drainage operation; subsequent chemotherapy under the FOLFOX/XELOX schemes combined with targeted therapy; status of the peritoneal carcinomatosis: P1-P2 in the Japanese classification; performance status: ECOG 2 and lower.

Exclusion criteria: patients refusing from specific treatment; patients with mCRC with symptom-free primary tumor; patients diagnosed with P3 peritoneal carcinomatosis in the Japanese classification; patients with colon cancer (lower and medium ampullas), and anal form of the rectal cancer; performance status above ECOG 2.

Prior to commencement of treatment, all patients underwent examination, their clinical diagnosis established and verified, staged under the TNM system, the number of organs affected by the metastases was identified. The participants of the study were divided into two groups. Group 1 included 119 patients after a debulking operation, the first stage of which was the R2 debulking resection of the primary tumor lesion. Group 2 included 83 patients after just the drainage symptomatic operation aimed at relief of intestinal obstruction without removal of the primary lesion.

In both study groups, patients exhibited either isolated metastatic involvement of a single organ or combined involvement of two or more organs. Patients in both groups were comparable in terms of sex, age, TNM stage, and primary tumor location. The study design is presented in **Fig. 1**.

Statistical analysis. The study results were processed in Statistica 10.0, SPSS 13. To assess the risk of one-year mortality, univariate binary logistic regression was first performed. Subsequently, predictors with a significance level below 0.1 were included in a multivariate binary logistic regression model using stepwise backward elimination based on the Wald algorithm. The quality of prediction was evaluated based on the statistical significance of the predictors included in the model and on sensitivity and specificity metrics. The algorithm for selecting the optimal surgical treatment method was developed using the Chi-Square Automatic Interaction Detection (CHAID) decision tree method. The CHAID

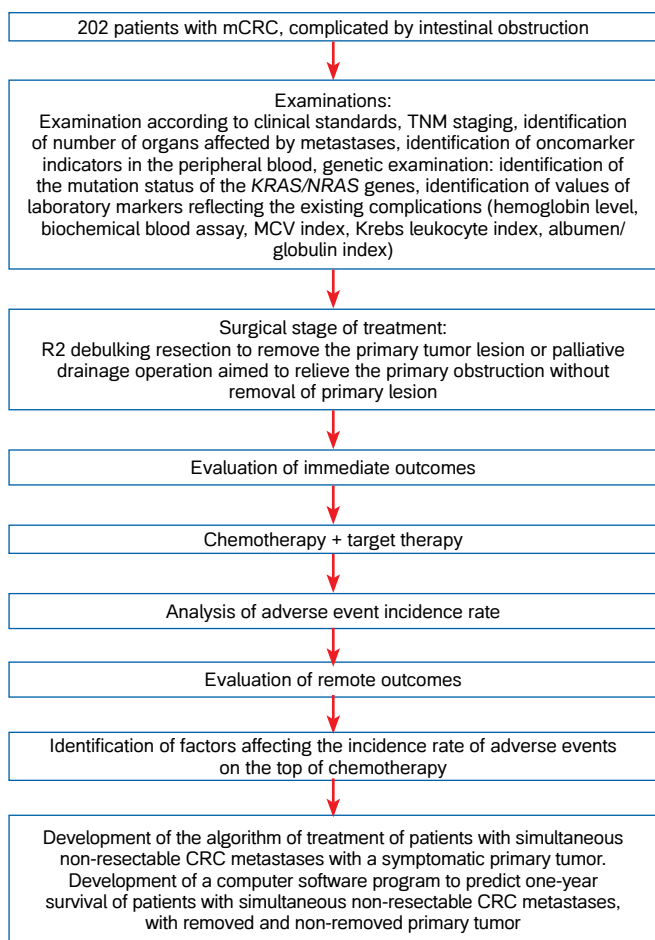


Figure 1. Study design.

Рисунок 1. Дизайн исследования.

method is based on testing the hypothesis of independence between two variables using the χ^2 (chi-square) test. Construction was performed using the SPSS 13 software package based on data from a training dataset comprising 202 observations. The significance level α was set at <0.05.

RESULTS

The following parameters were assessed: intraoperative blood loss and number of bed-days. The average intraoperative blood loss among patients in Group 1 was 150 ± 20 mL; among patients of Group 2, 80 ± 20 mL ($p = 0.000$). The average number of in-patient bed-days in Group 1 was 20 ± 2 , in Group 2, 12 ± 2 bed-days ($p = 0.000$). These indicators in the group with patients after the debulking surgery were significantly higher, which is accounted for by the volume of the surgery.

In the subsequent phase, postoperative complications were analyzed in patients in both study groups. In Group 1, postoperative surgeries developed in 37 patients (31.1%), which was significantly higher than in Group 2, where postoperative complications developed in 15 patients (18.1%) ($\text{Chi} = 4.336$; $\text{df} = 1$; $p = 0.037$).

The postoperative complications affected the time of start of chemotherapy: in Group 1, in patients after the debulking surgery to remove the primary lesion the average value of CT start after the surgery was 44.0 ± 2.0 days; in Group 2 of patients who had a colostomy, this value was 30.0 ± 1.0 days ($Z = 2.732$; $p = 0.006$).

Later, on the chemotherapy stage, adverse events were analyzed as they developed that required suspension of systemic treatment, dosage reduction or stoppage

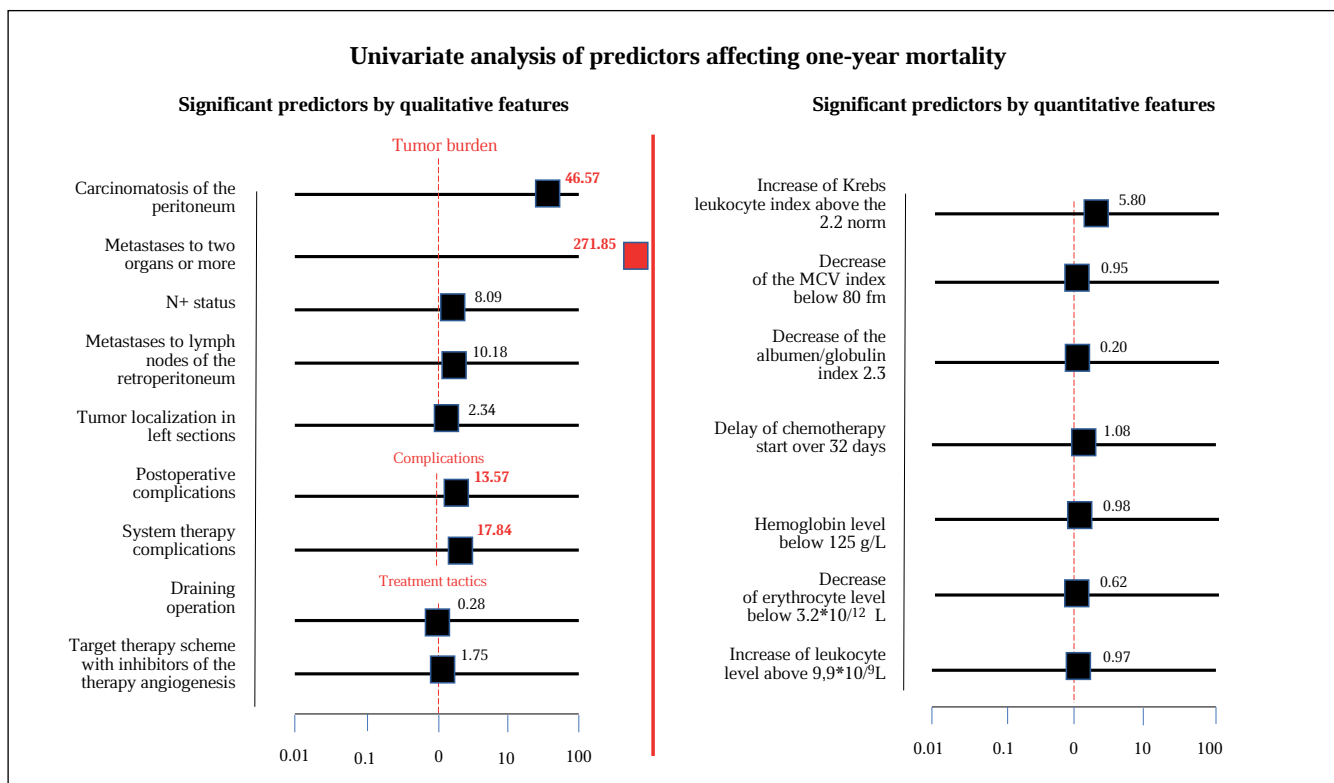


Figure 2. Univariate analysis of significant predictors influencing 1-year mortality in patients with metastatic colorectal cancer complicated by intestinal obstruction (qualitative and quantitative characteristics).

Рисунок 2. Однофакторный анализ значимых предикторов, влияющих на годичную летальность у пациентов с метастатическим КРР, осложненным кишечной непроходимостью (качественные и количественные признаки).

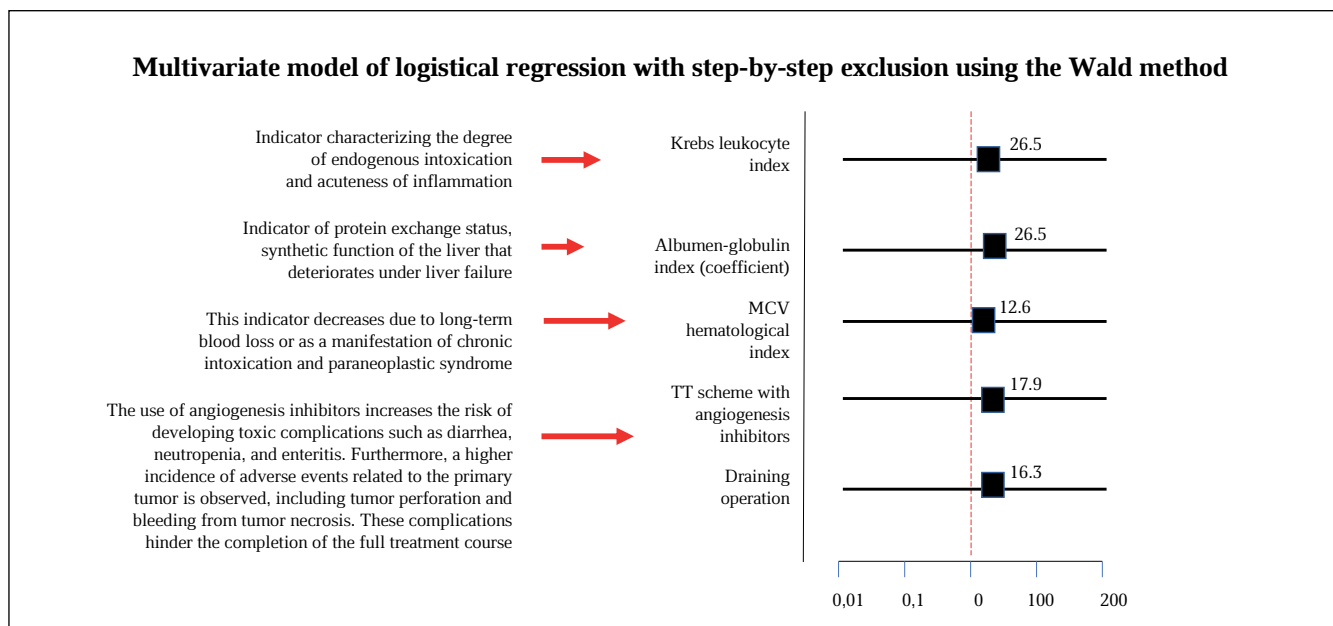


Figure 3. Multivariate analysis of variables associated with 1-year mortality in patients with metastatic colorectal cancer complicated by intestinal obstruction.

Рисунок 3. Многофакторный анализ переменных, ассоциированных с годичной летальностью у пациентов с метастатическим КРР, осложненным кишечной непроходимостью.

of the therapy. In Group 1 of the study, such adverse events were observed in 47 (39.6%), in Group 2, in 67 (80.9%) patients. In both groups, the following complications were observed: complications of the blood (leukopenia, thrombocytopenia), thrombotic and ulcerous complications. Such complications as tumor perforation and hemorrhage from the disintegrating tumor were not observed in the group of patients with the removed primary tumor. The developing complications in the course of the chemotherapy affected the number of cycles. The initially planned 12 CT cycles in the group with the primary tumor removed were delivered to 51.8% patients; in the group with non-removed primary tumor, only to 19.9% patients: it became necessary to stop special treatment for the majority of patients of this group due to development of adverse events on top of the systemic treatment ($p = 0.000$).

In the next stage, indicators of event-free and overall survival. One-year mortality in the Group 1 was 37 people (31.1%), in Group 2, 51 patients (61.4%) ($\chi^2 = 18.323$, $df = 1$; $p = 0.000$). In order to evaluate the significance of the factors influencing one-year mortality, univariate equations of logistic regression were derived and predictors were identified that significantly affected one-year mortality (**Fig. 2**).

Based on the identified significant predictors, a multivariate logistical regression model was constructed with step-by-step exclusion using the Wald method (**Fig. 3**). The predictors that had significant influence on one-year survival were the increase of the Krebs leukocyte index (KLI), decrease of the albumen-globulin index (AGI) and decrease of the MCV, affection by metastases of more than one organ and increase of incidence rate of postoperative complications. As far as the surgery method is concerned, the colostomy without removal of the primary tumor also increased probability of death within one year.

For the further assessment of the factors influencing patient survival depending on the volume of surgical intervention, we constructed the CHAID decision trees (**Fig. 4**). The identified factors that had significant impact on one-year mortality reflected the status of complications related to the presence of the primary tumor and the tumor burden.

Implementation of the algorithm

1. If metastases are found to affect two or more internal organs, primary tumor removal surgery is not indicated due to the lack of oncological practicability of such intervention.

2. If metastases are not found to affect two or more internal organs, the second step of analysis follows: if the albumen-globulin index decreases below 1.5, primary tumor removal surgery is also not indicated, for the patient has signs of liver failure, when drug therapy efficiency is significantly compromised.

3. If the albumen-globulin index does not decrease below 1.5, the third step follows: the analysis of the Krebs leukocyte index. If KLI is above 2.2, primary tumor removal surgery is indicated, for the relief of the respective inflammatory process related to the presence of the primary tumor will relieve, in the subsequent stages, the onset of adverse septic events on top of the system treatment.

4. If the Krebs leukocyte index is below 2.2, the fourth stage of analysis will follow: the analysis of the MCV index relation to the scheme of the future target therapy. If the MCV index is below 80 with the combination of angiogenesis inhibitor TT, the removal of primary tumor is indicated. The MCV marker reflects the presence of a chronic hemorrhage, the source of which in the majority of CRC cases is the primary tumor. Once angiogenesis inhibitors are added to the therapy scheme, the probability of development of such an adverse event as bleeding from

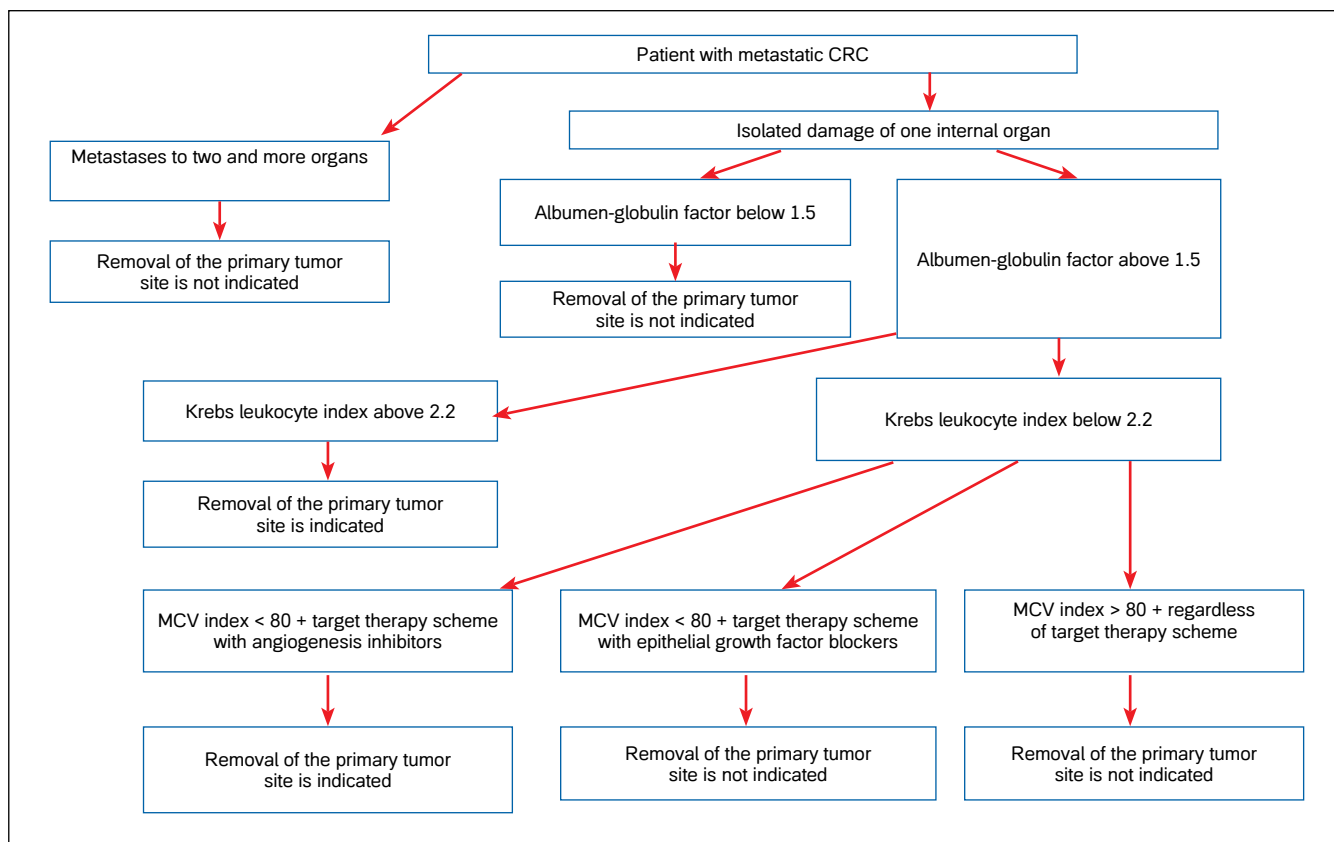


Figure 4. Decision tree.

Рисунок 4. Дерево принятия решений.

the disintegrating tumor increases significantly. If the MCV index is below 80 with the combination of epithelial growth factor blocker TT, regardless of the planned TT course, the removal of the primary tumor on the first stage of treatment is not indicated, and the formation of the colostomy would be sufficient. Since the risk of development of adverse events on the top of system therapy administration in this group of patients is minimal, it would be sufficient to relieve the manifestations of intestinal obstruction, start administration of chemotherapy in the shortest time possible, and later look into the possibility of R0 resection.

Based on this algorithm, a computer program was developed that calculates the risk of mortality within the first year in mCRC patients with a symptomatic primary tumor and determines the practicability of debulking surgery with respect to all of the above predictors.

In order to produce a prediction for a mCRC patient before the surgical stage of treatment, the following indicators are analyzed. Chest and abdomen CT scans are used to determine the number of internal organs affected by metastases. Biochemical blood assay is used to calculate the albumen-globulin coefficient. The values of the general blood test are used to calculate the MCV index, percentages of neutrophils and lymphocytes, and to calculate the Krebs leukocyte index.

The testing of the software performance quality involved its sensitivity and specificity. We tested the possible points of outcome discrimination, and the incidence of erroneous predictions was $1.0 \pm 0.7\%$.

DISCUSSION

Patients with mCRC are some of the most complicated groups to develop treatment tactics. They have an adverse long-term prognosis. According to practical recommendations of RUSSCO, in effect prior to 2018, it was recommended to perform the debulking surgery to remove the primary tumor before starting the chemotherapy. In the opinion of Yu.A. Barsukov, M.F. Cherkasov, debulking surgeries are aimed at reduction of the amount of tumor tissue and improve efficiency of the administered chemotherapy [4, 8, 9]. However, some studies report that complications after surgeries in CRC are seen in 19.3 – 26.7%, and mortality after these surgeries is 2.2 – 5.4% [10, 11]. Development of postoperative complications significantly delays the start of drug therapy and, in some cases, render further treatment impossible. According to the Clavien – Dindo classification of surgical complications, in 7.1% cases after surgery for CRC there occur fatal complications that render the patient’s further drug therapy impossible [12]. This is explained by the volume of the surgery and technical difficulties in the performance of the surgery. According to our data, the group with a history of debulking surgeries to remove the primary tumor, postoperative complications occurred more often than in the group without removal of the primary tumor (29.8% vs. 9.6%), which resulted later in the delay of start of chemotherapy. In Group 1, the average number of days the chemotherapy started after the surgery was 44.0 days, whereas in Group 2, this number was 30.0 days ($Z = 2.732$; $p = 0.006$), which had a respective impact on the treatment efficiency.

The complications that develop regularly and deteriorate the patients' quality of life became the cause for a number of international randomized studies. In 2016, 2019 and 2020 the following studies were completed: China Multicenter (China), JCOG1007 (Japan) and PTR Trial (South Korea). Their findings are as follows: in the symptom-free progression of the primary tumor, debulking operations to remove the primary tumor do not improve 1-, 2-, 3- and 5-year survival of mCRC patients.

At the moment, four European studies are in the process of enrolling patients: SYNCRONOUS (Germany), CAIRO4 (Netherlands), CCR-IV (Spain), CLIMAT (France). According to the published intermediate results of these studies, no connection is seen between the improved survival of patients with a history of debulking operations to remove the primary tumor [13].

This resulted in the modification of recommendations, and since 2018, recommendations have been in effect that call for a personalized approach to the removal of the primary tumor with respect to the risk of development of complications.

It should be mentioned that the above studies focused on the symptom-free (uncomplicated) progress of the primary tumor. The presence of a complicated (symptomatic) primary tumor necessitates removal of existing complications by removal of the primary tumor prior to administration of system treatment.

Remote outcomes strongly depend on the development of adverse events on top of the chemotherapy in progress. According to the data of the European Society for Medical

Oncology, adverse events accompany chemotherapy in more than 50% patients. E. Savu reports that the degree of their manifestation depends on the therapy scheme, dosage, tumor burden and individual factors, i.e. presence or absence of existing complications without clinical manifestation [14]. According to S.N. Fedorinov and A.Yu. Dobrodeev, the following adverse events may be seen in the course of the chemotherapy: hemorrhage from a disintegrating tumor, tumor perforation with subsequent development of septic complications [15, 16]. All of these complications are related to the presence of a non-removed primary tumor. In our observations, the number of adverse events in the group with the non-removed primary tumor was above the European level of 50% and was 68.2%, whereas in the group with the removed primary tumor this indicator was 33.3%. We believe that this is related with the presence of subclinical complications of the primary tumor that existed even before the start of the system treatment.

CONCLUSION

The proposed algorithm and the computer program developed on its basis consider the amount of metastatic affection of the internal organs and such indicators as albumin-globulin coefficient, Krebs leukocyte index, MCV index and the scheme of the chemotherapy to be administered. The algorithm and the program allow for a justification of necessity of removal of the primary tumor or formation of a colostomy and for improvement of outcomes of system treatment and levels of overall survival of patients with metastatic colorectal cancer. ■

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethics approval. Protocol No. 265 of June 21, 2023.	Этическая экспертиза. Протокол ЛЭК №265 от 21.06.2023 года.
Consent for publication. All patients signed a written informed consent form.	Согласие на публикацию. Все пациенты подписывали добровольное информированное согласие.
Study funding. The study was carried out with the support of the Samara Regional Clinical Oncology Dispensary.	Источник финансирования. Исследование выполнено при поддержке Самарского областного клинического онкологического диспансера.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Shvets D.S.: planning of the scientific work, study design, writing of the text. Mikolenko N.I., Kozlov A.M., Frolov S.A.: critical revision. Kaganova T.O.: statistical processing, concept development. Kaganov O.I., Orlov A.E.: study design, editing of the manuscript. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	Участие авторов. Швец Д.С. – планирование научной работы, дизайн исследования, написание текста. Миколенко Н.И., Козлов А.М., Фролов С.А. – критический пересмотр. Каганова Т.О. – статистическая обработка, разработка концепции. Каганов О.И., Орлов А.Е. – дизайн исследования, редактирование рукописи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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A new method for reconstruction of the lateral wall of the attic after atticotomy

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Abstract

An original way for reconstruction lateral wall of the attic after separate atticotomy is proposed and demonstrated using a clinical case. Patient P. (33 years old) with chronic left-sided epitympanoantral suppurative otitis media. Left-sided mixed hearing loss of grade 3 (air-bone interval 50-55 dB). Under general anesthesia, a retroauricular approach to the tympanic cavity was performed, separate atticotomy was performed, pathological contents of the middle ear cavities were removed, and autofascia and autcartilage were harvested. According to the original technique, the cartilage plates were placed together and sutured with a 4-0 size absorbable braided polyglactin 910 suture using an atraumatic needle. The needle was first inserted through the center of both cartilage plates from front to back, withdrawn, and re-inserted near the previous needle entry point from back to front. The resulting loop was not tightened. Next, the cartilage was re-inserted from front to back near the previous needle entry point, forming a second loop through which the end of the suture without the needle was threaded. Both loops were then tightened. The suture was passed from the external auditory canal through the attic into the antrum and out into the external auditory canal. The sutured plates were placed in the attic so that their ends were adjacent to the posterior wall of the external auditory canal. The ends of the sutures were tightened with a trial knot

so that the tension of the suture pressed the cartilaginous plates against the posterior wall of the external auditory canal. A mark was made where the knot touched the outer edge of the posterior bony wall of the external auditory canal, the knot was unraveled, a groove was made in the area of the mark, the ends of the suture were retightened, and a knot was tied in the groove. Ossicular chain reconstruction with a 2.25 mm partial prosthesis, tympanoplasty with fascia and cartilage, wound suturing, and packing of the external auditory canal were performed. After one year, the air-bone interval was 10 dB. Computed tomography of the temporal bones showed no recurrence of cholesteatoma, and reconstruction of the lateral wall of the attic was satisfactory.

Conclusion. The development and implementation of new reconstructive techniques in chronic suppurative otitis media surgery expands the capabilities and enhances the physician's skills. The proposed technique for forming the lateral attic wall after separate atticotomy effectively restores the anatomical relationship between the middle ear and the external auditory canal and has practical significance.

Keywords: attic, cartilaginous plate, chronic suppurative otitis media, attic reconstruction, atticotomy.

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Новый способ реконструкции латеральной стенки аттика при отдельной аттикоантотомии

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Аннотация

Предложена оригинальная методика реконструкции латеральной стенки аттика после отдельной аттикоантотомии, которая продемонстрирована на клиническом примере. Пациент П. (33 лет), диагноз: хронический левосторонний эпитимпаноантральный гнойный средний отит. Левосторонняя смешанная тугоухость 3 степени (костно-воздушный интервал 50–55 Дб). Под общей анестезией осуществлены ретроаурикулярный доступ в барабанную полость, отдельная аттикоантотомия, патологическое содержимое полостей среднего уха удалено, забор аутофасции, аутохряща. Пластинки хряща, согласно оригинальной методике, складывали вместе и прошивали рассасывающейся плетеной нитью из полиглactина 910 размер 4-0 с атравматичной иглой. Сначала прокалывали иглой по центру обе пластинки хряща спереди назад, выводили иглу и снова прокалывали рядом с предыдущим местом входа иглы сзади наперед, при этом сформированную петлю не затягивали, далее

повторно прокалывали хрящ спереди назад рядом с предыдущим местом входа иглы с формированием второй петли, в которую продевали конец нити без иглы, после чего затягивали обе петли. Из наружного слухового прохода нить проводили через аттик в антрум и выводили в наружный слуховой проход. Сшитые пластины помещали в аттик так, чтобы своим торцом они прилежали к задней стенке наружного слухового прохода. Концы нитей затягивали пробным узлом так, чтобы сила натяжения нити прижимала хрящевые пластинки к задней стенке наружного слухового прохода. В месте прилегания узла к наружному краю задней костной стенки наружного слухового прохода делали метку, узел распускали, в области метки делали углубление-паз, концы нити повторно натягивали и завязывали узел в области углубления-паза. Реконструкция цепи слуховых косточек частичным протезом 2,25 мм, тимпанопластика фасцией и хрящом, ушивание раны, тампонада наружного слухового прохода. Через

1 год – костно-воздушный интервал 10 Дб, на компьютерной томографии височных костей рецидива холестеатомы нет, реконструкция латеральной стенки аттика состоятельна.

Заключение. Разработка и внедрение новых способов реконструкции в хирургии хронического гнойного среднего отита расширяет возможности и развивает компетенции врача. Предложенная методика формирования

латеральной стенки аттика после раздельной аттикоантромии позволяет эффективно восстановить анатомическое взаимоотношение среднего уха и наружного слухового прохода и имеет практическую значимость.

Ключевые слова: аттик, хрящевая пластинка, хронический гнойный средний отит, реконструкция аттика, аттикоантромия.

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ХГСО – хронический гнойный средний отит; ЛСА – латеральная стенка аттика; НСП – наружный слуховой проход; МСКТ – мультиспиральная компьютерная томография.

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BACKGROUND

Separate atticoanthrotomy in chronic suppurative otitis media (CSOM) is one of 'closed type' sanitizing operations which, unlike 'open-type' surgeries include not only the stage of removal of the cholesteatoma and the pathological contents, but the stage of reparation of anatomic compatibility of the middle ear structures [1–3]. The sanitizing stage being over, reparation of the access to the antrum and the reconstruction of the later wall of the attic are performed, which is an integral part of formation of the frame and the support of the drum or the neotympanic membrane, especially in the event the hammer is absent [4].

The requirements for a graft used in the reconstruction of the attic lateral wall are rigidity and the ability to be shaped to fit the acquired defect of the attic lateral wall, resistance to inflammation in the setting of CSOM, and the absence of graft tissue resorption over time. Another important factor of successful reconstruction is the possibility of reliable fixation of the graft in the proper position to prevent its displacement to the antrum or the tympanic cavity in the early or remote post-surgery periods, which might necessitate revision surgery [2–6].

We proposed an original method of reconstruction of the lateral wall of the attic after separate atticoanthrotomy [7], which is illustrated on a specific clinical case.

CASE DESCRIPTION

Patient P. (33 years old). Clinical diagnosis: chronic left-sided epitympanoantral suppurative otitis media. Left-sided mixed hearing loss of grade 3. Admitted to the clinic with complaints of hearing loss and episodes of purulent discharge from the ear up to 2 times per year. CSOM over 12 years.

Examination: the left circumaural area is not altered, the ear canal shows traces of mucous discharge, the tympanic membrane is thickened and mildly hyperemic, with a perforation in the pars flaccida. The lateral wall of the attic is partially eroded by the inflammatory process. Hearing: whispered speech is perceived at 0 meters (Fig. 1).

Right ear: the tympanic membrane is gray and mobile. Hearing: whispered speech is perceived at 6 meters. No vestibular disorders.

According to the multi-spiral computed tomography (MSCT) of the temporal bones, the cells of the left mastoid

process are well developed, pneumatization is impaired; the antrum and attic are filled with pathological content. The lateral wall of the attic is partially eroded. The head of the malleus and the body of the incus show carious changes; the long process of the incus is destroyed by the inflammatory process. The stapes is preserved. The audiometry shows mixed loss of hearing of the left ear, the air-bone interval was 35–40 dB.

The surgical treatment was performed under combined general anesthesia. Under the control of an operating microscope, a postauricular approach to the tympanic cavity was performed. A disruption of the ossicular chain was identified, caused by resorption of the long process of the incus. The stapes was preserved and mobile. The cholesteatoma developed to the attic and the additus. The bore was used to incise the cells of the mastoid process, to perform the anthrotomy with preservation of the posterior wall of the external auditory tract (EAT). The pathological contents of the

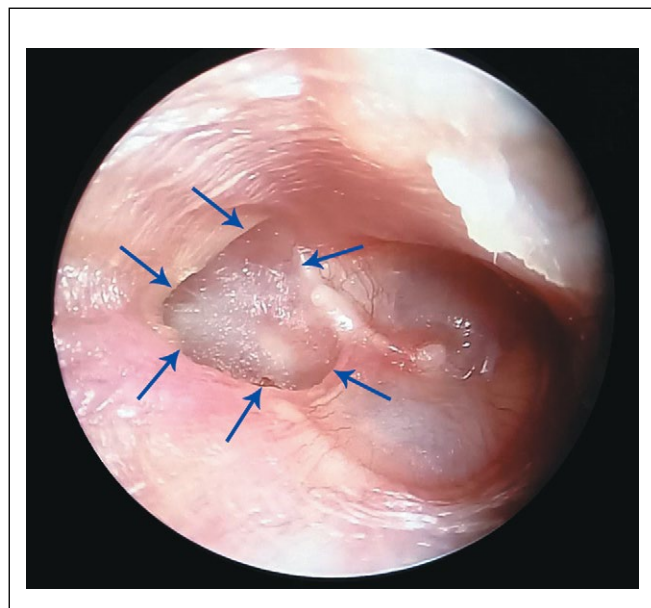


Figure 1. View of the tympanic membrane and bone defect in the area of the lateral wall of the attic (the boundaries of the defect are indicated by arrows).

Рисунок 1. Вид барабанной перепонки и костного дефекта в области латеральной стенки аттика (границы дефекта указаны стрелками).

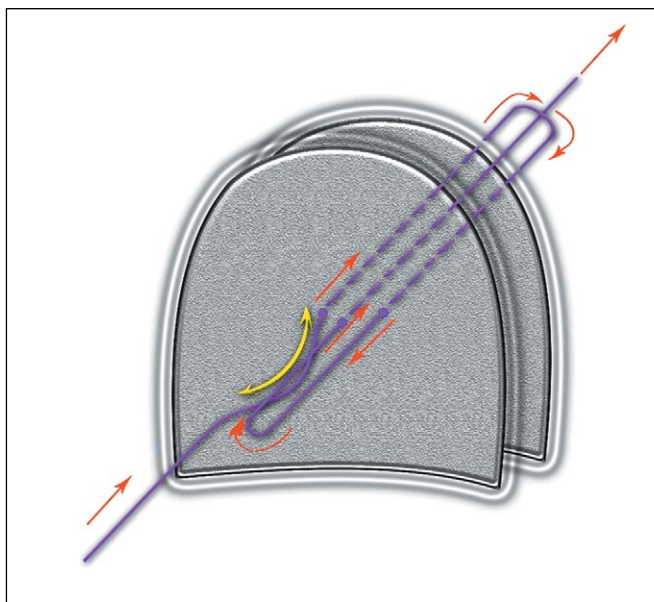


Figure 2. Schematic diagram of suture placement on two cartilaginous plates. Red arrows indicate the direction of needle and thread movement; the yellow arrow with two ends indicates insertion of the end of the thread without the needle into the second loop.

Рисунок 2. Схема наложения шва на две хрящевые пластины. Красные стрелки – направление движения иглы с нитью, желтая стрелка с двумя концами – вправление конца нити без иглы во вторую петлю.

antrum was removed until the body of the anvil was visualized from the side of the antrum, the remaining part of the anvil was removed. Atticotomy was performed using a drill. The head of the malleus was removed. Under endoscopic control (30°, 45°, and 70° scopes), sanitization of the tympanic cavity, attic, and antrum was carried out. Perichondrium, temporal fascia, and conchal cartilage were harvested from the left postauricular region for reconstruction of the lateral epitympanic wall and the access area to the antrum.

According to the original method, the cartilage plates were placed together and sutured with a 4-0 size absorbable braided polyglactin 910 suture using an atraumatic needle. The needle was first inserted through the center of both cartilage plates from front to back, withdrawn, and re-inserted near the previous needle entry point from back to front. The resulting loop was not tightened. Next, the cartilage was re-inserted from front to back near the previous needle entry point, forming a second loop through which the end of the suture without the needle was threaded. Both loops were then tightened (Fig. 2).

The suture was passed from the external auditory canal through the attic into the antrum and out into the external auditory canal. The sutured plates were placed in the attic so that their ends were adjacent to the posterior wall of the external auditory canal. The ends of the sutures were tightened with a trial knot so that the tension of the suture pressed the cartilaginous plates against the posterior wall of the external auditory canal. A mark was made where the knot touched the outer edge of the posterior bony wall of the external auditory canal, the knot was unraveled, a groove was made in the area of the mark, the ends of the suture were retightened, and a knot was tied in the groove (Fig. 3).

Ossicular chain reconstruction with a 2.25 mm partial titanium prosthesis. He access to the antrum was closed

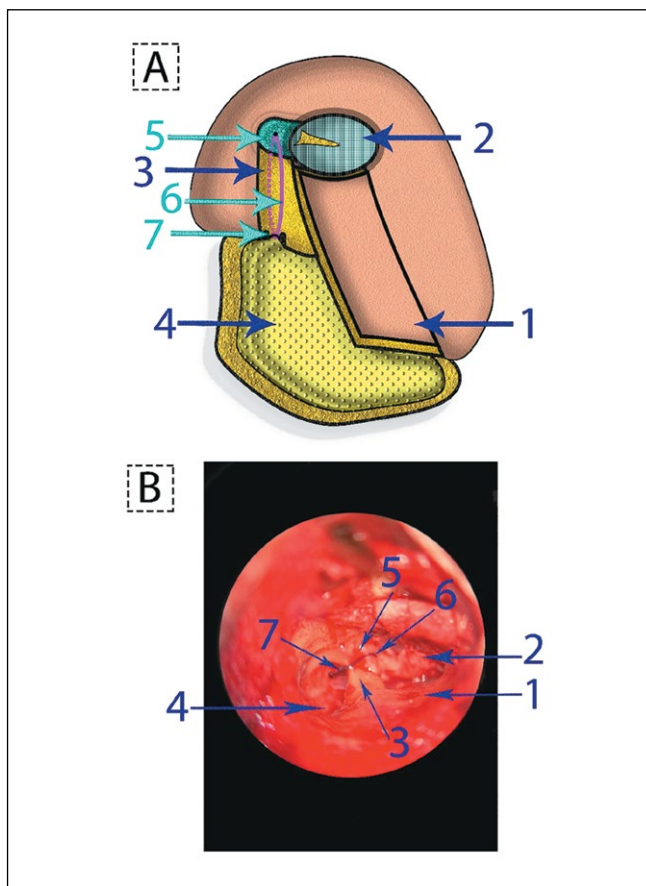


Figure 3. A - diagram showing the middle ear cavities and the walls of the external auditory canal after reconstruction of the lateral wall of the attic with a cartilaginous graft. B - intraoperative photograph of a similar stage of the operation; 1 - external auditory canal, 2 - projection of the neotympanic membrane, 3 - posterior wall of the external auditory canal, 4 - antromastoid cavity, 5 - cartilaginous graft, 6 - thread, 7 - knot in the depression-groove at the end of the posterior wall of the external auditory canal.

Рисунок 3. А – схема, на которой изображены полости среднего уха и стенки наружного слухового прохода после реконструкции латеральной стенки аттика хрящевым трансплантатом. В – интраоперационная фотография аналогичного этапа операции; 1 – наружный слуховой проход, 2 – проекция неотимпанальной мембраны, 3 – задняя стенка наружного слухового прохода, 4 – антромастoidalная полость, 5 – хрящевой трансплантат, 6 – нить, 7 – узел в углублении-пазу в торце задней стенки наружного слухового прохода.

with cartilage. Tympanoplasty was performed with temporal fascia. The meatal-tympanic flap was repositioned to its original position, the wound was sutured by layers, and the external auditory canal was packed with a hemostatic sponge.

Three weeks after removal of tampons from the external auditory tract, the examination revealed integrity of the neotympanic membrane, the repair area had no visible defects, the hearing improved, the bone-air interval was 15–20 dB. One year after the operation, the bone-air interval was 10 dB, and the MSCT of the temporal bones and the MRI showed no signs of recurrence of the cholesteatoma; the reconstruction was secure (Fig. 4).

DISCUSSION

Numerous methods of reconstruction of the lateral wall of the attic using transplants are reported in literature; all of them having their proper advantages and disadvantages.

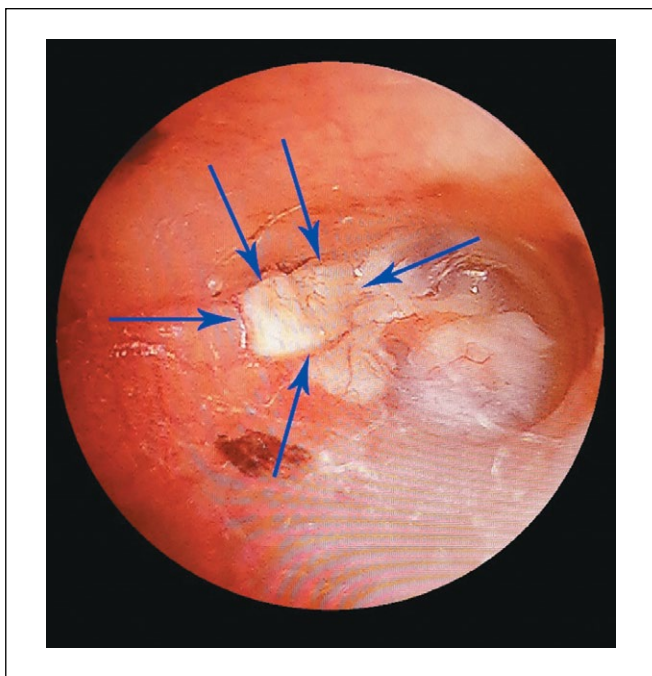


Figure 4. View of the tympanic membrane and reconstruction of the lateral wall of the attic 1 year after surgery (the boundaries of the cartilage transplant are indicated by arrows).

Рисунок 4. Вид барабанной перепонки и реконструкции латеральной стенки аттика через 1 год после операции (границы хрящевого трансплантата указаны стрелками).

Thus, the use of free bone grafts from the cortical layer of the temporal bone [8], on the one hand, enables anatomical reconstruction. On the other hand, it is technically challenging to first drill out and then shape the graft to the exact size of the defect using a bur. The absence of tight contact with the bony walls of the attic may compromise graft osteointegration, leading to sequestrum formation.

Reconstruction of the lateral wall of the attic is most commonly performed using a fragment of conchal or tragal cartilage. This preference is due to the graft's accessibility in sufficient quantity, ease of shaping to fit the acquired defect of the lateral wall of the attic, resistance to inflammation in the setting of CSOM, and lack of postoperative resorption. However, simply placing the cartilage plate over the defect without additional fixation can easily lead to graft displacement during healing [4].

In the event of use of allogeneic [9] or autogenous [10] cartilage plates, where fixation relies on the elastic properties of the cartilage plate itself, instability of the formed construct can lead to changes in its position and shape.

The use of a reconstruction technique for the lateral wall of the attic involving a chondroperichondrial graft offers a clear advantage. In this graft, the cartilage size matches the defect of the lateral wall of the attic, while the perichondrium exceeds it [11]. This provides excellent "primary" fixation of the graft to the walls of the external auditory canal, even in the absence of tight contact between the cartilage and the bony walls of the attic. The downsides of this method, in our opinion, are the displacement of the graft in the healing process due to scarring, tightening or, conversely, thinning and partial lysis of the perichondrium; the impossibility of changing the shape and increasing the thickness of the graft and, if necessary, reconstructing large defects of the lateral wall of the attic: the graft is attached to the perichondrium, and its thickness and shape depend on the cartilage of the donor area. Besides, an error on part of the surgeon in the selection of the size and form of the graft in this method of fixation would require harvesting a second graft, the source whereof is limited.

Our method utilizing two sutured cartilages allows for stabilization of the graft in the area of the defect of the lateral wall of the attic supported by the posterior wall of the external auditory tract and to prevent formation of retraction pockets thanks to an increased thickness of the graft. Suturing with single-thread absorbable 910 polyglactin through the cartilages involving the posterior osseous wall of the external auditory tract and fixation of the knot in the groove area prevents the thread from displacement relatively to the posterior wall of the external auditory tract and secures the graft in place in the early postoperative period.

CONCLUSION

Development and implementation of new reconstruction techniques in CSOM surgery broadens capabilities and enhances physician competencies. The proposed method for reconstructing the lateral wall of the attic after separate atticoantrotomy effectively restores the anatomical relationship between the middle ear and the external auditory canal and is of practical significance. ■

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
<p>Ethics approval. Compliance with ethical principles: the conducted study complies with the standards of the Declaration of Helsinki as amended in 2024. The compliance of the study protocol with ethical principles was confirmed by the Local Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education "ROSBIOTECH" (Protocol No. 7/2 dated February 25, 2025).</p>	<p>Этическая экспертиза. Соответствие принципам этики: проведенное исследование соответствует стандартам Хельсинкской декларации (Declaration Helsinki) в редакции 2024 г., соответствие протокола исследования этическим принципам было подтверждено локальным этическим комитетом ФГБОУ ВО «РОСБИОТЕХ» (протокол №7/2 от 25 февраля 2025 г.).</p>
<p>Consent for publication. Written consent was obtained from the patient for the depersonalized publication of relevant medical information and all of accompanying images in the journal.</p>	<p>Согласие на публикацию. Авторы получили письменное согласие пациента на публикацию в журнале медицинских данных и фотографий в обезличенной форме.</p>
<p>Study funding. The study was the authors' initiative without external funding.</p>	<p>Источник финансирования. Работа выполнена по инициативе авторов без привлечения финансирования.</p>
<p>Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.</p>	<p>Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.</p>
<p>Contribution of individual authors. Morozov I.I., Gorbuнова N.V.: study concept and design, manuscript editing. Bulanov K.V., Abdullaev A.G.: material collection, statistical data processing, writing of the text. Authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.</p>	<p>Участие авторов. Морозов И.И., Горбунова Н.В. – концепция и дизайн исследования, редактирование рукописи. Буланов К.В., Абдуллаев А.Г. – сбор материала, статистическая обработка данных, написание текста. Авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.</p>

<p>Statement of originality. No previously published material (text, images, or data) was used in this work.</p>	<p>Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).</p>
<p>Data availability statement. The editorial policy regarding data sharing does not apply to this work.</p>	<p>Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима.</p>
<p>Generative AI. No generative artificial intelligence technologies were used to prepare this article.</p>	<p>Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.</p>
<p>Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.</p>	<p>Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.</p>

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A new device for removing foreign bodies from soft tissues (experimental study)

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Abstract

Aim: to perform a comparative evaluation of a newly developed device for removing foreign bodies from soft tissues.

Material and methods. A minimally invasive endoscopic system has been developed to facilitate the removal of foreign bodies from soft tissues while decreasing the procedure duration and intervention-related injury. An experimental study was performed using a comparative group design. Blind gunshot wounds were simulated in porcine thigh specimens (pistol shots from a distance of 25 meters). In the main study group (20 wounds) extraction was performed using the developed device, in the comparison group (20 wounds), using a standard Grasper's clamp under ultrasound guidance. The bullet extraction time was measured with a stopwatch, and the extent of soft tissue damage was quantified by the volume of soft tissue excised.

Results. The duration of bullet extraction in the study group MED [Q1;Q3] 178,5 [148,5; 223,7] s was shorter than in the control group: MED [Q1;Q3] 322,0 [248,5; 350,0] s ($p=0.001$). The number of muscle fragments extracted along with bullets was higher in the control group (31 fragments) than in the study group (9 fragments). The novel device reduced intervention-related trauma in the study group compared to the control group.

Conclusion. The novel device for extraction of foreign bodies from soft tissues demonstrated a significant reduction in tissue trauma and a shorter procedure time in an experimental model. The combined use of endoscopic and ultrasound guidance enhances targeting precision, facilitates secure grasping and stable retention of the foreign body, and enables its minimally traumatic extraction.

Keywords: foreign bodies, wound debridement, endoscopic surgery.

Conflict of interest: nothing to disclose.

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Новое устройство для удаления инородных тел из мягких тканей (экспериментальное исследование)

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Аннотация

Цель: провести сравнительную оценку эффективности разработанного устройства для удаления инородных тел из мягких тканей.

Материал и методы. Для упрощения удаления инородных тел из мягких тканей, сокращения продолжительности и травматичности вмешательства была разработана малоинвазивная эндоскопическая система. Выполнено экспериментальное исследование в группах сравнения. Проводили моделирование огнестрельных пулевых слепых ранений на фрагменте свиного бедра (выстрелы из пистолета с дистанции 25 метров). В основной группе (20 шт.) удаление пуль осуществляли с применением разработанного устройства, в группе сравнения (20 шт.) – с применением зажима Граспера под ультразвуковым контролем. Оценивали продолжительность удаления пули с применением секундомера и травматичность манипуляции по количеству дополнительно удаленных мягких тканей.

Результаты. Продолжительность удаления пули в основной группе MED [Q1;Q3] 178,5 [148,5; 223,7] с была меньше, чем в группе сравне-

ния – MED [Q1;Q3] 322,0 [248,5; 350,0] с ($p=0,001$). В основной группе вместе с пулями дополнительно было извлечено 9 фрагментов мышцы, окружающих пули, в группе сравнения – 31 фрагмент. Травматичность вмешательства с использованием разработанного устройства в основной группе была ниже, чем в группе сравнения.

Заключение. Разработанное устройство для удаления инородных тел из мягких тканей позволяет снизить травматичность и сократить продолжительность экстракции предметов (в эксперименте). Применение в его составе эндоскопической визуализации совместно с ультразвуковой обеспечивает повышение точности позиционирования инородного тела в мягких тканях, а также способствует его захвату, надежному удержанию и малотравматичному удалению.

Ключевые слова: инородные тела, хирургическая обработка ран, эндоскопическая хирургия.

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■ INTRODUCTION

Traumatic injuries involving foreign bodies penetrating the tissue are quite complicated for diagnostics and treatment. Among the peacetime injuries, they account for approx. 50% of traumas and usually are household injuries [1]. The foreign bodies are, as a rule, fragments of wood, glass, metal cuttings, plastic, parts of components of high-speed household appliances.

Most frequently, foreign objects penetrate the patients' bodies during warfare. In the course of the Second World War, shrapnel (56.8%) and bullet (43.2%) gunshot wounds prevailed. In the warfare of the last decades, the most common gunshot wounds are mine-blast and explosion wounds [2, 3]. According to V.V. Solosin *et al.*, in the period of the special military operation (SMO) the incidence of shrapnel wounds was 79%, and bullet wounds, 10% [4]. In terms of localization of most injuries, wounds of the extremities account for 81.4% of all admitted wounded patients [5]. Such injuries are accompanied with damage of various anatomic areas with foreign bodies deeply penetrating the soft tissues and causing various complications. An unremoved foreign object is a source of infectious complications, it can cause pain, and, in case of its migration, cause damage of various structures, arrosion of vascular walls with formation of hematomas and development of bleeding. In the event of their migration in the vascular structure, urgent conditions may develop [6]. In the event of penetration of chemically active objects, intoxication of the surrounding soft tissues occurs [7, 8]. Another thing to be considered is the certain psychological discomfort that the patients feel when having unremoved foreign objects.

The analysis of literature shows that currently there are no clear indications for the removal of foreign bodies. The problem is approached on a case-by-case basis and depends on a variety of factors, such as position of the wound tract and the foreign body, its size and shape, presence of nervous and vascular branches in its vicinity. The surgeon always faces the question of what would cause the greater harm, the removal of the object or leaving it in the body. Standard operations to remove foreign objects are quite complicated and involve a great number of unsuccessful interventions, from 50 to 80% [9].

According to the Guidelines for Military Field Surgery, removal of foreign bodies (projectiles, their elements, secondary shrapnel, pieces of clothing) is one of the stages of primary surgical treatment of gunshot wounds. In the course of provision of qualified surgical treatment, only those foreign objects are removed that are located along the path of the wound tract. At this stage of medical evacuation, the foreign objects that are located near large vessels, deep

inside vital organs, and the foreign objects requiring complex additional access are not subject to removal [10].

Different methods of identification of location of foreign bodies have been developed. Usually, these methods involve X-ray irradiation of the patient, e.g. with the use of an electronic-optical image converter. It is to be noted that this method enables identification of the location of the foreign object and the surgical tool bit involves considerable radiation exposure of the patient and the medical staff. The use of an electronic-optical image converter enables visualization of the object to be removed only in one plane, which does not give the surgeon any information about the location of the object in three dimensions during the operation. Moreover, this method cannot be used in extraction of X-ray negative objects [11].

Ultrasonic-controlled removal of foreign objects via wound tract facilitates the work of the surgeons. At the same time, such manipulations necessitate respective highly precise manual skills on part of ultrasonic diagnosticians [12].

Currently, there are numerous surgical tools and operations for the extraction of different objects, yet they all come with certain shortcomings, restrictions in use, and are not universal. Traditional surgical access may not always be used to remove foreign objects, especially if they are positioned deeply, close to the passage of nervous and vascular bundles. In the event of a large number of foreign objects, e.g., in mine-blast injuries, their extraction with the use of traditional surgical intervention also does not look possible.

Thus, at the moment, it is necessary to develop low-invasive surgical tools incorporating components for navigation ensuring low-trauma removal of foreign objects from the soft tissues.

■ AIM

To perform a comparative evaluation of a newly developed device for removing foreign bodies from soft tissues.

■ MATERIAL AND METHODS

In order to simplify the removal of foreign objects from soft tissues, to reduce duration and trauma of the intervention, a special device was developed: "Device for foreign object removal from soft tissues" (patent of the Russian Federation for the invention No.2844631 dated 17.12.2024). The appearance of the working specimen in its carrying case is shown in **Fig. 1**.

The device is an endoscopic system that is inserted into the wound tract until contact with the foreign object. The process is controlled visually (on a monitor screen) and ultrasonically. In the wall of the casing there are channels for the water pump tubes, a tube for the removal of washing fluid, and clamps

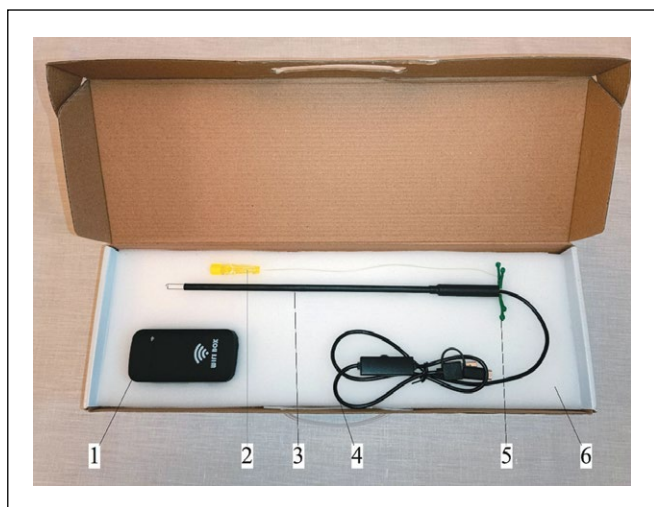


Figure 1. Functional prototype of the device: 1 – Wi-Fi transmitter, 2 – irrigation pump, 3 – main body of the device, 4 – flexible endoscope, 5 – fixation mechanism controls, 6 – storage case.

Рисунок 1. Действующий образец устройства: 1 – wi-fi передатчик, 2 – водяная помпа, 3 – корпус устройства, 4 – гибкий эндоскоп, 5 – органы управления внутренними фиксаторами, 6 – кейс.

to hold the foreign object. Wound washing is performed by a water pump, through which antiseptic solution or normal saline is fed. The removal of the foreign object is controlled endoscopically, once it is held in clamps (Fig. 2).

The L-shaped clamps are concealed in the channels of the casing and the grooves of its frontal surface. This ensures atraumatic insertion of the surgical tool in the wound tract until contact with the foreign body. Next, under visual control, the clamps are extended along and beyond the foreign body. The clamps are then rotated 90 degrees and closed beyond the object (Fig. 2). Once the foreign object is held with all clamps, the tool with the foreign object is retracted through the wound tract. Throughout the procedure of object extraction, the wound is washed with normal saline or antiseptic solution. The washing fluid is removed through the channel in the wall of the tool.

Once the foreign object is removed, the wound may be drained using the same tool. For that purpose, it is inserted in the wound tract under endoscopic control to reach the position of the removed object. The endoscope is then retrieved, and a perforated polyvinyl chloride tube is inserted in the channel

of the tool to the entire length of the wound tract. After that, the surgical tool is removed from the wound tract.

In order to test the proposed tool, experiments were performed on a fragment of a porcine ham on the base of the Department of Traumatology and Orthopedics of the Voronezh State Medical University named after N.N. Burdenko. At the outset, bullet gunshot wounds were modeled in the “Bunker-M” shooting gallery (Voronezh). The fragment of the porcine ham was shot at from a distance of 25 meters from a rifled-bore firearm: Chiappa 1911 pistol with .22LR (5.6 mm) cartridges, and Makarov pistol with 9×19 Luger cartridges. The result was the fragment of the ham with 20 blind-ended bullet wounds containing foreign objects, i.e. bullets (Fig. 3).

Two comparison groups were formed (20 manipulations in each). In the main group, the removal of the foreign objects from the fragment of the porcine ham was performed with the proposed tool. In the comparison group, the removal was performed with a Grasper clamp under ultrasonic control (Mindray DC-4, China). The comparison groups were comparable, for the bullets were removed from one fragment of the porcine ham. Since the majority of wounds were perforating, the bullets were implanted in the wound tracts to model the blind-ended wounds.

The study involved assessment of duration of foreign object removal. To that end, a SOPPr-2a-3-000 stopwatch was used. Another object of assessment was the trauma intensity of intervention judging by the presence of additionally removed fragments of soft tissue that were extracted together with the foreign object or apart from it.

Statistical analysis was performed using SPSS Statistics software suite, version 26. The distribution in both groups deviated from normality. The Shapiro–Wilk test was used to assess the normality of the distribution. Intergroup comparisons were made using the nonparametric Mann–Whitney U test.

RESULTS

The duration of the foreign object (bullet) removal in the main group was lower than in the comparison group (p=0.001). The data follows in Table 1.

In the comparison group, the duration of the foreign body extraction was greater: the removal process was complicated

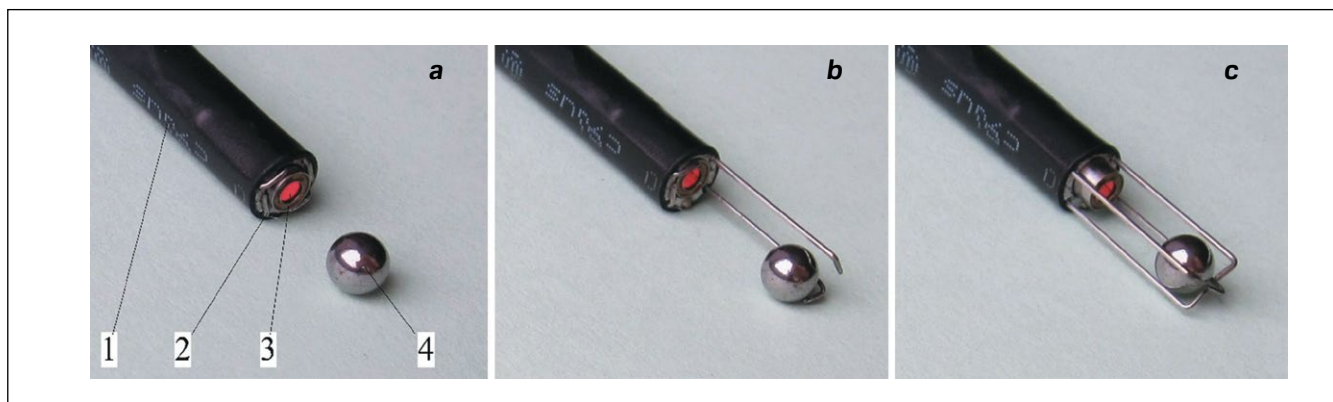


Figure 2. Foreign body grasping sequence: a – initial position, b – extension of clamps, c – rotation and grasping; 1 – mane body of the device, 2 – clamps, 3 – endoscope, 4 – foreign body (pellet).

Рисунок 2. Схема захвата инородного тела: а – начальное положение, б – выдвижение фиксаторов, с – поворот фиксаторов и захват инородного тела; 1 – корпус устройства, 2 – фиксаторы, 3 – эндоскоп, 4 – инородное тело (дробь).

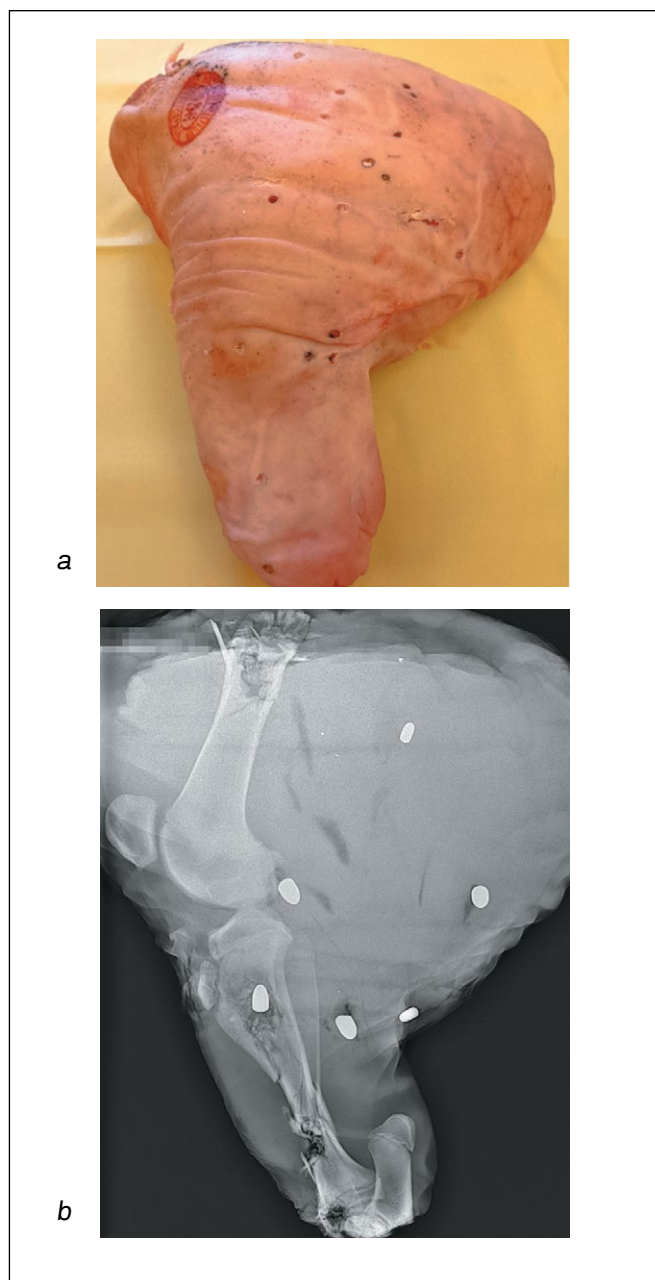


Figure 3. The appearance of the porcine thigh specimen (a) and its corresponding radiograph (b) during the experimental procedure.

Рисунок 3. Внешний вид фрагмента свиного бедра (а) и соответствующая ему рентгенограмма (b) во время эксперимента.

with technical difficulties on the stage of bullet grasping and with bullet slipping out in the course of movement in the wound tract. This necessitated repeated grasping of the foreign body extending the time of the manipulation. In the main group, in all cases the bullets were removed after the initial grasping with clamps of the proposed tool (**Fig. 4**).

One of the reasons of increased duration of bullet removal in the comparison group was the necessity of ultrasonic visualization of the foreign object and the Grasper clamp. In some cases, it was further complicated by the presence of air in the wound tract which rendered the process of foreign object removal more difficult. In the main group, the ultrasonic visualization of the bullet and the wound tract had a secondary role to identify the course of the wound tract and

Criteria	Main group	Comparison group
MED [Q1;Q3], s	178.5 [148.5; 223.7]	322.0 [248.5; 350.0]
Min; Max, s	92; 280	125; 403
MED±SD, s	183.7 ± 55.7	294.3 ± 88.1

Table 1. Results of foreign body removal in the comparison groups

Таблица 1. Результаты удаления инородных тел в группах сравнения

the position of the foreign object. All major manipulations to grasp the object were done under endoscopic control.

In the main group, 9 fragments of muscles surrounding the bullets were extracted together with the bullets, whereas in the comparison group the number of fragments was 31. Thus, the trauma intensity of the developed tool in the main group was lower than that in the comparison group.

In our study, when the foreign object was grasped with the jaws of the Grasper clamp, the tissues of muscles surrounding the foreign object would get between the jaws resulting in their further trauma. In the comparison group, when the bullet slipped out of the clamp in the course of its transportation in the wound tract, it had to be grasped again. Soft tissues would regularly get between the jaws of the Grasper clamp, and they were extracted with the bullet.

DISCUSSION

Foreign objects may penetrate the patients' body due to occupational or household trauma, blasts of mines or other ammunition and due to iatrogenic injury. Such objects are removed in two major stages: exact identification of the foreign body and its extraction.

Currently, there are different methods and tools for the extraction of objects from the patients' bodies. Traditional technologies (surgeries) are relatively traumatic, involve loss of blood and, in some cases, involve large incisions.

One of the methods of extraction of foreign bodies is their removal under ultrasonic control using various clamps: Mosquito, Crocodile, Grasper clamps. Ultrasonic navigation ensures precise visualization of foreign objects and their extraction. At the same time, this method requires good manual skills of the ultrasonic diagnostician. When using the above mentioned clamps, additional trauma of the soft tissues around the foreign object is possible since they may get between the jaws of the clamp. In the event the foreign object is located inside a bone or in the marrowy canal, this method may not be used due to limitations of the ultrasound. Another shortcoming of these clamps is the insufficient fixation of the foreign object between the jaws of the tool. In the process of extraction of foreign bodies, they might slip out necessitating repeated grasping [13, 14].

N.V. Momot et al. Suggest using angiographic tools in the course of the operation to speed up the procedure and to improve their efficacy and safety [15]. Without doubt, such intraoperative radiographic navigation ensures simplification and optimization of shrapnel removal technique from soft tissue; however, it requires costly radiographic equipment.

There are methods of removal of foreign object with the aid of magnets inserted in the wound tract. While the magnets are effective in the removal of ferromagnetic foreign objects [16], they cannot be used to remove paramagnetic objects.

One of the methods of extraction of foreign bodies is the use of endoscopic technologies. U. Haramoto et al. suggest

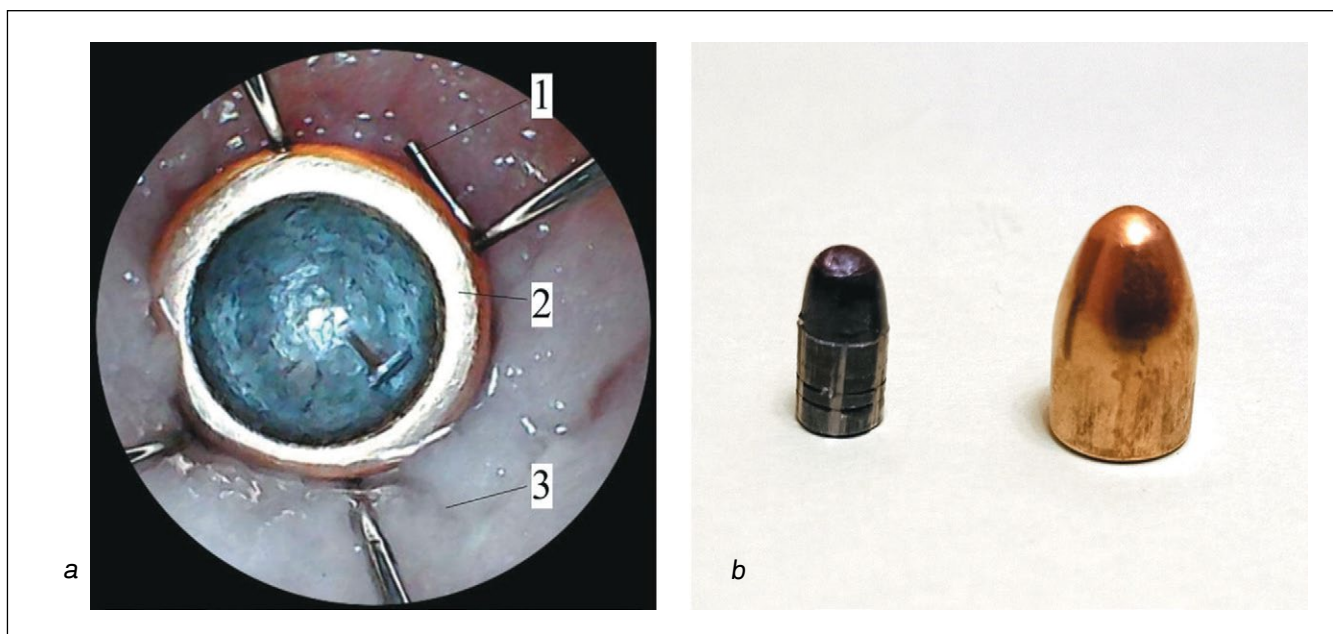


Figure 4. Endoscopic view of bullet extraction from the wound channel (a) and extracted bullets (b): 1 – retriever, 2 – bullet, 3 – muscle tissue.
Рисунок 4. Эндоскопическая картина удаления пули из раневого канала (a) и удаленные пули (b): 1 – фиксатор, 2 – пуля, 3 – мышечная ткань.

using the endoscope to wash the wound tract and remove foreign objects from it [17]. V.I. Egorov et al. recommend using videoendoscopic equipment combined with navigational systems [18].

The tool for the removal of foreign objects developed by us combines two types of navigation: ultrasonic and visual. The proposed tool has a system for grasping the foreign object that ensures secure fixation of the object and prevents its migration in the course of extraction. When removing sharp-edged fragments of ammunition via the wound tract, this system ensures protection of soft tissues. It is to be noted that the designed tool ensures fixation of foreign objects of any geometry. The availability of the endoscopic system ensures all manipulations are visually controlled, which contributes to decreased trauma during the procedure.

The tool is transported in a small-sized carrying case, which ensures easy transportation and use in any operating or dressing

room. The ultrasonic tools used can be portable ultrasonic devices. Their use assists identification of the position of the foreign object, vascular and nervous bundles nearby, and allows for control of the tool insertion in the wound tract.

CONCLUSION


The designed tool allows for reduced trauma and decreased duration of foreign object removal (experimentally). The use of endoscopic and ultrasonic visualization ensures increased precision in the positioning of the foreign objects in the soft tissue, and assists grasping, holding and low-trauma removal of foreign objects. The proposed tool may be used for removal of all types of objects that penetrated organs and tissues, magnetic and non-magnetic, radiographically positive and negative. The tool may become an auxiliary tool for orthopedic traumatologists in the treatment of patients with foreign objects in the soft tissues.

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Use of botulinum toxin type A in the preoperative preparation of patients with ventral hernias: effect on the postoperative period

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Abstract

Aim: to evaluate the effect of preoperative botulinum toxin type A (BoNT-A) administration on the early postoperative period in patients with large incisional ventral hernias (IVH) compared with a control group.

Material and methods. A retrospective analysis of 19 patients with IVH class W3 (EHS classification) was performed. The main group (n=9) included patients who received preoperative BoNT-A injections (Dysport 900-1000 U or Xeomin 200 U) into the lateral abdominal muscles under US guidance followed by TAR repair. The control group (n=10) included patients operated without BoNT-A preparation (methods: TAR, Rives-Stoppa, TAR+bridge). The operative time, intensity of pain syndrome according to VAS on days 1, 3 and 5, the duration of opioid analgesic use, the frequency and structure of complications, and the length of hospital stay were evaluated.

Results. In the BoNT-A group, pain intensity was significantly lower on day 1 (VAS median 18.0 [11.5; 26.0] mm vs. 43.5 [40.0; 52.8] mm in

control, $p < 0.001$), day 3 (11.0 [8.5; 13.0] mm vs. 41.5 [38.0; 42.8] mm, $p < 0.001$) and day 5 (2.0 [1.0; 3.5] mm vs. 31.5 [29.0; 33.0] mm, $p < 0.001$). The overall complication rate in the BoNT-A group was 11.1% (surgical site hematoma in 1 patient) vs. 70.0% in the control group ($p = 0.027$), with no infectious complications recorded in the BoNT-A group (0% vs. 40.0% in control, $p = 0.087$). The median length of hospital stay in the BoNT-A group was 8.0 [7.0; 8.0] days vs. 9.0 [8.0; 15.8] days in the control group ($p = 0.095$).

Conclusion. Preoperative botulinum therapy is a safe and effective method that significantly reduces the intensity of postoperative pain and the frequency of complications in patients with large ventral hernias.

Keywords: botulinum toxin type A, ventral hernia, preoperative preparation, postoperative period, chemical component separation, pain.

Conflict of interest: nothing to disclose.

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Применение ботулинического токсина типа А в предоперационной подготовке пациентов с вентральными грыжами: влияние на течение послеоперационного периода

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Аннотация

Цель: оценить влияние предоперационного введения ботулинического токсина типа А (БТА) на течение раннего послеоперационного периода у пациентов с большими послеоперационными вентральными грыжами (ПОВГ) в сравнении с контрольной группой.

Материал и методы. Проведен ретроспективный анализ 19 пациентов с ПОВГ класса W3 по классификации EHS. Основную группу (n=9) составили пациенты, получившие предоперационные инъекции БТА (Диспорт 900-1000 ЕД или Ксеомин 200 ЕД) в боковые мышцы живота под УЗ-контролем с последующей герниопластикой TAR. Контрольную группу (n=10) составили пациенты, оперированные без подготовки БТА (методы:

TAR, Rives – Stoppa, TAR+bridge). Оценивались время операции, интенсивность болевого синдрома по ВАШ (визуально-аналоговая шкала) на первые, третьи и пятые сутки, продолжительность применения опиоидных анальгетиков, частота и структура осложнений, длительность госпитализации.

Результаты. В группе БТА интенсивность боли была достоверно ниже на первые сутки (медиана ВАШ 18,0 [11,5; 26,0] мм против 43,5 [40,0; 52,8] мм в контроле, $p < 0,001$), на третьи сутки (11,0 [8,5; 13,0] мм против 41,5 [38,0; 42,8] мм, $p < 0,001$) и на пятые сутки (2,0 [1,0; 3,5] мм против 31,5 [29,0; 33,0] мм, $p < 0,001$). Общая частота осложнений в группе БТА составила 11,1% (гематома послеоперационной раны у одного пациента)

против 70,0% в контроле ($p=0,027$), при этом инфекционные осложнения в группе БТА зафиксированы не были (0% против 40,0% в контроле, $p=0,087$). Медиана длительности госпитализации в группе БТА составила 8,0 [7,0; 8,0] дня против 9,0 [8,0; 15,8] дня в контроле ($p=0,095$).

Закключение. Предоперационная ботулинотерапия является безопасным и эффективным методом, достоверно снижающим интенсивность по-

слеоперационной боли и частоту осложнений у пациентов с большими вентральными грыжами.

Ключевые слова: ботулинотерапия типа А, вентральная грыжа, предоперационная подготовка, послеоперационный период, химическая компонентная сепарация, боль.

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Список сокращений

БТА – ботулинотоксин типа А; ПОВГ – послеоперационная вентральная грыжа; TAR – transversus abdominis release; EHS – European Hernia Society; ВАШ – визуально-аналоговая шкала; УЗ – ультразвуковой.

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INTRODUCTION

Incisional ventral hernias (IVH) are a serious challenge of the modern medicine. Despite the advancements of low-invasive surgical interventions, the number of laparotomies remains quite high. IVH develop from disorders of tissue reparation in the anterior abdominal wall, infectious and inflammatory processes in the area of the surgical wound, and from technical defects in the closure of the fascia [1]. The incidence rate of IVH development is approx. 5% among adults [2].

The modern classification of IVH, according to the European Hernia Society, based on the stratification of defects of the anterior abdominal wall by localization, width of the hernia orifice and number of recurrences [3]. The repair of large IVH with the width of hernia defects more than 10 cm is a technically complicated task. The attempt of complete reconstruction of the anterior abdominal wall may require a wide mobilization of fascia and separation of components of the anterior abdominal wall. High tension of tissue is the key factor accounting for the rate of recurrence which, according to the literature data, may reach 54%. Each subsequent recurrence complicates surgical treatment and increases risks for the patient [4].

Progressive methods of repairing normal anatomy of the anterior abdominal wall in hernia repair is the TAR (*transversus abdominis* release) according to Y. Novitsky (2015) [5]. This surgical procedure involves mobilization of the retromuscular space of the *rectus abdominis* muscles, incision of their sheaths, and dissection of the plane between the *transversalis fascia* and the *transversus abdominis* muscle. Component separation increases the mobility of the anterior and posterior aponeurotic layers, thereby facilitating approximation of the hernia defect margins. The use of posterior component separation with TAR in the repair of large IVHs ensures complete abdominal wall reconstruction; however, this surgical technique is technically demanding and significantly traumatic [6].

The impossibility of primary closure of the fascial defect often stems from a marked retraction and tension of the muscles of the anterior abdominal wall. In 2009, a research team headed by Tomas R. Ibarra-Hurtado first used a

preparation of botulinum A toxin (BoNT-A is a neurotoxin that causes temporary chemical denervation of the muscles due to blockade of acetylcholine release in the neuromuscular synapse) to relax the lateral muscles of the abdomen and facilitate the approximation of the edges of the hernia defect. The authors reported successful results of the use of this method to facilitate the primary fascial closure of the hernia defect in ventral hernias [7]. Preoperative chemical component separation of the lateral abdominal muscles may reduce the invasiveness of hemioplasty and facilitate approximation of the hernia defect margins [4, 8]. This method is being investigated in the context of improving conditions for both open and laparoscopic surgery, enabling relaxation and elongation of the lateral abdominal muscles [8, 9].

The data on the safety of the method, especially in patients with concomitant pathologies, continue to accumulate. Large research demonstrate a good tolerance profile of the BoNT-A and its applicability for comorbid patients [10, 11].

Despite the available data on the effect of BoNT-A on intraoperative parameters, a comprehensive analysis of its impact on the early postoperative period remains insufficiently addressed in the literature.

AIM

To evaluate the effect of preoperative chemical denervation of muscles of the anterior abdominal wall with botulinum toxin type A (BoNT-A) on the early postoperative period in patients with large and giant incisional ventral hernias (IVH) compared to a control group.

MATERIAL AND METHODS

Study design and patients. The study is a retrospective analysis of our own clinical experience. It is an analysis of data of 19 patients (9 men and 10 women), average age of 59.5 ± 12.5 years (95% CI 53.4–65.5), divided into 2 groups. The main group (BoNT-A group) included 9 patients who had undergone preoperative treatment with BoNT-A and subsequent IVH repair. The control group ($n=10$) included the patients operated on without preliminary chemical

EHS			
Incisional Hernia Classification			
Midline	subxiphoidal	M1	
	epigastric	M2	
	umbilical	M3	
	infraumbilical	M4	
	suprapubic	M5	
Lateral	subcostal	L1	
	flank	L2	
	iliac	L3	
	lumbar	L4	
Recurrent incisional hernia?		Yes <input type="radio"/>	No <input type="radio"/>
length:	cm	width:	cm
Width	W1	W2	W3
	<4cm	≥4-10cm	≥10cm
cm	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Figure 1. EHS classification of incisional ventral hernia.

Рисунок 1. Классификация послеоперационных вентральных грыж EHS.

denervation. All hernias belonged to W3 class according to EHS classification (Fig. 1). This class includes the hernias the width of whose gates is 10 cm and more.

Formation of groups and selection criteria. For the purposes of this study, the patients were chosen retrospectively from the database of the Department of Surgery of the Clinics of the Bashkir State Medical University (Ufa, Russia). The resolution of administration of preoperative botulinum therapy was made by an interdisciplinary team including a surgeon and a neurologist specializing in botulinum therapy.

The main criterion for inclusion in the study was the presence of an incisional ventral hernia, EHS class W3 (Fig. 2).

Exclusion criteria: acute infectious processes and decompensation of chronic diseases at the moment of planning of surgery, patient's refusal from participation in the study.

Indications and decision-making algorithm. The use of BoNT-A was performed within chemical component separation off-label (outside registered indications) according to the approved internal clinical algorithm. The indications were the dystonia (hypersthneia) of the muscles of the anterior abdominal wall confirmed by clinical examination and loss of domain of the abdominal cavity, i.e. loss of volume of the abdominal cavity due to organs and tissues being permanently in the hernia sac. The resolution was initiated by the surgeon upon identification of the above mentioned indications. The patient was then routed to consult the neurologist for a detailed evaluation of the muscle tone and neurological status. The final decision of the team as to administration of the BoNT-A, choice of the drug, dosage and points of injection was then approved by the medical panel involving a surgeon and a neurologist. The procedure was performed upon obtaining of the patient's informed consent.

Technique. The injection was controlled by ultrasound 3–10 weeks before the planned surgery. The following drugs were

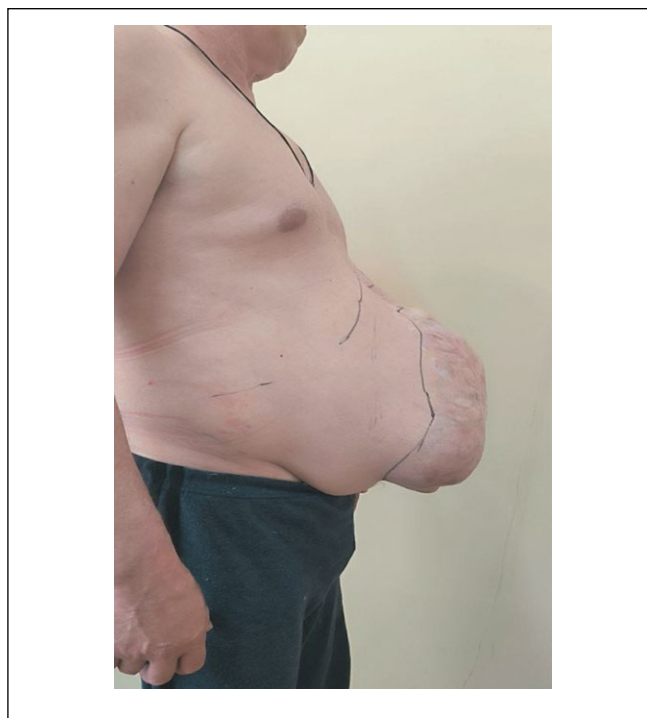


Figure 2. Preoperative appearance of a patient with a ventral hernia of the anterior abdominal wall before botulinum toxin type A injection.

Рисунок 2. Внешний вид пациента с вентральной грыжей передней брюшной стенки до инъекции ботулинического токсина типа А.

used: Dysport (IPSEN PHARMA, France) 900-1000 U or Xeomin (Merz Pharma GmbH & Co. KGaA, Germany) 200 U. The target muscles were the lateral abdominal muscles: external oblique, internal oblique and the transverse muscle of the abdomen. Three injections were made on either side (6 points in total). After administration of the BoNT-A, dynamic monitoring was performed for 3-4 weeks by the multidisciplinary team in order to evaluate the onset of muscular relaxation prior to surgery.

Choice of hernioplasty method. All patients underwent retromuscular hernioplasty whose method (TAR, Rives-Stoppa, TAR+bridge) was determined intraoperatively by the operating surgeon depending on the size of the defect, condition of the tissue and tension of the fascia. During approximation of the hernia defect margins, the surgeon subjectively assesses the tension of the tissue. To reduce tension, unilateral or bilateral posterior component separation is performed. If tissue tension persists after separation, corrective bridge repair is undertaken.

Evaluation of the pain syndrome. The intensity of postoperative pain was evaluated daily using the Russian language version of the visual analogue scale (VAS). The scale is a non-graded 10 cm horizontal line with finite points “no pain” and “worst pain imaginable”. The patients was asked to mark a point on the line that matched the intensity of their pain. The mark was measured in millimeters from zero and registered by the nurse of the Department of Surgery every day at 7:30 a.m. For the purposes of analysis, the values taken on days 1, 3 and 5 after the operation were used. In all cases, on the first day after the surgery, Promedol was administered.

Criteria of patient discharge after the surgery: lack of discharge in the drainage, regular spontaneous bowel movements and urination, lack of complications, lack of signs

Metric	Control group (n=10)	BoNT-A group (n=9)	Effect magnitude (95% CI)	p-value
Age, years (M ± SD)	56.50 ± 14.16	62.78 ± 10.24	MD = 6.28 (-5.73 to 18.29)	0.289
Sex, n (%)				
Male	6 (60.0)	3 (33.3)	OR = 0.33 (0.05 to 2.06) RD = -0.27 (-0.67 to 0.17)	0.370
Female	4 (40.0)	6 (66.7)	OR = 3.00 (0.49 to 19.60) RD = 0.27 (-0.17 to 0.67)	0.370
Defect width, mm (M ± SD)	115.00 ± 18.41	158.00 ± 32.86	MD = 43.00 (14.71 to 71.29)	0.002*
Repair method, n (%)				
TAR	3 (30.0)	9 (100.0)	RD = 0.70 (0.35 to 1.00)	0.001*
Rives Stoppa	5 (50.0)	0 (0.0)	OR = 0.04 (0.00 to 0.77) RD = -0.50 (-0.86 to -0.03)	0.026*
TAR + bridge	2 (20.0)	0 (0.0)	OR = 0.16 (0.01 to 3.61) RD = -0.20 (-0.58 to 0.26)	0.478

Notes: MD – Mean Difference; OR – Odds Ratio; RD – Risk Difference. For qualitative results with normal distribution data is presented as M ± SD; for categorical indicators, as n (%). * – statistically significant differences (p < 0.05).

Примечания: MD – разность средних (Mean Difference); OR – отношение шансов (Odds Ratio); RD – разность рисков (Risk Difference).

Для количественных показателей с нормальным распределением данные представлены как M ± SD; для категориальных показателей – как n (%).

* – статистически значимые различия (p < 0.05).

Table 1. Comparative characteristics of patients and treatment methods in the study groups

Таблица 1. Сравнительная характеристика пациентов и методов лечения в исследуемых группах

of inflammatory process. The minimum hospitalization period was 4 days.

Table 1 shows that the groups were comparable in the age (mean difference (MD) = 6.28 years, 95% CI: -5.73 to 18.29; p=0.289) and sex distribution (odds ratio (OR) = 0.33, 95% CI: 0.05 to 2.06; p=0.370). However, in the BoNT-A group, the patients had credibly larger hernia defects (MD = 43.00 mm, 95% CI: 14.71 to 71.29; p=0.002), and all of them (100%) underwent hernia repair according to the TAR method. In the control group, different methods were used: TAR (30.0%), Rives Stoppa (50.0%) and TAR + bridge (20.0%).

Assessed parameters: time of operation, pain syndrome intensity as per VAS on the first, third and fifth day after the surgery, duration of administration of opioid analgesics, incidence rate and structure of complications (hematoma of the surgical wound, wound infection) and duration of hospitalization (bed-days).

Statistical analysis. The analysis was performed in the StatTech v. 4.10.4 software suite (developer: StatTech LLC, Russia). The normality of the distribution of quantitative variables was assessed using the Shapiro–Wilk test. Data with a normal distribution are presented as arithmetic mean and standard deviation (M ± SD) with a 95% confidence interval

(CI) for the mean. For intergroup comparisons, Student's t-test was used, calculating the mean difference (MD) and its 95% CI. Data with a non-normal distribution are presented as median and interquartile range (Me [Q1; Q3]). Comparisons were made using the Mann–Whitney U test, calculating the Hodges–Lehmann shift estimator and its 95% CI. Categorical data are described as absolute numbers and percentages (n, %). For comparisons, Fisher's exact test was used, calculating the odds ratio (OR) and risk difference (RD) with 95% CIs. The statistical significance level was set at p < 0.05. Statistical analysis and reporting were performed in accordance with the SAMPL guidelines [12].

RESULTS

Surgical parameters and postoperative progress. The comparison of intra- and postoperative metrics between the groups revealed several significant differences.

It is seen from **Table 2** that the mean time of operation in the BoNT-A group was credibly longer than in the control group (MD = 84.78 min., 95% CI: 25.98 to 143.58; p=0.006). The intensity of pain syndrome in the BoNT-A group was statistically significant and clinically lower on all stages of the study: on day one (Hodges–Lehmann shift (H-L shift) = -25.5 mm, 95%

Metric	Control group (n=10)	BoNT-A group (n=9)	Effect magnitude (95% CI)	p-value
Time of operation, min. (M ± SD)	118.00 ± 46.32	202.78 ± 70.36	MD = 84.78 (25.98 to 143.58)	0.006*
Days until cessation of opioid administration, Me [IQR]	2.00 [1.00; 2.00]	2.00 [1.00; 2.00]	H-L shift = 0.0 (-0.5 to 0.5)	0.785
VAS day 1, mm, Me [IQR]	43.5 [40.0; 52.8]	18.0 [11.5; 26.0]	H-L shift = -25.5 (-30.0 to -20.0)	<0.001*
VAS day 3, mm, Me [IQR]	41.5 [38.0; 42.8]	11.0 [8.5; 13.0]	H-L shift = -30.0 (-34.0 to -26.0)	<0.001*
VAS day 5, mm, Me [IQR]	31.5 [29.0; 33.0]	2.0 [1.0; 3.5]	H-L shift = -29.0 (-32.0 to -26.0)	<0.001*
Bed-days, days, Me [IQR]	9.00 [8.00; 15.75]	8.00 [7.00; 8.00]	H-L shift = -1.0 (-3.0 to 0.0)	0.095
Any complications, n (%)	7 (70.0)	1 (11.1)	OR = 0.05 (0.00 to 0.64) RD = -0.59 (-0.89 to -0.09)	0.027*
Infectious complications, n (%)	4 (40.0)	0 (0.0)	OR = 0.10 (0.00 to 2.08) RD = -0.40 (-0.75 to 0.05)	0.087
Hematoma of the surgical wound, n (%)	3 (30.0)	1 (11.1)	OR = 0.30 (0.02 to 3.39) RD = -0.19 (-0.58 to 0.26)	0.582

Notes: MD – Mean Difference; H-L shift – Hodges – Lehmann shift; OR – Odds Ratio; RD – Risk Difference. The data are presented as M ± SD (normal distribution) or Me [IQR] (median and interquartile range). * – statistically significant differences (p < 0.05).

Примечания: MD – разность средних; H-L shift – сдвиг Ходжеса – Лемана; OR – отношение шансов; RD – разность рисков. Данные представлены как M ± SD (нормальное распределение) или Me [IQR] (медиана и межквартильный размах). * – статистически значимые различия (p < 0.05).

Table 2. Comparison of intra- and postoperative parameters

Таблица 2. Сравнение интра- и послеоперационных показателей



Figure 3. Intraoperative view after chemical component separation with botulinum toxin type A: condition of the anterior abdominal wall muscles after infiltration.

Рисунок 3. Интраоперационный вид после химической компонентной сепарации с применением ботулинического токсина типа А: состояние мышц передней брюшной стенки после инфильтрации.

CI: -30.0 to -20.0; $p < 0.001$), on day three (H-L shift = -30.0 mm, 95% CI: -34.0 to -26.0; $p < 0.001$) on day five (H-L shift = -29.0 mm, 95% CI: -32.0 to -26.0; $p < 0.001$). The median time to cessation of administration of opioid analgesics in both groups was 2.0 days, and no statistically significant differences were found (H-L shift = 0.0 days, 95% CI: -0.5 to 0.5; $p = 0.785$).

Incidence of complication and duration of hospitalization. The general incidence of postoperative complications in the BoNT-A group was credibly lower: 11.1% (1 patient) vs. 70.0% (7 patients) in the control group. The absolute risk difference (RD) was -0.59 (95% CI: -0.89 to -0.09), and OR was 0.05 (95% CI: 0.00 to 0.64; $p = 0.027$). In the BoNT-A group, no infectious complications were registered (0% vs. 40% in the control group, RD = -0.40, 95% CI: -0.75 to 0.05; $p = 0.087$). The incidence of hematomas of the surgical wound was not credibly different (11.1% vs. 30.0%, RD = -0.19, 95% CI: -0.58 to 0.26; $p = 0.582$). The median duration of hospitalization in the BoNT-A group was 1 day less, however, the difference did not reach statistical significance (H-L shift = -1.0 days, 95% CI: -3.0 to 0.0; $p = 0.095$).

DISCUSSION

This study demonstrates that preoperative botulinum toxin therapy is an effective and safe adjunct in the surgical treatment of complex ventral hernias, enabling superior outcomes even in patients with initially larger hernia defects.

The most significant findings include a reliable and clinically significant reduction in postoperative pain intensity in the BoNT-A group by 25–30 mm on the VAS, as well as a 59 percentage point reduction in the absolute risk of postoperative complications in the study group compared to controls. This result is consistent with the data reported by B. Zendejas et al. (2013) [13]. We believe that the key mechanism underlying the observed reduction in pain and complication rates is the achieved relaxation and increased length of the anterior abdominal wall muscles, which reduces tissue tension (**Fig. 3**). This pathogenetic effect of botulinum toxin therapy, leading to contraction of the hernia defect, is supported by the findings of our previously published systematic review [14].

The recorded incidence rate in the BoNT-A group (11.1%) was reliably lower than in the control group (70.0%), and there were no cases of infectious complications in the BoNT-A group. The decrease of the absolute risk of infection by 40 per cent points, while not reaching formal significance ($p = 0.087$), was an important clinical trend. The obtained data matches the favorable safety profile of the method described in the literature [10, 11], and emphasizes its potential role in the decrease of the risk of infectious processes, likely because of decrease of tissue tension and improvement of their perfusion.

The median operation time in the preoperative botulinum therapy group was reliably longer than in the control group (MD = 84.8 min., 95% CI: 26.0 to 143.6; $p = 0.006$). This difference is expected and can be explained by two factors: the TAR technique, which was performed in all patients in the study group, is more complex, and patients in the BoNT-A group had initially larger defects (MD = 43.0 mm, 95% CI: 14.7 to 71.3; $p = 0.002$).

Despite the greater complexity and longer duration of surgical intervention in patients with initially larger defects, the botulinum toxin therapy group demonstrated a trend toward a reduction in median hospital stay by 1 day. The lack of statistical significance ($p = 0.095$) is likely attributable to the limited sample size.

Limitations of the study include its retrospective character, small sample and initial differences between the groups in the width of the defect and in the surgical method applied, which could affect the results. However, this lack of balance reflecting the clinical practice of type A botulinum toxin in the most complicated cases, makes the demonstrated improvement of postoperative period in the BoNT-A group even more convincing.

CONCLUSION

Our findings demonstrate that preoperative botulinum toxin therapy significantly reduces postoperative pain intensity by 25–30 mm on the VAS and decreases the absolute risk of

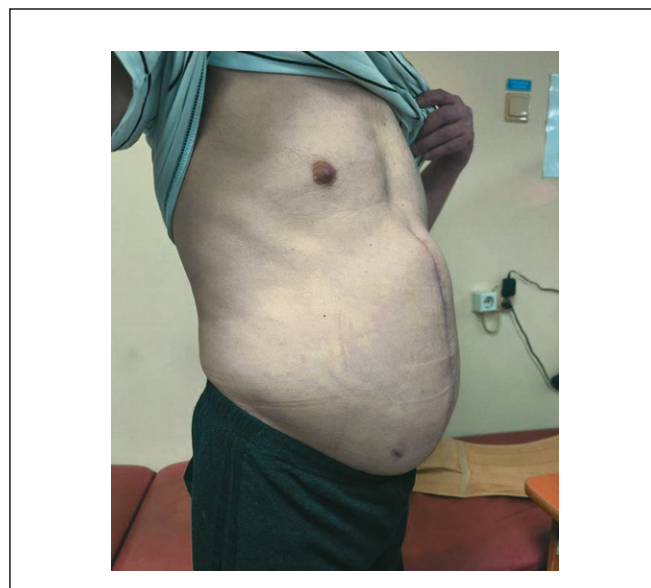


Figure 4. Postoperative view after reconstruction of the anterior abdominal wall and repair of the ventral hernia.

Рисунок 4. Послеоперационный вид после реконструкции передней брюшной стенки и пластики вентральной грыжи.

complications by 59 percentage points. These data contribute to the growing body of evidence presented in a recent systematic review, indicating that the method is safe, significantly increases the length of the lateral abdominal muscles, and improves the likelihood of fascial closure in complex ventral hernia repair [15]. Despite the retrospective design and initial differences between the groups that might have affected the evaluation of certain outcomes, the observed positive effects were achieved in the patients with wider initial defects, which

emphasizes the clinical significance of the method. Thus, the use of type A botulinum toxin is an effective clinically justified adjuvant component of complex management of patients with complex ventral hernias, which significantly improves direct postoperative outcomes (Fig. 4).

The major advantages of the method are considerable reduction of intensity of postoperative pain syndrome and reduction of incidence rate of early postoperative complications. ■

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical approval. The study was conducted in accordance with the ethical standards of the Helsinki Declaration and approved by the Local Ethics Committee of BSMU (Protocol No. 8 dated 24.12.2025).	Этическая экспертиза. Исследование выполнено в соответствии с этическими стандартами Хельсинкской декларации и одобрено ЛЭК ФГБОУ ВО «Башкирский государственный медицинский университет» (протокол № 8 от 24.12.2025).
Consent for publication. All study participants signed a written informed consent form.	Согласие на публикацию. Все участники исследования подписывали добровольное информированное согласие.
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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Akhmadeeva L.R., Galimov O.V.: idea, concept. Gizatullin R.R., Bakeev M.R., Valitova E.V.: collecting material, writing of the article. Allayarov N.D.: collection of material, research design, writing of the article. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	Участие авторов. Ахмадеева Л.Р., Галимов О.В. – идея, концепция. Гизатуллин Р.Р., Бакеев М.Р., Валитова Э.В. – сбор материала, написание статьи. Аллаяров Н.Д. – сбор материала, дизайн исследования, написание статьи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
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Molecular and cellular aspects of the pathogenesis of incisional hernias

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Abstract

The incisional hernias are one of the most common surgical pathologies worldwide. The achievements of medical science in recent decades have significantly improved the results of treatment of this disease, due to the justification and implementation of various methods of hernioplasty with implantation of synthetic endoprotheses. At the same time, the incidence rate of incisional hernias remains fairly high. For several years, research has been conducted to study the molecular and cellular mechanisms of incisional hernias formation. The key issue in the problem of tissue repair disorders after laparotomy is to understand the processes of extracellular matrix organization and fibroblast activation. The extracellular matrix appears to be a unique environment that promotes the proper structuring of collagen fibers, the acquisition of postoperative scar strength and timely wound cavity contraction. The regulation of extracellular matrix homeostasis depends on many factors that affect the timing and usefulness of tissue repair after surgical trauma. The main regenerative potential

consists of populations of fibroblasts responsible for the synthesis and degradation of collagen. Extracellular matrix and fibroblasts have a multifactorial effect on wound repair and imbalance of their interaction can contribute to the formation of incisional hernias. Molecular compounds synthesized by fibroblasts, which include matrix metalloproteinases, matrix metalloproteinase inhibitors, as well as actin and collagen proteins, play an important role both in the healing of surgical wounds and in the formation of hernias. Identification of critical points in the pathogenesis of incisional hernias at the molecular and cellular levels will make it possible to predict and prevent their formation. This opens up new opportunities for precision stratification of patients before abdominal wall hernia repair and the choice of personalized surgical tactics.

Keywords: incisional hernias, extracellular matrix, fibroblasts, collagen, molecular mechanisms of repair.

Conflict of interest: nothing to disclose.

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Молекулярные и клеточные аспекты патогенеза послеоперационных вентральных грыж

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Аннотация

Послеоперационные вентральные грыжи являются одними из самых распространенных хирургических патологий во всем мире. Достижения медицинской науки за последние десятилетия позволили значительно улучшить результаты лечения данного заболевания вследствие обоснования и внедрения различных способов герниопластики с имплантацией синтетических эндопротезов. В то же время частота возникновения послеоперационных вентральных грыж остается на достаточно высоком уровне. На протяжении нескольких лет проводятся исследования, направленные на изучение молекулярных и клеточных механизмов формирования послеоперационных грыж. Ключевым вопросом в проблеме нарушения репарации тканей после лапаротомии является понимание процессов организации внеклеточного матрикса и активизации фибробластов. Внеклеточный матрикс предстает той уникальной средой, способствующей правильной структуризации коллагеновых волокон, приобретению прочности послеоперационного рубца и своевременной контракции раневой полости. Регуляция гомеостаза внеклеточного матрикса находится в зависимости от многих факторов, влияющих на сроки и полноценность репарации тканей после операционной травмы.

Основной регенераторный потенциал составляют популяции фибробластов, ответственных за синтез и деградацию коллагена. Внеклеточный матрикс и фибробласты оказывают многофакторное влияние на репарацию раны, и нарушения баланса их взаимодействия может способствовать формированию послеоперационных вентральных грыж. Синтезируемые фибробластами молекулярные соединения, к которым относятся матричные металлопротеиназы, тканевые ингибиторы металлопротеиназ, а также актиновые и коллагеновые белки, играют важную роль как в заживлении операционной раны, так и в формировании грыж. Определение критических точек патогенеза послеоперационных вентральных грыж на молекулярном и клеточном уровнях позволит прогнозировать и профилактировать их образование. При этом открываются новые возможности для прецизионной стратификации пациентов перед оперативным лечением грыж и выбора персонализированной хирургической тактики.

Ключевые слова: послеоперационные вентральные грыжи, внеклеточный матрикс, фибробласты, коллаген, молекулярные механизмы репарации.

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ПОВГ – послеоперационная вентральная грыжа; ВКМ – внеклеточный матрикс; ММП – матричная металлопротеиназа; ТИМП – тканевый ингибитор металлопротеиназы.

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■ INTRODUCTION

Anteroventral hernias remain some of the long-standing unresolved problems of surgical science. The history of the problem is decades old originating from the moment of formation of surgery as a medical science [1]. The most complicated and socially impactful are the hernias related to previous surgeries of the abdomen [2-5]. Recent data shows that the incisional ventral hernias (IVH) occur after 10-20% laparotomies; at the same time, in high-risk patients, the incidence may reach 70% [6]. Throughout XX century, experience and knowledge has been accumulated in the area of surgical treatment of IVH, in that way, many original and progressive methods have been created to restore the normal anatomy of the abdomen after herniotomy. From the time of advent and large-scale implementation of mesh endoprosthesis to reinforce the anterior abdominal wall in reparative surgeries of hernias, the outcomes of treatment of IVH patients improved significantly. At the same time, even with the development and improvement of surgical methods, significant reduction of IVH formation incidence and IVH recurrence is still a standing problem.

Surgical access during different operations of the abdomen has always been selected from the standpoint of comfortable visualization of the surgery area without regard to the common factors of tissue regulation of the wound repair and formation of the surgical scar. In order to understand the problem of IVH formation, it is important to know the specifics of not only the macroscopic but cellular composition of the structures of the anterior abdominal wall. The interaction between the cells and molecules involved in the tissue reparation and regeneration following the surgical wound becomes especially important. The re-conceptualization of the process of formation of the surgical scar, and discovery of new correlations of the formation and structurization of connective tissue may significantly improve both the outcomes of surgical treatment of IVH and reduce the incidence of IVH formation and recurrence [7, 8]. In the recent decades, the pathogenesis of IVH on various levels of biological organization has been the focus of many studies. Papers published by Russian and foreign authors show a distinct shift from the anatomical level of studies to histological and molecular. This is well justified by the necessity of search for pathogenic links of hernia formation on the initial level of cellular and subcellular organization [9, 10]. The study of molecular mechanisms of formation of IVH opens new horizons for the prediction, prevention and treatment of the pathology [11, 12].

The goal of this review is to update the latest achievements in the studies of molecular and cellular mechanisms of IVH formation, to give a critical view of specific pathogenic processes of reparation of surgical wound tissues, and to look for new diagnostic and treatment targets of antero-ventral hernias.

Method of search for sources. The search for literature was performed in the RSCI and PubMed databases using the following keywords: incisional hernias, molecular mechanisms of hernia formation, cellular mechanisms of hernia pathogenesis, extracellular matrix, the importance of fibroblasts in the formation of incisional hernias. Only the papers published in the past 20 years were selected. For the purposes of our review, we selected the systematic reviews and meta-analyses, randomized controlled studies, international recommendations and literature reviews. We also reviewed references of the selected papers. Subsequently, we chose the papers based on the analysis of the full text, abstract, level of validity and statistical significance of presented results. The search for sources for this review produced 65 articles to be included.

■ HOMEOSTASIS OF THE EXTRACELLULAR MATRIX IN THE REPARATION OF THE LAPAROTOMY WOUND

The incision of the anterior abdominal wall to provide surgical access is a serious injury that is accompanied with a classic inflammatory reaction that progresses in aseptic conditions. The reparative processes after laparotomies are aimed not only on the closure of the wound and the isolation of the abdomen, but on the reinforcement of the injured area by excessive synthesis of connective tissue. In the early post-surgery period, the strength of the incision line is secured with sutures on the layers of the anterior abdominal cavity thus creating conditions for a favorable progression of the wound process. The complete reparation of the tissues after the laparotomy occurs 100 days after the surgery, and the strength of the scar is up to 90% from that of the physiologically normal tissue of the anterior abdominal wall [13]. The highest importance in the process of healing of the tissues of the abdominal wall, aponeurosis in the first place, is attached to the structure and the composition of the extracellular matrix (ECM). In response to the alternation and the inflammation, thrombocytes, neutrophils, macrophage and lymphocytes migrate from the systemic blood flow to the wound area. These cells form a spatial structure without a distinct organization, or the temporary ECM [14]. Multiple proinflammatory cytokines responsible

for cellular adhesion are produced, viz. interleukin-1 beta (IL-1 β), tumor necrosis factor alpha (TNF- α) and gamma interferon (IFN- γ) [15, 16]. The mechanical strength of the temporary ECM is low and depends on the thrombocytes and fibrin. At this initial stage of tissue reparation, integrity of the temporary ECM until formation of the collagen matrix is especially important. The insufficient intraoperative hemostasis results in the formation of a hematoma; at the same time, the temporary ECM is disorganized and the time of wound healing increases [17, 18]. This phenomenon contributes to the formation of IVH and recurrent of hernias after hernioplasty.

The study of properties of intracellular interactions in the spatial model produced the notion of the matrisome, a complete set of all proteins and genes encoding them that form the ECM. The view of the ECM as a dynamically changing cytological platform opens a new view of the processes of reparation of connective tissue and formation of hernias. The changes of the matrisome and the loss of mechanical strength of the ECM are associated with the proliferation of an abnormal population of fibroblasts. Some studies showed an increase of atypical fibroblasts responsible for the disruption of normal synthesis of collagen in early incontinence of the laparotomy wound [19, 20]. The analysis of the matrisome provides an opportunity of identification of the leading cascades of molecular reactions and cellular interactions responsible for the mechanotransduction of tissues [21-23]. The study of the matrisome may enable identification of genetic determinants and predictors of formation of hernias of the anterior abdominal wall.

Thus, various components of the ECM may influence the processes of reparation of the laparotomy wound and participate in the formation of IVH. The complex analysis of the composition of the ECM in the formation of IVH will identify the pathogenic targets in order to address the disorders of tissue homeostasis in advance.

■ REGULATION OF COLLAGEN METABOLISM AND ITS ROLE IN THE PATHOGENESIS OF IVH

The primary granulation tissue of the wound surface after the laparotomy predominantly consists of elastin and type III collagen. As healing progresses and phases of regeneration change, there occurs a significant reorganization of the ECM and its elements. The formation of a strong scar stems from the replacement of cellular and molecular components in the place of the surgical wound. The restructuring of the ECM is related to the loss of type III collagen by the granulation tissue, its replacement with type I collagen, contraction of the wound due to fibroplasia and mechanotransduction of myofibroblasts [24, 25]. These key processes underlie the acquisition of mechanical strength and decrease of the size of the wound, processes, whose disruption is of highest importance for the formation of IVH. At the same time, the significance of other types of collagen is also studied; type IV collagen involved in the formation of the basal membrane of cells, and type V collagen regulating the processes of fibrillogenesis, are in the focus

of scientific interest. The work of N. Henriksen *et al.* (2015) demonstrated the changes in the quantities of type IV collagen in patients with and IVH and patients without hernias. Thus, the IHV group showed a greater activity in the processes of denaturation and resynthesis of this protein [26]. L. Lorentzen *et al.* (2018) also demonstrated higher metabolic activity with respect to type V collagen in patients with IVH [27].

The processes of physiological remodeling of the ECM are mediated by the activity of matrix metal proteinases (MMP). The MMP family includes 23 proteins with a wide variety of biological substrata and respective functions. The major role of all proteins in this family is involvement in the ECM homeostasis in the healing of wounds. Some studies demonstrated their activation by numerous proinflammatory cytokines, hormonal substances and growth factors, most important of which are the IL-1 β , TNF- α and tissue inhibitors of metal proteinases (TIMP) [28-31]. The TIMP are zinc-mediated endopeptidases capable of breaking down all types of ECM proteins. There are four types of these enzymes, viz. TIMP-1, TIMP-2, TIMP-3 and TIMP-4 [32]. In physiological conditions, the distribution of MMP and TIMP is 1:1, which ensures the continuity of protein composition of the tissue and the ECM. The change in the MMP to TIMP ratio may influence the metabolism of collagen, which was seen in patients with IVH. In their work, J. Guillen-Marti *et al.* (2009) demonstrated a correlation between MMP and TIMP in the tissues of IVH patients. The authors noted the decrease of RNA TIMP-3 transcripts in the aponeurosis and TIMP-4 in the skeletal muscles, as well as TIMP-3 in the tissues of hernia defect in IVH patients [33].

Exposed to MMP proteins, type III collagen denaturates, and the fibroblasts receive the signal for the synthesis of type I collagen, whereupon gradual replacement of protein in the tissue occurs [34]. The process progresses in a dynamic equilibrium, which ensures a balance between the synthesis of collagen and its breakdown, and the ECM and the forming scar acquire the necessary mechanical strength. What is interesting is that the regulation of the ECM homeostasis is highly variable and depends not only on the synthesis of collagen forms but on its degradation as well, which may directly influence the formation of IVH. Some studies demonstrated a correlation between the disorganization of the ECM and increased activity of MMP-1, MMP-2, MMP-9 and MMP-13, and a correlation with the formation of hernias of the anterior abdominal wall [35, 36]. The proven role of changes in the type I collagen to type III collagen ratio in the regulation of the ECM homeostasis allowed for a detailed study of the molecular mechanism of IVH formation. At the same time, the regulation of processes of collagen degradation may have no lesser meaning than that of its synthesis. The work of R. Rosch *et al.* (2006) studies the influence of MMP on the formation of IVH. The authors reported elevated expression of MMP-2 in the connective scar tissue of IVH patients [37]. At the same time, the work of J. Salameh *et al.* (2007) also demonstrated high expression of MMP-2 in IVH; however, the analysis involved the tissues remote from the hernia defect [38]. This phenomenon shows the

systemic pathology of the metabolism of connective tissue involving MMP, not the local dysregulations.

The products of collagen breakdown in the course of the ECM remodeling or its abnormal synthesis go to the systemic blood and may be detected as serum biomarkers. The level of markers of collagen breakdown circulating in the bloodstream characterizes its homeostasis on the organismic level, since this protein and its forms are seen in various organs and systems [39]. Some studies were performed that demonstrate the correlation between the indicators of collagen breakdown and status of IVH [40]. H. Kayashima et al. (2015) studied serum levels of fragments of type IV collagen in IVH patients. They found that the level of serum N-terminal propeptide of the 7S domain of type IV collagen (P4NP-7S) was elevated in patients with IVH and was related to the development of ventral hernias [41]. It is not out of the question that there are other serum markers of collagen degradation influencing its metabolism and the fibroblast function. These circulating oligopeptides may serve as valuable tools for IVH prediction.

The analysis of collagen-mediated molecular reactions in the process of wound reparation is vital to the understanding of IVH pathogenesis. Elevated synthesis of type I collagen on the tissue level may preclude formation of IVH after any kind of laparotomy, since this protein is the main component of the ECM that determines the strength and integrity of the scar. On the other hand, suppression of type I collagen degradation has a positive effect on its metabolism and functional activity. In recent years, there were some breakthroughs in the identification of points of impact on collagen exchange regulation in order to prevent IVH and plan the treatment thereof.

■ FIBROBLAST POPULATIONS AND THEIR SIGNIFICANCE IN IVH FORMATION

Laparotomy induces a fibroproliferative response mediated by endogenous inflammatory factors. Fibroblasts are major participants of regenerative processes in the wound that synthesize collagen and form the ECM structure. Under physiological repair conditions, fibroblasts migrate into the injury site starting from day two and participate in granulation tissue formation over a four-day period. In response to the inflammation mediators, the intercellular interactions stimulate fibroblasts to synthesize collagen, the main 'construction' protein [42]. The accumulation of collagen ensures strength of the ECM, which regulates its normal functioning and supports its homeostasis [43]. The disruption of collagen metabolism in the formation of the ECM is a known factor of IVH development. Predominance of type III collagen over type I reduces the mechanical strength of ECM and alters its architecture [44]. Of particular interest are the causes of abnormal collagen synthesis during tissue repair, which are associated with the functional activity and phenotype of fibroblasts, which constitute the main regenerative cell pool of the ECM [45].

Migration, proliferation and activation of collagen synthesis by fibroblasts are regulated by cytokines, platelet-derived (PDGF) and vascular endothelial (VEGF) growth

factors [46]. Molecular mechanisms of tissue repair directly depend on synthetic activity of fibroblasts. The key feature of fibroblasts as participants of IVH pathogenesis is the change of their functional activity and synthesis of type III collagen instead of type I collagen. Other processes of biological tissue repair demonstrate decrease or cessation of synthetic activity of fibroblasts, e.g. process of healing of trophic and ulcerous defects of various tissues [47]. The analysis of morphological characteristics of tendon and fascial elements of the anterior abdominal wall in IVH revealed significant specific features of their cellular composition and structure. The histological analysis of sections of IVH tissue showed deficiency of the ECM, decreased quantity of fibroblasts and immune cells. The cytological analysis of fibroblasts from the IVH tissue showed their significant deficiency: spindle morphology, vacuolated cytoplasm, swollen mitochondria and elevated expression of vimentin. Another important feature of fibroblasts from IVH is their increased apoptotic activity and propensity for autophagy [48]. Differentiation of fibroblasts is highly important in the processes of tissue repair after laparotomy. Selection of cell populations occurs due to unfavorable conditions of wound healing (suppurative inflammation, eventration, hematoma), which promotes degradation of the ECM, synthesis of type III collagen and mediates the formation of IVH.

In the structure of the ECM cells, there is a population of fibroblasts that is a component of connective tissue before the onset of the surgical wound. This cellular pool is referred to as resident fibroblasts that stay at rest without any endogenous stimulation. As compared to dermal fibroblasts, the resident fibroblasts have a greater plastic potential with respect to collagen. The greatest amount of resident fibroblasts was found in the fascial structures of the anterior abdominal wall. Laparotomy stimulates proliferation and migration of fascial fibroblasts, which fosters proper organization of the ECM. Recent data shows that the functional activity of fascial fibroblasts and dermal fibroblasts is different [49]. The special feature of resident fibroblasts is the synthesis of various components of the matrisome including proteoglycans, fibronectin and hyaluronic acid [50]. At the same time, resident fibroblasts are not only sources of collagen but also of enzymes involved in its breakdown. These cells synthesize MMP-1, MMP-2, MMP-9, MMP-19, and TIMP-1, TIMP-2, TIMP-3 [51]. This fact provides a completely new view of fibroblasts in the tissue repair process after laparotomy, including in the process of IVH formation. The regulation of synthetic activity of fibroblasts allows for changes in the strength of the connective-tissue scar on various stages of its organization. It would be logical to suggest, therefore, that such regulation is mediated both by exogenous stimuli and by the endogenous stimuli, including genetically determined ones.

Another important feature of fibroblasts is their differentiation to myofibroblasts, a contractile phenotype synthesizing the smooth muscle alpha-actin (α -SMA). Myofibroblasts are unique cells of connective tissue that are capable of mechanotransduction. The contraction of actin proteins causes contraction of the ECM and alignment of the edges of the wound cavity [52]. The stress

in the intercellular interaction of the ECM fibroblasts triggers a cascade of specific reactions resulting in the activation of mechano-sensitive genes of the matrisome. Mechanotransduction of the ECM also initiates the differentiation of fibroblasts to myofibroblasts. In the process of wound repair, the latter act as additional markers of scarring and fibrosis [53, 54]. Myofibroblasts are also involved in the remodeling of the ECM at later stages of repair and ensure wound contraction by stress fibers and formation of α -SMA. As repair processes come to an end, the number of myofibroblasts decreases due to their apoptosis [55]. The main source of myofibroblasts is in the connective tissue: the resident pool of fibroblasts [56]. When the tissues of the anterior abdominal wall are damaged by laparotomy, the reserve of myofibroblasts is replenished from the populations of dermal and fascial fibroblasts [57]. Another important source of myofibroblasts is the fibrocytes. These cells circulate in the bloodstream and are able to migrate to any tissues of the body, performing various functions. Fibrocytes attain a special significance in the tissue repair after laparotomy; they are capable of impacting the IVH formation, being involved in the regulation of the ECM remodeling and wound contraction. Fibrocytes can synthesize different subtypes of collagen, vimentin and fibronectin, which are the substrate of the ECM and which mediate activity of fibroblasts [58]. At the same time, due to inflammatory endogenous stimulation, fibrocytes can differentiate to myofibroblasts thereby increasing the contraction of the ECM and its strength. Fibrocytes also trigger the inflammatory reactions in the surgical wound and increase synthesis of structural components of the ECM involving the signaling pathway of the beta-1 transforming growth factor (TGF- β 1) [59]. Myofibroblasts are unique participants of the repair process greatly involved in the repair of the defect of the anterior abdominal wall after the surgical injury. The regulation of differentiation and apoptosis of fibroblasts occurs by mechanotransduction of the ECM and the TGF- β 1 signaling pathway [60]. TGF- β 1 is a regulatory cytokine peptide involved in numerous physiological cellular processes. In the first place, the synthesis and the activation of this peptide ensures the differentiation, proliferation, migration, adhesion and apoptosis of various cells in the body. In the ECM, the TGF- β 1 is linked to its prodomain, the latency-associated peptide (LAP). The TGF- β 1–LAP complex dissociates during tissue repair, including under the influence of myofibroblasts and the integrin α V synthesized by the [61]. Thus, a positive feedback loop is observed between the processes of proliferation, differentiation of myofibroblasts, and contraction during post-laparotomy wound repair.

Fibroblasts are instrumental in reparative processes after laparotomies. They are vital for the formation of a strong post-operative scar. These cells regulate the synthesis of collagen, its breakdown, they ensure the homeostasis of the ECM, trigger the myofibroblasts and differentiate into them contributing to the wound contracture. The detailed study of fibroblast populations, their genetic and epigenetic characteristics, as well as the means of regulation of their

synthesis function, will enable control and programming of regeneration of connective tissue in the location of the surgical wound. At the same time, the functional and morphological features of specific populations of fibroblasts influences the formation of IVH via collagen metabolism and degradation of the ECM. Studying the characteristics of fibroblasts in the anterior abdominal wall of patients with IVH will enable the modulation of wound healing processes after the hernioplasty, the selection of a synthetic mesh implantation technique, and the prediction of recurrences.

■ ROLE OF INFLAMMATION AND HYPOXIA IN THE IVH PATHOGENESIS

Laparotomy-induced surgical wound of the anterior abdominal wall is an alteration of tissue and the first phase of the regenerative process. The specific feature of surgical wounds is that they are sterile, therefore, the inflammatory reactions occur in aseptic conditions. The aseptic inflammatory process differs from the infectious one by the lack of exogenous mediators of inflammation (infectious agents). The activation of aseptic inflammation occurs under the influence of the damage-associated molecular pattern (DAMP). The DAMP comprises different protein molecules within the nucleus of the cell and in the intracellular liquid of the tissues of the body that trigger immune processes due to sterile alteration and inflammatory reaction [31]. One of the main component of the DAMP is a protein from the group of nuclear non-histone proteins (high-mobility group protein B1 - HMGB-1). This molecule is one of the earliest to react to the damage and stimulates the immune system to trigger to inflammatory cascade [62]. The HMGB-1 ensures cell migration to the aseptic focus of inflammation and chemotaxis, and triggers immune-mediated cellular reactions and cytokine production [63]. Following the laparotomy, the HMGB-1 is involved in the MMP overexpression by triggering the TNF- α , IL-1 β , IL-1 α , IL-2, IL-8, IL-18 and type I IFN I, which results in the degradation of type I collagen and its replacement with type III [31].

Another aspect of the surgical wound is the hypoxic stress of the tissues in the area of the wound. Deficit of oxygen inhibits processes of angiogenesis and repair in the laparotomy area [21]. Hypoxia also precludes differentiation of fibroblasts into myofibroblasts, reduces expression of type I collagen and α -SMA [64]. One of the principal molecular responses to hypoxia is the increased expression of the hypoxia-induced 1-alpha factor (HIF-1 α). The activation of this protein triggers processes of neoangiogenesis in the area of the surgical wound, leading to revascularization and faster repair of tissues. Enhanced tissue trophism directly influences fibroblast activity and their synthetic capacity, leading to increased synthesis of type I collagen and improved ECM strength [65].

Investigating the expression of DAMPs and HIF-1 α may allow for predicting the occurrence of IVH after primary laparotomies. Studying the activity of these compounds will help optimize surgical strategies for the operative treatment of IVH and recurrent hernias by

mitigating the impact of inflammation and hypoxia in the intra- and postoperative periods.

CONCLUSION

Over several decades, regenerative processes have attracted active scientific interest. This area of studies attained special significance in the investigation of mechanisms of IVH formation. The analysis of molecular and cellular processes of healing of the surgical wound may allow for a more detailed insight in the reasons of formation of secondary abdominal hernias. The mechanisms of repair of connective tissue after laparotomy differ greatly

from other types of injuries and damage to the anterior abdominal wall. The specifics of formation and structure of ECM, collagen, fibroblasts, myofibroblasts, and the tissue response to aseptic inflammation and hypoxia allow for a completely new view of the process of IVH formation. Biochemical reactions and intercellular interactions are no less important for tissue healing than proper laparotomy wound closure technique. It is now becoming evident that understanding critical disturbances in physiological repair processes opens up opportunities for the improvement of early diagnosis, refinement of surgical correction, and development of methods for recurrence prevention. ■

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Galimov O.V.: contribution to analyzing literature data and making significant important edits to the manuscript in order to increase the scientific value of the article. Khanov V.O.: contribution to obtaining, analyzing literature data, editing of the text of the article. Bakeev M.R.: development of the article concept, data analysis, writing of the text of the article. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	Участие авторов. Галимов О.В. – вклад в анализ данных литературы, внесение в рукопись существенно важной правки с целью повышения научной ценности статьи. Ханов В.О. – вклад в получение, анализ данных литературы, редактирование текста статьи. Bakeev M.R. – разработка концепции статьи, анализ данных, написание текста статьи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
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Surgical treatment of patient with osteomyelitis of the hip using preoperative 3D modeling and “Autoplan” software suite

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Abstract

The article presents a clinical case of treatment of a patient with chronic post-traumatic osteomyelitis of the femur. A fundamentally important point was the analysis of the CT scan results in the Autoplan hardware and software complex (APC) system according to the developed method and the construction of a 3D model of the lower extremities. As a result, the osteomyelitis focus was visualized. Based on the 3D model and using the intraoperative navigation

of the “Autoplan” software suite, the patient underwent a femoral sequester-necrectomy. The assessment of the immediate and long-term treatment results was carried out.

Keywords: osteomyelitis, 3D modeling, sequester-necrectomy, intraoperative navigation.

Conflict of interest: nothing to disclose.

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Хирургическое лечение пациента с остеомиелитом бедренной кости с использованием предоперационного 3D-моделирования и аппаратно-программного комплекса «Автоплан»

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Аннотация

Представлен клинический случай лечения пациента с хроническим посттравматическим остеомиелитом бедренной кости. Принципиально важным моментом стал анализ результатов КТ-исследования в системе аппаратно-программного комплекса (АПК) «Автоплан» по разработанному способу и построение 3D-модели нижних конечностей. В результате был визуализирован очаг остеомиелита. На основе 3D-модели и интра-

операционной навигации АПК «Автоплан» пациенту была выполнена секвестрнекрэктомия бедренной кости. Произведена оценка ближайших и отдаленных результатов лечения.

Ключевые слова: остеомиелит, 3D-моделирование, секвестрнекрэктомия, интраоперационная навигация.

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■ BACKGROUND

Osteomyelitis is a purulent-inflammatory disease affecting all bone elements and adjacent soft-tissue structures, leading to deformity and functional impairment in organs and body systems [1–5]. Among all purulent and septic diseases, osteomyelitis accounts for 6.8–12%, and in 3–5% cases, the disease is the cause of damage to the locomotion apparatus [6].

Chronic osteomyelitis is considered an incurable disease due to its severe and long-term progression, complicated treatment and development of complications. Despite the strong technological progress, implementation of new pathogenic approaches towards treatment of the disease with consideration of etiological factors, the outcomes of treatment leave room for improvement. The recurrence rate within one year is at least 30% of all post-surgery patients, with 42.1% to 74.3% in remote periods. The patients require multiple surgeries [5, 7]. The success of treatment largely depends on the radicality of the operation and adequate sanitation of the focus of the infection. Use of preoperative 3D-modeling and intraoperative navigation is highly instrumental in the efficacy of surgical treatment.

We propose a clinical study that enables evaluation of surgical tactics and long-term outcomes of treatment of the patient with osteomyelitis of the femur, in which preoperative 3D-modeling and software and hardware suite Autoplan were used.

■ CASE DESCRIPTION

Patient M., aged 71, was admitted to the department of surgery on March 25, 2024. The patient considers his disease to date back to 2004, when in a traffic accident he had a closed displaced fracture of the medium third of the left femur. He underwent an intramedullary nailing. One month after the operation, despite the marked tendency for the fracture union, there appeared a fistula opening on the left hip. Three months after the operation, a follow-up X-ray examination was performed showing consolidation of the fracture, and the nail was removed. In 2010, the patient underwent an operation for osteomyelitis

of the left femur, and sequestrectomy was performed, following which clinical healing was reported with lack of infection process in the injury area. In 2024, the fistula reappeared. The patient himself put bandages using wet-to-dry dressings with aqueous solutions of antiseptics (Mestamidin, Chloroxehidine) and salve dressings (Levomecol, Oflomelid), with no positive dynamics. The patient received outpatient consultations of the surgeon and was recommended planned surgical treatment.

On admission, the patient underwent a standard examination including total blood count, clinical urine analysis, blood coagulation test, biochemical blood test, microbiology examination of the wound fluid for susceptibility to antibiotics, as well as X-ray examination of the right femur.

The examination found that the patient had multiple postoperative scars on the hip, and on the anteriomedial and lateral surface there were two fistula openings up to 1.0 cm in diameter with moderate purulent discharge (up to 5 mL per day). The revision of the fistulas with a bulb-headed probe, the end of the probe touched the femoral bone. Both active and passive movement in the knee and hip joint were preserved. Pulsation of the main arteries was satisfactory; the sensitivity was preserved.

The microbiological examination of the wound fluid identified *Pseudomonas aeruginosa* 105. Following the antibiotic susceptibility pattern, the patient was prescribed respective etiological antimicrobial therapy.

In the preoperative preparation phase, a CT scan of the lower extremities was performed (**Fig. 1**). The series of CT scans in the multi-plane and 3D projections periosteal layering was observed in the lower third of the femoral shaft, accompanied by focal disruption of the cortical layer. In the upper and medium thirds, bone expansion was visualized, the cortical layers were sclerotized and deformed; there were areas of periosteal reaction on the lateral surface of the femoral bone. The fistula tract was identified at the level of the middle third of the thigh, extending up to 20 mm to the lateral surface. Additionally, formation of the fistula tract at the level

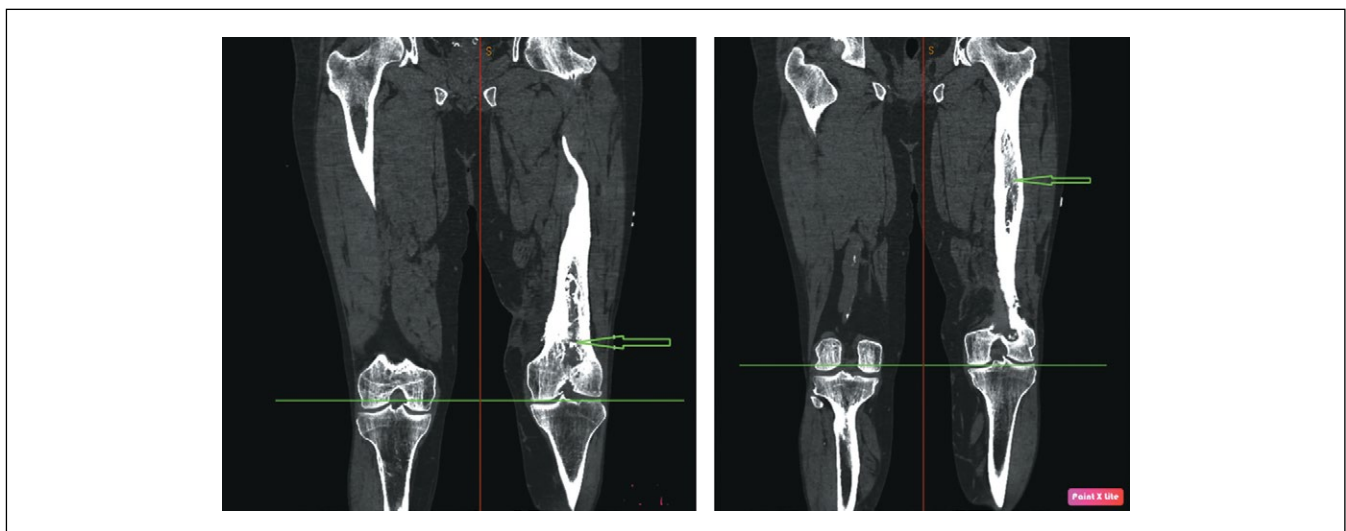


Figure 1. CT scan of the lower extremities, frontal projection. Arrows indicate the osteomyelitis focus.

Рисунок 1. КТ нижних конечностей, фронтальная проекция. Стрелками указан очаг остеомиелита.

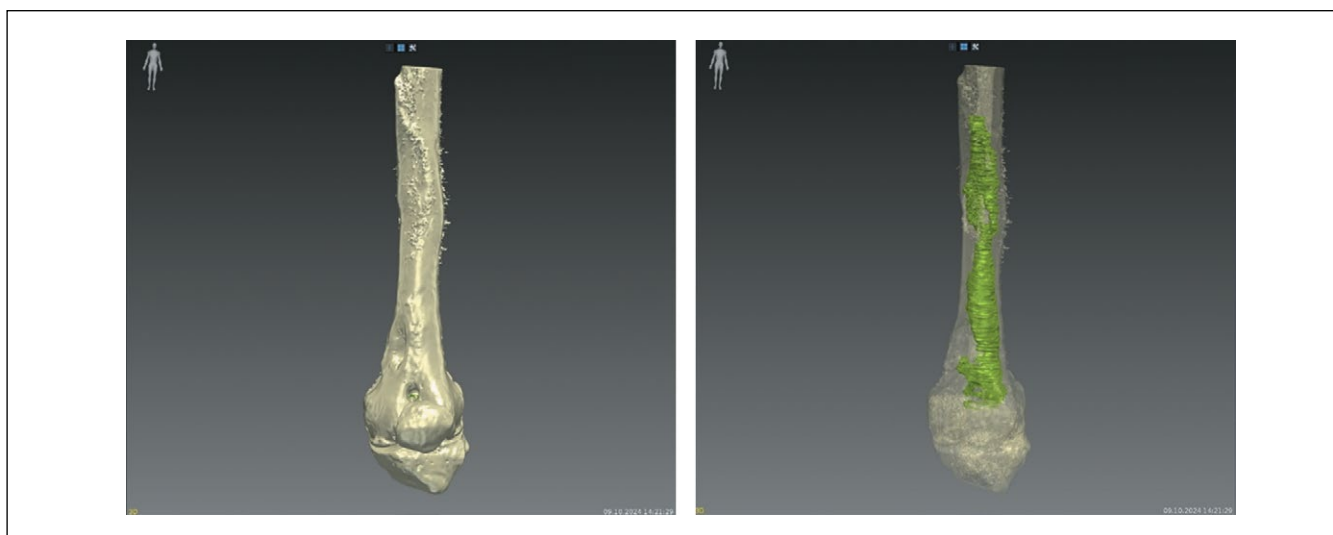


Figure 2. 3D model of the femur based on the CT scan. The osteomyelitis lesion is shown in green.

Рисунок 2. 3D-модель бедренной кости на основе КТ-исследования. Зеленым цветом обозначен очаг остеомиелита.

of the lower third, extending to the medial surface of the thigh, was noted.

Based on the CT examination, a 3D-model of the femoral bone was built visualizing the focus of osteomyelitis¹. DICOM data was uploaded to Autoplan, and the following transformations were performed: 1) alignment of separate CT scan series to a unified coordinate system; 2) segmentation (marking) of boundaries of anatomical structures on the images; 3) construction of three-dimensional polygonal models based on the segmented boundaries of anatomical structures (**Fig. 2**).

In order to reconstruct the shape of anatomical objects between the visible scans, 2D and 3D interpolation algorithms were used. 3D polygonal models of the finest anatomical structures were constructed without smoothing, while surface smoothing was applied to models of larger anatomical structures. For each model, the color and transparency degree were chosen to ensure the informative value of the entire three-dimensional scene.

On the surgical field, prior to skin incision, anatomical guides were chosen (in this case, the upper and the lower, medial and distal edges of the kneecap, and femoral condyles), on which the anchor points were marked that were fixed on the virtual model using a special pointer with light-reflective markers. At the same time, the virtual model of the focus of osteomyelitis was aligned with its actual position in this patient in the single coordinate system. After that, it became possible to visualize the virtual model of the hip bone with the focus of osteomyelitis and the pointer on the screen in real time. By moving the pointer in the points of the topical

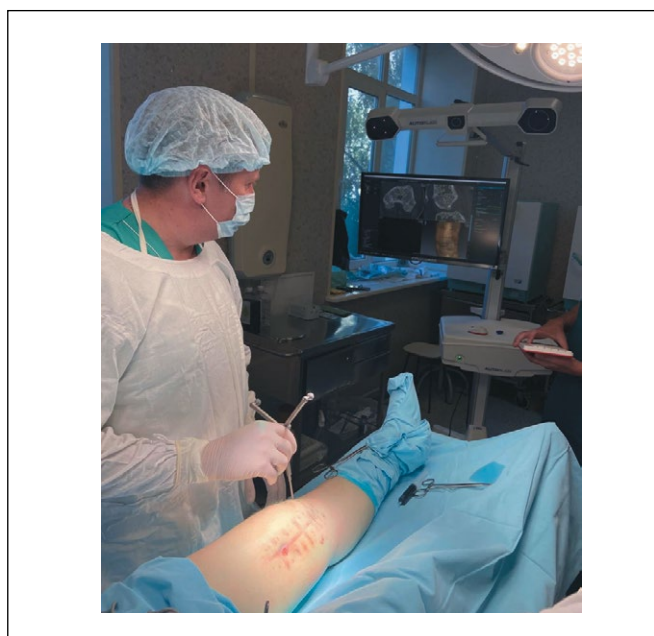


Figure 3. Combining the position of a virtual model of the osteomyelitis focus with its real location into a single coordinate system using the Autoplan APCS and a pointer with reflective markers.

Рисунок 3. Совмещение положения виртуальной модели очага остеомиелита с его реальным расположением в единую систему координат с использованием АПК «Автоплан» и указки со светоотражающими маркерами.

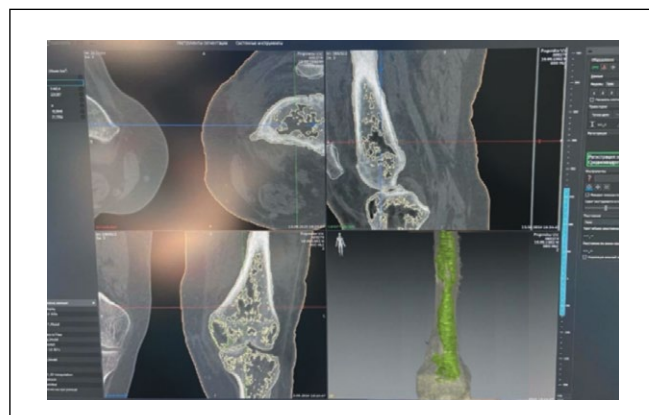


Figure 4. Computed tomography of the femur with the focus of osteomyelitis and the 3D model.

Рисунок 4. Компьютерная томография бедренной кости с очагом остеомиелита и 3D-модель.

¹ Filing receipt No.2025107993 for the invention "Method of topical diagnostics and visualization of lesion of osseous tissue destruction in chronic osteomyelitis of long tubular bones" dated 21.02.2025.

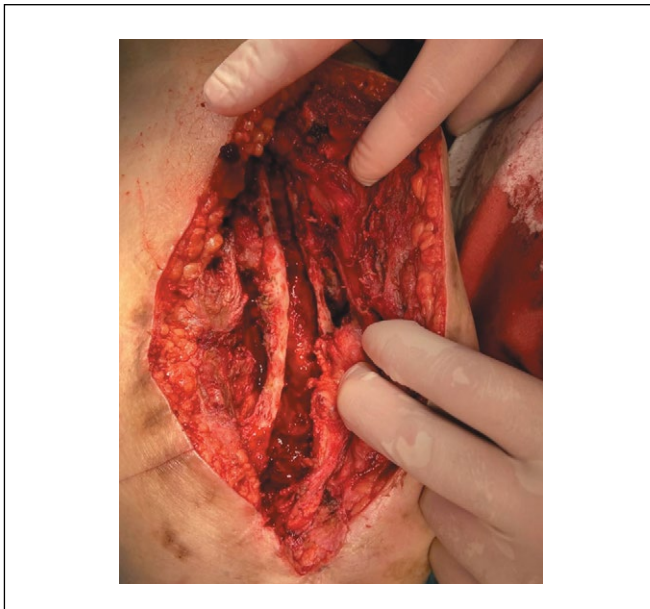


Figure 5. Bone cavity after sanitation of the osteomyelitis focus.
Рисунок 5. Костная полость после санации очага остеомиелита.



Figure 6. Bone cavity closure with a pedicled muscle flap.
Рисунок 6. Пластика костной полости мышцей на питающей ножке.

position of the focus of osteomyelitis and referring its position with intact sections of the bone, the access to the focus of pathology was selected, and its actual localization was found during the surgery with consideration of the patient's individual anatomic features (**Fig. 3, 4**).

After delineating the osteomyelitic focus boundaries, sequestrectomy of the femoral bone was performed. The fistula opening on the anteromedial surface of the left thigh was excised. Infected tissues and pathological granulations were removed. The wound was closed with sutures. Converging incisions up to 15 cm long, incorporating excision of the fistula opening on the lateral surface of the left thigh, were made to dissect the soft tissues down to the bone. The eroded femoral bone was exposed. The periosteum was elevated with a periosteal elevator. Using a chisel and mallet, trepanation of the femoral bone was performed along the entire extent of the lesion, guided by the 3D model. A 15 cm long cavity was created (**Fig. 5**). Curettage was performed with a Volkman spoon until punctate bleeding was achieved. Antiseptic lavage with Mestamidin was performed, followed by plasty of the bone cavity using a portion of the quadriceps femoris muscle on a distal pedicle (**Fig. 6**). The wound was closed in layers.

The postoperative period had no complications. The wound healed by primary intention. The stitches were removed on day 8 after the surgery (**Fig. 7**). The patient was discharged in a satisfactory condition to be followed up by a surgeon in the local medical facility.

Follow-up examinations were performed in 1, 3, and 6 months from the operation. No wound defects, fistula openings, pain at rest or in motion, no restrictions under exercise were seen.

The quality of life was analyzed using the questionnaire specifically developed for patients operated for chronic osteomyelitis. It is an enhanced international questionnaire to assess quality of life SF-36 (HEALTH STATUS SURVEY). The changes were observed in the value of

pain intensity: before the surgery, it was 38%, after the surgery, 100%. This shows that the sensation of pain was practically relieved and did not restrict the patient's activity. The value of vitality increased twofold. The value of 'social functioning' domain increased from 62.5 to 95.5%, i.e. by 33%; therefore, the patients physical and emotional condition had less limitations on their capability and desire to communicate. The value on the 'mental health' domain increased by 56%, a significant improvement of the patient's mental status.



Figure 7. Photo of the lower limb of patient M., 71 years old, 8 days after surgery.

Рисунок 7. Фото нижней конечности пациента М., 71 года, на 8 сутки после оперативного вмешательства.

The physical and mental components of health status were also calculated. Before the surgery, the physical component was 36.1%, after the surgery, 55.6%: an increase by 19.5%. The mental component of health status before the surgery was 29.3%, after the surgery, 73.1%: an increase by 43.8%.

DISCUSSION

Treatment of patients with osteomyelitis of long tubular bones is a most complex challenge of purulent surgery. The problem of chronic osteomyelitis remains vital not only due to difficulties of its diagnostics, treatment and prevention, but also due to high costs of patient treatment, long-term incapacity to work, high incidence of disablement, which, according to Russian authors, is 55–65%, and, according to foreign authors, may reach 90% [8–10].

Sequestrectomy became the most significant of radical surgical interventions in the treatment of osteomyelitis [11].

Currently, clinical practice places significant emphasis on the application of a personalized approach, innovative imaging modalities, and preoperative surgical planning. One of perspective areas is the preoperative 3D-modeling based on CT examination and intraoperative navigation

using the Autoplan¹ hardware and software complex [12]. For the surgical treatment of osteomyelitis, this method provides precise visualization of the pathological focus, determination of its boundaries before and during the surgery based on individual anthropometric data of each patient [13, 14]. The use of the personalized approach allows for reduction of surgery time, maximum preservation of intact bone tissue, and the best aesthetic outcome [15].

CONCLUSION

The use of preoperative 3D-modeling and intraoperative navigation with the Autoplan hardware and software complex in sequestrectomy allows for a radical excision of the focus of infection, preservation of a maximum amount of healthy soft and bony tissue, and achievement of osteomyelitis remission.

An individualized approach to the patient, accounting for their anatomical specificities, combined with the correctly chosen treatment strategy, yielded favorable short- and long-term outcomes while preserving quality of life. The 6-month postoperative follow-up of our patient revealed improved quality of life and no disease recurrence, confirming the high efficacy of the method. ■

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Makarov I.V.: concept and design of the study, analysis and interpretation of data, editing of the article. Ladonin S.V.: writing of the text and its editing. Bondareva D.A.: writing of the text. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	Участие авторов. Макаров И.В. – концепция и дизайн исследования, анализ и интерпретация данных, редактирование статьи. Ладонин С.В. – написание текста и его редактирование. Бондарева Д.А. – написание текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Consent for publication. Written consent was obtained from the patient for the depersonalized publication of relevant medical information and all of accompanying images in the journal.	Информированное согласие на публикацию. Авторы получили письменное согласие пациента на публикацию в журнале медицинских данных и фотографий в обезличенной форме.
Statement of originality. No previously published material (text, images, or data) was used in this work.	Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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