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ORIGINAL RESEARCH
ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Meta-analysis of mid-term survival and clinical results of left ventricular surgical reconstruction

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Abstract. *Relevance*. Post-infarction aneurysm of the left ventricle significantly reduces the length and quality of life of patients. The results of comparisons of different methods for surgical restoration of the left ventricle are ambiguous and often contradictory, complicating the choice of an effective treatment strategy and the ability to objectively assess the survival prospects of such patients. *The aim* of the meta-analysis is to assess the one-year survival of patients after surgical reconstruction of the left ventricle, to determine the functional class of heart failure, and to study the morphological and functional characteristics of the heart. A comparative analysis of the results of the meta-analytic assessment of patient survival after left ventricle reconstruction using the DOR (SAVER) method will be performed in comparison with other treatment methods. *Materials and Methods.* As a result of a systematic search in two specialized databases (PubMed, Google Scholar), 1,875 articles were selected. A total of 15 studies were included in the final analysis. The total number of patients in these studies was 1,089. To objectify the assessment of the effectiveness of different surgical approaches, two patient groups were formed. The first group underwent only surgical reconstruction of the left ventricle using the Dor procedure or surgical anterior ventricular endocardial restoration (SAVER); the second group received other methods of surgical ventricular reconstruction, depending on the surgical feasibility. *Results.* The mean age of the examined patients was 62.1 (95% CI: 60.2–64.1) years. The study included 56% (95% CI: 42–69) men. Anterior aneurysm occurred in 87% (95% CI: 74–99) of patients. The mean EuroSCORE value corresponded to 9.7% (95% CI: 7.3–12.1). Before the operation, the patients had a high functional class of heart failure according to NYHA [3 functional class (95% CI: 2.82–3.1)], low left ventricular ejection fraction [31.3% (95% CI: 29.2–33.3)], dilation of the heart chambers [EDVI — 131.7 mL/m2 (95% CI: 113.1–150.2)]. Meta-analysis of the difference in mean values of ejection fraction in patients before and 1 year after surgery showed an increase of 10.1% (95% CI: 8.01–12.1, $p < 0.001$). Meta-analysis of the difference in mean values of EDVI and NYHA functional class of heart failure in patients before and 1 year after surgery showed a decrease

of 38.8 ml/m2 (95% CI: 28.1–49.6, p < 0.001) and 1.52 (95% CI: 1.3–1.8, p < 0.001), respectively. *Conclusion.* The meta-analysis showed that one year after surgery, survival rates are 94%, with statistically significant increases in ejection fraction and decreases in functional class of heart failure according to the NYHA scale. The studies did not reveal significant differences in patient survival and clinical outcomes one year after operations performed using different surgical methods. The results indicate the effectiveness of left ventricular surgical reconstruction, providing prolonged improvement in patients' functional status. However, it should be noted that there was significant heterogeneity among the studies.

Keywords: postinfarction left ventricular aneurysm, surgical ventricular reconstruction; ventricular restoration; dor procedure; ventricular, endoventricular plasty, mid-term survival

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Introduction

Left ventricular dysfunction caused by ischemic heart disease and myocardial infarction is the main cause of chronic heart failure worldwide [1–5]. One of the most severe complications of acute myocardial infarction is post-infarction left ventricular aneurysms [6, 7]. This condition significantly reduces the duration and quality of life for patients. The incidence of left ventricular aneurysm in patients after myocardial infarction ranges from 10 to 35% [8]. More than 95% of true left ventricular aneurysm cases are the result of transmural myocardial infarction caused by acute occlusion of the left anterior descending artery or the dominant right coronary artery.

Postinfarction disorders lead to scar transformation, thinning of the wall of the left ventricle and its ischemic remodeling [9]. Subsequently, compensatory hypertrophy of the remaining cardiomyocytes occurs with a change in their spatial location, which is accompanied by a change in the normal geometry, volume and mass of the left ventricle. Echocardiography at an early stage of remodeling reveals a local violation of contractility (akinesis, dyskinesis) with thinning of the wall, dilation and sphericization of the left ventricle [10]. These spatial and geometric changes lead to an increase in tension of the wall of the left ventricle, deterioration of microcirculation and further tonic dilation of its cavity. Deterioration of the systolic function of the left ventricle and its dilation cause the progression of heart failure.

Due to the insufficient effectiveness of conservative treatment methods, there is a need to search for and

develop new surgical approaches, as well as to evaluate long-term treatment outcomes and analyze their effectiveness [11–14]. Current guidelines recommend considering left ventricular aneurysmectomy during coronary artery bypass grafting for patients with NYHA functional class III–IV heart failure, large left ventricular aneurysms, high risk of thromboembolism, or ventricular arrhythmias. Surgical reconstruction of the left ventricle can be considered as an operation aimed at reducing the adverse effects of remodeling by excluding dyskinetic and scarred areas of the left ventricle, preventing further dilatation and restoring geometry [15–18].

The basic principles of surgical treatment of left ventricular aneurysms and their modifications were proposed by Cooley, Jatene and Dor more than half a century ago. In general, these methods can be divided into two categories: linear and geometric reconstruction. Currently, the Dor procedure and its modifications are widely used. The analysis of the results of studying the anatomical and physiological features of the heart in the case of post-infarction aneurysm, as well as the concepts of surgical treatment and methods of performing operations in leading medical institutions around the world, has allowed us to formulate the principles of optimal correction of all affected heart structures in patients with post-infarction left ventricular aneurysms.

In the process of reconstructing post-infarction left ventricular aneurysms, it is crucial to achieve an optimal balance between the benefits of reducing left ventricular wall stress due to volume reduction and the necessary cavity size that ensures adequate stroke volume [9]. At present, there are no reliable methods of predicting postoperative morphofunctional changes in the heart, which makes it difficult to calculate an adequate end-diastolic volume and ejection fraction. This causes certain difficulties in clinical practice, since prognostic assessment of these indicators before surgery is extremely important for determining the effectiveness of its performance, choosing further treatment strategies and evaluation of patients' condition in the long term. In addition, the results of studies aimed at comparing different methods of surgical left ventricular repair are often ambiguous and even contradictory, which does not allow making unambiguous conclusions and complicates the choice of an effective treatment strategy. Unfortunately, the available data on the mid-term and long-term results of surgical treatment of such patients remain very limited. This creates certain difficulties in understanding how different treatment methods affect the survival and quality of life of patients.

The aim of the meta-analysis is to assess the one-year survival of patients after surgical reconstruction of the left ventricle, to determine the functional class of heart failure, and to study the morphological and functional characteristics of the heart. A comparative analysis of the results of the meta-analytic assessment of patient survival after left ventricle reconstruction using the DOR (SAVER) method will be performed in comparison with other treatment methods.

Materials and methods

Search for Publications and Selection of Studies

Information was searched for the period from January 1, 2000 to December 31, 2024 in electronic databases using the PubMed and Google Scholar platforms. The search algorithm was developed in strict accordance with the requirements set out in the PRISMA guidelines governing the preparation of reports for systematic reviews and meta-analyses [19]. It included research searches using search queries, keywords (including MeSH), and logical operators. The search queries and data selection were conducted only in English. In order to maximize the sensitivity of the search and obtain the most complete results, various terms and keywords related to the topic under study were combined. Keywords in the research in the PubMed database: (Surgical ventricular reconstruction) OR (Surgical ventricular restoration) OR (Dor procedure) OR (ventricular aneurysmectomy) OR (Ventriculoplasty) OR (Ventricular aneurysm repair) OR (endoventricular plasty) OR (ventricular endocardial restoration) OR (endocardial patch) OR (ventricular infarct

exclusion) AND ((medium-term results) OR (long-term results))).

The following word combinations were searched in the Google Scholar database: Surgical ventricular reconstruction, surgical ventricular restoration, Dor procedure, ventricular aneurysmectomy, ventriculoplasty, ventricular aneurysm repair, endoventricular plasty, ventricular endocardial restoration, endocardial patch, ventricular infarct exclusion.

Inclusion/exclusion criteria

This meta-analysis analyzed only full-text studies of adult patients who underwent left ventricular reconstruction for ischemic cardiomyopathy. It should be emphasized that all included studies had to have a follow-up duration of at least one year after surgery. This condition made it possible to obtain more accurate and reliable data on the results of surgery and on the patients' condition in the mid-term period. All methods of surgical reconstruction of the left ventricle were included in the meta-analysis, which makes it more comprehensive, covering a wide range of approaches used in cardiac surgery.

In addition, a detailed subanalysis of patients after surgical reconstruction of the left ventricular using the Dor procedure or surgical anterior ventricular endocardial restoration (SAVER) was performed. These types of surgical operations have common principles with minimal differences and are often considered equivalent in the literature [9]. Studies in which left ventricular reconstruction was not performed, as well as patients with non-ischemic cardiomyopathy, were excluded. In addition, the analysis did not include publications in which the duration of follow-up of patients after left ventricular reconstruction was less than one year. This decision is due to the fact that the limited follow-up period will not allow for a full assessment of the results of the operation and the potential risks of complications in the medium term.

The meta-analysis included publications describing the preoperative period (stage I), the short-term postoperative period (stage II), and one year after surgery (stage III). In order to objectively evaluate the effectiveness of different surgical approaches, two groups were distinguished: group 1 patients underwent only surgical reconstruction of the left ventricular using the Dor procedure or surgical anterior ventricular endocardial restoration (SAVER); Group 2 patients underwent various surgical ventricular reconstruction methods, depending on surgical expediency (Table 1). In the second group, surgeons chose the method of surgical reconstruction based on their own preferences and the clinical situation. Publications of clinical cases, abstracts, conference presentations, editorials, reviews, and expert opinions were also excluded, as these materials do not contain sufficient systematic data necessary for conducting a meta-analysis.

Extraction and synthesis of study data

As a result of a systematic search in two specialized databases, a total of 1875 articles dedicated to surgical reconstruction of the left ventricle in patients with ischemic cardiomyopathy were identified. This list included both prospective and retrospective studies on the subject. After careful analysis and exclusion of duplicate materials that could affect data objectivity, a final total of 962 publications remained. A detailed selection process was then conducted, during which the titles and abstracts of each article were assessed. This allowed for the exclusion of 698 articles that did not meet the pre-established criteria.

Thus, a total of 264 articles were included in the final list, which underwent full-text analysis. Out of these, only 15 studies met all the necessary inclusion criteria. The total number of patients involved in these studies amounted to 1089. The PRISMA diagram (Figure 1) clearly illustrates the search, filtering, and selection strategy of the articles, which is crucial for understanding the methodology of this meta-analysis.

The validity and methodological quality of the selected non-randomized studies were assessed using the Newcastle-Ottawa Scale (NOS), which is recommended by the Cochrane Collaboration. The average score on the NOS for the included studies was 6.5. Table 1 provides detailed information regarding the design of individual studies as well as the baseline characteristics of the patients.

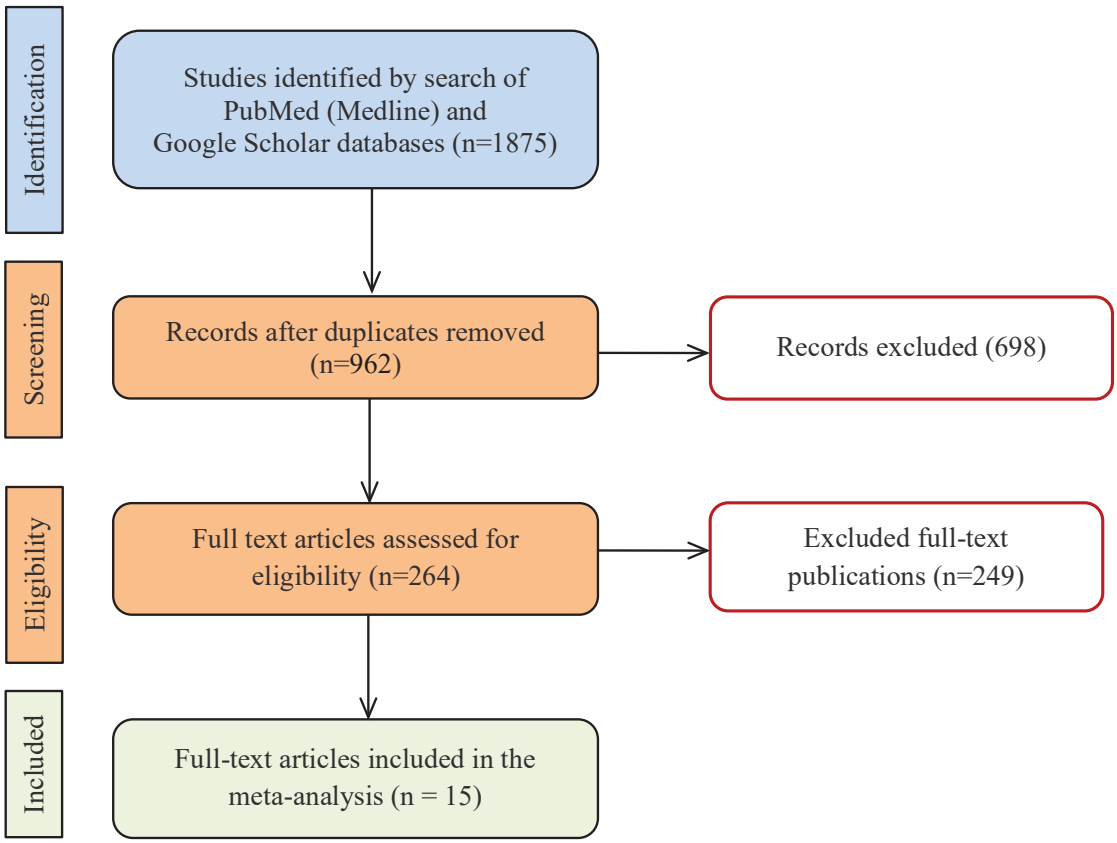

Fig. 1. PRISMA schematic diagram of the search strategy.
Note: PRISMA — Preferred Reporting Items for Systematic Reviews and MetaAnalysis.

Table 1

Overview of the studies included in the systematic review

Author, year of publication	Number of patients	Study type	Average age, years (*M* ± SD)	Study period	Surgical techniques
Donato et al., 2001a [20]	207	Retro-spectively	58 ± 6	January 1991 — December 1996	Surgical reconstruction of the left ventricle by the Dor procedure
Donato et al. (1), 2001b [21]	44	Retro-spectively	58 ± 6	June 1997 — August 1998	Surgical reconstruction of the left ventricle by the Dor procedure
Fujii et al., 2004 [22]	14	Pro-spectively	67 ± 10	-	Endoventricular circular patch plasty (Dor procedure)
Kokaji et al., 2004 [23]	30	Pro-spectively	61 ± 11	1996–2003	Endoventricular circular patch plasty (Dor procedure)
Lee et al., 2007 [24]	49	Pro-spectively	59.7 ± 9.88	2001–2006	Surgical ventricular reconstruction by means of the Dor procedure or surgical anterior ventricular endomyocardial restoration (SAVER)
Bove et al., 2009 [25]	23	Pro-spectively, retro-spectively	68 ± 8	2005–2008	Endoventricular circular patch plasty (Dor procedure)

Table 1 Continued

Author, year of publication	Number of patients	Study type	Average age, years (*M* ± SD)	Study period	Surgical techniques
Tekumit et al., 2010 [8]	67	Retro-spectively	64.8 ± 8.9	February 2001 — June 2009	Surgical reconstruction of the left ventricle by the Dor procedure
Pocar et al., 2010 [15]	31	Retro-spectively	65.2 ± 7.6	January 2000 — December 2007	Endoventriculoplasty; modified Dor procedure; linear repair techniques
Skelley et al., 2011 [16]	87	Retro-spectively	61 ± 10	January 2002 –April 2008	Endoventriculo-plasty
Marchenko et al., 2011 [17]	116	Retro-spectively	-	2005–2008	Autoventriculoplasty (septalplasty of LV and IVS, modified Stoney technique); endoventriculoplasty with a synthetic patch (Dor–Cooley–Matas technique)
Cho et al., 2012 [14]	60	Retro-spectively	65 ± 8	September 2002 — September 2010	Dor procedure; linear closure; septal anterior ventricular exclusion (SAVE)
Hwang et al., 2014 [12]	63	Retro-spectively	62.7 ± 9	1999–2005	Surgical anterior ventricular endocardial restoration (SAVER)
Kato et al., 2015 [13]	15	Retro-spectively	63.2 ± 9.5	2004–2012	Septal anterior ventricular exclusion (SAVE); overlapping procedure; linear closure
Chen et al., 2022 [18]	78	Retro-spectively	55.3 ± 11.4	From January 1999 — March 2021	Linear ventriculoplasty, endocardial patch reconstruction (Dor procedure); modified left ventricular reconstruction
Solowjowa et al., 2022 [27]	205	Retro-spectively	63.4 ± 11.2	November 2005 — January 2016	Modified Dor procedure

Methods of left ventricular surgical reconstruction presented in the meta-analysis

In the publications of Donato, M. et al. (2001a, b) analyzes surgical reconstruction of the left ventricle by the Dor procedure in patients with anterior transmural myocardial infarction [20, 21]. Coronary artery bypass grafting was performed simultaneously with the reconstruction of the left ventricle. Both publications are included in the meta-analysis, because the retrospective analysis collected information about patients who underwent surgery at different time periods, and the patient groups did not overlap. This ensures the independence of the results and allows for a more accurate interpretation of the data obtained.

In the Fujii H. study and co-authors (2004), the author discusses the use of endoventricular circular patch plasty, performed according to the Dor procedure [22]. The technique described in the publication Kokaji K. et al. (2004), is largely similar to the approaches proposed earlier by Dor V. [23].

In a clinical study conducted by Lee S. et al. (2007), patients underwent surgery for left ventricular surgical reconstruction using the Dor procedure or surgical anterior ventricular endomyocardial restoration (SAVER) [24]. At the same time, 45 patients underwent concomitant coronary artery bypass grafting. Ventricular and mitral valve function was assessed using transesophageal echocardiography.

In the publication by Bove T. and co-authors. (2009) the authors reported that the reconstruction was performed using endoventricular patch plasty as described by Dor et al. An intraventricular balloon was used to give the left ventricle an elliptical shape and control the volume of the left ventricle [25].

In 2010, Tekumit H. et al. performed surgery to remove a left ventricular aneurysm using the

Dor procedure [8]. In cases where coronary artery bypass surgery was performed, grafts taken from the left internal thoracic artery and/or saphenous vein were used to restore blood flow. In addition, mitral annuloplasty was performed in patients diagnosed with grade III or IV mitral regurgitation. None of the patients required the implantation of a permanent pacemaker.

In a study conducted by Pocar M. and co-authors. (2010), the author discusses various approaches to surgical reconstruction of the left ventricle of the heart [15]. Several methods were used, among which were: implantation of an oval bovine pericardial or Dacron patch; modified Dor procedure with no internal patch; linear closure when the residual area was small. One of the features of this study was the use of longitudinal septal plication with interrupted sutures. This method was used in 10 cases, of which 8 additionally used an intracavitary patch, and in 2 cases not. The Guilmet overcoat technique was used to close the ventricular septal defect in two patients. Bypass surgery of the left anterior descending artery was performed in 26 patients (84%).

According to a publication by Skelley N.W. et al. (2011), before the reconstruction of the left ventricle, coronary artery bypass grafting was performed [16]. Depending on the condition of the heart valve apparatus, annuloplasty or mitral valve replacement was performed during the operation. Surgical reconstruction of the left ventricle was performed through ventriculotomy, which was performed in the distal part of the anterior wall. After the thrombus was removed, the left ventricle was carefully examined for scar tissue. In most patients, an intraventricular balloon was inserted into the left ventricle, which allowed the chamber size to be controlled and provided optimal conditions for further reconstruction. At the next stage, a purse-string suture was placed around the edge of the intraventricular balloon. In cases where ventricular defects exceeded 2–3 cm, Dacron polyester patch was used to close them. Otherwise, for smaller defects, linear closure was used.

In the study of Marchenko A. and co-authors. (2011), the author performed surgical reconstruction of the left ventricle using autoventriculoplasty in 49% of cases [17]. It was septaloplasty of the left ventricle and the interventricular septum using the modified Stoney technique. In 51% of cases, endoventriculoplasty with a synthetic patch was performed using the Dor–Cooley–Matas method. Surgical correction of the mitral valve was performed in 34 patients with grade 3–4 mitral regurgitation. At the same time, annuloplasty with rigid ring was preferred in 60% of cases. Suture annuloplasty or annuloplasty with xenopericardium band was performed in 28% of patients, and mitral valve replacement was performed in 12% of patients.

Cho Y. and co-authors. (2012) compared different surgical methods of left ventricular reconstruction. In most cases, surgical reconstruction of the left ventricle using the Dor procedure was performed (40 patients) [14]. Septal anterior ventricular exclusion (SAVE) was applied to 8 patients with ischemic cardiomyopathy and severe scarring who underwent repeated anterior-septal infarction using a large xenogenic patch measuring 8 × 4 cm. Linear left ventricular plasty was performed in 12 patients. During the operations, an intraventricular balloon inflated to the estimated diastolic volume of the left ventricle was used to avoid excessive volume reduction.

Hwang H.Y. et al. (2014) analyzed the results of surgical anterior ventricular endocardial restoration (SAVER) [12]. The left ventricle opened parallel to the left anterior descending coronary artery. An endoventricular circular pursestring suture was placed circumferentially in the transitional zone between the normal and diseased myocardium. An intraventricular balloon was used during the operation. Coronary revascularization was performed after the SAVER operation. Most revascularizations were performed under an on-pump beating heart. Mitral annuloplasty was performed in patients in whom preoperative echocardiography revealed moderate or greater mitral regurgitation. One patient underwent mitral valve replacement.

According to some authors Kato Y. et al. (2015), the choice of the most optimal cardiac surgical methods of ventriculoplasty surgery is significantly determined by the localization of the postinfarction scar [13]. In patients with anterior septal infarction, the septal anterior ventricular exclusion (SAVE) or overlapping procedure

was used, and in patients with posterior infarction, linear closure was used.

In later studies, Chen L. and co-authors. (2022) raised questions about the main approaches to surgical reconstruction of the left ventricle, which are applied depending on the characteristics of the aneurysm and the preferences of surgeons [18]. These methods include Cooley linear ventriculoplasty, endocardial patch reconstruction (Dor procedure), and modified left ventricular reconstruction. Modified reconstruction of the left ventricle described by Zheng Z. et al. [26], includes several key stages. First of all, the surgeon applies an endoventricular pursuestring suture using a linear suture in the area of scar tissue. The suture is then tightened to form an opening of about 2 cm in diameter, thus reducing the volume of the ventricle and maintaining its satisfactory geometry. The operation is completed by analogy with standard linear ventriculoplasty, which implies further closure of the ventricle and restoration of its normal structure.

Solowjowa et al. (2022), analyzed the results of left ventricular reconstruction surgery using a modified Dor procedure with multiple Fontan sutures around the perimeter of the aneurysm without the use of a patch in combination with coronary artery bypass grafting [27]. In 12.2% of patients with specific local findings, for example, a defect in the interventricular septum after extensive anteropical myocardial infarction, a patch was required to close the defect. Mitral valve surgery was performed in patients with echocardiographically confirmed mitral regurgitation ≥ grade 2.

Statistical analysis

Statistical data processing was carried out using the OpenMeta software (Beta 1.0 version, 2015). The baseline characteristics of patients and clinical outcomes are presented as mean values with 95% confidence intervals (CI). Continuous data were combined using meta-analysis with a random effects model. The heterogeneity of the data was assessed using Cochran's Q test and the I^2 test. Survival data 1 year after surgery, collected from each study, were pooled to obtain a weighted average and a 95% confidence interval.

Results

General characteristics of patients

The mean age of the examined patients was 62.1 years (95% CI: 60.2–64.1). The heterogeneity indicators are presented in Table S1. The study included 56% (95% CI: 42–69) men. Angina pectoris occurred in 79% (95% CI: 68–90) of the patients. The time from the onset of myocardial infarction to the surgical reconstruction of the left ventricle was 6.3 years (95% CI: 2.9–9.7). An anterior localization aneurysm was found in 87% (95% CI: 74–99) of patients. At the same time, a thrombus in the ventricle was detected preoperatively in 27% (95% CI: 19–35) of cases. The mean EuroSCORE was 9.7% (95% CI: 7.3–12.1).

The most commonly associated diseases in patients in the meta-analysis are diabetes mellitus [36.7% (95% CI: 31.1–42.3)], atrial fibrillation [10.7% (95% CI: 4.5–16.9)], ventricular extrasystole [23.1% (95% CI: 14–32.2)], stroke or transient ischemic attack [10.4% (95% CI: 8.7–12.2)], and impaired kidney function [13.7% (95% CI: 9.8–17.5)].

Preoperative characteristics

In most cases, before surgery, patients had a high functional class of heart failure according to NYHA [3 functional class (95% CI: 2.82–3.1)], which is caused by morpho-functional disorders of the heart. Such patients have low left ventricular ejection fraction [31.3% (95% CI: 29.2–33.3)], dilated heart cavities [EDVI — 131.7 mL/m^2 (95% CI: 113.1–150.2); ESVI — 91.8 mL/m^2 (95% CI: 79.6–104.1)], increased pulmonary capillary wedge pressure [15.4 mmHg (95% CI: 13.4–17.5)]. Despite severe impairments, relatively satisfactory cardiac index values were maintained in patients [2.7 L/min/m^2 (95% CI: 2.4–2.9)] and the stroke volume index ndex [45.5 mL/m^2 (95% CI: 30.9–60.1)]. The average degree of mitral regurgitation was at the level of 1.72 (95% CI: 1.4–2.04).

Operative characteristics

The duration of cardiopulmonary bypass was 144.8 minutes (95% CI: 118–171.6), and the aortic cross-clamping time was 82.7 minutes (95% CI: 72.2–93.3). In 88.7% (95%

CI: 81.5–95.9) of cases, coronary artery bypass grafting was performed simultaneously with left ventricle reconstruction. The average number of grafts during coronary artery bypass grafting was 2.5 (95% CI: 2.2–2.8). Additionally, mitral valve surgery was required in 20.1% (95% CI: 14.3–25.8) of cases. An intra-aortic balloon pump was used in 25.5% (95% CI: 17–34) of cases.

Postoperative results

After surgical reconstruction of the left ventricle, the patient demonstrated a significant reduction in volumetric parameters [EDVI — 81.71 ml/m² (95% CI: 70.5–92.9); ESVI — 50.7 ml/m² (95% CI: 44.5–56.9)], which was maintained during the first year after the operation [EDVI — 85.96 ml/m² (95% CI: 72.9–99.07); ESVI — 52.1 ml/m² (95% CI: 45.7–58.5)]. After the surgical intervention, the cardiac index was 2.8 L/min/m² (95% CI: 2.48–3.18), and the stroke index was 38.9 mL/m² (95% CI: 24.4–53.6). The left ventricular ejection fraction after geometric reconstruction in the early postoperative period reached 40%, and one year after the operation — 41%. The pulmonary capillary wedge pressure and mitral regurgitation after the operation were 11.5 mmHg (95% CI: 8.9–13.9) and 0.7 grade (95% CI: 0.22–1.16), respectively, and one year after the operation, these indicators reached 12.97 mmHg (95% CI: 8.64–17.3) and 1.14 grade (95% CI: 0.85–1.44). The NYHA functional class after surgery was 1.58 (95% CI: 1.4–1.7), and one year after the operation it was 1.57 (95% CI: 1.3–1.83).

Dynamics of the left ventricle end-diastolic volume index

The study included 11 publications with a total of 759 patients. A meta-analysis was performed on the difference in mean values of EDVI in patients before and after surgery. As shown in forest plot (Figure 2), after surgery, the final value of this indicator statistically significantly ($p<0.001$) decreased by 46.8 ml/m² (95% CI: 35–58.5). We adopted the random-effects model because heterogeneity was significant ($Tau^2 = 293.9$; $Q(df - 10) = 97.7$; $p < 0.001$; $I^2 = 90.8$). According to the data presented in forest plot (Figure 3), before surgery and one year after it, the value of EDVI decreased by 38.8 ml/m² (95% CI: 28.1–49.6, $p<0.001$) with significant heterogeneity ($Tau^2 = 198.8$; $Q(df -10) = 53.01$; $p < 0.001$; $I^2 = 84.9$). In the course of the meta-analytic assessment conducted to determine changes in EDVI, no statistically significant changes were identified a year after surgery compared to the early postoperative period (MD= –5; 95% CI= –12.9–2.9; $p = 0.21$). Heterogeneity was significant ($Tau^2 = 85.4$; $Q(df - 9) = 31.9$; $p < 0.001$; $I^2 = 78.0$).

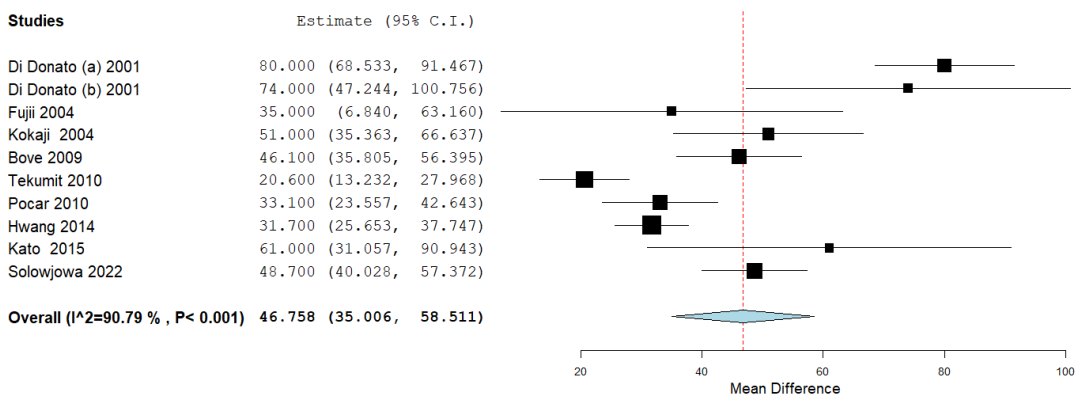

Fig. 2. Forest plot for the meta-analysis of EDVI before and after surgery

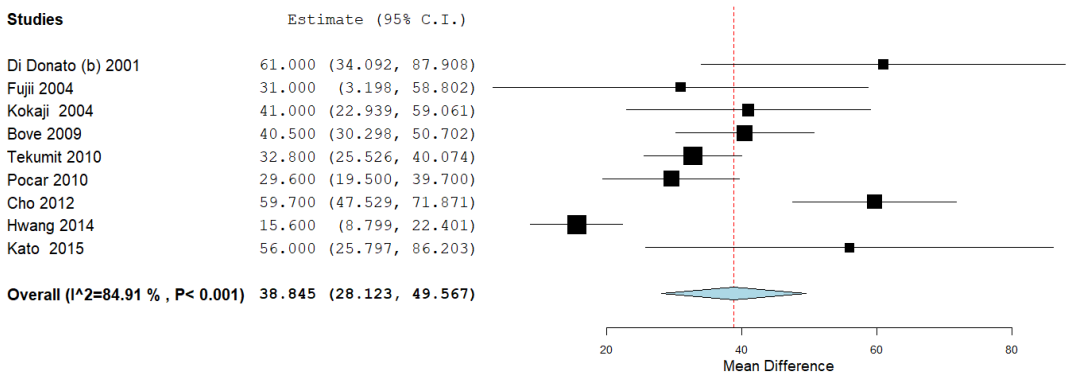

Fig. 3. Forest plot for the meta-analysis of EDVI before and one year after surgery

Dynamics of the left ventricle end-systolic volume index

In the study, a meta-analysis of 10 publications was conducted, which included 434 patients. A meta-analysis of the difference in mean values of ESVI in patients was performed before and after surgery. According to the data presented in forest plot (Figure 4), after surgery, the final value of this indicator decreased by 39.4 ml/m² (95% CI: 29.6–49.2, $p < 0.001$) with significant heterogeneity ($Tau^2 = 223.4$; $Q(df - 9) = 87.6$; $p < 0.001$; $I^2 = 88.6$). The data displayed in forest plot (Figure 5) indicate a reduction in ESVI before surgery and one year after the surgical intervention by 35.15 ml/m² (95% CI: 27.4–42.6, $p < 0.001$), though substantial heterogeneity was observed among the studies ($Tau^2 = 105.2$; $Q(df - 9) = 38.8$; $p < 0.001$; $I^2 = 76.8$). The results of the meta-analysis did not reveal significant differences in the end-systolic volume index between the measurements recorded one year after the surgical intervention and those in the early postoperative period (MD = –0.95; 95% CI: –4.6–2.74, $p = 0.62$). The studies showed moderate heterogeneity ($Tau^2 = 12.75$; $Q(df - 9) = 15.7$; $p = 0.05$; $I^2 = 49.2$).

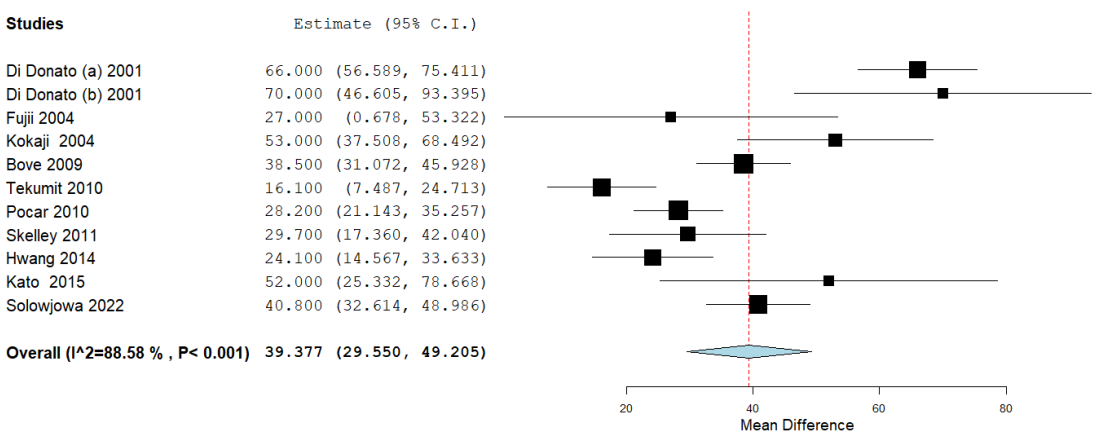

Fig. 4. Forest plot for the meta-analysis of ESVI before and after surgery

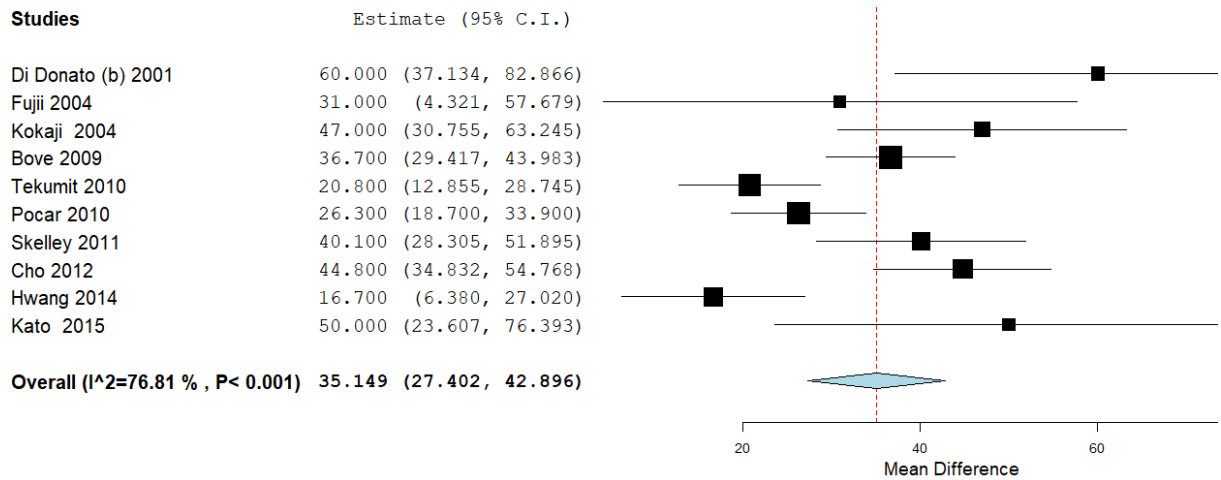

Fig. 5. Forest plot for the meta-analysis of ESVI before and 1 year after surgery

Dynamics of left ventricular ejection fraction

In the study, 11 publications were analyzed, involving 657 patients. As shown in forest plot (Figure 6), after the surgery, the final value of EF significantly increased ($p < 0.001$) by 9% (95% CI: 6.6–11.4). Adopting the random-effects model, the heterogeneity between the studies was significant ($Tau^2 = 13.8$; $Q(df - 10) = 67.3$; $p < 0.001$; $I^2 = 83.7$). Forest plot (Figure 7) presents data indicating that one year after the operation, EF increases by 10.1% (95% CI: 8.01–12.1, $p < 0.001$) compared to preoperative levels. Heterogeneity was significant ($Tau^2 = 6.7$; $Q(df-10) = 29.5$; $p < 0.001$; $I^2 = 69.5$). Through the meta-analysis of EF, we studied the treatment outcomes after surgery and one year post-operation. No statistically significant differences in EF were obtained (MD = –2.41; 95% CI: –4.9–0.072, $p = 0.057$). Significant heterogeneity was observed between the studied stages ($Tau^2 = 7.39$; $Q(df - 11) = 19.6$; $p = 0.007$; $I^2 = 64.2$).

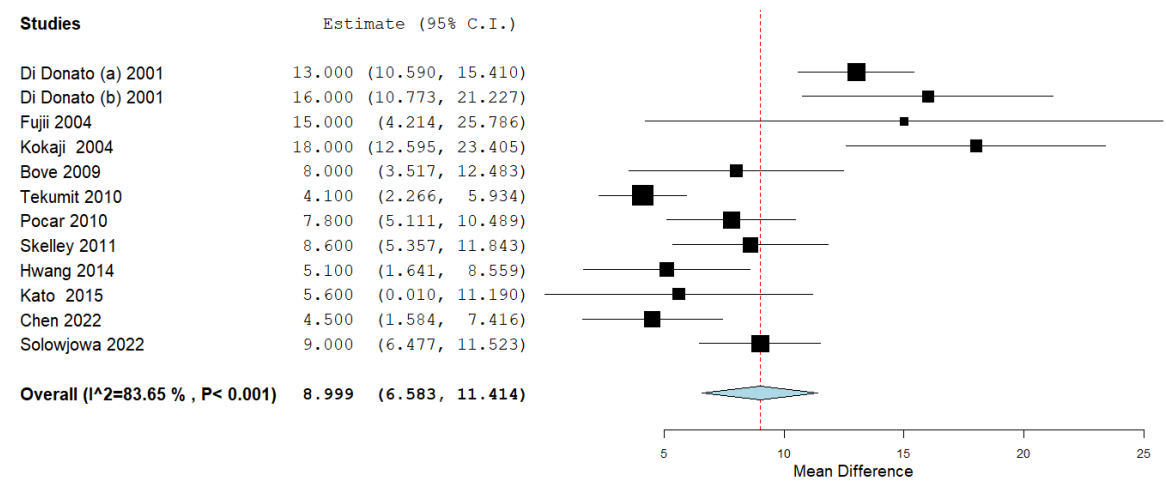

Fig. 6. Forest plot for the meta-analysis of EF before and after surgery

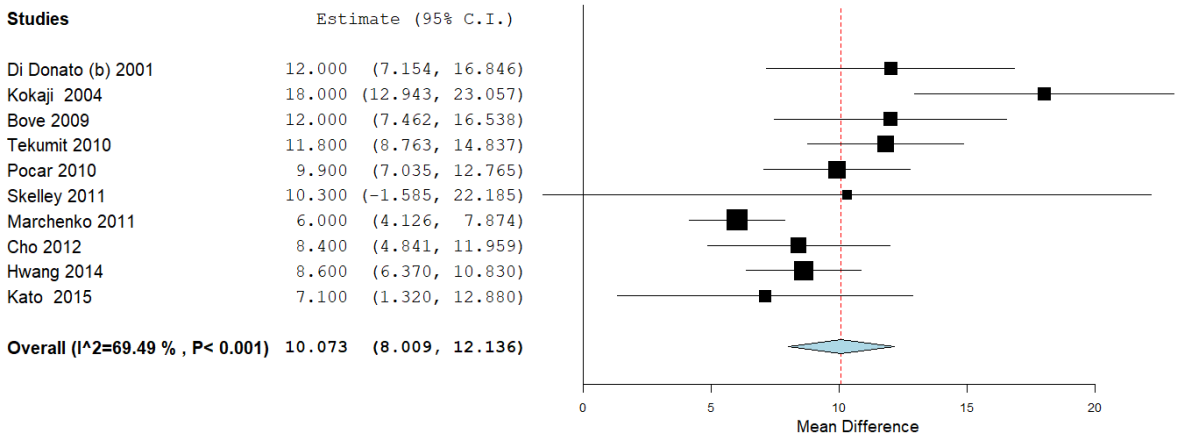

Fig. 7. Forest plot for the meta-analysis of EF before and one year after surgery

Dynamics of pulmonary capillary wedge pressure (PCWP)

In this study, 4 publications were analyzed, which described the results of examinations of a total of 348 patients. The main focus was on the change in the PCWP indicator before and after surgical intervention. For a deeper analysis, a meta-analytic assessment of the differences in mean PCWP values in patients before and after the operation was conducted. The results presented in forest plot (Figure 8) demonstrate a statistically significant (p = 0.001) overall reduction of this indicator in the early period after surgery by 4 mmHg (95%CI: 1.6–6.3), with significant heterogeneity observed (Tau^2=3.6; Q(df – 3) = 8.13; p=0.043; I^2 = 63.1). The meta-analytic assessment did not reveal significant changes in PCWP one year after the operation compared to preoperative levels (MD = 3.4 mmHg; 95% CI: –0.74–7.5, p = 0.107). Significant heterogeneity was noted among the studied parameters (Tau^2 = 9.32; Q(df-2) = 6.6; p = 0.037; I^2 = 69.7).

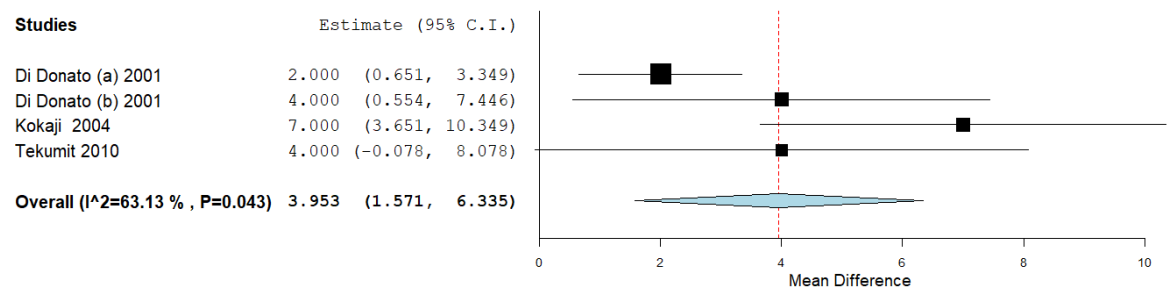

Fig. 8. Forest plot for the meta-analysis of PCWP before and after surgery

Dynamics of changes in cardiac index and stroke volume index

In this study, a meta-analysis of four scientific publications was conducted, which described the results of examinations of a total of 486 patients. A meta-analysis of the difference in mean cardiac index (CI) values in patients before and after the operation was performed (Figure 9). During the meta-analytic assessment aimed at identifying changes in cardiac index, no significant changes were found postoperatively compared to the preoperative period (MD = –0.11; 95% CI: –0.23–0.01, p = 0.07). The heterogeneity observed was moderate (Tau^2 = 0.007; Q(df – 3) = 5.5; p = 0.14; I^2 = 45.3).

A meta-analysis of stroke volume index (SVI) based on three scientific publications, including 312 patients (Figure 10), revealed a reduction in this indicator in the early postoperative period by 7.47 mL/m² (95% CI: 5.7–9.2, p < 0.001) with insignificant heterogeneity (Tau² = 0; Q(df – 2) = 0.315; p = 0.854; I² = 7.47).

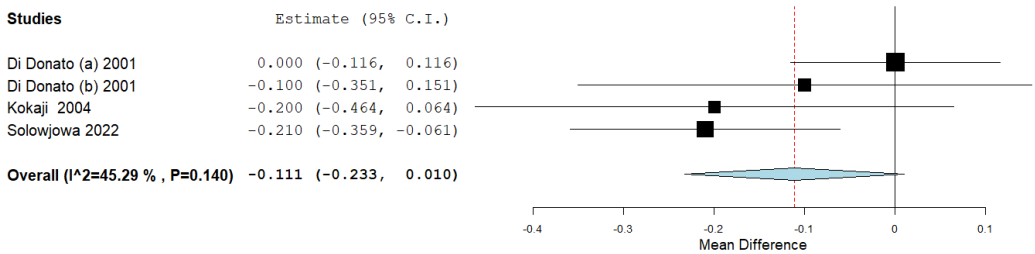

Fig. 9. Forest plot for the meta-analysis of cardiac index before and after surgery

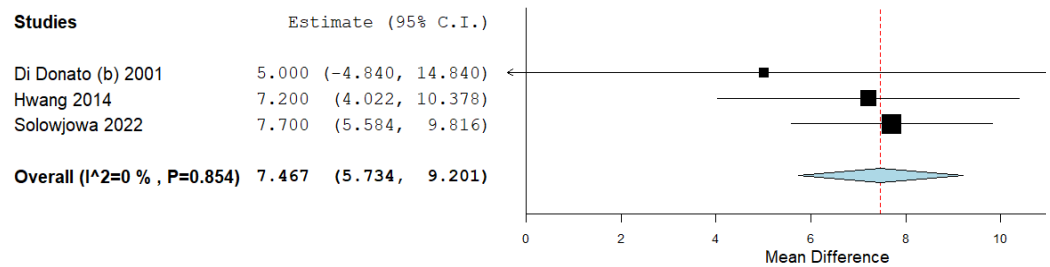

Fig. 10. Forest plot for the meta-analysis of stroke volume index before and after surgery

Dynamics of Mitral Regurgitation

The study included 4 publications, with a total of 318 patients. A meta-analysis was performed to assess the difference in mean MR values in patients before and after surgery. As indicated by the forest plot (Figure 11), after the surgery, the overall value of this parameter decreases by 0.75 grade (95% CI: 0.25–1.25, p = 0.003). There was great heterogeneity between studies (Tau² = 0.244; Q(df – 3) = 68; p < 0.001; I² = 95.6), so we pooled the data under the random-effects model. According to the data presented in the forest plot (Figure 12), one year after surgery, there was a reduction in MR by 0.62 grade (95% CI: 0.2–1.04, p = 0.004) with significant heterogeneity (Tau² = 0.25; Q(df – 5) = 81.5; p < 0.001; I² = 93.8). Additionally, one year after surgery, an increase in MR by 0.2 grade (95% CI: 0.05–0.33, p = 0.009) was observed compared to the early postoperative period, with no heterogeneity observed among the studies (Tau² = 0; Q(df – 2) = 0.043; p = 0.98; I² = 0).

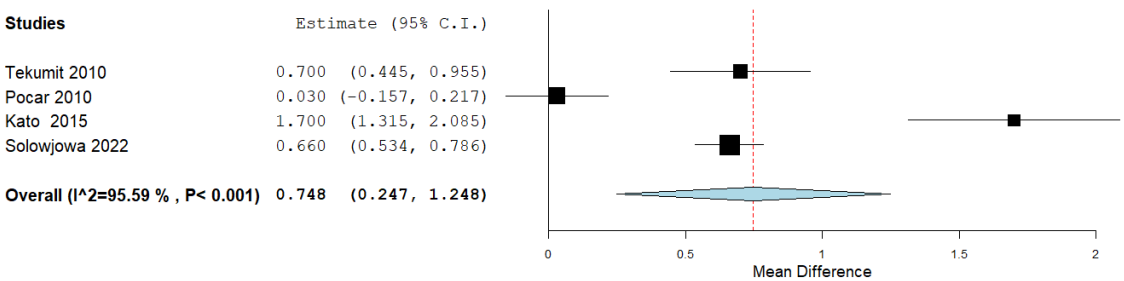

Fig. 11. Forest plot for the meta-analysis of mitral regurgitation before and after surgery

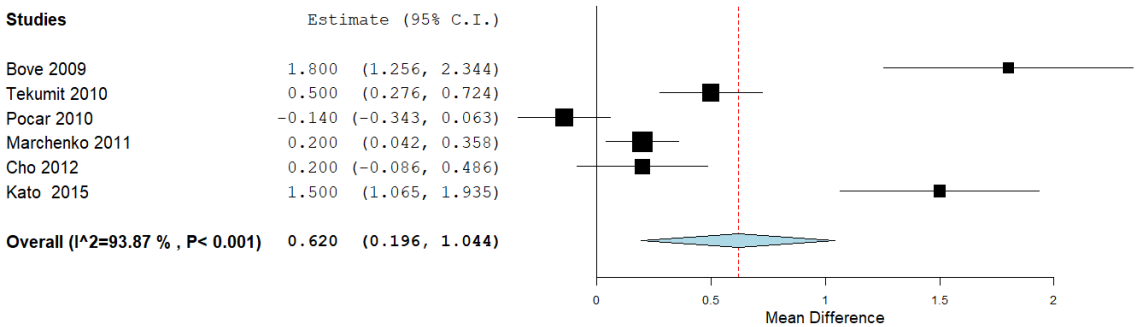

Fig. 12. Forest plot for the meta-analysis of mitral regurgitation before and one year after surgery

Dynamics of NYHA Functional Class in Heart Failure

This study analyzed data from 325 patients presented in four publications. Meta-analysis allowed for the assessment of the difference in mean NYHA functional class values before and after surgery. According to the results shown in forest plot (Figure 13), after the operation, the overall value of this parameter significantly decreases by 1.5 (95% CI: 1.28–1.72, $p < 0.001$). Heterogeneity was significant ($Tau^2 = 0.03$; $Q(df - 3) = 9.73$; $p = 0.021$; $I^2 = 69.1$). The obtained results confirm the effectiveness of surgical intervention, which contributes to the improvement of patients' functional state. According to the data presented in the forest plot (Figure 14), there was a reduction in NYHA by 1.52 (95% CI: 1.3–1.8, $p < 0.001$) before surgery and one year after it, with significant heterogeneity ($Tau^2 = 0.08$; $Q(df - 5) = 35.35$; $p < 0.001$; $I^2 = 85.8$). This indicates an improvement in patients' condition that persists for a long time after surgery.

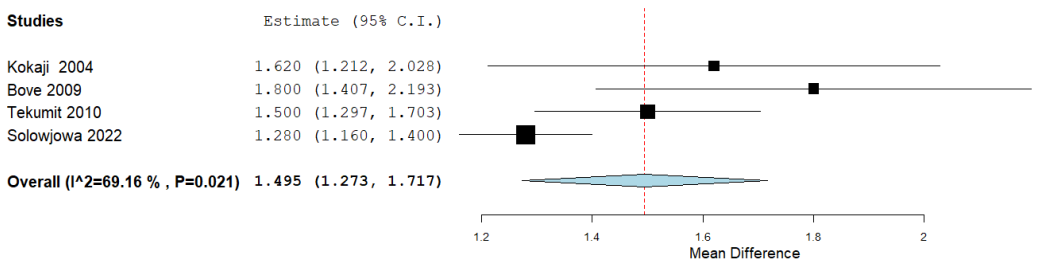

Fig. 13. Forest plot for the meta-analysis of NYHA functional class before and after surgery

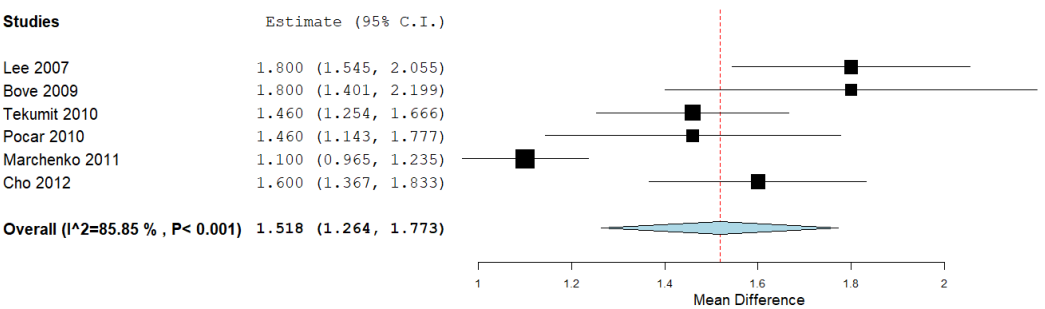

Fig. 14. Forest plot for the meta-analysis of NYHA functional class before and one year after surgery

Postoperative mortality and one-year survival after surgical left ventricular reconstruction

The meta-analytic assessment conducted to study postoperative mortality includes 11 different publications, analyzing a total of 951 patients. According to the data presented in the forest plot (Figure 15), the level of postoperative mortality was 5.4% (95% CI: 3.8–7.1). There was great heterogeneity between studies ($Tau^2 = 8.6$; Q(df – 10) = 1998.6; $p < 0.001$; $I^2 = 99.5$), so we pooled the data under the random-effects model.

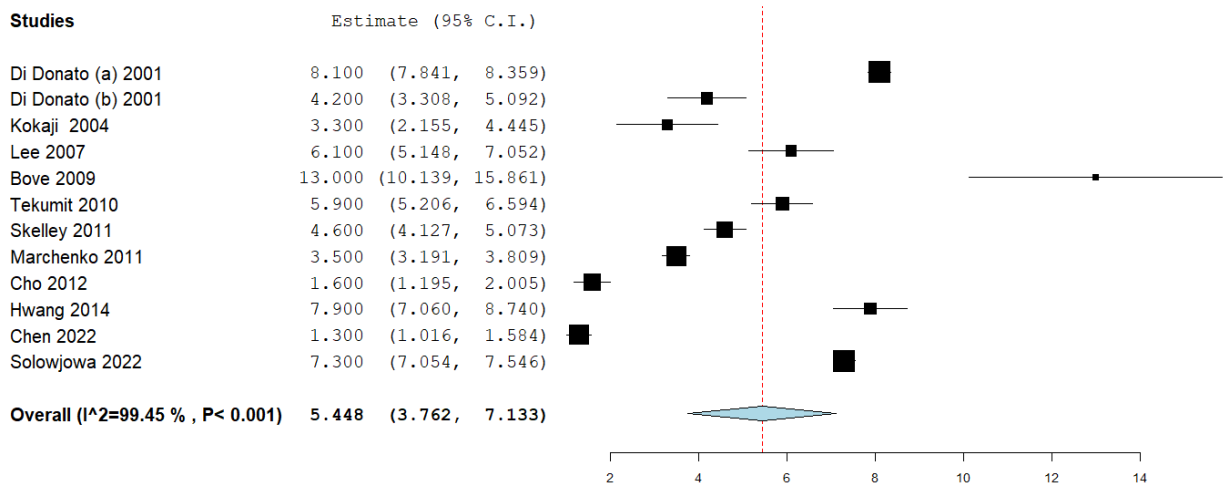

Fig. 15. Forest plot for the meta-analysis of postoperative mortality

The study of patient survival after surgical left ventricular reconstruction has provided fundamentally important information about the mid-term outcomes of this procedure (Figure 16). This research analyzed eight scientific articles involving 788 patients who underwent the surgery. The results indicated that one year after the surgical intervention, the survival rate was 94% (95% CI: 90–98), with significant heterogeneity ($Tau^2 = 0.003$; Q(df-7) = 6023.9; $p < 0.001$; $I^2 = 99.8$).

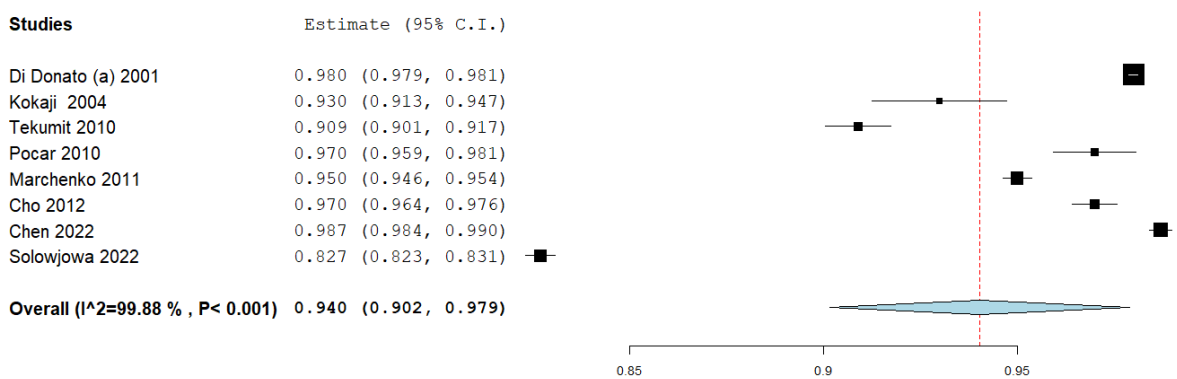

Fig. 16. Forest plot for the meta-analysis of patient survival one year after left ventricular reconstruction surgery

Subanalysis of patients after surgical reconstruction of the left ventricle using the Dor (or surgical anterior ventricular endocardial restoration) technique

Surgical reconstruction of the left ventricle using the Dor technique is one of the most frequently performed operations in patients with complicated forms of coronary heart disease. It should be noted that the surgical anterior ventricular endocardial restoration (SAVER) surgery technique described in the literature has minimal differences from the Dor operation, and in the English literature it is often considered as an analog of the Dor procedure [9]. Therefore, in the meta-analysis, these types of surgical ventricular reconstruction were considered in one group. The subanalysis of patients who underwent surgical reconstruction of the left ventricle is an important stage in assessing the medium-term results of this surgical procedure. A meta-analytical study conducted a detailed assessment of a sample of patients who underwent surgical ventricular reconstruction. During the study, two groups were identified: group 1 patients underwent only surgical reconstruction of the left ventricular using the Dor procedure or surgical anterior ventricular endocardial restoration (SAVER); Group 2 patients underwent various surgical ventricular reconstruction methods, depending on surgical expediency (Table 1).

The main purpose of the subanalysis was to assess the survival rate of patients who underwent surgical reconstruction of the left ventricular using the Dor procedure or SAVER, compared with patients who underwent various surgical ventricular reconstruction methods, depending on surgical expediency.

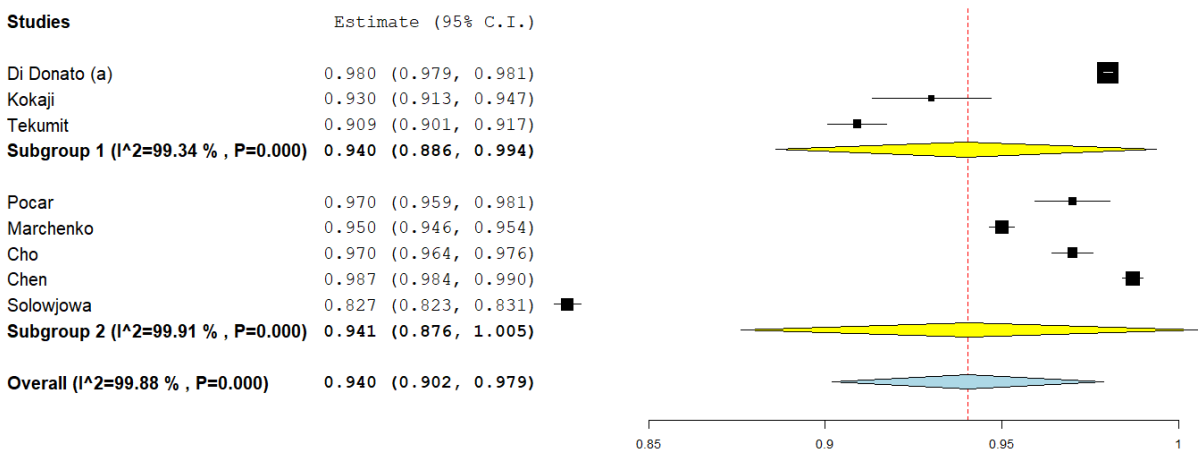

Fig. 17. Meta-regression analysis of patient survival in groups 1 and 2 one year after surgical reconstruction

The subanalysis was performed on the basis of 8 publications with a total of 497 patients. The results of the studies did not reveal a statistically significant difference between the groups by age, preoperative EDVI, ESVI, EF, and NYHA class of heart failure. In group 1, the degree of mitral regurgitation was 0.8 grade higher (95% CI: 0.28–1.25) compared to group 2 (p=0.002). There was no difference in the number of shunts and coronary artery bypass grafting operations in combination with surgical ventricular reconstruction. The meta-regression analysis of survival (Figure 17) did not reveal statistically significant differences between the two groups (p = 0.98).

The restoration of blood flow in hibernating areas of the myocardium after surgical reconstruction of the left ventricle and aortocoronary bypass leads to an improvement in systolic function [9, 10]. Additionally, reverse remodeling results in a reduction of hypertrophy, volume of the left ventricle, and restoration of its structural and geometric parameters. Since this process takes several weeks to months, assessing the patient's condition in the mid-term period is particularly important for predicting the clinical status of the patient.

The results of the meta-analysis showed that the increase in the ejection fraction after surgery was 9% (95% CI: 6.6–11.4). Moreover, these changes are maintained throughout the first year. Thus, one year after the surgery, no statistically significant differences in EF were found (MD = 2.1; 95% CI = –0.21–4.4; p=0.075) compared to the early postoperative period. In the meta-analysis presented in the study by Ferrell (2022), it was found that before the surgery, the ejection fraction increased by 30% [28.8–31.2], and in the early postoperative period, it increased by 40.9% [39.4–42.4] [11]. Similar results were obtained in the study by Dor et al. (2011), according to which, one year after left ventricular surgical reconstruction, the left ventricular ejection fraction (LVEF) increased from 26% to 44% [28].

Unlike these data, the STICH (Surgical Treatment for Ischemic Heart Failure) study provides important information about the impact of coronary artery bypass grafting on patients with ischemic cardiomyopathy [29, 30]. According to these results, in the studied patients, the ejection fraction after surgery increased only from 21 to 27%. Apparently, the peculiarities of the surgical strategy for patients with ischemic cardiomyopathy indicated that coronary artery bypass grafting combined with drug therapy in such patients was associated with a higher risk of mortality within the first month compared to the group receiving only optimal medical treatment. The results of most studies have shown that, after surgical reconstruction of the left ventricle, there is a significant increase in ejection fraction. This is due to a decrease in wall stress and an increase in the contractile ability of the heart muscle following the removal of scar changes and the restoration of the elliptical shape of the left ventricle [31]. However, when considering the long-term perspective, especially in the 10-year interval, the results of the STICH study indicate that the group of patients receiving coronary artery bypass grafting combined with drug therapy demonstrated higher survival rates compared to those who underwent only medical treatment without surgical intervention.

The study by Cleland J.G. et al. (2003) found a positive effect of carvedilol on left ventricular ejection fraction. This is likely related to the improvement in the function of both hibernating and ischemic myocardium [32]. The use of carvedilol may serve as an important alternative or adjunct to revascularization in patients with hibernating myocardium. Similar results have been observed with other beta-blockers. Their use contributes to an increase in myocardial perfusion duration during diastole and a reduction in heart rate, which creates the conditions for reverse ventricular remodeling.

According to the results of the meta-analysis, in 88.7% (95% CI: 81.5–95.9, $p < 0.001$) of cases, coronary artery bypass grafting (CABG) was performed simultaneously with left ventricle reconstruction. During the CABG procedure, the number of bypasses averaged 2.5 (95% CI: 2.2–2.8, $p < 0.001$). Several studies have highlighted the significant role of revascularization in improving clinical symptoms and patient survival [14, 15, 17]. For instance, in the meta-analysis conducted by Allman (2002), a strong correlation was found between myocardial viability, assessed through non-invasive testing methods, and improved survival of patients post-revascularization [33]. The study involved 3088 patients, with a mean ejection fraction of 32 ± 8%. The follow-up for these patients lasted an average of 25 ± 10 months. The results indicated that among patients with viable myocardial regions, revascularization was associated with a 79.6% reduction in annual mortality (16% vs. 3.2%, chi-square = 147, $p < 0.0001$). Furthermore, a direct correlation was observed between the degree of left ventricular dysfunction and the effectiveness of revascularization ($p < 0.001$). All of this underscores the necessity of assessing myocardial viability before making decisions regarding revascularization. Meanwhile, among patients without viable myocardial regions, the mortality rate was intermediate.

According to the results of the study, there was a reduction in mitral regurgitation of 0.75 grade (95% CI: 0.25–1.25, $p = 0.003$) after the operation. The decrease in MR before the surgery and one year postoperatively was 0.6 grade (95% CI: 0.2–1, $p=0.004$). In the meta-analytic assessment conducted one year after the operation, an increase in MR of 0.2 grade (95% CI: 0.05–0.33, $p = 0.009$) was observed compared to the early postoperative period. Surgical

intervention on the mitral valve was required in 20.1% (95% CI: 14.3–25.8, $p < 0.001$) of cases.

Mitral insufficiency is a common complication of heart failure, occurring in 50% of patients. The degree of mitral insufficiency directly correlates with patient survival [9]. Mitral insufficiency can develop as a result of dilation of the fibrous ring, prolapse of the mitral valve due to left ventricular geometry alteration, and ischemic dysfunction of the papillary muscles. In most cases, patients with post-infarction left ventricular aneurysm develop secondary mitral insufficiency, often referred to as "functional." In this case, the leaflets, fibrous ring, and papillary muscles remain unchanged, but there is inadequate coaptation or restriction of mobility. The dysfunction of the papillary muscles, which leads to their lateral displacement along with the posterior lateral wall of the left ventricle, is often mentioned in the pathogenesis of mitral insufficiency. Risk factors contributing to the development of mitral insufficiency include age, sex, previous myocardial infarction, extent of myocardial infarction, recurrent myocardial ischemia, and multivessel disease [9]. Currently, the question of the appropriateness of performing mitral valve repair in patients with moderate insufficiency remains a topic of discussion.

According to the results of the meta-analysis, after the surgery, the NYHA functional class decreased by 1.5 (95% CI: 1.28–1.72, $p < 0.001$). One year after surgical reconstruction of the left ventricle, the NYHA functional class remained reduced by 1.5 (95% CI: 1.26–1.8, $p < 0.001$) compared to the preoperative level. This decrease indicates the effectiveness of the surgical intervention aimed at improving the functional status of patients and confirms that the achieved effect is maintained for 1 year post-surgery.

Recent scientific studies have confirmed that surgical reconstruction of the left ventricle can be an effective treatment method for patients with ischemic cardiomyopathy, which is characterized by severe left ventricular dysfunction and the formation of aneurysms. The application of this strategy leads to a statistically significant improvement in left ventricular ejection fraction (LVEF), a reduction in functional class according to the New York Heart Association (NYHA) scale, and an increase in patient survival [34].

A retrospective analysis by Williams et al. demonstrated improvement in NYHA functional class in patients with severe heart failure who underwent left ventricular reconstruction. The results confirm the safety and efficacy of left ventricular reconstruction, both as a standalone procedure and in combination with coronary artery bypass grafting (CABG). The choice of the optimal surgical strategy depends on the individual characteristics of the patient, the severity of heart failure, the presence of comorbidities, and the anatomical features of the left ventricle. It should be emphasized that the need for left ventricular reconstruction is determined using modern imaging techniques, such as multi-slice computed tomography and cardiac magnetic resonance imaging, which allow for detailed visualization of the left ventricle's anatomy and help determine the optimal volume of surgical intervention. The postoperative period requires careful monitoring and rehabilitation, including medication therapy, physiotherapy, and assessment of left ventricular function.

The meta-analysis of the survival of patients who underwent surgical reconstruction of the left ventricle of the heart provided clinically significant information on the mid-term outcomes of this operation. The results of the studies showed that one year after the surgical intervention, the survival rate was 94% (95% CI: 90–98). The meta-regression analysis did not reveal statistically significant differences in the survival of patients undergoing surgical reconstruction of the left ventricle using the Dor procedure or SAVER, compared to patients who underwent surgical ventricular reconstruction using other surgical approaches ($p = 0.98$).

It should be emphasized that the prognosis for patients with post-infarction left ventricular aneurysms is largely determined by the baseline ejection fraction value. In the Artery Surgery Study (CASS), it was found that the 12-year survival rate for patients with an ejection fraction of less than 35% receiving medical treatment does not exceed 12%. In contrast, for patients with an ejection fraction between 35 and 50%, this rate is 54% [9].

Limitations

A comparative analysis of data between patients who underwent left ventricular reconstruction in conjunction with coronary artery bypass grafting and those who only had coronary artery bypass grafting could not be conducted. The reason was the lack of comprehensive information on this topic in scientific research.

In this systematic review, publications were analyzed regardless of the sample size of patients. The number of participants ranged from 14 to 207. It is possible that if we had limited the minimum number of participants, the results could have been different. Furthermore, one of the limitations can be considered the selection of studies in which patient observations were conducted for at least one year.

In the future, it seems reasonable to conduct a more detailed study of mitral valve surgeries, as well as to evaluate the effectiveness of different surgical methods for left ventricular reconstruction.

Conclusion

The meta-analysis showed that one year after surgery, survival rates are 94%, with statistically significant increases in ejection fraction and decreases in functional class of heart failure according to the NYHA scale. The studies did not reveal significant differences in patient survival and clinical outcomes one year after operations performed using different surgical methods. The results indicate the effectiveness of left ventricular surgical reconstruction, providing prolonged improvement in patients' functional status. However, it should be noted that there was significant heterogeneity among the studies.

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Мета-анализ среднесрочной выживаемости и клинических результатов хирургической реконструкции левого желудочка

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Аннотация. *Актуальность*. Постинфарктная аневризма левого желудочка значительно снижает продолжительность и качество жизни пациентов. Результаты сравнения разных способов хирургического восстановления левого желудочка неоднозначны и нередко противоречивы, что усложняет выбор эффективной стратегии лечения и возможность объективно оценить перспективу выживаемости таких пациентов. Цель мета-анализа — оценить выживаемость пациентов через 1 год после хирургической реконструкции левого желудочка, определить функциональный класс сердечной недостаточности и изучить морфо-функциональные характеристики сердца. Выполнить сравнительный анализ результатов мета-аналитической оценки выживаемости пациентов после хирургической реконструкции левого желудочка по методике DOR (SAVER), в сопоставлении с другими методами лечения. *Материалы и методы*. В результате систематического поиска по двум специализированным базам данных (PubMed, Google Scholar) отобрано 1875 статей. В окончательный анализ было включено 15 исследований. Общее количество пациентов в этих исследованиях составило 1089. В целях объективизации оценки эффективности разных хирургических подходов было сформировано две группы пациентов. В первой — проводилась только хирургическая реконструкция левого желудочка по методике Дора или операция SAVER (surgical anterior ventricular endocardial restoration); во второй — применялись и другие методы хирургической реконструкции левого желудочка, в зависимости от хирургической целесообразности. *Результаты и обсуждение*. Средний возраст обследованных пациентов составил 62.1 (95% CI: 60.2–64.1) года. В исследовании принимали участие 56% (95% CI: 42–69) мужчин. Аневризма передней локализации встречалась у 87% (95% CI: 74–99) пациентов. Среднее значение EuroSCORE соответствовало 9.7% (95% CI: 7.3–12.1). До операции у пациентов отмечался высокий функциональный класс сердечной недостаточности по NYHA [3 functional class (95% CI: 2.82–3.1)], низкая фракция выброса левого желудочка [31.3% (95% CI: 29.2–33.3)], расширение полостей сердца [EDVI — 131.7 mL/m^2 (95% CI: 113.1–150.2)]. Мета-анализ разности средних значений фракции выброса у пациентов до и через 1 год после операции свидетельствует о ее повышении на 10.1% (95% CI: 8.01–12.1, $p < 0.001$). Мета-анализ разности средних значений EDVI и функционального класса сердечной недостаточности по NYHA у пациентов до и через 1 год после операции показал снижение на 38.8 мл/м^2 (95% CI: 28.1–49.6, $p < 0.001$) и 1.52 (95% CI: 1.3–1.8, $p < 0.001$) соответственно. *Выводы.* Мета-анализ показал, что через год после операции выживаемость составляет 94%, при этом статистически значимо увеличивается фракция выброса и снижается функциональный класс сердечной недостаточности по шкале NYHA. Исследования не выявили значимых различий выживаемости пациентов и их клинических результатов через год после операций, выполненных разными хирургическими методами. Полученные результаты свидетельствуют об эффективности хирургической реконструкции левого желудочка, обеспечивающей пролонгированное улучшение функционального состояния пациентов. Однако необходимо отметить, что между исследованиями наблюдалась значительная гетерогенность.

Ключевые слова: Постинфарктная аневризма левого желудочка, хирургическая реконструкция желудочка, операция Дора, эндовентрикулопластика, среднесрочная выживаемость

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ОБЗОР
REVIEW

Хирургическая тактика при тяжелой травме и обморожениях в полярных регионах в условиях ограниченных ресурсов

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Аннотация. *Актуальность.* Тяжелая травма остается одной из ведущих причин предотвратимой смерти в мире. В условиях развитой инфраструктуры стандартом является раннее выполнение окончательного хирургического вмешательства в специализированном центре. В удаленных арктических поселениях, на полярных станциях и судах такая стратегия недостижима из-за дефицита ресурсов, отсутствия специалистов и задержек эвакуации, поэтому хирург и врач общей практики вынуждены принимать критические решения, от которых напрямую зависят исходы лечения. Цель. Обобщить международный опыт оказания хирургической помощи при тяжелой травме и обморожениях в полярных регионах, проанализировать применение принципов damage control surgery/damage control resuscitation (DCS/DCR) и prolonged field care (PFC) в условиях ограниченных ресурсов, а также показать роль телемедицины и сотрудничества в поддержке хирургических решений. *Материалы и методы*. Проведен нарративный (scoping) обзор литературы за 1990–2025 гг. по базам PubMed/MEDLINE, Embase, Scopus, РИНЦ и Cochrane Library, а также по национальным руководствам по военной, полевой и полярной медицине. Включались публикации по DCS/DCR/PFC, полярной хирургии, обморожениям, эвакуации, телемедицине и организации медицинской помощи в Арктике и Антарктике. *Результаты и обсуждение*. Показано, что принципы DCS/DCR, сформировавшиеся в военной хирургии, адаптируемы к полярным условиям и позволяют поэтапно вести пациентов с тяжелой травмой и обморожениями при длительной эвакуации и дефиците ресурсов. Ключевым становится выбор места и объёма вмешательства с учетом логистики, возможностей анестезиологии и реанимации, состава команды и рисков эвакуации в сложных метеоусловиях. Обоснована концепция “полярного хирургического модуля” как компактного автономного операционно-реанимационного блока, а также описаны подходы к сортировке и хирургической тактике при обморожениях в условиях длительной изоляции. *Выводы.* Поэтапная тактика лечения травмы с применением DCS/DCR/PFC в полярных регионах позволяет согласовать объём операции с реальными ресурсами и эвакуационными возможностями, снижая риск фатальных осложнений. Обобщенный опыт военно-полевой и полярной хирургии может использоваться при разработке протоколов помощи при тяжелой травме в северных регионах и формировать задел для дальнейших исследований травмы в высокогорных районах и перспективных космических миссиях.

Ключевые слова: тяжелая травма; обморожения, полярные регионы, хирургическая тактика, хирургия контроля повреждений (DCS), реанимация контроля повреждений (DCR), пролонгированное полевое ведение (PFC), военно-полевой травматизм, эвакуация, телемедицина, полярная медицина

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Surgical strategy for severe trauma and frostbite in polar regions under limited resource conditions

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Abstract. *Relevance.* Severe trauma remains one of the leading causes of preventable death worldwide. In well-resourced systems, early definitive surgery in a specialized trauma center is the standard of care. In remote Arctic settlements, polar stations and ships, this approach is often unattainable because of limited equipment and personnel, lack of specialists, and prolonged evacuation delays; therefore, a surgeon or general practitioner must make time-critical decisions that directly determine outcomes. Aim: To summarize international experience in surgical care for severe trauma and frostbite in polar regions, analyze the applicability of damage control surgery/damage control resuscitation (DCS/DCR) and prolonged field care (PFC) in resource-limited settings, and outline the role of telemedicine and inter-facility collaboration in supporting surgical decision-making. *Materials and methods.* A narrative (scoping) review of the literature (1990–2025) was performed using PubMed/MEDLINE, Embase, Scopus, RSCI, and the Cochrane Library, as well as national and institutional guidelines on military, field, and polar medicine. Publications addressing DCS/DCR/PFC, polar surgery, frostbite, evacuation, telemedicine, and organization of medical care in the Arctic and Antarctica were considered. *Results and Discussion.* Principles of DCS/DCR, originating from military surgery, are adaptable to polar conditions and enable staged management of severe trauma and frostbite when evacuation is delayed and resources are scarce. Key determinants include selecting the location and extent of intervention with respect to logistics, anesthesia and

critical care capacity, team composition, and evacuation risk in adverse weather. The concept of a “polar surgical module” is justified as a compact autonomous operating and critical care unit; approaches to triage and surgical tactics for frostbite during prolonged isolation are also discussed. *Conclusion*. A staged strategy using DCS/DCR/PFC in polar regions aligns operative scope with real resources and evacuation capabilities, reducing the risk of fatal complications. The synthesized experience from military-field and polar surgery can inform protocols for severe trauma care in northern regions and provide a foundation for further research in high-altitude environments and prospective space missions.

Keywords: severe trauma, frostbite, polar regions, surgical management, damage control surgery, damage control resuscitation, prolonged field care, combat-related trauma, evacuation, telemedicine, polar medicine

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Введение

Тяжелая травма остается одной из ведущих причин предотвратимой смертности в мирное и военное время. В классической модели травматологической помощи ключевым считается как можно более раннее выполнение окончательного хирургического вмешательства в условиях хорошо оснащенного стационара. Однако в ситуациях ограниченных ресурсов — на театре военных действий, в изолированных арктических поселках, на полярных станциях и удаленных островах — такая стратегия нередко оказывается невыполнимой: сроки эвакуации исчисляются часами и сутками, возможности анестезиологии и реанимации ограничены, а один хирург или врач общей практики вынужден принимать решения, от которых напрямую зависят исходы [1–7].

Ответом на эти вызовы стала концепция поэтапного лечения травмы с использованием damage control surgery (DCS — хирургия контроля повреждений), damage control resuscitation (DCR — реанимация контроля повреждений) и prolonged field care (PFC — пролонгированное полевое ведение). Эти подходы ориентированы на ранний контроль жизнеугрожающих нарушений и выполнение минимально достаточного объёма вмешательства на каждом уровне с последующим переносом окончательной хирургии в более подготовленный стационар [2–4, 8–11].

Отдельный пласт данных по оказанию помощи в условиях длительной изоляции и ограниченной эвакуации представлен в работах, посвященных хирургическим случаям и организации медицинской помощи на антарктических станциях, включая

телемедицинскую поддержку и описанные кейсы самопомощи [12–15]. Организационные и тактические аспекты медицинского обеспечения, а также оценка эффективности военно-медицинских систем и подходов к догоспитальной помощи при современных конфликтах дополняют рамку принятия решений в условиях ограниченных ресурсов [16–18].

Арктика и Антарктика представляют собой предельный вариант такой среды: крайне низкая плотность населения, сложные климатические условия, зависимость от авиационной эвакуации и длительные периоды фактической изоляции сочетаются с широким спектром патологии — от травм и обморожений до неотложной абдоминальной и гнойной хирургии [19–27]. При дефиците профильных специалистов и ограниченном анестезиологическом обеспечении именно тактический выбор — «выполнить ограниченное вмешательство на месте» или «стабилизировать и эвакуировать» — становится центральной задачей полярного хирурга.

Несмотря на наличие обзоров по военной травме и медицинскому обеспечению полярных регионов, вопросы хирургической тактики при тяжелой травме и обморожениях в полярных регионах, выбор объёма вмешательства и организационных моделей помощи чаще всего рассматриваются фрагментарно. Практикующему хирургу трудно сопоставить опыт разных стран и понять, какие элементы можно прямо перенести в его реальность [1–4, 19–32]. Настоящий обзор адресован хирургам, анестезиологам-реаниматологам и врачам скорой помощи, работающим или планирующим работу в условиях ограниченных ресурсов.

Цель настоящего обзора — обобщить международный опыт оказания хирургической помощи при тяжелой травме и обморожениях в полярных регионах, проанализировать применение принципов DCS/DCR/PFC в условиях ограниченных ресурсов, а также показать роль телемедицины и международного сотрудничества в поддержке хирургических решений: выполнять ограниченное вмешательство на месте или стремиться к максимально ранней эвакуации [1–18, 23–27].

Материалы и методы

Проведен нарративный (scoping) обзор литературы за период 1990–2025 гг. Поиск выполнялся в базах PubMed/MEDLINE, Embase, Scopus, Cochrane Library и РИНЦ, а также по спискам литературы в ключевых обзорах и руководствах по военной, полевой и полярной медицине и телемедицине [1–7, 12, 15, 18, 20–23, 26, 28–33]. Дополнительно учтены руководства и доктринальные документы по медицинскому обеспечению современных вооруженных конфликтов и операций в условиях ограниченных ресурсов [1–6, 8, 9, 16–18, 23–25], а также материалы национальных антарктических программ и работы по медицине Крайнего Севера [12, 15, 20–22, 28–32].

В обзор включались:

- международные и национальные руководства по военной и полевой хирургии, а также по концепциям DCS/DCR/PFC [1–11, 16–19, 23–27];
- работы по организации медицинской и хирургической помощи в Арктике и Антарктике, на удаленных островах и судах [12, 15, 20–22, 28–32];
- публикации по телемедицине и эвакуации в полярных регионах [13, 30–34];
- исследования по обморожениям и другим холодовым поражениям, включая данные полярных экспедиций и антарктических станций [2–4, 8–11, 20–22, 28–32, 35–40];
- клинические наблюдения и серии случаев, отражающие реальные сценарии полярной хирургии и длительной эвакуации [12–15, 22, 28–32, 34].

Поиск проводился с использованием комбинаций ключевых слов на английском и русском языках: severe trauma, damage control surgery, damage control resuscitation, prolonged field care, frostbite, cold injury, polar medicine, Arctic, Antarctic, evacuation, telemedicine, austere environment, полярная медицина, Арктика, Антарктика, тяжелая травма, обморожения, телемедицина, эвакуация и др. [1–18, 20–34].

Основное внимание уделялось публикациям, содержащим данные о структуре травмы, особенностях обморожений, возможностях хирургического вмешательства на разных уровнях медицинской

помощи, а также факторам, влияющим на хирургическое решение: сроки и способ эвакуации, оснащенность учреждений, опыт команды, доступность телемедицины и интенсивной терапии [12–15, 20–22, 28–32, 34].

Военно-полевая хирургия и концепции DCS/DCR/PFC

Эволюция damage control surgery и damage control resuscitation

Концепция damage control surgery (DCS) была сформулирована в начале 1990-х гг. Rotondo и соавт. как ответ на высокую летальность при экстренных вмешательствах у пациентов с массивной кровопотерей и выраженной коагулопатией [2]. Основная идея заключалась в выполнении ограниченного объёма операции, направленного на быстрый контроль кровотечения и загрязнения (контроль источника), с намеренным отказом от немедленного восстановления анатомии. После стабилизации в отделении реанимации и коррекции гипотермии, коагулопатии и ацидоза проводился второй этап — окончательная реконструктивная хирургия [2–4].

Параллельно развивалась концепция damage control resuscitation (DCR), ориентированная на раннюю гемостатическую ресусцитацию, минимизацию кристаллоидов, прицельное использование компонентов крови и коррекцию коагулопатии [3, 8, 13, 14]. В дальнейшем эти подходы были интегрированы в руководства Joint Trauma System и Tactical Combat Casualty Care (TCCC) и стали основой стандартизированных алгоритмов догоспитальной и госпитальной помощи при тяжелой травме [8, 11–13, 17].

DCS/DCR сместили акцент с попытки «идеальной» одномоментной операции на контроль физиологии (кровотечения, коагулопатии, гипотермии) и «разбиение» хирургии на два этапа: спасение жизни и последующую реконструкцию. В полярных условиях именно эта логика — минимально достаточное вмешательство вместо полного, но рискованного — оказывается критически важной.

1.2. Prolonged field care и опыт современных конфликтов

В современных конфликтах (Афганистан, Ирак, операции специальных сил) на первый план вышла проблема prolonged field care (PFC) — ситуации, когда тяжело раненый пациент вынужден находиться в условиях ограниченных ресурсов многие часы до эвакуации [9, 10, 12]. Принципы PFC включают:

- приоритет контроля кровотечения и дыхательных путей;
- раннее применение гемостатических средств и трансфузии крови/плазмы;
- поддержание температуры тела и профилактику гипотермии;
- мониторинг жизненно важных функций в полевых условиях [9–11, 15–17].

Анализ данных военной травмы показал, что систематическое внедрение DCS/DCR/PFC и стандартов TCCC (tactical Combat Casualty Care, тактическая помощь пострадавшим в бою) привело к снижению предотвратимой летальности и улучшению исходов в боевых действиях [11–13, 17, 18]. Для полярного хирурга это означает, что проверенные в боевых условиях алгоритмы могут служить готовым каркасом тактики в условиях Крайнего Севера, где время до травмоцентра сопоставимо с военной эвакуацией.

Особенности травмы и хирургической помощи в полярных регионах

Российская Арктика и Крайний Север

В российской Арктике и на Крайнем Севере сеть медицинских учреждений представлена фельдшерско-акушерскими пунктами, амбулаториями, небольшими районными больницами и несколькими межрайонными центрами, оснащенными операционными [20, 21]. Санитарная авиация позволяет эвакуировать пациентов в региональные и федеральные центры, но возможности эвакуации ограничены погодой, световым днем и доступностью бортов.

При тяжелой травме или острой хирургической патологии врач малой больницы должен решить, возможно ли локальное ограниченное вмешательство (например, лапаротомия с тампонадой, наложение стомы, фасциотомия) или нужно предпринимать попытку немедленной эвакуации [20, 26, 27]. В обоих случаях значимы гипотермия, трудности мониторинга и дефицит крови и препаратов. Для хирурга здесь принципиально важно не столько «уметь всё», сколько точно понимать пределы безопасного объёма операции в данных ресурсных условиях.

Норвегия и архипелаг Шпицберген (Лонгйирбюен, Баренцбург)

На Шпицбергене базовым учреждением является госпиталь в Лонгйирбюене, способный выполнять ограниченный объём экстренной хирургии и стабилизацию травмированных; российский поселок Баренцбург ориентирован на более простые вмешательства с последующей эвакуацией пациентов в Лонгйирбюен или на материковую Норвегию [21, 22, 29].

Трехлетний анализ травм, связанных в основном со снегоходами, показал, что большинство повреждений приходится на конечности, однако встречаются разрывы селезенки и почек, тяжелые переломы и ЧМТ; летальных исходов не зарегистрировано, что связывается с четко отлаженной системой эвакуации и готовностью госпиталя к экстренной хирургии [22, 29]. С точки зрения тактики это пример модели, где локальный уровень выполняет роль DCS-этапа, а материковые центры — этапа окончательной реконструкции.

Гренландия (Королевство Дания)

Медицинская система Гренландии представляет собой многоуровневую структуру: фельдшерские пункты и небольшие больницы в поселках, несколько более крупных региональных центров и возможность эвакуации в Данию при тяжелой патологии [21, 30, 31].

Телемедицина позволяет консультировать сложные случаи и выбирать между локальным вмешательством и эвакуацией. В серии наблюдений по острым неотложным состояниям телемедицинские консультации в ряде случаев позволили избежать эвакуации, а в других — стабилизировать пациентов до прибытия санитарной авиации [30, 31]. Для хирурга это означает, что решение о необходимости DCS или, наоборот, об отказе от операции принимается не в одиночку, а совместно с экспертами центра.

Антарктические станции

Антарктические станции разных стран обычно обслуживаются одним врачом (иногда хирургического профиля), который несет ответственность за весь спектр патологии — от стоматологии до экстренной хирургии [12, 15, 28]. Scoping review по хирургической эпидемиологии антарктических станций за 1904–2022 гг. показал, что наиболее частыми вмешательствами являются аппендэктомии, операции по поводу грыж, гнойная хирургия и травматологические процедуры [12, 28].

При невозможности эвакуации здесь часто реализуется крайняя форма DCS: ограниченные по объёму операции, выполнение манипуляций немедицинским персоналом под руководством врача, телемедицинская поддержка специалистов на «большой земле». В таких условиях именно строгая самоограниченность хирурга в выборе объёма вмешательства и поэтапность лечения определяют исход.

Север США и Канады

В северных регионах США и Канады (Аляска, север Канады) широко используются принципы PFC и DCR, заимствованные из военной медицины, в сочетании с воздушной эвакуацией на большие расстояния [9–11, 19, 21, 22, 25]. Здесь, как и в Арктике, ключевыми ограничивающими факторами являются погода, наличие бортов и длительное время доставки пациента в травмоцентр. Хирурги и врачи удаленных стационаров в Северной Америке работают в логике, близкой к полярной: локальный контроль повреждений + планируемая эвакуация в центр уровня I–II. Сравнительная характеристика моделей организации хирургической помощи в полярных регионах представлена в табл. 1.

Таблица 1

Сравнительная характеристика моделей организации хирургической помощи в полярных регионах

Регион / Страна	Базовый уровень помощи	Наличие хирурга	Возможности локальной хирургии	Время эвакуации в высокоспециализированный центр	Основные инструменты улучшения исходов
Российская Арктика и Крайний Север	ФАП, малые районные больницы, межрайонные центры	Не всегда (часто врач общей практики или анестезиолог, хирург по вызову)	Небольшие полостные операции, простая травматология, DCS-вмешательства по показаниям	Часы-сутки, зависит от погоды, наличия санавиации и расстояния	Принципы DCS/DCR, санавиация, телемедицина с федеральными центрами, обучение персонала
Норвегия / Шпицберген	Госпиталь Лонгйирбюена, амбулатория Баренцбурга	Дежурный врач с хирургическими навыками	Экстренная хирургия средней сложности, стабилизация тяжелых пациентов, подготовка к эвакуации	Как правило часы (до материковой Норвегии), возможны задержки из-за погоды	Четкая система эвакуации, развитая телемедицина, участие в национальной системе здравоохранения
Гренландия (Дания)	Малые больницы в городах, региональные центры	В ряде центров есть хирурги; в малых больницах — врачи общей практики	Базовая общая и травматологическая хирургия, DCS по показаниям	Часы-сутки до крупных центров и Дании	Телемедицина, стандартизированные протоколы эвакуации, интеграция в систему здравоохранения Дании
Антарктические станции разных стран	Один врач на станции (часто без узкой спец. по хирургии)	Обычно один врач, иногда с хирургическим опытом	Ограниченный спектр вмешательств (аппендэктомия, герниопластика, дренирование, простая травматология)	Сутки-недели, зависит от сезона, погоды и логистики	DCS-подход, телемедицина, международная кооперация, тщательный отбор персонала
Север США и Канады	Районные больницы, опорные пункты, региональные центры	В крупных центрах -хирурги и травматологи; в удаленных пунктах — врачи общей практики	Базовая общая и травматологическая хирургия, стабилизация состояния, подготовка к эвакуации	Часы-сутки до травмоцентров уровня I–II	Применение принципов PFC и DCR, развитая санитарная авиация, использование военных протоколов (TCCC и др.)

Table 1

Organisation of surgical care for severe trauma in selected polar regions

Region / Area	Basic level of medical facility	Surgical provider	Available surgical procedures	Evacuation time to a high-specialty center	Main tools to improve outcomes
Russian Arctic and Far North	Feldsher-midwife stations, small district hospitals, inter-district centers	Not always a surgeon; often a general practitioner or anaesthesi-ologist, surgeon on call	Minor abdominal procedures, simple trauma surgery, DCS interventions when indicated	Hours to days, depending on weather, availability of air medical transport and distance	DCS/DCR principles, air medical evacuation, telemedicine with federal centers, staff training
Norway / Svalbard	Longyearbyen Hospital, Barentsburg outpatient clinic	On-call physician with surgical skills	Emergency surgery of moderate complexity, stabilization of severely injured patients, preparation for evacuation	Usually hours (to mainland Norway); delays possible due to weather	Well-defined evacuation system, developed telemedicine, integration into the national health-care system
Greenland (Kingdom of Denmark)	Small hospitals in towns, regional centers	Surgeons in some centers; in small hospitals — general practitioners	Basic general and trauma surgery, DCS when indicated	Hours to days to large centers and to Denmark	Telemedicine, standardized evacuation protocols, integration into the Danish health-care system
Antarctic stations of different countries	One physician at the station (often without formal surgical specialty)	Usually a single physician, sometimes with surgical experience	Limited range of procedures (appendectomy, hernia repair, drainage, simple trauma surgery)	Days to weeks, depending on season, weather and logistics	DCS approach, telemedicine, international cooperation, careful selection and training of staff

Таблица 1 Continued

Region / Area	Basic level of medical facility	Surgical provider	Available surgical procedures	Evacuation time to a high-specialty center	Main tools to improve outcomes
Northern USA and Canada	Rural hospitals, outposts, regional centers	Surgeons and trauma surgeons in major centers; general practitioners in remote outposts	Basic general and trauma surgery, stabilization and preparation for evacuation	Hours to days to level I–II trauma centers	Application of PFC and DCR principles, well-developed aeromedical evacuation, use of military trauma protocols (e. g. TCCC)

Применение принципов DCS/DCR/PFC в полярных условиях

В полярных регионах концепции DCS/DCR/PFC становятся практическим инструментом адаптации помощи к реальным ресурсам. На уровне малых стационаров и полярных станций основной задачей является стабилизация пациента, контроль источника кровотечения и инфекционного загрязнения, минимизация операционной агрессии и обеспечение условий для дальнейшей эвакуации [1–7, 15–22, 24, 27].

Практические хирургические задачи полярного хирурга

В реальных условиях арктических стационаров и полярных станций круг вмешательств, выполняемых по принципам DCS, относительно типичен и включает:

- экстренную лапаротомию с тампонадой брюшной полости, контролем источника кровотечения и временным закрытием брюшной стенки (открытая лапаростома, вакуум-ассистированная повязка);
- спленэктомию при некупируемом кровотечении из селезенки;
- наружное дренирование и разгрузочные вмешательства при перфорации полых органов (формирование стом, выведение петли кишки) вместо сложных реконструкций и анастомозов;
- временную стабилизацию переломов (внешняя фиксация, скелетное вытяжение) при отсутствии условий для окончательного остеосинтеза;
- декомпрессивные вмешательства (фасциотомии при компартмент-синдроме, декомпрессивная краниотомия/краниэктомия в исключительных ситуациях при наличии минимального инструментария и опыта);
- обработку комбинированных и инфицированных ран с радикальным иссечением некротических тканей и открытым ведением раны [1–4, 5–7, 15–18, 21–22, 24].

Выбор конкретного объёма вмешательства определяется не только анатомией повреждения, но и ресурсами пункта: наличием крови и кровезаменителей, возможностями анестезии и мониторинга, квалификацией единственного хирурга или врача общей практики, а также прогнозируемыми сроками эвакуации [8–11, 15–17, 19–22, 27]. В этом контексте принципы DCS/DCR/PFC перестают быть абстрактной доктриной и превращаются в практический алгоритм принятия **конкретных хирургических решений —** от отказа от анастомоза в пользу стомы до выбора внешней фиксации вместо внутреннего остеосинтеза.

Температурный менеджмент тяжелой травмы в условиях холода

В полярных регионах проблема гипотермии приобретает ключевое значение: пострадавший часто поступает в стационар уже охлаждённым, а транспортировка и операционная не всегда обеспечивают адекватный тепловой режим. Гипотермия усиливает коагулопатию и метаболический ацидоз, формируя «летальную триаду» травмы и повышая риск неконтролируемого кровотечения и несостоятельности DCS-вмешательств [3, 18, 27]. Одновременно экспериментальные и клинические данные показывают, что контролируемое снижение температуры тела при массивной кровопотере может замедлять метаболизм и продлевать время,

доступное для хирургического контроля повреждений, что легло в основу концепции emergency preservation and resuscitation (EPR) [20, 35, 36]. В полярной практике эти два аспекта — профилактика случайной гипотермии и осторожное использование потенциала контролируемой гипотермии — должны рассматриваться как единая задача температурного менеджмента: активное согревание пациента, подогрев инфузий и компонентов крови, минимизация экспозиции, использование теплых операционных и, при критической задержке эвакуации, обсуждение возможности применения протоколов глубокой гипотермии EPR (emergency preservation and resuscitation, экстренное сохранение и реанимация в специализированных центрах) [18, 27, 35, 36].

Point-of-care диагностика (POCUS и экспресс-лаборатория)

Ограниченный доступ к КТ (компьютерная томография), круглосуточной лаборатории и рентгену делает point-of-care диагностику одним из ключевых инструментов полярного хирурга. Портативное ультразвуковое исследование у постели больного (point-of-care ultrasound, POCUS) позволяет выполнять FAST/eFAST-протоколы, оценивать наличие свободной жидкости, повреждения паренхиматозных органов, плевральные осложнения и базовые параметры функции сердца, а также контролировать эффективность DCS-вмешательств [8, 11, 22]. Дополнение POCUS экспресс-лабораторией (лактат, гемоглобин, гематокрит, коагуляция, кислотно-основное состояние) позволяет более обоснованно решать, возможно ли ограничиться локальным вмешательством или необходима срочная эвакуация в центр более высокого уровня [21, 22, 31, 37].

Современные обзоры подчеркивают, что POCUS в полевых и ресурсно-ограниченных условиях — от военных конфликтов до высокогорья и микрогравитации — повышает диагностическую точность и влияет на выбор хирургической тактики [9–11, 25, 31, 37]. Для полярного хирурга и врача общей практики освоение POCUS и базового набора point-of-care тестов становится таким же обязательным навыком, как владение типичными DCS-операциями.

Инфекции и сепсис в изолированных базах

Задержка эвакуации, ограниченный доступ к повторной хирургической санации и антибиотикам, высокая плотность проживания в зимующих коллективах и наличие инвазивных устройств (катетеры, дренажи) повышают риск ранних инфекционных осложнений после травмы и ургентных операций. В антарктических сериях наблюдений отмечена значительная доля гнойно-воспалительных заболеваний (раневые инфекции, абсцессы, флегмоны, пневмонии), нередко требующих повторных вмешательств и длительного наблюдения [12, 15, 28].

Для полярной хирургии принципиальны: максимально радикальная первичная хирургическая обработка ран, формирование стом вместо рискованных анастомозов, короткие рациональные курсы антибиотиков из ограниченного формуляра, строгий контроль за катетерами и дренажами, ранняя мобилизация пациента, а также использование телемедицины для раннего выявления признаков сепсиса и корректировки антибактериальной терапии [12, 15, 21, 28, 31]. При невозможности эвакуации именно сочетание адекватного DCS-вмешательства и грамотной противоинфекционной тактики определяет исход.

Обморожения и комбинированные холодовые травмы

В полярных регионах тяжелая механическая травма часто сочетается с локальными обморожениями и системной гипотермией: снегоходные и лыжные аварии, падения в полынью, травмы на палубе или льду, длительное пребывание на холодном ветру [20–22, 28–31]. В этих условиях переломы длинных костей, ЧМТ (черепно-мозговая травма) и повреждения мягких тканей нередко сопровождаются обморожениями кистей, стоп, лица и ушей, причем частота таких сочетаний возрастает по мере удаления от крупных стационаров и увеличения времени до эвакуации [20–22, 29–31].

С хирургической точки зрения обморожения требуют коррекции стандартной тактики damage control. На первичном этапе приоритетом остаются жизнеспасающие вмешательства:

остановка кровотечения, декомпрессия (включая фасциотомии при синдроме компартмента), ограниченная ревизия и туалет ран, стабилизация нестабильных переломов с помощью аппаратов внешней фиксации [20, 22, 27]. Радикальные некрэктомии и тем более ампутации на фоне глубоких обморожений, как правило, откладывают до стабилизации гемодинамики, согревания и формирования четкой демаркационной линии; на полярном этапе допустимы только ограниченные некрэктомии и открытое ведение раны при угрозе инфекции или некротического сепсиса [20, 22, 27, 35].

Временное хирургическое ведение включает применение вакуум-терапии (при наличии оборудования), использование временных покрытий (кожные и синтетические покрытия, «биологические повязки»), этапные ревизии раны с интервалом 24–72 часа и планирование уровня ампутации или реконструктивного вмешательства после телемедицинской консультации с центром, имеющим опыт хирургии холодовых поражений [20–22, 30, 31, 33, 35]. В проектируемые протоколы полярного хирургического модуля целесообразно включать чек-листы оценки степени обморожения, критерии для срочной хирургической декомпрессии и ранних некрэктомий, а также стандартизированные сроки и объемы отсроченных ампутаций и реконструкций, согласованные с опорным центром. Ключевые клинические степени обморожения и практические ориентиры для принятия решений приведены в табл. 2.

Таблица 2

Клинические степени обморожения и ключевые ориентиры для хирурга в полярных условиях

Степень обморожения	Клинические признаки (после согревания)	Значение для хирурга / тактика в полярных условиях
I степень (поверхностная)	Побледнение, цианоз кожи, преходящая анестезия, отек; пузырей нет, чувствительность частично восстанавливается	Как правило, консервативное ведение, хирургическое вмешательство не требуется. Важно исключить более глубокие зоны, документировать объем поражения и не перегружать полярный модуль пациентами, не требующими оперативной помощи.
II степень (поверхностная с пузырями)	Пузыри с прозрачным содержимым, умеренный отек, выраженная болезненность после согревания; сохранение капиллярного кровотока	Хирургическая тактика минимальна: вскрытие напряженных пузырей при угрозе разрыва, асептическая повязка, иммобилизация. Радикальные некрэктомии и ампутации не показаны. Пациент может оставаться на полярном этапе при наличии возможности наблюдения и регулярных перевязок.
III степень (глубокая)	Пузыри с геморрагическим содержимым, выраженный отек, снижение или отсутствие чувствительности, цианотичная или черная окраска кожи, тугорелые («древесные») ткани.	Требуется этапное хирургическое ведение: ограниченные некрэктомии при признаках инфекции или влажной гангрены, открытое ведение раны, при наличии оборудования — VAC-терапия. Уровень окончательной ампутации, кожно-пластические вмешательства и остеосинтез по возможности откладывают до формирования демаркационной линии и телемедицинской консультации со специализированным центром.
IV степень (тотальный некроз)	Глубокий некроз кожи, подкожной клетчатки, мышц и/или костей; «мумификация» сегмента, отсутствие чувствительности и кровотока, укорочение при поражении пальцев	В условиях полярного модуля приоритет — стабилизация пациента и профилактика сепсиса. Окончательный уровень ампутации (на уровне жизнеспособных тканей проксимальнее зоны некроза) планируют после согревания, повторных ревизий и консультации опорного центра. На первичном этапе допустимы только срочные некрэктомии при инфекционных осложнениях, дренирование, временная внешняя фиксация при сочетании с переломами и подготовка к эвакуации.
Комбинированная травма + обморожение (любая степень)	Сочетание переломов, ЧМТ, травмы груди/живота и различных степеней обморожения конечностей, лица, ушных раковин; часто — выраженная системная гипотермия	Объем вмешательств на зоне обморожения подчинен принципам damage control: приоритет — остановка кровотечения, декомпрессия, наружная фиксация переломов, контроль источника перитонита. Агрессивные ампутации и обширные некрэктомии на холодовых сегментах откладываются до стабилизации пациента и перевода в специализированный центр; обязательно активное согревание и телемедицинская консультация.

Table 2

Clinical degrees of frostbite and key surgical decision points for the surgeon in polar conditions

Degree of frostbite	Clinical signs (after rewarming)	Implications for the surgeon / tactics in polar conditions
Grade I (superficial)	Pallor and cyanosis of the skin, transient anesthesia, oedema; no blisters, sensation partially returns.	Management is usually conservative; surgical intervention is not required. It is important to exclude deeper zones of injury, document the extent of frostbite and avoid overloading the polar module with patients who do not need operative care.
Grade II (superficial with blisters)	Clear fluid-filled blisters, moderate oedema, marked pain after rewarming; capillary refill is preserved.	Surgical tactics are minimal: decompress tense blisters at risk of rupture, apply aseptic dressings and immobilise the affected part. Radical necrectomies and amputations are not indicated. The patient can remain at the polar level provided that observation and regular dressing changes are feasible.
Grade III (deep)	Haemorrhagic blisters, marked oedema, reduced or absent sensation, cyanotic or black skin, firm «wooden» tissues.	Staged surgical management is required: limited necrectomies when there are signs of infection or wet gangrene, open wound management, and VAC therapy if equipment is available. The definitive level of amputation, reconstructive procedures and osteosynthesis should, whenever possible, be postponed until a clear demarcation line forms and a telemedicine consultation with a specialist center has been obtained.
Grade IV (total necrosis)	Deep necrosis of the skin, subcutaneous tissue, muscles and/or bones; «mummification» of the segment, absence of sensation and blood flow, shortening of the digit in finger involvement.	In the polar module the priority is to stabilize the patient and prevent sepsis. The definitive level of amputation (at the level of viable tissues proximal to the necrosis zone) is planned after rewarming, repeated inspections and consultation with a referral center. At the primary stage only urgent necrectomies for infectious complications, drainage, temporary external fixation in cases with associated fractures and preparation for evacuation are acceptable.
Combined trauma + frostbite (any degree)	Combination of fractures, traumatic brain injury, chest/abdominal trauma and various degrees of frostbite of the extremities, face and ears; pronounced systemic hypothermia is common	Interventions on frostbitten areas follow damage-control principles: priorities are hemorrhage control, decompression, external fracture fixation and control of intra-abdominal sepsis. Aggressive amputations and extensive necrectomy on cold-injured segments are postponed until the patient is stabilized and transferred to a specialized center; active rewarming and telemedicine consultation are mandatory.

Телемедицина в полярной хирургии

Телемедицина является ключевым инструментом поддержки хирургов и врачей общей практики в изолированных регионах, где доступ к специализированной помощи ограничен, а эвакуация может быть отложена на часы и сутки [28–32]. Для полярной медицины она фактически становится «виртуальным многопрофильным консилиумом», к которому один-единственный врач может подключаться из арктического посёлка, с борта судна или антарктической станции. При этом телемедицина прямо влияет на хирургическую тактику: позволяет уточнить показания к операции, скорректировать объём вмешательства и оптимально спланировать эвакуацию.

Арктическая зона: Россия и другие страны Севера

В Арктической зоне России телемедицинские консультации используются для дистанционной интерпретации диагностических данных, обсуждения тактики при ургентной патологии и принятия решения об эвакуации [28]. На практике это включает:

- передачу ЭКГ (электрокардиография), рентгенограмм и результатов УЗИ (ультразвуковое исследование) в региональные и федеральные центры;
- телеконсилиумы по поводу острых хирургических заболеваний (аппендицит, перфорация полого органа, ущемленные грыжи) и травматологических повреждений;
- совместное с врачами старшего уровня решение, возможна ли локальная операция по прин-

ципам damage control или необходимо максимально быстро организовывать эвакуацию.

Систематический обзор телемедицинских сервисов в Арктике показывает, что телемедицина применяется для широкого спектра задач — от телерадиологии и телеконсультаций до дистанционного мониторинга пациентов в экспедициях [33]. В ряде стран (Норвегия, Канада, Дания/Гренландия, северные регионы США) описаны модели, где врач в удаленном поселке или на судне может круглосуточно связаться с травматологом, хирургом или анестезиологом университетского госпиталя, передать им изображения и видео, а затем реализовать рекомендованный объём вмешательства или подготовить пациента к эвакуации [29–31, 33].

Хирургический акцент. В арктических условиях телемедицина позволяет не только уточнять диагноз, но и разделить ответственность за выбор объёма вмешательства между местным врачом и экспертами опорного центра. Для хирурга малой больницы это снижает риск как чрезмерно агрессивной, так и недостаточной операции и облегчает решение в пользу DCS или отсроченной окончательной хирургии после эвакуации. Следовательно, на арктическом направлении телемедицина решает сразу несколько задач:

- диагностическую (телерадиология, дистанционное УЗИ, оценка тяжести травмы);
- тактическую (выбор между локальным DCS-вмешательством и эвакуацией);
- организационную (оптимизация маршрутизации и времени старта санитарной авиации).

Телемедицина на антарктических станциях

На антарктических станциях телемедицинская поддержка стала стандартом. Японские и британские программы описывают регулярные телеконсилиумы с университетскими клиниками, использование телерадиологии, дистанционной ЭКГ и видеосвязи для обсуждения хирургических случаев [30, 31].

Фактически один врач на станции получает возможность:

- консультироваться с хирургами, анестезиологами-реаниматологами, травматологами и другими специалистами;
- обсуждать показания к операции, её объём и технику в условиях ограниченных ресурсов;
- получать поддержку при ведении пациентов в послеоперационном периоде и при осложнениях.

При этом телемедицина выступает не только как инструмент выбора тактики, но и как средство психологической поддержки врача, который несёт единоличную ответственность за исход тяжёлых случаев в полной изоляции.

Хирургический акцент. Для врача антарктической станции телемедицина часто является единственным способом получить подтверждение или коррекцию решения «оперировать / не оперировать». В условиях, когда повторная эвакуация или повторное вмешательство могут быть невозможны, такая поддержка снижает вероятность фатальных ошибок при перитоните, травме живота или тяжёлой черепно-мозговой травме.

Особые формы полярной телемедицины и самолечения

Отдельный, во многом показательный эпизод телемедицинской помощи в условиях полной изоляции описан Taub и соавт.: врач, работавший на станции на Южном полюсе, проводил самолечение под дистанционным наблюдением специалистов на «большой земле», используя телемедицинские консультации для выбора тактики и контроля за своим состоянием [32]. Этот случай подчёркивает, что телемедицина в полярных регионах может использоваться не только для поддержки врачей в отношении других пациентов, но и для организации относительно безопасного самолечения при отсутствии возможности эвакуации и замены медицинского персонала.

В других публикациях описаны:

- дистанционное сопровождение пациентов с ОКС (острый коронарный синдром) на борту судов в антарктических водах;
- телеконсультации при подозрении на острый аппендицит или осложнённые травмы, когда решение об операции или выжидательной тактике принималось совместно судовым врачом и береговыми специалистами;

- мониторинг состояния участников экспедиций с использованием телеметрии и периодических телеконсультаций [30–32].

Хирургический акцент: наличие телемедицинской поддержки позволяет расширить допустимый диапазон выжидательной тактики, не пропуская при этом момента, когда пациента всё-таки необходимо оперировать или срочно эвакуировать. Это критично для условий, где повторная эвакуация или повторная операция могут быть невозможны.

В полярной хирургии телемедицина не заменяет очного хирурга, но делает его «частью» распределённой команды, связывая отдалённый пост с многопрофильным центром и позволяя переносить опыт крупного стационара в условия одной палаты или маленькой операционной на краю света.

Перспективы искусственного интеллекта, систем поддержки решений и телероботики

В рамках полярной медицины перспективным направлением является использование систем поддержки принятия решений и алгоритмов машинного обучения для триажа и тактического планирования при травме. На основе данных о механизме повреждения, жизненно важных показателях и времени до эвакуации такие системы могут предлагать врачу варианты: локальное DCS-вмешательство, отсроченная операция или немедленная эвакуация, оставаясь при этом надстройкой над клиническим мышлением, а не его заменой [30–32, 41–44].

Дополнением к телемедицине выступают экспериментальные модели телероботики: дистанционно управляемое ультразвуковое исследование, робот-ассистированные манипуляции и тренажёры с обратной связью, позволяющие отрабатывать навыки DCS-операций в условиях ограниченных ресурсов [41–44]. Пока эти технологии остаются на уровне пилотных проектов, однако для полярной хирургии они потенциально могут стать способом «доставить» экспертизу крупного центра на изолированный пост и представляют одно из ключевых направлений будущих исследований.

Международное сотрудничество в полярной хирургии

Международное сотрудничество является вторым ключевым опорным столбом полярной хирургии наряду с телемедициной. Практически ни одна страна не в состоянии обеспечивать полный спектр высокотехнологичной помощи и эвакуации во всех точках Арктики и Антарктики только своими силами; поэтому маршруты медицинской эвакуации, телеконсилиумы и обучение персонала изначально строятся как многосторонние.

Арктическое сотрудничество

В Арктике действуют международные соглашения по поиску и спасению (SAR), санитарной авиации и обмену ресурсами. При крупных инцидентах медицинская помощь часто оказывается силами нескольких стран, а маршруты эвакуации тяжёлых пациентов проходят через ближайшие арктические аэродромы и порты, независимо от государственных границ.

Для северных регионов России международное сотрудничество практически проявляется в:

- координации поисково-спасательных операций (SAR) в приграничных морских акваториях;
- обмене опытом по организации санавиации и применению DCS/DCR-подходов в отдалённых стационарах;
- участии полярных врачей в международных семинарах и тренингах по травме в экстремальных условиях.

Телемедицинские сети, описанные выше, фактически являются рабочим инструментом реализации этих договорённостей: они позволяют оперативно консультировать пациентов, выбирать маршруты эвакуации и согласовывать объём вмешательства между несколькими центрами.

Хирургический акцент. Для хирурга в арктическом стационаре международное сотрудничество означает возможность опираться не только на собственный опыт и ресурсы, но и на поддержку центра более высокого уровня, в том числе находящегося за пределами своей страны.

Антарктида как модель многостороннего взаимодействия

Антарктида представляет собой уникальную модель многосторонней кооперации. Станции разных стран функционируют в рамках общей договорной базы, предусматривающей:

- обмен информацией о медицинской обстановке и возможностях помощи;
- взаимную поддержку в экстренных ситуациях (эвакуация тяжёлых пациентов через ближайшую по расположению станцию, независимо от флага);
- использование общих логистических ресурсов (судов, авиации) для транспортировки пациентов и медикаментов [12, 15, 28, 32, 33].

Телемедицинские решения, разработанные для полярных экспедиций, включают согласованные форматы передачи изображений и данных мониторинга, общие протоколы телеконсультаций и участие в многоцентровых исследованиях полярной медицины [30–33].

Международное сотрудничество в Антарктиде включает три уровня:

- **Стратегический** — договоры и соглашения, определяющие принципы взаимопомощи и использования инфраструктуры.
- **Оперативный** — соглашения между программами отдельных стран, фиксирующие конкретные маршруты эвакуации и обмен ресурсами.
- **Клинический** — ежедневные телеконсилиумы и консультации по реальным пациентам, когда хирурги и анестезиологи из разных стран совместно принимают тактические решения.

Хирургический акцент. Наличие многосторонних соглашений и отлаженных телемедицинских каналов позволяет врачу антарктической станции применять принципы DCS, рассчитывая на последующую эвакуацию и реконструкцию в центре более высокого уровня, даже если он находится под флагом другой страны.

Визуализация сети сотрудничества

Основные направления международного взаимодействия, маршруты эвакуации и ключевые телемедицинские узлы в Арктике и Антарктиде могут быть представлены в виде единой сети, объединяющей национальные программы и полярные станции [12, 15, 28, 32, 33].

Клинические и организационные примеры

Наиболее известным клиническим примером хирургического вмешательства в полярных условиях остаётся самооперация Л.А. Рогозова по поводу острого аппендицита на антарктической станции. Ограниченный объём вмешательства, выполнение лишь жизненно необходимой операции в условиях минимального набора инструментов и отсрочка реконструктивного этапа хорошо иллюстрируют принцип DCS: устранить непосредственную угрозу жизни и не выходить за пределы возможностей среды.

Другим широко цитируемым примером является история врача J. Nielsen на станции Амундсен-Скотт на Южном полюсе. В период полярной зимы, когда эвакуация была полностью невозможна, у неё выявили подозрительное образование в молочной железе. Диагностика и выбор тактики лечения целиком опирались на телемедицину: по каналам связи проводились телеконсилиумы с хирургами и онкологами, под их контролем Nielsen выполнила под местной анестезией биопсию и начала противоопухолевое лечение, препараты и расходные материалы для которого были доставлены авиасбросом. До возобновления полётов наблюдение и коррекция терапии также осуществлялись дистанционно [13, 33]. Этот сценарий показывает, что в условиях полной изоляции телемедицина может частично компенсировать отсутствие очного специализированного консилиума и обеспечить проведение необходимых малых хирургических вмешательств и сложного лечения без ожидания восстановления транспортного сообщения. В обзорах по полярной медицине описаны и другие ситуации, когда телемедицина использовалась для поддержки сложных решений: дистанционное ультразвуковое исследование, оценка показаний к лапароскопии или лапаротомии, выбор объёма вмешательства при ограниченном анестезиологическом обеспечении и возможной задержке

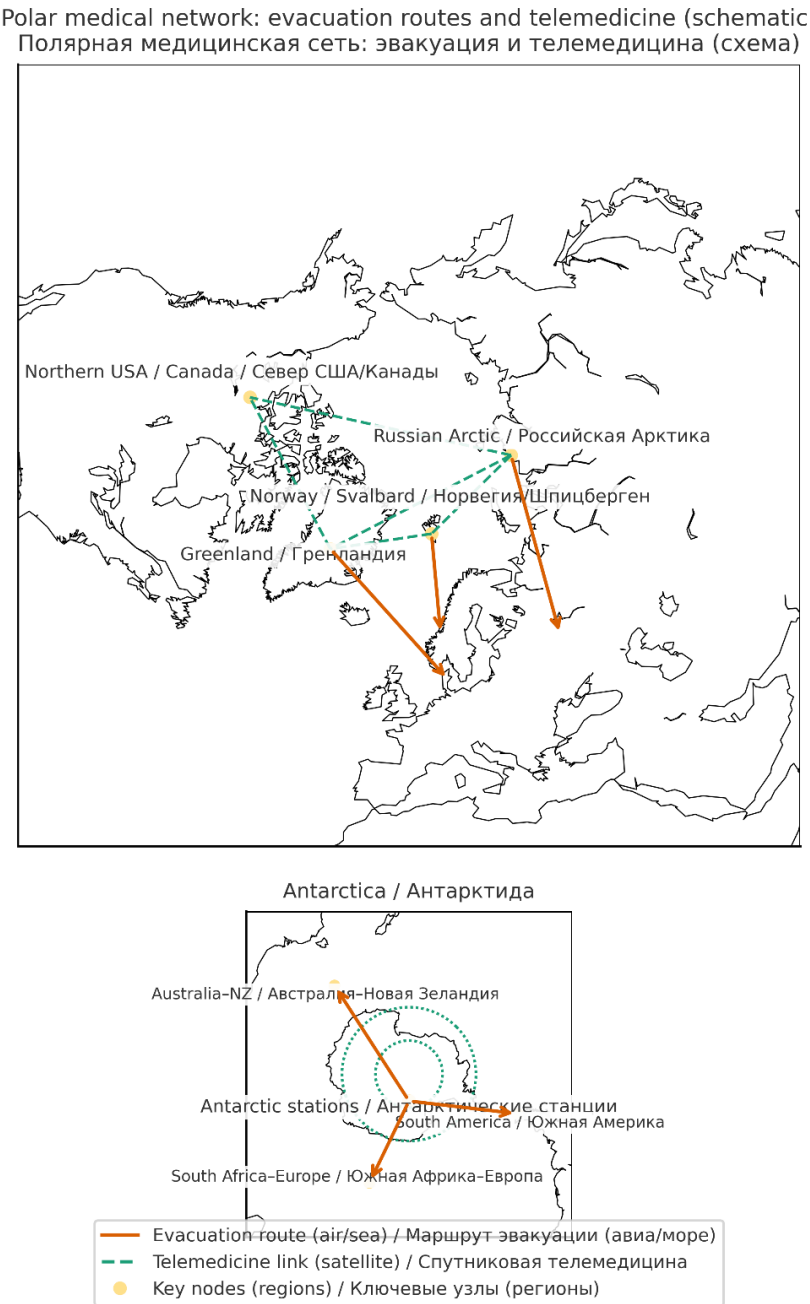

Рис. 1. Полярная медицинская сеть: маршруты эвакуации и телемедицины (схема)

Примечание: На схеме показаны ключевые регионы Арктики (Российская Арктика, Норвегия/Шпицберген, Гренландия, Аляска, Северная Канада) и отдельные станции в Антарктиде, соединённые линиями возможной эвакуации и телемедицинских каналов. Стрелками обозначены вероятные маршруты транспортировки пациентов и направления телеконсилиумов между арктическими узлами и антарктическими станциями.

Fig. 1. Polar medical network: evacuation routes and telemedicine links (schematic)

Note: The map shows key Arctic regions (Russian Arctic, Norway/Svalbard, Greenland, Alaska, Northern Canada) and selected Antarctic stations, connected by potential evacuation routes and telemedicine links. Arrows indicate probable patient transfer pathways and directions of teleconsultations between Arctic hubs and Antarctic stations.

эвакуации. Часть этих сценариев отрабатывалась в виде симуляций с задержкой сигнала, имитирующей спутниковую связь [12, 28, 33].

Кардиологический опыт также демонстрирует роль телемедицины: удалённое интерпретирование ЭКГ и эхокардиографии используется для решения, следует ли выполнять на месте минимально инвазивное вмешательство, продолжать консервативную терапию или инициировать немедленную эвакуацию, не подвергая пациента неоправданному риску транспортировки или операции.

Крупные серии наблюдений показывают, как эти подходы реализуются в повседневной практике при острых хирургических состояниях (острый живот, травма, осложнённые инфекции). Широкое использование телемедицинских консультаций, стандартизированных протоколов DCS/DCR и поэтапного планирования эвакуации ассоциировано с снижением летальности и частоты осложнений при сохранении приемлемого уровня риска на каждом этапе дистанционного обсуждения и динамического наблюдения [30–32].

Хирургический акцент. Перечисленные клинические примеры демонстрируют общий принцип: в полярной среде ключевым ресурсом является не набор инструментов, а организация маршрута пациента и доступ к экспертному мнению. DCS/DCR/PFC, поддержанные телемедициной и международным взаимодействием, позволяют выбирать минимально достаточный объём вмешательства с приемлемым уровнем риска на каждом этапе.

Концепция полярного хирургического модуля

Опыт военно-полевой хирургии и полярной медицины позволяет сформулировать концепцию стандартизированного **«полярного хирургического модуля»** — компактного блочного подразделения, способного обеспечить выполнение жизнеспасающих вмешательств по принципам DCS/DCR/PFC в условиях Крайнего Севера, Антарктики и других изолированных регионов [1–4, 8–12, 15, 19–21, 28–31, 33].

С практической точки зрения такой модуль представляет собой сочетание:

- **приёмно-реанимационной зоны**, где выполняются сортировка, первичная оценка по принципам ABCDE, интенсивная терапия и реализация DCR (контроль дыхательных путей, гемостатическая ресусцитация, профилактика гипотермии) [3, 8–11, 17, 18, 23–25, 27];
- **малой операционной**, оснащённой для выполнения ограниченного спектра вмешательств damage control (лапаротомия с тампонадой, спленэктомия, формирование стом, внешняя фиксация переломов, фасциотомии, дренирующие операции) [1–4, 6, 7, 15, 19, 20, 22, 26, 27];
- **зоны кратковременного наблюдения**, где пациент может находиться до эвакуации или перевода на следующий этап [12, 15, 20–22, 28, 30, 31];
- **технического блока**, включающего систему подогрева инфузионных растворов, минимальный набор стерилизационного оборудования, кислород, аппараты ИВЛ и мониторинга [15, 20–22, 26, 27];
- **узла связи и телемедицины**, обеспечивающего круглосуточный доступ к телеконсилиумам с крупными центрами [13, 28–31, 33, 34].

Ключевой принцип полярного хирургического модуля **— ориентация на DCS, а не на «полный» объём хирургии.** Оборудование и логистика подбираются исходя из необходимости быстро выполнить ограниченное, но жизнеспасающие вмешательства в условиях дефицита времени, крови и анестезиологических ресурсов, а не из стремления к универсальности любой ценой [2–4, 6, 8–11, 17–19, 23–25].

Состав оснащения модуля может включать:

- базовый набор инструментов для лапаротомии и тампонады брюшной полости;
- набор для наружной фиксации длинных костей и таза;
- инструменты для выполнения трепанации или декомпрессивной краниотомии в исключительных ситуациях;
- оборудование для регионарной анестезии и базовой общей анестезии;

- расходные материалы для активного согревания пациента, согревания инфузий и крови;
- комплект средств для быстрой трансфузии и, при возможности, заготовки крови на уровне модуля [1–4, 6, 7, 15, 19, 20, 22, 26, 27].

Отличительной особенностью полярного хирургического модуля является тесная интеграция с телемедицинскими системами. Рабочее место хирурга или врача общей практики предполагает возможность:

- передачи в реальном времени ЭКГ, УЗИ, рентгеновских и, при наличии, КТ-изображений;
- видеосвязи с хирургами, анестезиологами и травматологами опорных центров;
- совместного планирования объёма вмешательства (например, выбор в пользу стомы, а не анастомоза; наружной фиксации, а не внутреннего остеосинтеза) [13, 28–31, 33, 34].

В перспективе концепция полярного хирургического модуля может быть использована как **унифицированная платформа** для проектирования:

- стационаров в удалённых арктических посёлках;
- медицинских блоков научно-исследовательских станций;
- хирургических модулей для экспедиционных кораблей и судов снабжения;
- прототипов автономных медицинских модулей для высокогорных лагерей и длительных космических миссий [12, 15, 20–22, 24, 28, 30, 31, 33, 34].

Полярный хирургический модуль представляет собой не только архитектурное или инженерное решение, но и **концентрированное воплощение принципов DCS/DCR/PFC** в структурированном пространстве, где каждый метр и каждый прибор подчинён задаче сохранения жизни пациента до передачи его в центр более высокого уровня [1–4, 6, 8–11, 17–19, 23–25, 28–31, 33].

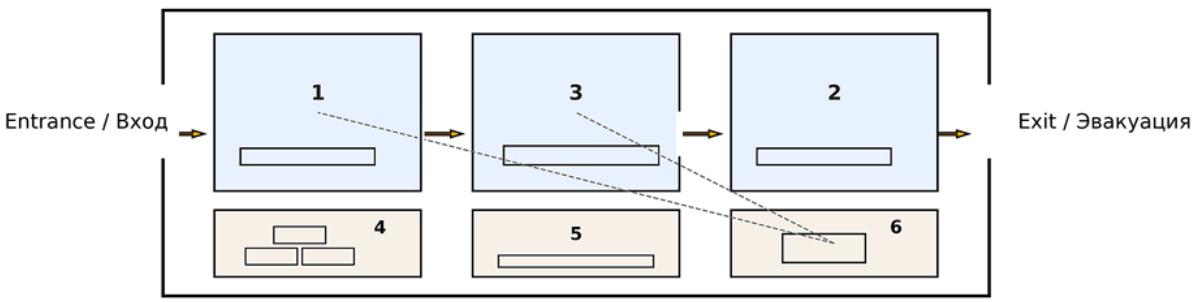

Рис. 2. Полярный хирургический модуль: схематическое устройство компактного контейнерного блока

Примечание: Модуль разделён на шесть пронумерованных зон: (1) реанимация и сортировка с проведением ABCDE-оценки, DCR и гемостатической ресусцитации; (2) зона кратковременного наблюдения перед эвакуацией или переводом; (3) операционная для вмешательств в формате damage-control surgery (DCS); (4) склад и логистическая зона для запаса расходных материалов, тёплой одежды, носилок и резервного оборудования. Стрелками показан типичный путь пациента от входа через реанимацию и DCS к наблюдению и дальнейшей эвакуации; (5) технический блок с системами подогрева инфузий и крови, источниками кислорода, аппаратами ИВЛ, мониторинга и базовой стерилизации; (6) узел телемедицины для телеконсилиумов и передачи ЭКГ, УЗИ, рентген- и КТ-изображений в опорные центры. Нумерация зон соответствует функциональному назначению, а не линейному расположению; маршрут пациента: Entrance → 1 → 3 → 2 → Exit.

Fig. 2. Polar surgical module: schematic layout of functional zones in a container-based unit

Note: The module is divided into six numbered areas: (1) resuscitation and triage zone for ABCDE assessment, DCR and haemostatic resuscitation; (2) short-term observation bay before evacuation or transfer; (3) operating room for damage-control surgery (DCS); (4) storage and logistics area for consumables, warm clothing, stretchers and reserve equipment. Arrows indicate the typical patient pathway from entrance through resuscitation and DCS to observation and further evacuation; (5) technical block with fluid and blood warming systems, oxygen supply, ventilators, monitoring and basic sterilization; (6) telemedicine unit providing real-time teleconsultations and transfer of ECG, ultrasound and X-ray/CT images to higher-level centers. Zone numbering reflects function rather than left-to-right placement; patient pathway: Entrance → 1 → 3 → 2 → Exit.

Практические задачи полярного хирурга

В практической работе полярного хирурга или врача-универсала ключевым становится не столько владение максимально широким спектром оперативных техник, сколько умение выбрать минимально достаточный и безопасный объём вмешательства в конкретной ресурсной ситуации. Наиболее типичные задачи включают:

- **Принятие решения о месте и времени операции.** Выбор между немедленным вмешательством на станции/в малом стационаре и отсроченной операцией в опорном центре с учётом времени эвакуации, погодных условий и состояния пациента.
- **Выполнение ограниченных DCS-вмешательств.** Лапаротомия с тампонадой и временным закрытием брюшной полости, спленэктомия, формирование стом, внешняя фиксация переломов, фасциотомии и радикальная хирургическая обработка ран в условиях ограниченного инструментария и анестезиологических ресурсов [1–4, 5–7, 15–18, 21–24].
- **Управление риском осложнений при невозможности эвакуации.** Оценка допустимой степени «недолеченности» (например, выбор в пользу стомы вместо анастомоза), профилактика инфекционных и тромбоэмболических осложнений, активная борьба с гипотермией и коагулопатией [3, 8, 13–16, 23].
- **Интеграция телемедицинской поддержки в тактику.** Запрос телеконсультаций, дистанционная интерпретация данных визуализации (ЭКГ, УЗИ, КТ), совместное с экспертами планирование операции и послеоперационного наблюдения [28–33].
- **Организационная роль.** Координация работы команды (даже если она включает в себя немедицинский персонал), распределение ресурсов, ведение документации для последующего анализа и обучения.

Управление болью и сознанием при дефиците ресурсов

Отдельной задачей является управление болью и сознанием при дефиците ресурсов. В полярных условиях далеко не всегда доступны ингаляционные анестетики, многоуровневая инфузионная аналгезия и мониторинг глубины седации; при этом пациенты часто находятся в пути многие часы или даже сутки. Руководства по тактической помощи пострадавшим в бою и полевой анестезиологии рекомендуют опираться на комбинации кетамина, опиоидов, нестероидных противовоспалительных средств и регионарной анестезии, адаптированные к возможностям конкретного пункта [5, 6, 18, 19, 23]. Для полярных стационаров целесообразно заранее отработать стандартные схемы анальгезии и седации для типичных сценариев (нестабильный пациент с тяжёлой травмой, длительная эвакуация, повторные санационные операции) и обучить персонал распознавать ранние признаки передозировки, делирия и дыхательной недостаточности на фоне холода, гипоксии и недосыпания [18, 20, 23, 24].

Планирование возвращения к профессиональной и физической активности

Ещё одна недооценённая область — планирование возвращения к профессиональной нагрузке (return-to-duty / return-to-climb) у полярников, военнослужащих, альпинистов, моряков и спасателей. Даже после успешно выполненного DCS-вмешательства и реконструкции пациент может иметь длительные ограничения по нагрузке, работе в холоде, на высоте или в условиях изоляции. Долгосрочные наблюдения за участниками полярных и высотных экспедиций показывают, что травмы опорно-двигательного аппарата и последствия хирургических вмешательств существенно влияют на возможность продолжать работу по специальности [21, 22, 28]. Это подчёркивает необходимость регистров, оценивающих не только выживаемость, но и функциональные исходы и способность возвращения к прежнему уровню активности в экстремальных профессиях, включая высокогорный и космический компонент будущих миссий [17, 21, 28, 39, 40].

Человеческий фактор и когнитивная нагрузка

Отдельным ограничивающим звеном полярной хирургии выступает человеческий фактор. Исследо-

вания команд, выполняющих травматологическую реанимацию, показывают, что качество коммуникации, распределение ролей, ситуационная осведомлённость и лидерство напрямую влияют на полноту выполнения протоколов и частоту ошибок, нередко не меньше, чем уровень технического оснащения [44]. В экспериментальных работах предложены количественные индикаторы согласованности действий команды и продемонстрировано, что целевые тренинги и симуляционные занятия улучшают координацию и объективные показатели качества помощи при тяжёлой травме [44].

В полярных условиях к этим факторам добавляются хронический недосып, полярная ночь, изоляция, ограниченный состав команды и необходимость совмещать несколько ролей (хирург, анестезиолог, организатор эвакуации). Современные обзоры по human factors подчёркивают, что подобная комбинация повышает когнитивную нагрузку, способствует срывам внимания и увеличивает риск тактических ошибок, особенно при редких, но критических сценариях [45]. Это делает обязательными использование простых чек-листов, заранее отработанных алгоритмов, регулярных коротких симуляционных тренингов и активное внедрение когнитивных «подсказчиков» (в том числе основанных на ИИ), которые не заменяют клиническое мышление, но страхуют от наиболее типичных пропусков. Свод ключевых практических задач полярного хирурга в условиях ограниченных ресурсов представлен в табл. 3.

Таблица 3

Ключевые практические задачи полярного хирурга в условиях ограниченных ресурсов

Задача	Уровень помощи	Содержание	Практические комментарии
Применение принципов DCS	Малый стационар, полярная станция, судно	Минимально необходимое вмешательство (контроль кровотечения, временная стабилизация повреждений) с отказом от окончательной реконструкции в условиях нестабильной физиологии	Требует предварительной отработки алгоритмов и чёткого понимания границ вмешательства
Реализация DCR и PFC	Догоспитальный этап, малый стационар	Ограничение кристаллоидов, приоритет крови/плазмы (при наличии), контроль гипотермии и коагулопатии, длительное поддерживающее лечение до эвакуации	Нужны запасы расходников, протоколы мониторинга, обучение персонала
Телемедицинская поддержка решений	Все уровни, особенно изолированные пункты	Организация круглосуточного доступа к телеконсилиумам (хирург, анестезиолог, кардиолог), передача изображений (ЭКГ, УЗИ, КТ)	Важны стандартизированные протоколы связи и резервные каналы (интернет/спутник/радио)
Маршрутизация и планирование эвакуации	Станция, малый стационар, региональный центр	Оценка времени эвакуации, погоды, доступности бортов, готовности принимающего центра; использование «окна погоды»	Необходимы заранее отработанные схемы взаимодействия с SAR (поиск и спасение) и авиацией, несколько резервных маршрутов
Профилактика гипотермии и коагулопатии	Догоспитальный этап, операционная	Активный контроль температуры (утепление, подогрев инфузий), ранняя диагностика и коррекция коагулопатии, минимизация кровопотери	В полярных условиях борьба с гипотермией — ключевой элемент DCR
Подготовка команды и взаимодействие	Все уровни	Тренировки по сценариям тяжёлой травмы, чёткие роли в бригаде, взаимодействие со спасателями, авиацией, экипажами судов	В условиях кадрового дефицита важна рациональная распределённость задач между врачом, фельдшером, медсестрой и немедиками

Table 3

Key practical tasks for a polar surgeon in limited-resource settings (task, level of care, content, practical comments)

Task	Level of care	Content	Practical comments
Application of DCS principles	Small hospital, polar station, ship	Only the minimum necessary intervention (haemorrhage control, temporary stabilization of injuries), with deferral of definitive reconstruction in the setting of physiological instability	Requires prior rehearsal of algorithms and a clear understanding of the limits of the intervention
Implementation of DCR and PFC	Prehospital stage, small hospital	Restriction of crystalloids, priority use of blood/plasma (if available), control of hypothermia and coagulopathy, prolonged supportive care until evacuation	Requires adequate stock of consumables, monitoring protocols and staff training
Telemedicine support for decision-making	All levels of care, especially isolated sites	Organisation of 24/7 access to teleconsultations (surgeon, anaesthesiologist, cardiologist); transmission of images (ECG, ultrasound, CT)	Standardized communication protocols and backup channels (internet / satellite / radio) are essential
Routing and evacuation planning	Station, small hospital, regional centre	Assessment of evacuation time, weather, aircraft availability, readiness of the receiving center; use of «weather windows»	Requires pre-established schemes of interaction with SAR (search and rescue) and aviation services and several backup routes
Prevention of hypothermia and coagulopathy	Prehospital stage, operating room	Active temperature control (insulation, warming of infusions), early diagnosis and correction of coagulopathy, minimization of blood loss	In polar conditions, prevention and treatment of hypothermia is a key element of DCR
Team training and coordination	All levels	Scenario-based training for severe trauma, clearly defined roles within the team, coordination with rescue services, aviation and ship crews	Under staff shortage, rational distribution of tasks between the physician, paramedic, nurse and non-medical personnel is critical

Фигура полярного хирурга объединяет клиническую, организационную и коммуникационную компоненты. От его готовности к DCS-подходу, владения базовыми техниками и умения использовать международные сети сотрудничества зависит исход единичных, но крайне тяжёлых случаев травмы и острой хирургической патологии в полярных регионах. Предлагаемая маршрутизация тяжело травмированного пациента в полярном регионе и алгоритм выбора между локальным вмешательством формата damage-control и эвакуацией показаны на рис. 3 и 4.

Рис. 3. Маршрутизация тяжёлого полярного пациента

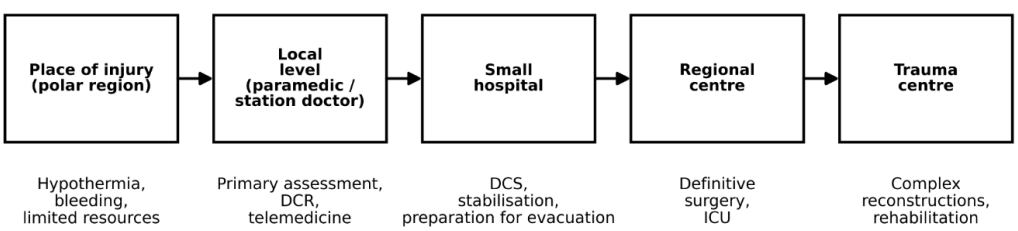

Fig. 3. Care pathway for a severely injured patient in polar regions

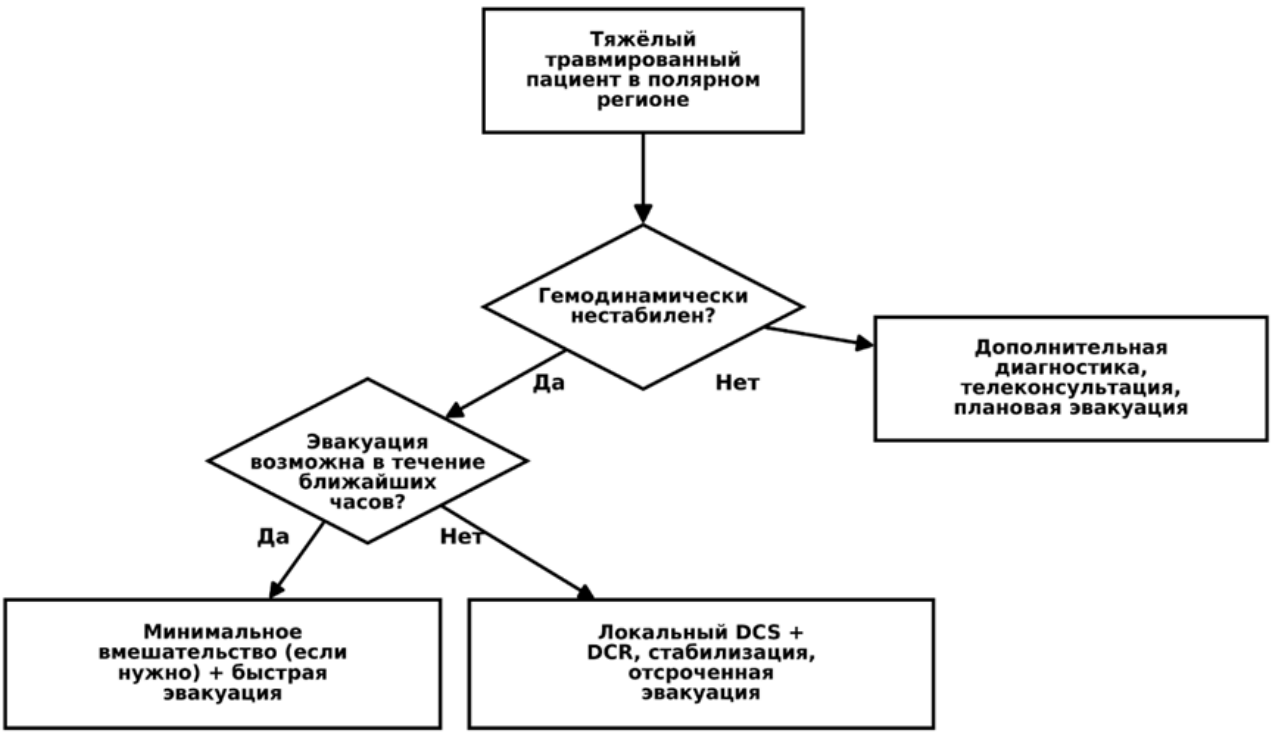

Рис. 4. Упрощённый алгоритм выбора: локальный DCS или эвакуация

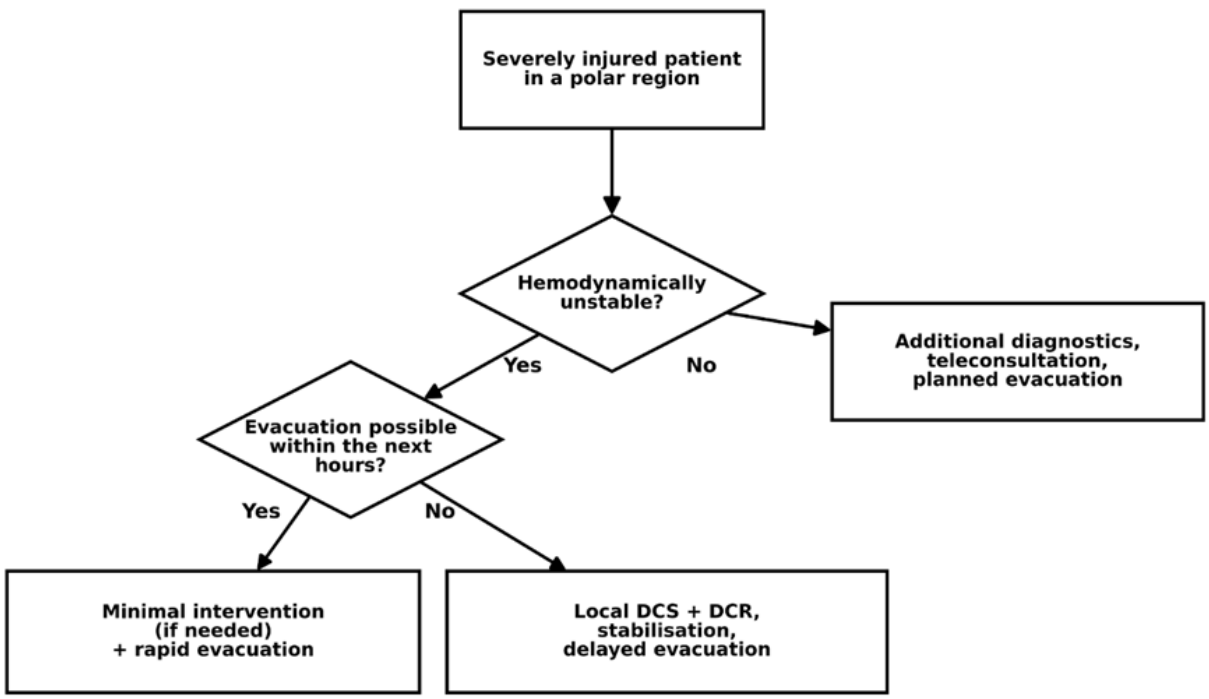

Fig. 4. Simplified decision algorithm: local DCS versus evacuation

Ограничения и направления будущих исследований

Имеющаяся литература по хирургии травмы в полярных регионах характеризуется рядом ограничений. Большинство публикаций представляют собой ретроспективные серии наблюдений, описания отдельных клинических случаев или отчёты экспедиций, что затрудняет количественную оценку исходов и сравнение различных моделей помощи [19–24]. Данные по российской Арктике и Крайнему Северу представлены крайне ограниченно и фрагментарно [25–27]. В ряде случаев DCS/DCR/PFC в полярных условиях описываются через экстраполяцию опыта военно-полевой хирургии и экспедиционной медицины без детальной адаптации к специфике северных территорий [1–4, 5–7, 8–11, 19–22, 27].

Перспективными направлениями исследований являются создание международных регистров полярного травматизма и неотложной хирургической патологии, стандартизация протоколов DCS/DCR/PFC для Арктики и Антарктики, разработка единых критериев принятия решения об операции и эвакуации, а также оценка эффективности телемедицинских моделей поддержки хирургов и врачей общей практики в изолированных регионах [19–22, 24, 28, 30–32]. Особое внимание заслуживают три сквозных направления, интегрирующие полевую, полярную, горную и космическую хирургию: (1) проектирование и тестирование автономных хирургических модулей для арктических посёлков, высокогорных лагерей, морских экспедиций и перспективных орбитальных/лунных миссий; (2) изучение управляемой гипотермии и методик emergency preservation and resuscitation как инструмента «защитного гипобиоза» при тяжёлой травме; (3) исследование регенерации и заживления костной и мягких тканей в условиях холода, гипоксии и микрогравитации с целью последующего переноса этих знаний в обычную хирургическую практику [20, 27, 35–40].

Выводы

Поэтапная тактика лечения травмы с применением DCS/DCR/PFC в полярных регионах позволяет адаптировать объём операции к реальным ресурсам и эвакуационным возможностям, снижая риск фатальных осложнений. Обобщенный опыт военно-полевой и полярной хирургии может быть использован при разработке протоколов помощи при тяжёлой травме в северных регионах России и других стран, а также служить методологической основой для последующих исследований травмы в высокогорных районах и перспективных космических миссиях. Перспективные направления включают разработку автономных хирургических модулей, протоколов контролируемой гипотермии (EPR), создание телемедицинских систем и регистров полярной травмы с моделированием эвакуационных сценариев, а также изучение регенерации тканей в экстремальных условиях. Дополнительно следует учитывать влияние локальной (в том числе аппаратной) гипотермии на клеточные процессы и микроциркуляцию, что может иметь значение при выборе тактики температурного менеджмента в условиях холода [46, 47].

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ORIGINAL RESEARCH
ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Employing seamless mesh implants during Lichtenstein hernia repair with the use of insights enabled by artificial intelligence

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Abstract. *Relevance*. Globally, there are now 32.53 million hernia cases, up from about 23.92 million during the previous 3 decades. Many authors lack statistical knowledge, which could jeopardize healthcare. *The aim* was to use artificial intelligence as a statistical technique to assess the potential effects of Adhesix™ self-gripping mesh implants, Hertra™ mesh implants, and Lintex™ glue-fixed mesh implants on the outcomes of inguinal hernia patients who underwent open inguinal hernia repair in Lichtenstein. *Materials and Methods.* We performed 120 Liechtenstein-compliant inguinal hernia repair procedures on three evenly split patient groups (n = 40) using Adhesix™, Hertra™, and Lintex™ mesh implants. The parameters for comparison were the time-frame of the procedure, hospital-stays, challenges afterwards surgery, and issues that arose during the brief follow-up. *Results and Discussion*. Patients of the first group were hospitalized for shorter periods of time than those in the second and third groups (group A-4.9 bed /day, group B-4.9.5 bed /day, and group C-4.95 bed /day), with no statistically significant differences. Patients in the first group experience a significantly shorter procedure time, followed by those in the second and third groups (27.8 min, 31.4 min, and 38.9 min respectively). Unlike the third group, which included 3 patients with postoperative discomfort and 1 with postoperative seroma formation, the first and second groups' postoperative hospitalization stays were free of complications. In contrast to the third group's 2 patients who experienced mesh migration and hernia recurrence, the first and second groups' patients experienced no complications during the short-term follow-up. *Conclusion*. Compared to Lintex™ mesh implants, the operative times using Adhesix™ and Hertra™ are significantly shorter with no post-operative complications or hernia recurrence.

Keywords: hernia, mesh implants, polypropylene, glue, artificial intelligence

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Conflicts of interest statement. Authors declare no conflict of interest.
Ethics approval. The study was approved by the bioethics commission of the Federal State Budgetary Institution Research Institute of Human Morphology (Protocol № . 3, 01.02.2019).

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Consent for publication. All patients provided informed voluntary consent to participate in the study according to the Helsinki Declaration of the World Medical Association (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013) and personal data processing.

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Introduction

When it comes to surgical mesh fabrication, polypropylene (PP) is the most widely used material worldwide [1]. It is nonabsorbable, electrostatically neutral, extremely hydrophobic, nonpolar, and has a high tensile strength. It can be found in mono or multifilaments, coated or uncoated, heavy or lightweight forms [2]. Fuse Deposition Modelling (FDM) in 3D printing surgical meshes [3] reduces the tensile strength of the mesh and creates multiple contact points between the mesh and surrounding tissues, as opposed to the mobile joint points that are achieved through knitting in non-pre-shaped meshes. This results in a significant reduction in both operative time and postoperative pain [4].

In terms of surgical time, postoperative seroma/hematoma production, urinary retention, and even more, recurrence rates, the use of pre-shaped surgical meshes is better to that of non-pre-shaped suture-fixed ones [5, 6]. Many theories explain why the application of self-adhering pre-shaped meshes causes less postoperative pain than sutured ones by linking the pathophysiology of early postoperative inguinal pain to not only surgery-related causes but also tissue trauma from surgical field preparation, mesh inflammatory reaction, and mesh fixation. Furthermore, cost-effective research demonstrated that self-adhering pre-shaped meshes were more cost-effective to use than ordinary sutured meshes, despite their higher price [7, 8].

Tissue adhesives have been proposed as an alternative to permanent fixation devices in hernia repair with the aim of reducing perforation-associated complications and chronic pain. The adhesives can be divided into three main categories: biologic products (e.g., fibrin), synthetic glues (e.g., cyanoacrylate based), and genetically engineered polymer protein glues. Fibrin sealant has been used extensively in all surgical disciplines for tissue adhesion, suture support, hemostasis, wound care, and endoscopic treatment of bleeding. Cyanoacrylate based glues have been investigated in numerous scientific studies as hemostatic agents, topical dressing, and adhesives in soft tissues, in ophthalmology, odontostomatology, osteosynthesis of bone fracture and, recently, as drug carriers. They were also used in gastroenterology for

esophagus varix treatment, in maxillo-facial surgery, and in vascular surgery for arterious anastomoses [9].

The accuracy of diagnoses, clinical judgment, and patient outcomes have all been transformed by the application of artificial intelligence and statistical science in medicine, especially surgery. The crucial significance statistical frameworks play in organizing and approving medical research is shown by current research. When assessing clinical outcomes, especially in surgical operations, fundamental statistical parameters like sensitivity, specificity, and predictive values are still crucial. Likewise, statistically verified artificial intelligence (AI) models improve surgical accuracy and outcome prediction [10,11].

Another popular statistical technique is regression analysis, for which Lee suggests standardized uses for continuous variables in clinical research [12]. Machine learning algorithms are becoming more widely used in a variety of fields, including radiology and surgical risk assessment. These algorithms provide doctors with dynamic models that get better with time and additional data [13]. The strength of statistical science in controlling chronic illnesses is further demonstrated by the use of machine learning in complicated areas, such as blood glucose prediction in Type 1 diabetes. In this situation, the precision, scalability, and reproducibility of research are greatly impacted by the data analysis methods selected. Although many people use Microsoft Excel for simple data management and visualization, Python offers more flexibility and computational resilience. With the help of libraries like Pandas, NumPy, SciPy, and scikit-learn, Python allows for sophisticated statistical modeling, real-time data analysis, and automation on a scale that Excel is unable to rival [14, 15].

The growing relevance of machine learning in medical research was reviewed by Garg and Mago [16], who emphasized how Python makes it easier to construct algorithms for diagnostic and therapy planning. Additionally, Fang explains how statistical techniques guarantee increased reproducibility and transparency in biological research when applied using programming environments such as Python. Additionally, Python is a better option for medical researchers working with high-dimensional clinical datasets due to its connection with hospital information systems and compatibility with big data platforms. With these developments, Python is now more suited to construct intelligent healthcare systems and serves as a supplement to statistical science [17].

The aim of this work is to enhance the results of Lichtenstein, the gold standard technique for anterior hernia repair [18], given that the global market for hernia repair is expected to reach $6.3 billion in the next few years [19].

Materials and methods

Patients

Between January 2022 and March 2025, our team conducted 120 patients with inguinal hernias who underwent anterior inguinal hernioplasty with seamless implants during Liechtenstein. The study took place at RUDN University's Department of Operative Surgery and Clinical Anatomy, located at the Clinical Federal Hospital № 85 in Moscow, Russia. We used patient card control, which allowed us to select all of the relevant help criteria. As summarized in Table 1.

Inclusion criteria

1. Patients with a unilateral, main inguinal hernia and no additional hernias.
2. Patients in the age range of 21 to 71.
3. Both men and non-pregnant women.
4. Patients were treated using the Lichtenstein method.
5. Patients beforehand.

Disqualification standards

1. People who have bilateral, recurrent inguinal hernias or other hernias that occur concurrently are excluded.
2. Individuals who are over 71 or under 21.
3. Expectant mothers.
4. Patients who expressed their desire for laparoscopic surgery.
5. Individuals in need of urgent care.

Table 1

Control card for the patients

1) Admission timing and date.
2) The release date and time.
3) Total hospital stay (beds per day).
4) Preoperative information on the patient:
   a. Name, surname, and middle name.
   b. The card's number.
   c. Gender.
   d. Age.
   e. Profession.
   f. Address.
   g. Telephone number.
   h. Patient grievance.
   i. The length of the hernia.
   j. Hernia size.
   k. Hernia site (left or right).
   l. Type of hernia: direct or oblique.
   m. The external inguinal ring's dimensions.
   n. Related comorbidities: assessing the influence of connective tissue diseases and figuring out the risk factors affecting the patient's quality of life.
5) Information obtained during surgery:
   a. Anathesia kind.
   b. The mesh implant that was used (kind, size, and technique of anchoring the mesh).
   c. Size of the hernial sac.
   d. Surgery-related issues.
   e. Time of operation.
6) Post-operative care:
   a. Complications during hospitalization.
   b. Concerns arose during the six-month postoperative short-term follow-up.

Research methodology

A combination of a prospective and retrospective analysis.

For the purposes of our investigation, we divided the 120 participants in our clinical trial into three equal groups (n = 40).

Adhesix™ self-gripping mesh implants (Figure 1) were used in Group A; 40 male patients make up this group. The average age was 51.45. Thirty-two patients had a right inguinal hernia, while eight patients had a left. There is a 24:16 ratio of oblique to straight inguinal hernias. The averages of age, duration of herniation, hernial and external henial ring, are summarized in Table 2.

Table 2

Averages of age, duration of herniation, dimensions of hernia and external henial ring for group A

Metric	Mean	Standard Error	Median	Mode	Standard deviation	Range	Min	Max
Age (years)	51.45	3.03	53	70	13.56	43	27	70
Duration of Herniation (months)	24.75	8.58	7.5	6	38.39	117	3	120
Hernia Length (cm)	6.9	0.61	6	6	2.71	9	3	12
Hernia Width (cm)	4.68	0.28	4.5	4	1.26	4.5	2.5	7
Hernia Height (cm)	3.75	0.45	3.5	3	1.28	4	2	6
Hernia Volume (cm^3)	85.35	21.11	39	12	94.41	276	12	288
External Inguinal Ring Size (cm)	2.5	0.11	2.5	2.5	0.51	2	1.5	3.5

Hertra™ pre-fitted mesh implants (Figure 2) were used in Group B; 36 men and 4 women. 55.95 years old was the average. This group consists of twenty patients with right inguinal hernias and twenty patients with left inguinal hernias. Oblique to direct inguinal hernias is 20:20 in ratio. The averages of age, duration of herniation, hernial and external henial ring, are summarized in table 3.

Glue-repaired Lintex™ mesh implants (Figure 3) were used in Group C; there were also 14 female patients and 26 male patients. The average age was 58.89 years. Of the patients, 26 had a right inguinal hernia and 14 had a left. 21:19 is the oblique to direct inguinal hernia ratio. The averages of age, duration of herniation, hernial and external henial ring, are summarized in Table 4.

Table 3

Averages of age, duration of herniation, dimensions of hernia and external henial ring for group B

Metric	Mean	Standard Error	Median	Mode	Standard deviation	Range	Min	Max
Age (years)	55.95	2.96	63	64	13.26	41	27	68
Duration of Herniation (months)	22.7	4.41	18	24	19.70	58	2	60
Hernia Length (cm)	7.35	0.88	6	5	3.95	13	2	15
Hernia Width (cm)	4.7	0.33	4.5	4	1.49	5	2	7
Hernia Height (cm)	3.29	0.61	3	2	1.60	4	2	6
Hernia Volume (cm^3)	86.3	28.05	31	25	125.46	498	6	504
External Inguinal Ring Size (cm)	2.35	0.19	2.5	1.5	0.83	2.5	1.5	4

Table 4

Averages of age, duration of herniation, dimensions of hernia and external henial ring for group C

Metric	Mean	Standard Error	Median	Mode	Standard deviation	Range	Min	Max
Age (years)	58.89	1.66	62	62	10.07	40	30	70
Duration of Herniation (months)	58.89	1.66	24	24	39.13	178	2	180
Hernia Length (cm)	58.89	1.66	7	6	3.71	15	2	17
Hernia Width (cm)	58.89	1.66	4	4	1.83	8	2	10
Hernia Height (cm)	58.89	1.66	3	3	1.79	7	2	9
Hernia Volume (cm^3)	58.89	1.66	48	48	259.29	1524	6	1530
External Inguinal Ring Size (cm)	58.89	1.66	25	25	0.76	2.5	1.5	4

Fig. 1. Adhesix™ self-gripping mesh implant

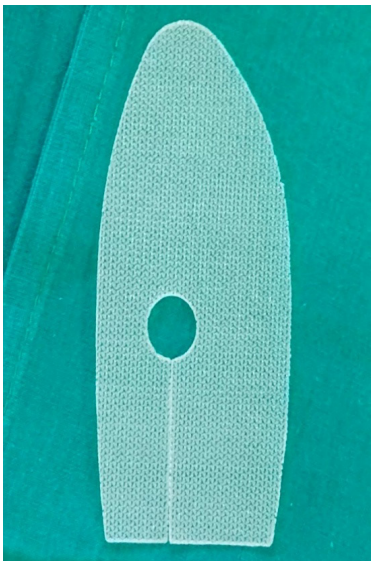

Fig. 2. Hertra™ pre-fitted mesh implant

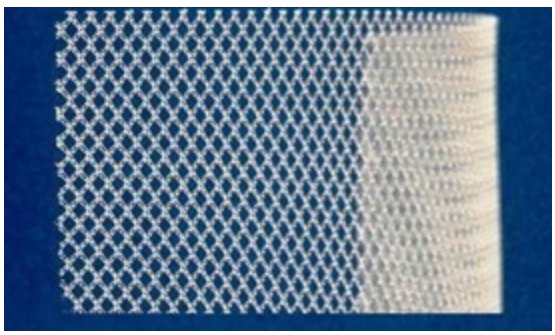

Fig. 3. Glue-repaired Lintex™ mesh implant

The main complaints of the patients are summarized in Table 5.

After collecting the medical histories of the patients in the three groups, we discovered the following comorbidities as summarized in Table 6.

Table 5

Main complaints of the patients

	Group A	Group B	Group C	Grand total
Painless Slowly growing inguinal mass	30/40 (75%)	18/40 (45%)	17/40 (42.5%)	65/120 (54.167%)
Constant inguinal pain during rest	3/40(7.5%)	7/40 (17.5%)	10/40(25%)	20/120 (16.67%)
Groin pain during standing	4/40(10%)	7/40 (17.5%)	6/40(15%)	17/120(14.167%)
Groin pain upon lifting heavy objects	2/40(5%)	6/40(15%)	7/40(17.5%)	15/120(12.5%)
Pulling pain in the groin	1/40(2.5%)	2/40(5%)	0/40(o%)	3/120(2.5%)
Grand total	40/40 (100%)	40/40 (100%)	40/40(100%)	120/120(100%)

Table 6

Patients' associated comorbidities

	Group A	Group B	Group C	Grand total
HTN	-	-	2/40 (5%)	2/120 (1.67%)
HTN+CHF	-	10/40 (25%)	4/40 (10%)	14/120 (11.67%)
HTN+CHD	-	4/40 (10%)	2/40 (5%)	6/120 (5%)
HTN+ Ch. Gastritis	-	4/40 (10%)	2/40 (5%)	6/120 (5%)
HTN+ Ch. Cal. Cholecystitis	-	2/40 (5%)	1/40 (2.5%)	3/120 (2.5%)
HTN+ Varicose veins	-	2/40 (5%)	1/40 (2.5%)	3/120 (2.5%)
HTN+ Type II D.M.	-	2/40 (5%)	1/40 (2.5%)	3/120 (2.5%)
HTN+ Dyslipidemia	-	2/40 (5%)	-	2/120 (1.67%)
HTN+AF	-	-	1/40 (2.5%)	1/120 (0.83%)
Sinus Bradycardia	-	-	1/40 (2.5%)	1/120 (0.83%)
COPD	2/40 (5%)	-	1/40 (2.5%)	3/120 (2.5%)
Varicose veins	4/40 (10%)	-	1/40 (2.5%)	5/120 (4.17%)
Urolithiasis	-	-	1/40 (2.5%)	1/120 (0.83%)
Type II D.M.	2/40 (5%)	-	-	2/120 (1.67%)
Grand total	8/40 (20%)	26/40 (65%)	18/40 (45%)	52/120 (43.3%)

Statistical analysis

The statistics module of the Python programming language, which is machine learning-based statistical software with artificial intelligence support, was used to perform the calculations. Descriptive statistics, such as arithmetic mean (M), standard error, median, mode, standard deviation (s), range, minimum (Min), and maximum (Max), were used to statistically examine the collected data. Windows 11 was the operating system. 8 GB of RAM is needed for the system.

Results and discussion

The comparison-based criteria

I. The time for operation.

The average operating time for patients in group (A) who had surgery with Adhesix™ self-gripping mesh implants was 27.8 minutes; for patients in group (B) who had surgery with Hertra™ mesh implants fixed by a single polypropylene suture to the pubic bone, it was 31.4 minutes; and for patients in group (C) with Lintex™ glue-fixed mesh implant was 38.9 minutes as summarized in Table 7.

The average operating duration of 3.6 minutes does not appear to differ statistically significantly between groups A and B, according to the p-value of 0.90.

The p-value (< 0.0001) shows a statistically significant difference in operative time between groups A and C, with an average of roughly 11.1 minutes.

The p-value (< 0.0001) shows a statistically significant difference in the average operating duration (~7.5 minutes) between groups (B) and (C).

In terms of operating time, these figures show a statistically significant difference between the use of Adhesix™ self-gripping mesh, Hertra™ mesh fastened by single stitch, and Lintex™ mesh fixed by glue.

Table 7

The average operative-time for the 3 group

Metric	Group A(Adhesix™)	Group B(Hertra™)	Group C (Lintex™)
Mean	27.8	31.4	38.9
Standard Error	1.5	1.76	2.17
Median	26.5	28.1	33.75
Mode	25	28.1	30
Std Dev	6.7	7.88	13.24
Range	21.8	30.6	63.75
Min	21	26.25	18.75
Max	38	35	82.5

II. Hospitalization (day/bed)

Hospital stays for group (A) patients who had surgery with Adhesix™ self-gripping mesh implants lasted an average of 4.9 days; group (B) patients who had surgery with Hertra™ mesh implants that were secured to the pubic bone with a single polypropylene suture lasted 4.95 days; and group (C) patients who had surgery with Lintex™ implants that were secured with glue lasted 4.95 days, as summarized in Table 8.

The average length of stay in the hospital was about five days, similar for all groups.

The p-value of 0.90 indicates that there is no statistically significant difference in the length of hospitalization for either group.

These numbers showed that the three study groups' hospital stays did not differ statistically significantly.

III. Recovery issues after surgery

During their hospital stay following surgery, we found that everyone in group (A) was trouble-free.

No problems exist between any of the group members for the patients in group (B).

Conversely, we found that three patients in group (C) had postoperative pain that was reduced following NSAID use. One patient had seroma. The other group members did not experience any pain. During the hospital stay following surgery, none of the patients in group (C) experienced any further issues.

Table 8

Hospitalization (day/bed)

Metric	Group A(Adhesix™)	Group B(Hertra™)	Group C (Lintex™)
Mean	4.9	4.95	4.95
Standard Error	0.34	0.23	0.19
Median	4.5	5	5
Mode	4	5	5
Std Dev	1.52	1.05	1.15
Range	5	4	5
Min	3	3	3
Max	8	7	8

IV. Issues with the short-term follow up.

During the six-month short-term follow-up, we noticed that all of the patients in group (A) had no issues. There were no repetitions.There are no problems among the patients in Group (B). There were no repetitions. Among the patients in group (C), we found two who had mesh migration and recurrence.

So, the three types of seamless implants that Lichtenstein uses for open inguinal hernioplasty are self-gripping mesh (Adhesix), mesh implants (Hertra) that are fastened to the pubic bone with a single wire, and mesh implants (Lintex) that are fixed with glue.

Discussion 1. Patients who had surgery in the first group were hospitalized for shorter periods of time than those in the second and third groups (group A-4.9 b/d, group B-4.9.5 b/d, and group C-4.95 b/d), but there were no statistically significant differences.

Discussion 2. Patients in the first group take a lot less time to complete the process than patients in the second and third groups (groups A, B, and C, respectively; 27.8 minutes, 31.4 minutes, and 38.9 minutes).

Discussion 3. Unlike the third group, which included three patients with postoperative discomfort and one with postoperative seroma formation, the first and second groups' postoperative hospitalization stays were free of complications.

Discussion 4. Unlike the third group, which included two patients with mesh migration and hernia recurrence, the first and second group patients experienced no complications during the short-term follow-up.

Conclusion

Compared to Lintex mesh implants, the operative times for inguinal hernioplasty with an anterior approach using self-gripping mesh (Adhesix), mesh implants (Hertra) fixed by a single polypropylene to the pubic bone, and mesh implants (Lintex) fixed by glue are significantly shorter (11. minutes and 7.5 minutes, respectively). In contrast to Lintex™, which experienced three post-operative pain cases and one seroma case, Adhesix™ and Hertra™ experienced no issues during the post-operative hospital stay. In the short-term follow-up, the first group experienced no issues, the second group experienced none, and the third group experienced two mesh migrations and a hernia recurrence.

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Использование бесшовных сетчатых имплантатов при герниопластике по методу Лихтенштейна с использованием технологий искусственного интеллекта

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Аннотация. *Актуальность*. В настоящее время во всем мире зарегистрировано 32,53 миллиона случаев грыжи, по сравнению с примерно 23,92 миллионами за предыдущие 3 десятилетия. Многим авторам не хватает статистических знаний, что может поставить под угрозу здравоохранение. Цель состояла в том, чтобы использовать искусственный интеллект в качестве статистического метода для оценки потенциального влияния Самофиксирующихся сетчатых имплантатов AdhesixTM, HertraTM и LintexTM на результаты лечения пациентов с паховой грыжей, перенесших открытую пластику паховой грыжи Лихтенштейн. *Материалы и методы*. Мы выполнили 120 процедур паховой гарниопластики по Лихтенштейну, у трех равномерно распределенных групп пациентов (n = 40) с использованием сетчатых имплантатов Adhesix™, HertraTM и LintexTM. Параметрами для сравнения были продолжительность процедуры, продолжительность пребывания в больнице, осложнения в послеоперационном периоде, возникшие во время краткого наблюдения. *Результаты и обсуждение*. Пациенты первой группы были госпитализированы на более короткие сроки, чем пациенты второй и третьей групп (группа А — 4,9 дня в сутки, группа В-4,9,5 дня в сутки и группа С-4,95 дня в сутки), без статистически значимых различий. У пациентов из первой группы время процедуры значительно сокращается, за ними следуют пациенты из второй и третьей групп (27,8 мин, 31,4 мин и 38,9 мин соответственно). В отличие от третьей группы, в которую вошли 3 пациента с послеоперационным дискомфортом и 1 с образованием послеоперационной серомы, послеоперационное пребывание в стационаре первой и второй групп протекало без осложнений. В отличие от двух пациентов третьей группы, у которых наблюдалась миграция сетки и рецидив грыжи, пациенты первой и второй групп не испытывали осложнений в течение короткого периода наблюдения. *Выводы*. По сравнению с сетчатыми имплантатами LintexTM, время операции при использовании AdhesixTM и HertraTM значительно сокращается без послеоперационных осложнений или рецидива грыжи.

Ключевые слова: грыжа, сетчатые имплантаты, полипропилен, клей, искусственный интеллект

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CLINICAL CASE REPORT
КЛИНИЧЕСКИЙ СЛУЧАЙ

Auto-graft vs 3D printed implant in reconstruction of frontal bone region

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Abstract. *Relevance*. Fibrous dysplasia is a pathological condition characterized by the substitution of normal bone with fibrous tissue. The progression of this disorder generally stabilizes with increasing age. Clinically, it may manifest as painless swelling and facial asymmetry. Radiographic examination reveals well-defined margins, intramedullary expansion, maintenance of a smooth cortical contour, and ground-glass appearance. Histologically, the condition is distinguished by the presence of fibrous tissue replacing bone, along with irregularly arranged and randomly oriented bony trabeculae. Current treatment approaches frequently involve surgical intervention utilizing custom-fabricated polyether ether ketone (PEEK) implants or autogenous bone grafts, such as calvarial grafts. *Materials and Methods.* In the Department of Maxillofacial Surgery of the Russian Children's Clinical Hospital (RCCH) — a branch of the Federal State Autonomous Educational Institution of Higher Education Russian National Research Medical University named after. N.I. Pirogov of the Ministry of Health of the Russian Federation of Moscow, 65 patients, from 2016 to 2023, were treated for histologically confirmed fibrous dysplasia in the frontal bone. Among them, 2 patients (7 years old girl, and 17 years old boy) were treated with 3D implants made from PEEK, and 2 patients (6 years old boy, and 9 years old girl) were treated with calvarial graft. *Results and Discussion.* The application of 3D implants has effectively enforce the primary stability of the reconstructed area. The lesion was successfully addressed, achieving an optimal aesthetic outcome characterized by a combination of strength, lightweight properties, and biocompatibility, without any observed complications or failures. Notably, recurrences have been recognized in patients who underwent treatment with calvarial grafts over five years after the operation. *Conclusion.* PEEK is a thermoplastic polymer characterized by its non-absorbable and nonporous properties, which allows for intraoperative modifications and provides optimal imaging characteristics in the postoperative period. On the other hand, it has been observed that auto-grafts may exhibit a higher risk of failure compared to custom-fabricated implants.

Keywords: frontal bone, fibrous dysplasia, polyether ether ketone, 3D implant, calvarial graft
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Author contributions. A.Yu. Kugushev — concept and design of the study, assumed a significant role in the analysis of the raw data, engaged in critical revisions of essential intellectual content, and provided final approval. Dr. Kugushev served as the surgeon responsible for the patient's surgical treatment and participated in the determination of the appropriate drug dosages. Farah Sadek and Suzan Dagher took part in the writing process, drafting of the manuscript, analyzing the data, and reviewing publications related to the topic of the article. A.V. Lopatin — scientific consulting, final approval of the manuscript. The manuscript has been read and approved by all the authors, and all the requirements for authorship have been met. Each author believes that the manuscript represents honest work.

Conflicts of interest statement. The authors declare no conflict of interest.

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Consent for publication. Voluntary written consent was obtained from the patients or their parents for the investigation, processing of personal data and publication of relevant medical information according to WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013.

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Introduction

Fibrous dysplasia (FD) is primarily a benign, hamartomatous, developmental dysplastic bone lesion that impacts multiple skeletal bones [1]. The majority of affected individuals are female, presenting with bone tumors and tumor-like lesions [2]. FD is characterized by a developmental anomaly that results in the replacement of normal bone tissue with fibro-osseous material, which exhibits varying degrees of osseous metaplasia [3–5]. This condition is not limited to a single bone; rather, it may be localized to a specific anatomical region [3]. While these lesions primarily affect the maxilla, they can also extend across sutures to involve adjacent or contiguous bones, including the sphenoid, zygomatic, temporal bones, frontonasal bones, and the base of the skull [6, 7]. Craniofacial fibrous dysplasia can lead to facial deformities, asymmetry, and, in severe instances, blindness due to the involvement of the orbital bones and subsequent compression of the contents within the orbital canal [8–10].

In addition, the diagnosis is complicated by the variety of radiographic manifestations due to the staging of the disease [11]. The principal classifications of fibrous dysplasia include monostotic, polyostotic, and craniofacial forms [12, 13]. Polyostotic fibrous dysplasia may be associated with McCune-Albright syndrome and Mazabraud syndrome [14]. In the case of McCune-Albright syndrome, multifocal FD is often accompanied by café au-lait spots, endocrine abnormalities, and precocious puberty. Conversely, Mazabraud syndrome

is characterized by the association of fibrous dysplasia with muscular myxomas [14, 15].

The radiographic findings are characteristic. There is a diffuse enlargement of the affected region accompanied by the destruction of bone tissue, which presents as alternating small areas of increased density and decreased density. This results in a "ground glass" appearance [16].

Reconstruction of frontal bone has been explored in the literature, and various materials are available for rehabilitation, like auto/allografts, and alloplastic materials, including bone cement, titanium meshes, and patient-specific implant (PSI) [17, 18].

Materials and methods

In the Department of Maxillofacial Surgery of the Russian Children's Clinical Hospital of the Russian National Research Medical University named after N.I. Pirogov of the Ministry of Health of the Russian Federation in Moscow, 65 children received surgical treatment for a frontal bone dysplasia from 2016 to 2023. The beginning of treatment for all these patients started with bi-coronal incision, following by anterior scalp flap, then craniotomy of the frontal bone was performed for resection of the affected area. Among the 65 children, 52 of them were treated with 3D implant made from PEEK implant and the remaining 13 patients had auto bone graft (calvarial graft).

From this group, 4 patients were selected for this article; 2 patients (7 years old girl, and 17 years old boy) which had multi-spiral computed tomography (MSCT) followed by 3D implant (PEEK) reconstruction. Other patients (6 years old boy, and 9 years old girl) had the same diagnosis process but were treated differently by using calvarial graft from cranial partial bone. A post-operation CT scan was made for a check-up every one year until the next eight years.

The diagnose of all cases was conformed with post-operation histological examination results that showed multiple bone fragments with pathological tissue of moderate cellularity with irregular shape, areas of maturation along the periphery, and moderate cellularity with irregular shape convoluted bone trabeculae of non-lamellar structure without osteoblastic.

The choice of treatment was taken on the bases of patient's ages, volume of affected area and the parents' own wish.

Results and discussion

Clinical case 1

Description of the clinical case

A 7-years-old girl presented with painless swelling over the left side of her frontal bone region since 2019, CT scan of the skull was performed, and she was primary diagnostic with polyostotic form of fibrous dysplasia. The patient had no history of trauma, or other associated disease related to FD. Consulted in the outpatient department of the RCCH for the first time in 2022, where hospitalization was recommended and the patient was admitted to the maxillofacial surgery department.

Diagnosis

The MSCT imaging revealed affected osseous structure diffuse ill-defined expansible ground glass lesion appearance involving craniofacial region. Notably there was a periosteal thickening along the anterior surface of the left frontal and partial bone. Clinically, a change in the configuration of the face was visualized without pain (Figures 1, 2).

Treatment

The reconstruction of the orbital roof and frontal bone was planned and conducted by using a customized modeled implant based on polyetheretherketone (PEEK). Fibrous dysplasia of parietal bone was removed and the defect was closed using a custom made hydroxyapatite prosthesis (Figure 3).

Observation

Following an improvement in the patient's condition after 2 weeks post-operative follow-up, the child was discharged under the care of specialists at

their place of residence. During the 3 years of follow up observation, MSCT scan control did not reveal any data of progression of the disease. Additionally a successful osteogenesis was noted between the PEEK implant and the bone (Figure 4).

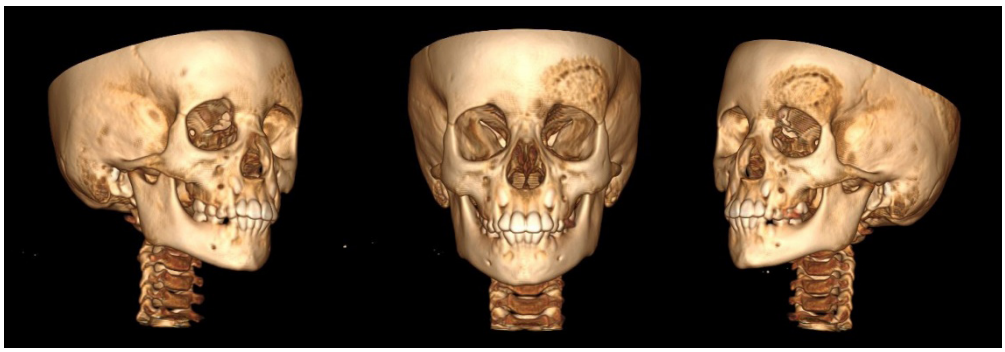


Fig. 1. MSCT (3D cut) showing bony expansion over the left frontal bone region in preoperative stage on 2022

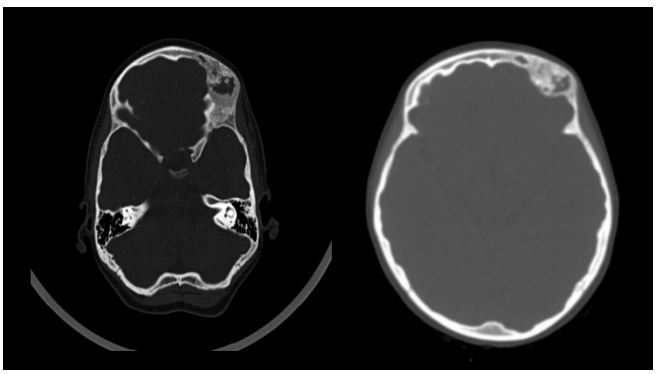


Fig. 2. Preoperative axial computed tomographic image exhibiting characteristic ground-glass opacification of fibrous dysplasia involving the left frontal

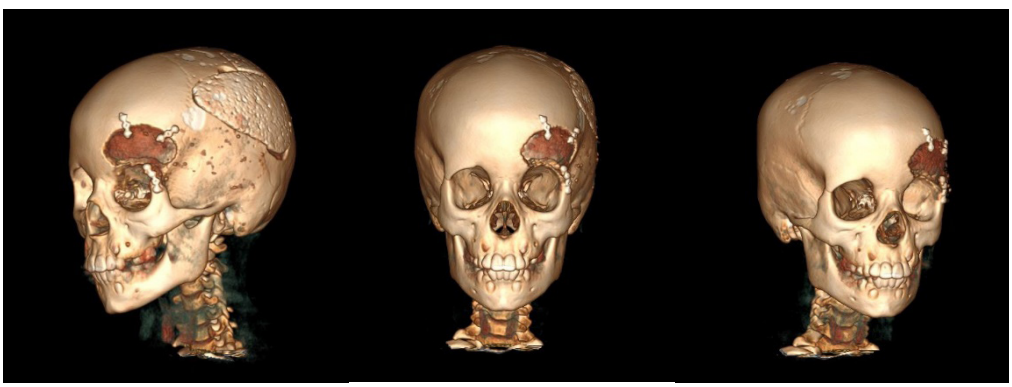
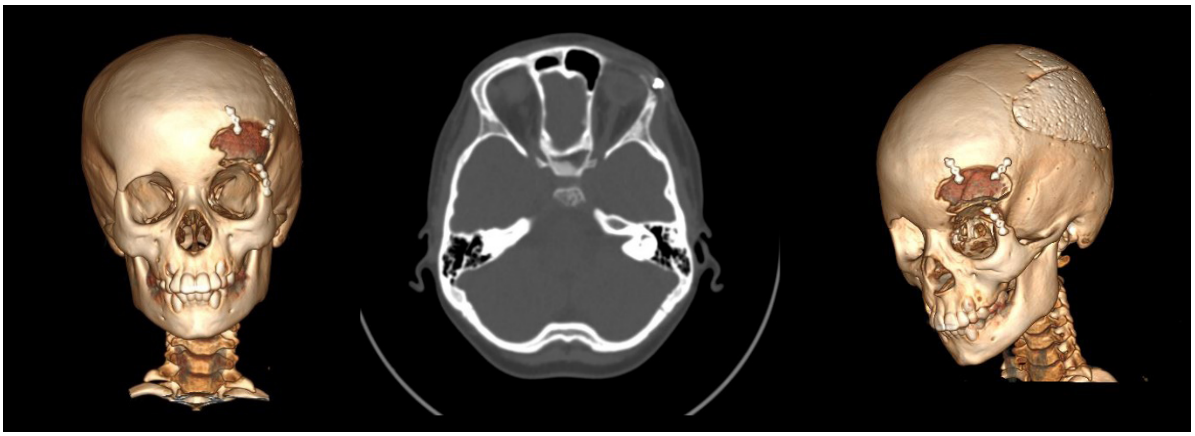
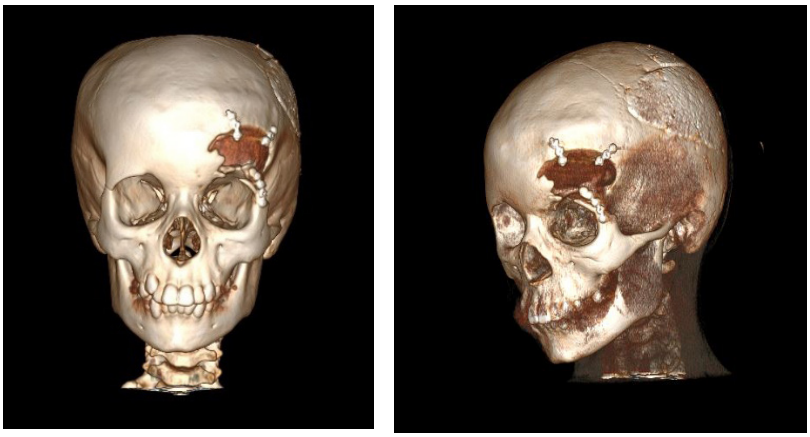


Fig. 3. MSCT (3D cut) scan showing post-operative surgery in 2022, with implant fixed by mini plates and mini screws on the left frontal bone and hydroxide appetite *prosthesis* in the left partial bone



a



b *c*

Fig. 4. Three years follow up control by MSCT on: *a* — 2023; *b* — 2024; *c* — 2025

Clinical case 2

Description of the clinical case

A 17-year-old male had a multi-slice computed tomography MSCT scan due to asymmetry observation in his forehead on the end of September 2023 which raised suspicions of a pathological formation. Upon consultation at RCCH at the beginning of July 2024, the patient was admitted in to the maxillofacial surgery department for further treatment and observation.

Diagnosis

The MSCT imaging revealed edema, deformity structure exhibits uneven compaction resembling a “ground glass” appearance in the right frontal bone (Figure 5). A diagnosis of fibrous dysplasia of the right frontal bone was established.

Additionally, a preoperative three-dimensional image and axial computed tomographic scan illustrate the distinctive ground-glass opacification characteristic of fibrous dysplasia affecting the left frontal, temporal, and sphenoid bones.

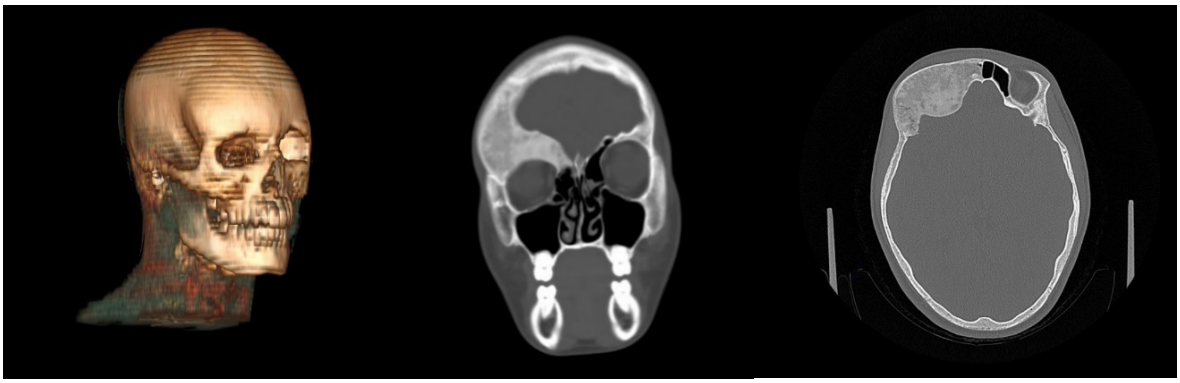


Fig. 5. A preoperative coronal computed tomographic image obtained on September 2023, reveals dysplastic growth of the left temporal bone, which is associated with frontal involvement and displacement of the orbital contents

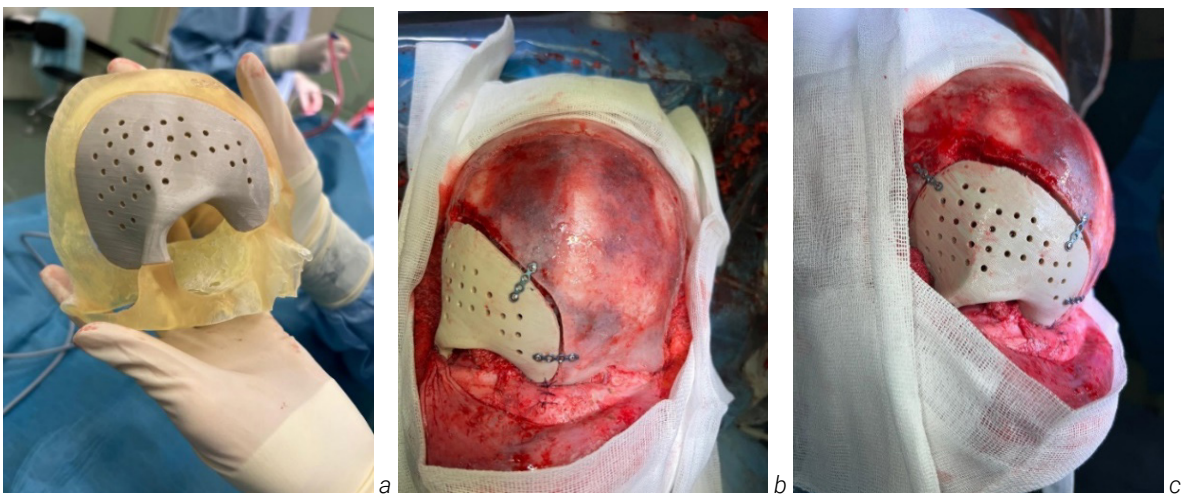


Fig. 6. A synthesis polyethertherketone (PEEK) implant. *a* — 3D PEEK Customized Implants designed individually for the patient to replace bony voids in the cranial and craniofacial skeleton; *b* and *c* — intraoperative view following fixation of polyetheretherketone (PEEK) implant with mini-plate and mini-screws

Treatment

A synthesis polyethertherketone (PEEK) implant was fixed by mini plate and mini screw to the affect area (Figure 6).

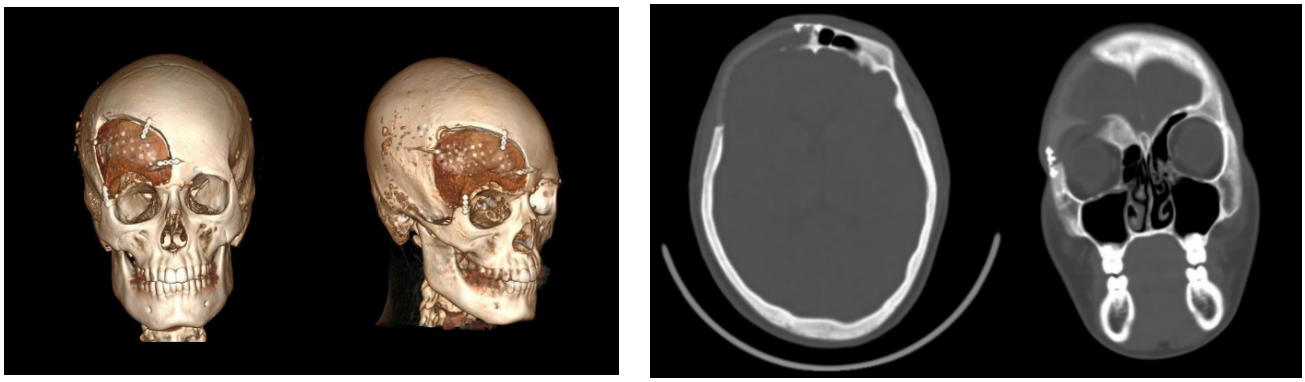
Observation

In the postoperative period, the patient received antibacterial therapy with combination of infusion pain killer and dexamethasone. The patient was discharged home in a stable condition after 2 weeks from operations.

Clinical Case 3

Description of the clinical case

A 6 years old boy has been ill since 2016, when a forehead asymmetry was first noticed by his parents. After one month later, a CT scan was performed and a bone density formation was found in the area of the zygomatic arch of the frontal bone and in the area of the parietal bone on the left (Figure 8). The patient was admitted to the maxillofacial surgery department for treatment in RCCH on 2016 after consultation.



a *b*

Fig. 7. MSCT postoperative on July 2024. (*a*) MSCT with three-dimensional reconstruction checkup (*b*) postoperative coronal and axial computed tomographic image with 3D, showing no recurrence signs of the disease

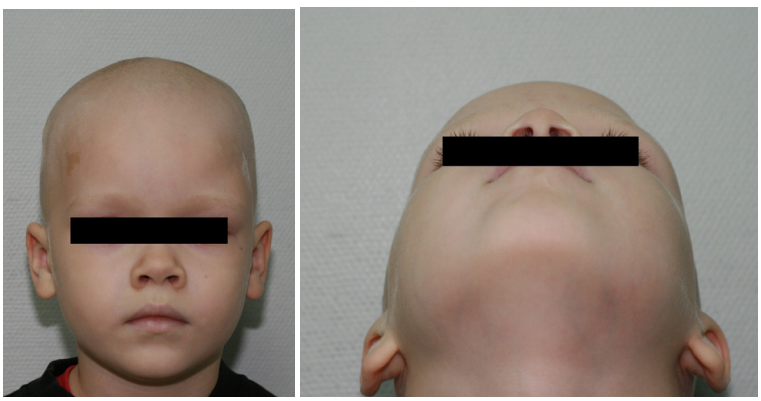


Fig. 8. Appearance of the child upon admission at RCCH on 2016, with forehead highlighting the gross asymmetry of the left supraorbital rim in comparison to the contralateral side. The skin above the formation is unchanged

Diagnosis

MSCT of the skull shows the affected osseous which is related to polyostotic craniofacial form of fibrous dysplasia in the left frontal bone and left parietal bone (25×40 mm in size and 7 mm in thickness). Locally, a bone density formation is visualized and palpated in these areas, originating from the bones (Figure 9).

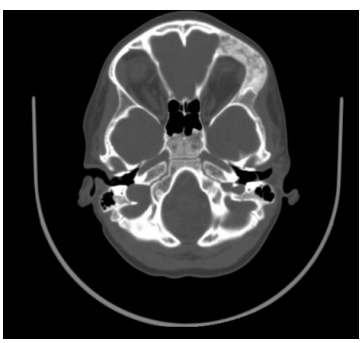


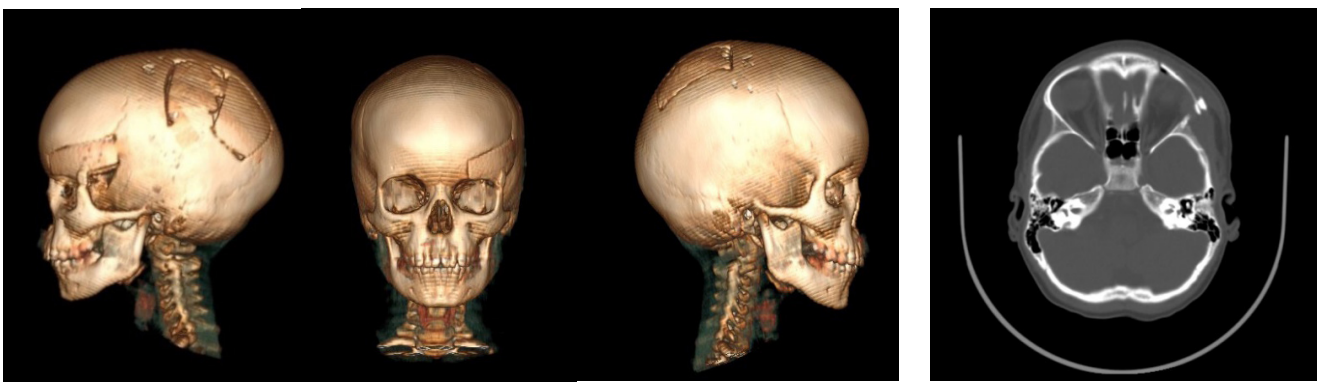
Fig. 9. Preoperative axial CT image exhibiting characteristic homogeneously dense appearance of fibrous dysplasia involving the left frontal bone

Treatment

A split auto-graft taken from the left parietal bone was remodeled to fit in the left frontal bone defect then fixed by mini-plate and mini-screw following by placing and fixing the internal cortical graft in the defect of the left parietal region (Figure 10).

Observation

In the postoperative period, the patient received antibacterial, infusion and symptomatic therapy. Healing by primary intention with the bone configuration looking normal. The patient was discharge home after 2 weeks from the operation day. He was monitored each year in RCCH by a follow up MSCT of skull. Recurrent episodes of this condition was revealed in 2022. MSCT showed evidence of bone regeneration and recurrence, with "hazy ground glass" appearance again in the same treated area in the left frontal bone region. (Figure 11). In 2025, a MSCT has been done again, and we noticed fast progression of FD in the same affected area (Figures 12, 13).



a *b*

Fig. 10. A split auto-graft. *a* — MSCT with three-dimensional reconstruction check-up, one day after the operation; *b* — Postoperative axial CT image

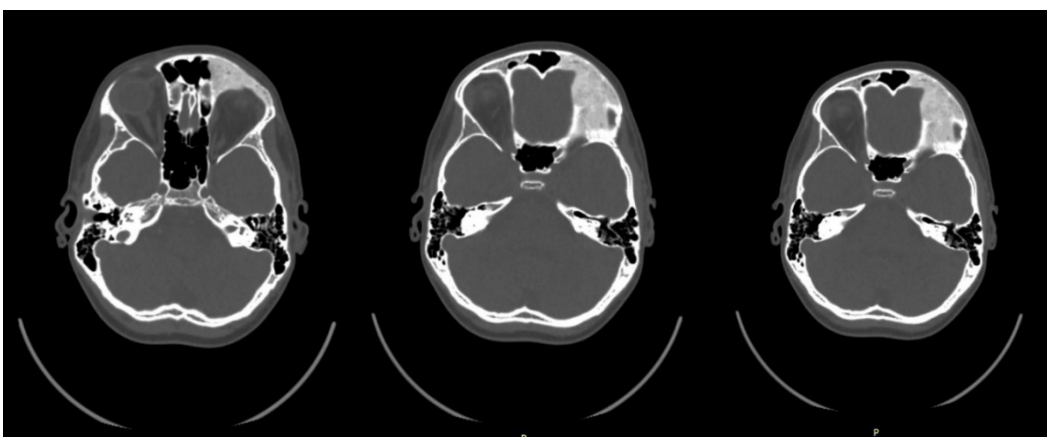


Fig. 11. MSCT scan showing recurrence of FD on the left frontal bone in 2022

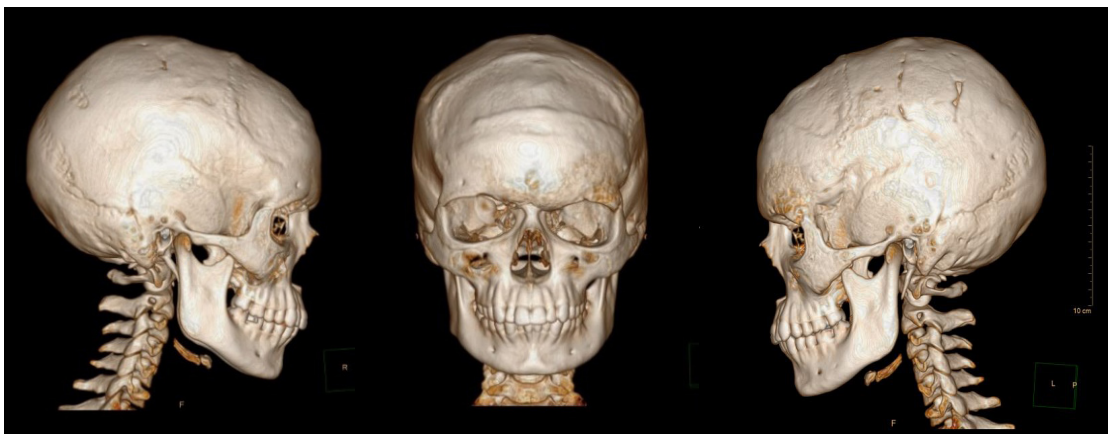


Fig. 12. MSCT revealed of fibrous dysplasia on the left frontal bone in 2025

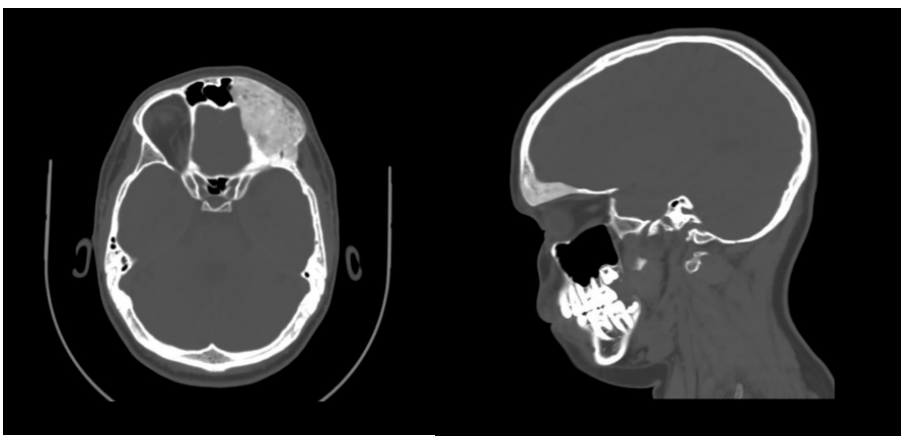


Fig. 13. Axial and sagittal computed tomographic image exhibiting characteristic ground-glass opacification of fibrous dysplasia involving the left frontal bones in 2025

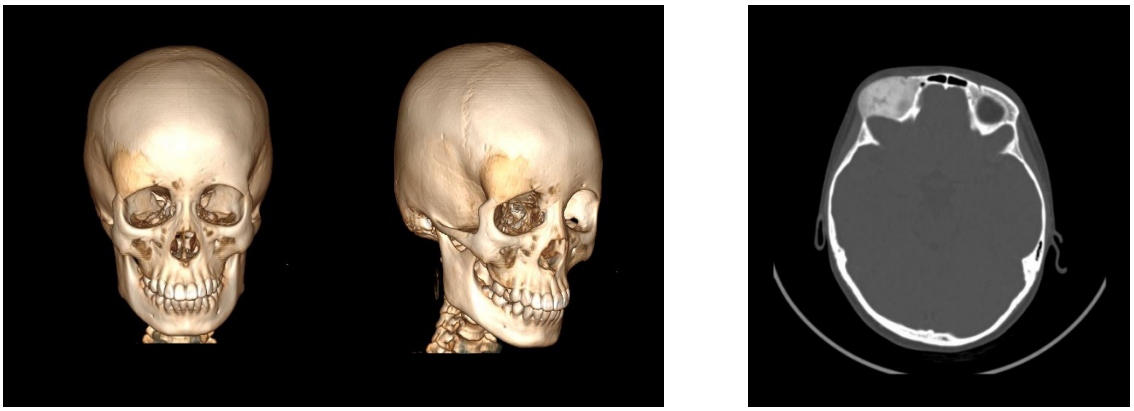
Clinical Case 4

Description of the clinical case

A 9 year old girl presented volume formation and growth in the right frontal bone in the winter of 2021. Due to no complain by this formation, the patient did not received any treatment back then. The patient was admitted to the RCCH for the first time for examination and treatment 2022, where a MSCT was done, due to notable facial asymmetry.

Diagnosis

MSCT of the skull shows monostatic fibrous dysplasia in the right frontal bone (5x5 cm). A focus of fibrous dysplasia with damage to the frontal bone and orbital roof was revealed**.** Additionally, edema and deformity in the right frontal bone was observed (Figure 14).



a *b*

Fig. 14. The edema and deformity in the right frontal bone.
a — 3D computed tomography image shows increased dimensions of the right frontal bone;
b — axial computed tomography image with expansion of right frontal bone

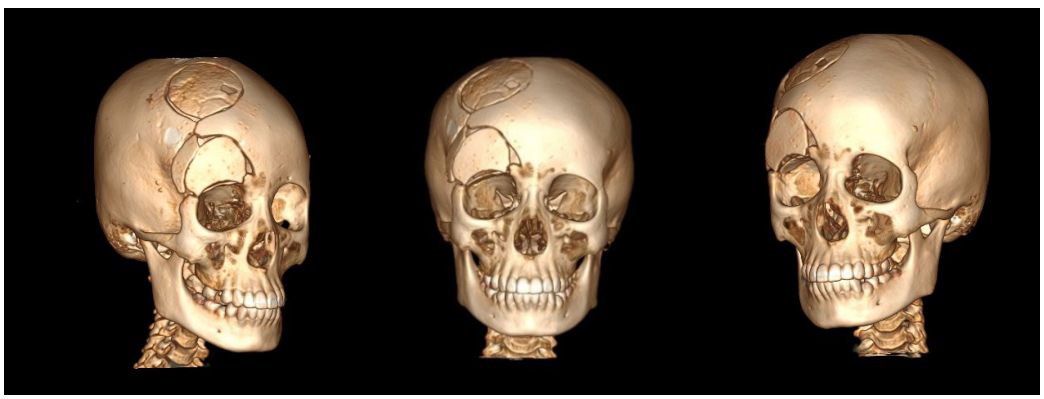


Fig. 15. Post-operation MSCT with three-dimensional reconstruction check-up

Treatment

A split graft from the cranial vault was planned. A 5×5 cm fragment was taken from the adjacent area of the unchanged frontal bone, which was subsequently split into 2 fragments with the return of the inner cortical plate to the donor area, and the outer cortical layer was cut into 3 fragments and re-modeled. The graft fragments were fixed to each other and to the skull bones (Figure 15).

Observation

In the postoperative period, the girl was under observation in the intensive care unit for 24 hours. The postoperative period is satisfactory and a course of antibiotic, infusion, and symptomatic therapy was administered.

The patient had some complications and changes in the right frontal region, with the presence of an epidural hematoma and air spreading to the area of the supra- and lateral walls of the right orbit after few days from the operation. In the soft tissues of the right orbit there are postoperative consolidations and edema. The lymph nodes of the neck, parotid and submandibular regions are enlarged, with a cyst of the temporomandibular joint. After treating and stabilizing the condition with analgesics and antibiotics, the patient was discharged 2 weeks later, after completing course of treatment under intensive observation in the department.

The recommended treatment modalities for craniofacial dysplasia can be categorized into three distinct groups: observation, pharmacological intervention, and

surgical intervention. Surgical treatment remains the preferred approach for this condition, as it aims to rectify or prevent deformities and functional impairments [19]. Furthermore, multi-slice computed tomography (MSCT) is instrumental in the diagnosis and treatment planning for fibrous dysplasia (FD) [20, 21]. The optimal surgical intervention for FD in the craniofacial region involves the utilization of customized polyetheretherketone (PEEK) implants or calvarial autografts [22]. Numerous studies have highlighted the advantages of employing PEEK, particularly in our clinical case studies, which indicate that the regions of the frontal bone treated with prefabricated PEEK implants — designed using preoperative CT scans — exhibited no signs of recurrence and maintained stable operative areas with favorable osteogenic conditions. PEEK has gained prominence in the medical field as an implant material, particularly in surgeries addressing fibrous dysplasia, due to its excellent thermal stability and biocompatibility, which promote osteointegration alongside its antibacterial and mechanical properties [23].

Conversely, some researchers advocate for the use of calvarial auto-grafts as a treatment option, citing benefits such as reduced issues related to bone availability, diminished donor site morbidity, and favorable tissue compatibility, which allows for a precise fit [24]. However, the findings presented in this article reveal certain limitations associated with this treatment approach. Notably, the surgical procedure often necessitates additional sites, which can lead to various complications, including exposure of the biomaterial (membrane or graft) to postoperative infections, neuro-sensory disturbances, and extended time required for bone reshaping, as well as the potential for hemorrhage and pain. Therefore, careful consideration of donor site selection and associated morbidity is essential.

The optimal treatment for craniofacial fibrous dysplasia involves the complete resection of the affected bones followed by immediate reconstruction using unaffected cranial bone grafts. Recently, the use of polyetheretherketone (PEEK) implants for reconstructing the affected area has become the predominant strategy for managing fibrous dysplasia in the craniofacial region, and is now considered the first-line intervention for this condition. The advantageous properties of PEEK, including its biocompatibility, flexibility for anatomical reshaping, and the ability to contour independently, contribute to the stability of the reconstructed area. This technology enables the achievement of aesthetically favorable cranioplasty outcomes at a cost-effective rate, without compromising patient results, and has demonstrated good stability with no indications of recurrence. In contrast, auto-grafts have shown limitations in achieving stable clinical outcomes and have been linked to a recurrence of fibrous dysplasia, along with postoperative complications.

Conclusion

Even though auto bone implant have been the go-to treatment plan for fibrous dysplasia in the most studied literature for its biocompatibility and have been considered as the first line treatment, but PEEK implants have showed promised results for its 3D shape, less trauma for patient (no need for donor site), and we are not limited in volume, the looking at the fact that fibrous dysplasia can affect multiple bone, polyetheretherketone (PEEK) 3D printed implants are the suitable type of implants and are recommended as a first line treatment.

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Аутотрансплантат и 3D-печатный имплантат при реконструкции лобной области

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Аннотация. *Актуальность.* Фиброзная дисплазия — патологическое состояние, характеризующееся замещением нормальной кости фиброзной тканью. Прогрессирование этого расстройства обычно стабилизируется с возрастом. Клинически это может проявляться в виде безболезненного отека и асимметрии лица. Рентгенологическое исследование

выявляет четко очерченные края, интрамедуллярное расширение, сохранение гладкого кортикального контура и вид матового стекла. Гистологически это состояние отличается наличием фиброзной ткани, заменяющей кость, а также нерегулярно расположенными и беспорядочно ориентированными костными трабекулами. Современные подходы к лечению часто включают хирургическое вмешательство с использованием изготовленных на заказ имплантатов из полиэфирэфиркетона (ПЭЭК) или аутогенных костных трансплантатов, таких как трансплантаты свода черепа. *Материалы и методы.* В отделении челюстно-лицевой хирургии Российской детской клинической больницы (РДКБ) — филиала ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» с 2016 по 2023 г. проводилось лечение 65 пациентов с гистологически подтвержденной фиброзной дисплазией лобной кости. Из них 2 пациентам (девочке 7 лет и мальчику 17 лет) были выполнены операции с использованием 3D-имплантатов из PEEK, а 2 пациентам (мальчику 6 лет и девочке 9 лет) — операции с использованием трансплантата из кости свода черепа. *Результаты и обсуждение.* Применение 3D-имплантатов эффективно усилило первичную стабильность реконструированной области. Поражение было успешно устранено, достигнув оптимального эстетического результата, характеризующегося сочетанием прочности, легкости и биосовместимости, без каких-либо наблюдаемых осложнений или неудач. В частности, рецидивы были выявлены у пациентов, прошедших лечение с использованием трансплантатов свода черепа в течение пяти лет после операции. *Выводы*. PEEK — это термопластичный полимер, характеризующийся своими нерассасывающимися и непористыми свойствами, что позволяет проводить интраоперационные модификации и обеспечивает оптимальные характеристики визуализации в послеоперационный период. С другой стороны, было отмечено, что аутотрансплантаты могут демонстрировать более высокий риск неудач по сравнению с изготовленными на заказ имплантатами.

Ключевые слова: лобная кость, фиброзная дисплазия, полиэфирэфиркетон, 3D-имплантат, трансплантат свода черепа

Информация о финансировании. Исследование не получало никаких специальных грантов от финансирующих агентств в государственном, коммерческом или некоммерческом секторах.

Вклад авторов. А.Ю. Кугушев — концепция, дизайн, хирургическое лечение, анализ исходных данных, написание рукописи. А.В. Лопатин — научное консультирование, окончательное одобрение рукописи. Ф. Садек, С. Дагер — участие в анализе данных, обзоре публикаций и написания рукописи. Рукопись была прочитана и одобрена всеми авторами, и все требования к авторству были соблюдены. Каждый автор считает, что рукопись представляет собой честную работу.

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ORIGINAL RESEARCH
ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Musculoaponeurotic layer structural alterations of the anterior abdominal wall in ventral hernias: insights from CT texture analysis

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Abstract. *Relevance*. Postoperative ventral hernias (POVH) remain a significant surgical challenge, characterized by remodeling of the musculoaponeurotic layer of the anterior abdominal wall and loss of functional integrity. Computed tomography (CT) texture analysis enables an objective assessment of tissue microarchitecture, facilitates the identification of structural changes, and optimizes preoperative planning and surgical decision-making. *Aim*. To evaluate structural changes in the musculoaponeurotic layer of the anterior abdominal wall in healthy individuals and patients with W2 and W3 POVH using texture analysis, identify intergroup differences, and determine the topographic-anatomical characteristics of affected tissues. *Materials and Methods*. This study included 90 patients (30 without hernias, 30 with W2-POVH, 30 with W3-POVH) examined between 2020 and 2024. All patients underwent multislice computed tomography (MSCT), and axial slices were segmented using Roboflow. The resulting masks were analyzed for texture characteristics, including brightness (mean_gray), contrast (contrast), correlation (correlation), kurtosis (kurtosis_gray), skewness (skewness_gray), standard deviation (std_gray), LBP, wavelet analysis, and gabor filtering. Statistical analysis included ANOVA, the Kruskal–Wallis test, and Tukey's post-hoc analysis. *Results and Discussion*. Texture analysis revealed significant differences in Wavelet and Gabor response ($p < 0.0001$). Group 2 exhibited marked structural alterations, while Groups 1 and 3 demonstrated similar tissue characteristics ($p > 0.05$), suggesting adaptive remodeling in patients with severe hernia defects. Further, Group 2 showed significant changes in contrast ($p < 0.0001$), correlation ($p < 0.0001$), and kurtosis ($p = 0.001$), while brightness (mean_gray) and homogeneity (homogeneity) did not differ significantly ($p > 0.05$). *Conclusion*. The most pronounced structural disorganization was observed in W2-POVH patients, indicating morphofunctional instability. In contrast, W3-POVH patients exhibited adaptive changes, suggesting compensatory remodeling. These findings confirm the progressive nature of morphological changes in POVH and highlight the importance of texture analysis for personalized surgical planning.

Keywords: textural analysis, postoperative ventral hernia, musculo-aponeurotic layer, structural changes, adaptive changes, fibrosis, surgical tactics

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All authors made significant contributions to the conception, conduct of the study and preparation of the article, and read and approved the final version before publication.

Consent of interest statement. All patients provided informed voluntary consent to participate in the study according to the Helsinki Declaration of the World Medical Association (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013) and personal data processing.

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Introduction

Postoperative ventral hernia (POVH) is a common complication following abdominal surgeries, with an incidence rate ranging from 9% to 20% within the first year postoperatively [1]. According to studies, this rate increases to 22.4% within three years after laparotomy [2]. The primary pathogenic factors contributing to the development and progression (recurrence) of POVH include degenerative changes in the postoperative scar area and the musculoaponeurotic layer of the anterior abdominal wall, particularly in patients with high-risk factors for hernia formation [3, 4].

From a biomechanical perspective, the linea alba endures the highest mechanical loads in patients with postoperative ventral hernias [3]. Consequently, deformation of the linea alba results in unbalanced lateral forces due to intra-abdominal pressure and involuntary contractions of the oblique and transverse muscles, leading to their retraction and shortening. This muscle shortening may cause irreversible contractures or reversible spasticity, further contributing to the lateral displacement of the rectus abdominis muscles, hernia formation, and its progression.

Prolonged herniation, especially in large and giant hernias, leads to remodeling of the abdominal wall muscles. Chronic exposure to pathological protrusion results in muscle atrophy, excessive fibrosis, and microcirculatory disturbances [5]. These changes are associated with a loss of muscle elasticity and strength, complicating surgical treatment and increasing the risk of recurrence. However, depending on the defect size and the extent of tissue involvement, the morphological and functional changes in the anterior abdominal wall may vary significantly. Preoperative assessment of the musculoaponeurotic layer remains a complex task, as conventional imaging techniques do not always allow for quantitative evaluation of structural alterations.

Modern approaches to medical image analysis include texture analysis, which enables the detection of subtle changes in tissue structure by assessing its heterogeneity, density, and spatial organization.

Computed tomography (CT) is an X-ray-based imaging modality that registers the attenuation of X-ray radiation as it passes through biological tissues. CT images are generated due to variations in the linear attenuation coefficient (μ), which is determined by the tissue's composition and density. The primary

quantitative parameter used in CT imaging is the Hounsfield Unit (HU, Hounsfield Units), calculated using the following equation [6]:

$$HU = 1000 \times \frac{\mu - \mu_{\text{water}}}{\mu_{\text{water}} - \mu_{\text{air}}}$$

where μ_{water} — is the attenuation coefficient of water, a μ_{air} — is the attenuation coefficient of air, μ — represents the attenuation coefficient of the tissue.

Each tissue type has a specific range of Hounsfield Units (HU): air (≈ –1000 HU), fat (≈ –100 HU), soft tissues (0–80 HU), and bones (700–3000 HU). Thus, the grayscale intensity in CT imaging is directly correlated with the radiological density of tissues and their atomic composition.

Traditional visual analysis of CT slices is limited by subjective interpretation in disease diagnostics, whereas quantitative methods, such as texture analysis, enable a detailed assessment of tissue heterogeneity.

Traditional diagnostic approaches, including visual assessment, morphometry, and manual classification, remain fundamental tools in medical imaging. Visual interpretation of images, based on subjective evaluation of grayscale gradients and anatomical structures, is widely used in clinical practice. However, this approach is characterized by a high degree of subjectivity, influenced by the individual perception of the physician, which can lead to variability in diagnostic outcomes. Additionally, the sensitivity of visual analysis is limited, making it challenging to detect subtle structural changes, while the absence of quantitative parameters prevents standardization in diagnostics.

Morphometry, as a method of quantitative assessment of anatomical structures, involves measuring their size, shape, and volume. In medical practice, morphometric parameters such as tissue thickness, pathological volume, and degree of deformation are used for disease diagnosis and prognosis. However, this method is limited by its inability to account for histological tissue heterogeneity, making it insufficient for a comprehensive characterization of structural changes. Furthermore, morphometric analysis requires significant time investment and manual data processing, reducing its efficiency in routine clinical applications.

The application of texture analysis in CT imaging allows for a quantitative assessment of tissue heterogeneity, revealing structural patterns that are not detectable through conventional diagnostic methods. Unlike visual analysis and morphometry, texture analysis relies on numerical parameters, eliminating subjective bias and improving reproducibility. This method exhibits high sensitivity to microscopic structural alterations and enables multiparametric analysis, including the evaluation of contrast, homogeneity, correlation, and other characteristics. Automating data processing significantly accelerates diagnosis and facilitates large-scale data analysis, which is particularly critical for personalized treatment planning. Thus, the integration of texture analysis into clinical practice enhances medical imaging capabilities by providing a standardized, reproducible, and precise method for diagnosing structural tissue changes.

Texture analysis is based on mathematical modeling of the spatial distribution of pixel intensities and enables the computation of parameters such as contrast, correlation, homogeneity, entropy, and other statistical features [7, 8].

One of the most widely used methods is the Gray-Level Co-occurrence Matrix (GLCM), which models the probability of pairs of pixels with specific grayscale values occurring at a fixed spatial distance from each other [9]. The key parameters of GLCM include: contrast, which characterizes the degree of difference between neighboring pixels and is calculated using the formula:

$$\text{Contrast} = \sum_{i=0}^{N-1}\sum_{j=0}^{N-1} P(i,j)(i-j)^2$$

Correlation, which measures the linear dependence between grayscale levels and is calculated using the formula:

$$Correlation = \sum_{i=0}^{N-1}\sum_{j=0}^{N-1} P(i,j)\frac{(i-\mu_i)(j-\mu_j)}{\sigma_i\sigma_j}$$

where μ_j are the mean grayscale values, and σ_i and $\sigma_j$are the standard deviations of grayscale levels in the image. Homogeneity, which evaluates the degree of texture smoothness and is calculated using the formula:

$$\text{Homogeneity} = \sum_{i=0}^{N-1}\sum_{j=0}^{N-1}\frac{P(i,j)}{1+(i-j)^2}$$

This parameter measures how uniform the distribution of grayscale intensities is, assigning higher values to images with low contrast and smooth transitions between pixel intensities.

The Local Binary Patterns (LBP) method analyzes the microtexture of an image by encoding differences between the central pixel and its neighboring pixels into a binary code. First introduced by Ojala et al., LBP is a powerful tool for microtexture analysis [10]. It is based on comparing the intensity of the central pixel with its surrounding pixels and generating a binary code that reflects local variations in brightness.Formally, LBP is defined as follows:

$$LBP = \sum_{p-0}^{P-1} s\,(I_P - I_c)\times 2^p, s(x) = \begin{cases}1, x \geq 0\\ 0, x < 0\end{cases}$$

where I_c — the intensity of the central pixel, I_P — represents the intensities of the neighboring pixels, P — number of neighbors, $s(x)$ is a step function that assigns binary values based on the difference in intensity.

The LBP method enables texture classification based on local gradient variations, making it a valuable tool for analyzing medical images, including oncological diagnostics, the assessment of structural tissue changes, and the identification of pathological features in histological specimens.

Wavelet analysis is a multi-scale image processing technique that decomposes texture into components with different spatial-frequency characteristics [11, 12]. Unlike the traditional Fast Fourier Transform (FFT), which analyzes an image in a fixed frequency domain, Wavelet transformation provides simultaneous localization in both space and frequency, allowing for a more detailed characterization of structural patterns. Mathematically, the Wavelet decomposition of a signal is defined as the convolution of the original image f(*x*, *y*) with a basis function ψ(*x*, *y*):

$$W(x,y,s) = \\ = \int\int f(x',y')\psi*(sx'-x, sy'-y)dx'dy'$$

where s — denotes the scale parameter, which controls the level of decomposition, $\psi(x,y)$ — represents the scaled and translated wavelet function

The application of Wavelet Energy allows for the assessment of texture energy distribution across different frequency ranges, making this method particularly useful for analyzing soft tissue structures, identifying anomalies, and predicting pathological changes [13, 14].

Gabor filters are directional filters that enable the analysis of periodic structures and spatial-frequency characteristics of an image [15]. They model the spatial-frequency sensitivity of visual cortex receptors and are widely used in texture analysis for extracting distinctive image features. The two-dimensional Gabor function is defined by the following equation:

$$G(x,y,\lambda,\theta,\psi,\sigma,\gamma) = \\ = \overline{\exp}\left(-\frac{x'^2+\gamma^2y'^2}{2\delta^2}\right)\cos\left(2\pi\frac{x'}{\lambda}+\psi\right)$$

where $\boldsymbol{x'=x\cos\theta+y\sin\theta}$, $\boldsymbol{y'=-x\sin\theta+y\cos\theta}$, $\boldsymbol{\lambda}$ (wavelength) controls the spatial frequency of the filter, **θ** (orientation) defines the direction of the filter, **σ** (scale) determines the standard deviation of the Gaussian envelope, **γ** (aspect ratio) adjusts the ellipticity of the Gaussian function, **ϕ** (phase offset) shifts the cosine function.

In addition to the Gray-Level Co-occurrence Matrix (GLCM), texture analysis of medical images utilizes statistical parameters that characterize the distribution of pixel intensities. One of the key metrics is the mean gray level (mean_gray), which represents the average intensity of pixels and reflects the density of the examined tissue. Another essential parameter is the standard deviation of the gray level (std_gray), which quantifies the variability of intensity values, allowing

for an objective assessment of structural heterogeneity in the image.

To analyze the shape of the intensity distribution, the skewness (skewness_gray) metric is used, which indicates the asymmetry of the distribution relative to the mean intensity. Negative skewness suggests the presence of predominantly darker regions, whereas positive skewness indicates the dominance of brighter areas. Another critical metric is kurtosis (kurtosis_gray), which reflects the "sharpness" of the intensity distribution and is particularly useful for detecting outliers and anomalous pixel values, making it especially important for evaluating heterogeneous structures.

The application of these statistical characteristics in CT texture analysis enables a detailed assessment of tissue microarchitecture, identification of deviations from normal structure, and classification of pathological changes. Texture analysis not only reveals the morphological features of tissues but also provides a quantitative assessment of their alterations, making it a promising tool in the diagnosis of various pathologies.

The use of Wavelet analysis, Gabor filtering, and Local Binary Patterns (LBP) for evaluating the textural characteristics of the musculoaponeurotic layer of the anterior abdominal wall offers greater precision in differentiating tissue conditions in patients with ventral hernias [16, 17].

Modern quantitative CT image analysis techniques continue to evolve, providing new opportunities for objective assessment of anatomical structures and pathological alterations. Beyond classical texture analysis — comprising methods such as GLCM, LBP, Wavelet analysis, and Gabor filtering — deep neural networks, machine learning, and radiomics have gained significant attention. These advanced techniques allow for a more detailed analysis of medical images by automatically extracting features and incorporating them into predictive models.

Deep learning is a powerful tool for medical image processing, enabling automatic segmentation, classification, and pathology detection. The foundation of these methods lies in convolutional neural networks (CNNs), which can extract relevant features without the need for manual selection of textural characteristics [18].

The architecture of Convolutional Neural Networks (CNNs) consists of several key components:

- Convolutional layers, which apply filters to input images and extract texture-based features.
- Pooling layers, which reduce the dimensionality of the feature space and enhance robustness to spatial shifts.
- Fully connected layers, which are used for classification or regression based on the extracted features.

One of the most effective architectures for medical imaging is U-Net [19]. This neural network model is specifically designed for image segmentation and is widely applied in radiology. Unlike traditional segmentation algorithms, U-Net employs an encoder-decoder strategy, allowing it to capture both local and global image features simultaneously.

Deep neural networks are also utilized in automated pathology detection, including the recognition of tumors, fibrosis, and degenerative tissue changes [20]. However, the primary limitations of this approach include high computational complexity, the need for large annotated datasets, and limited model interpretability.

In addition to neural network-based approaches, classical machine learning algorithms play a significant role in CT image analysis. Techniques such as gradient boosting (XGBoost, LightGBM), random forests (Random Forest), and support vector machines (SVM) [21] enable the development of predictive models based on quantitative image features, including textural, morphometric, and intensity-based parameters.

A key advantage of machine learning algorithms is their ability to combine diverse datasets and efficiently operate on relatively small sample sizes. For instance, the random forest method constructs ensembles of decision trees, reducing overfitting risk and enhancing model stability. Meanwhile, gradient boosting demonstrates high accuracy in classification and regression tasks by sequentially training weak models and integrating them into a unified system.

Radiomics is a methodology for multiparametric image analysis, involving the extraction and quantitative assessment of textural, morphometric, and spatial features. This approach enables the identification of hidden patterns that are inaccessible through traditional

visual analysis or even through individual machine learning techniques [22].

The radiomics pipeline consists of several key stages:

- Image segmentation, identifying the region of interest (ROI).
- Feature extraction, including textural characteristics, shape descriptors, and intensity metrics.
- Data filtering, removing non-informative parameters.

Model development, creating predictive models using machine learning techniques.

One of the primary advantages of radiomics is its potential for personalized diagnostics and prognostic analysis. In oncology, this method is widely applied for tumor aggressiveness assessment, therapy response prediction, and patient risk stratification [23]. By analyzing the textural characteristics of tumor formations, it is possible to identify radiomic signatures that correlate with molecular tumor features and clinical outcomes.

Deep learning, machine learning, and radiomics represent promising approaches for quantitative CT image analysis, expanding the capabilities of traditional visual assessment and textural feature extraction. Deep learning enables the automatic extraction of meaningful features, machine learning facilitates predictive modeling based on textural parameters, and radiomics integrates a broad spectrum of quantitative image characteristics.

Despite their high accuracy, the clinical implementation of these methods requires standardization, validation, and the development of reproducible data processing protocols. Further research on the integration of AI-driven approaches will contribute to enhancing diagnostic accuracy and improving the personalization of medical decision-making.

Aim

The objective of this study was to assess structural changes in the musculoaponeurotic layer of the anterior abdominal wall in healthy patients and those with ventral hernias of W2 and W3 categories using texture analysis of CT images. The study aims to identify quantitative and qualitative differences between groups based on key textural parameters and to evaluate the nature of structural tissue changes depending on the stage of the pathological process.

Materials and methods

This study was conducted at the Federal State Budgetary Healthcare Institution Clinical Hospital No. 85 of the Federal Medical and Biological Agency of Russia and the Private Healthcare Institution "Clinical Hospital RZD-Medicine" named after N.A. Semashko. The dataset included 90 patients who underwent examination or treatment between January 2020 and September 2024. All patients provided informed voluntary consent to participate in the study according to the Helsinki Declaration of the World Medical Association (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013) and personal data processing. The study was approved by the Ethics Committee of the Medical Institute of the RUDN University, Moscow, Russia (protocol No. 28 dated May 16, 2024).

For analysis, three independent groups were formed: group 1 (N=30): patients without postoperative ventral hernias (POVH) who were examined or treated for unrelated chronic pathology. Group 2 (N=30): patients diagnosed with W2 POVH. Group 3 (N=30): patients with large or giant ventral hernias (W3), who were candidates for preoperative botulinum therapy before surgical intervention.

All patients underwent computed tomography (CT) of the thoracic cavity, abdominal cavity, and pelvic organs (three anatomical regions) (Figure 1).

In the axial CT series, segmentation of the anterior abdominal wall muscles was performed, including the external oblique muscle (m. obliquus externus abdominis), internal oblique muscle (m. obliquus internus abdominis), and transverse abdominal muscle (m. transversus abdominis) on both the right and left sides. The segmentation of anatomical structures was carried out using the Roboflow platform (https://app.roboflow.com) through automated segmentation methods with manual correction when necessary. The U-Net convolutional neural network was used as the baseline algorithm for segmentation (Figure 2).

Fig. 1. Example of a CT series in the axial projection for segmentation

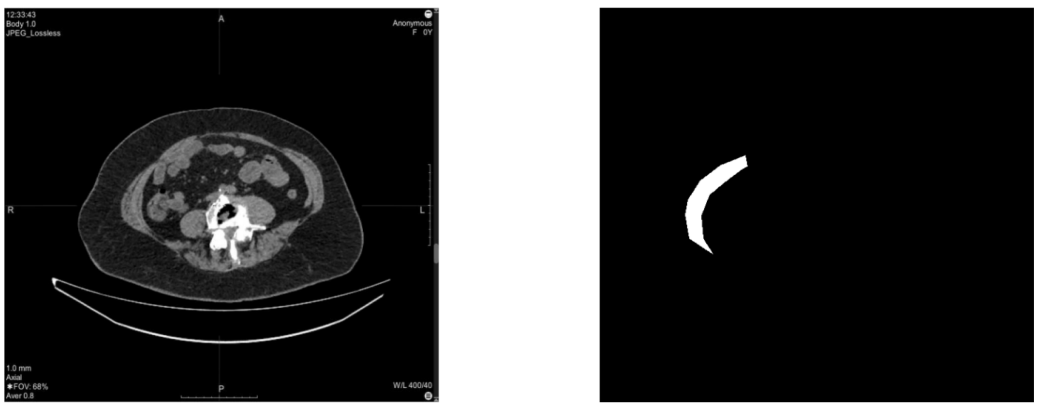


Fig. 2. An example of a CT scan and the corresponding mask of the musculo–aponeurotic layer of the anterior abdominal wall on the right

To enhance the accuracy of annotation, manual correction of segmentation masks was performed following automated segmentation, allowing for the minimization of errors associated with tissue heterogeneity and intensity gradient variability.

For the correct analysis of CT image texture characteristics, preprocessing was applied, including pixel intensity normalization, artifact suppression, and contrast optimization. Normalization was performed using intensity standardization, following the formula:

$$I' = \frac{I - \mu}{\delta}$$

where: I' — is the normalized intensity, I — the original pixel intensity, μ — the mean intensity of the image, δ — the standard deviation of intensity values.

This procedure minimized variability in scanning conditions and standardized gray-level intensity across all images. To eliminate artifacts caused by noise, metallic objects, and tissue density variations, a Gaussian filter and bilateral filtering were applied.

Contrast enhancement was performed using histogram equalization, which redistributes gray-level intensities based on their cumulative distribution. The integration of a comprehensive preprocessing approach, including normalization, artifact suppression, and automated segmentation, ensured standardization of CT images and improved the reproducibility of subsequent texture analysis.

For data processing and analysis, statistical methods, machine learning techniques, and visualization tools were employed. Descriptive statistics included the computation of mean values, standard deviations, and parameter distribution analysis within each group.

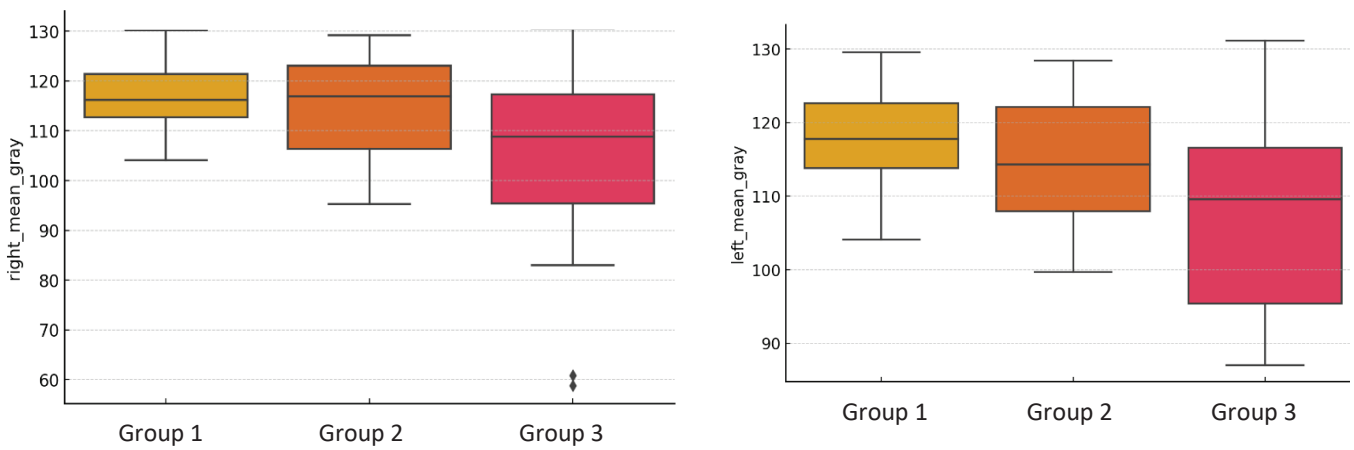
Texture analysis was conducted across the three patient groups, evaluating parameters such as mean gray level (mean_gray), contrast, homogeneity, correlation, kurtosis (kurtosis_gray), skewness (skewness_gray), standard deviation of gray levels (std_gray), Local Binary Patterns (LBP), lbp_mean, and lbp_var. The analysis utilized LBP, wavelet transform, and Gabor filtering.

To assess group differences, analysis of variance (ANOVA) and the nonparametric Kruskal–Wallis test were applied, enabling the identification of statistically significant differences. In cases where significant differences were detected, post-hoc Tukey's test was performed for multiple group comparisons.

All computations and visualizations were conducted using Python 3.11 libraries, including NumPy, SciPy, scikit-learn, Matplotlib, and Seaborn.

Results and discussion

The gray density (brightness) analysis of the segmentation masks revealed that Group 1 exhibited the brightest masks (right_mean_gray = 116.41, left_mean_gray = 117.82), which may indicate lower tissue density (Figure 3).



a *b*

Fig. 3. The density of gray in masks between groups (*a* and *b*). Kruskal–Wallis test with post-hoc Tukey's test, **p* < 0.05 considered significant

Group 3 exhibited the darkest masks (right_mean_gray = 106.46, left_mean_gray = 107.82), suggesting a potential increase in tissue density or the presence of fibrotic changes. Group 2 demonstrated intermediate values (right_mean_gray = 115.14, left_mean_gray = 114.89), reflecting a transitional nature of structural alterations in the musculoaponeurotic layer of the anterior abdominal wall (Figure 4).

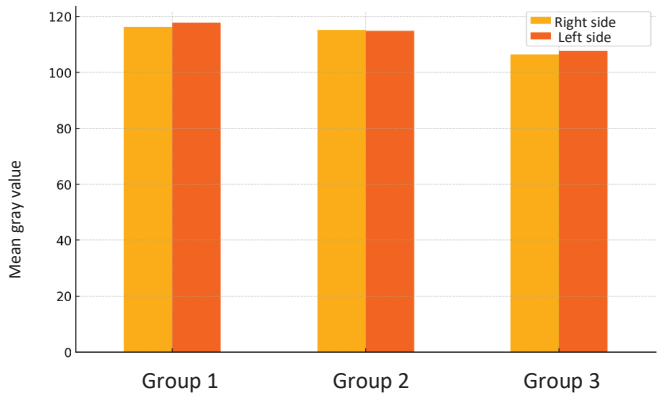


Fig. 4. Graph of gray level distribution (gray density in masks) by groups

Descriptive statistics revealed differences between groups in several key characteristics, as confirmed by analysis of variance (ANOVA) and the Kruskal–Wallis test. Statistically significant differences ($p < 0.05$) were observed for contrast and correlation on both the right and left sides, specifically: right_contrast ($p < 0.0001$), right_correlation ($p < 0.0001$), right_homogeneity ($p < 0.001$), left_contrast ($p < 0.0001$), and left_correlation ($p < 0.0001$). At the same time, features such as right_energy, right_lbp_mean, left_energy, and left_lbp_mean did not exhibit significant differences between groups, suggesting the similarity of these parameters across different clinical categories. Texture analysis demonstrated that the Wavelet Energy metric differed significantly between groups (ANOVA: $p < 0.0001$, Kruskal–Wallis test: $p < 0.0001$) (Figure 5).

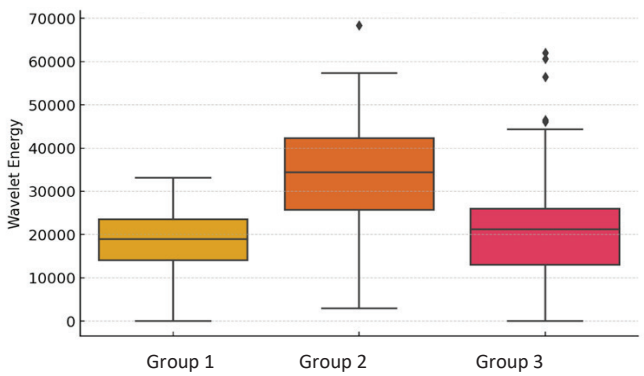


Fig. 5. Wavelet Energy indicator between groups. ANOVA: *$p < 0.0001$, Kruskal–Wallis test: * $p < 0.0001$

Post-hoc Tukey's test confirmed significant differences between Groups 1 and 2 ($p < 0.0001$) as well as between Groups 2 and 3 ($p < 0.0001$). However, no statistically significant differences were observed between Groups 1 and 3 ($p = 0.3279$), indicating that the muscle structure in Group W3 (Group 3) is more similar to normal tissue (Group 1) than to Group 2 (W2). The Gabor filtering method also identified significant differences between the groups (ANOVA: $p < 0.0001$, Kruskal–Wallis test: $p < 0.0001$) (Figure 6).

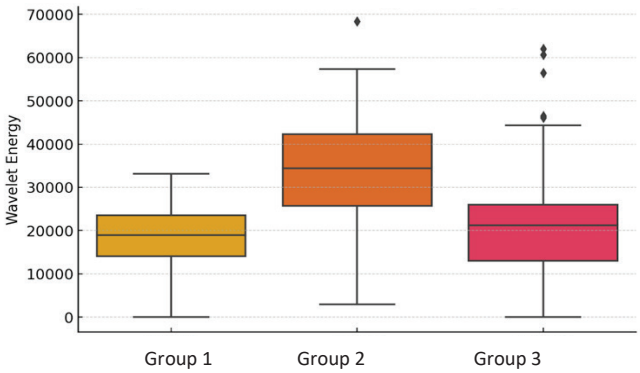


Fig. 6. Gabor filtering indicator between groups. Statistical analysis: ANOVA and Kruskal–Wallis test; *$p < 0.0001$ considered significant

Statistically significant differences were observed between Groups 1 and 2 ($p < 0.0001$), whereas differences between Groups 1 and 3 did not reach statistical significance ($p = 0.0801$). These findings suggest a trend toward normalization of muscle structure in Group 3.

Comparison of the right and left sides within each group revealed significant differences in Group 3 for the contrast parameter ($p = 0.00015$), which may indicate asymmetrical tissue changes. In Group 1, a significant difference was observed for correlation ($p = 0.033$), reflecting structural muscle characteristics. In Group 2, no statistically significant differences between sides were detected ($p > 0.05$), indicating symmetrical tissue properties in this group.

The results confirm that different stages of ventral hernias are associated with distinct types of changes in

the musculoaponeurotic layer of the anterior abdominal wall. Our findings are consistent with the results reported by Parshikov V.V. et al. [24], who demonstrated that the anatomical structure of the musculoaponeurotic layer undergoes significant alterations in ventral hernias, including changes in tissue density, fibrosis, and muscle remodeling.

Furthermore, it is well established that the use of botulinum toxin in preoperative preparation is based on the phenomenon of muscle contracture, which is particularly pronounced in W3 hernias [25]. The results of our study also support this finding, showing increased tissue density and reduced elasticity in W3 patients, which necessitates preoperative muscle relaxation for successful surgical treatment.

Thus, the observed structural changes complement existing scientific data on the mechanisms of ventral hernia formation and may contribute to the optimization of treatment strategies. Texture analysis of CT images provides an objective, quantitative assessment of pathological changes, making it a valuable tool for diagnostics and surgical decision-making. However, further research is required to evaluate the prognostic significance of the identified textural characteristics and their impact on surgical outcomes.

Conclusion

According to the obtained data, Group 1 (healthy patients) exhibits the most homogeneous muscle tissue structure, with the least changes in contrast and correlation, confirming their functional integrity and absence of pathological alterations. Group 2 (W2) demonstrates the most pronounced structural muscle changes, characterized by decreased contrast, altered pixel correlation values, and modified texture parameters, as identified through Wavelet analysis and Gabor filtering. The darkest segmentation masks were observed in Group 3, suggesting hypertrophic or compensatory changes in W3 patients, whereas tissues in W2 patients appear to be in a state of dysfunction and instability.

In terms of textural characteristics, Group 3 (W3) is closer to healthy patients (Group 1) than to Group 2, suggesting the presence of compensatory mechanisms in muscle tissue under conditions of long-standing hernias. This hypothesis is supported by the stable and homogeneously increased muscle density, along with similarity in the distribution of textural parameters between Group 3 and the control group.

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Структурные изменения мышечно-апоневротического слоя передней брюшной стенки при вентральных грыжах: данные текстурного анализа КТ

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Аннотация. *Актуальность.* Послеоперационные вентральные грыжи (ПОВГ) представляют собой серьезную хирургическую проблему, характеризующейся ремоделированием мышечно-апоневротического слоя передней брюшной стенки и потере его функциональной целостности. Применение текстурного анализа в КТ позволит объективно оценить микроархитектонику тканей, выявить структурные изменения и оптимизировать предоперационное планирование и тактику хирургического лечения. Цель — оценить структурные изменения мышечно-апоневротического слоя передней брюшной стенки у здоровых пациентов и пациентов с W2 и W3 — ПОВГ с помощью текстурного анализа, выявить межгрупповые различия и особенности топографо-анатомической организации тканей. Материалы и методы. В ретроспективное исследование включены 90 пациентов (30 без грыж, 30 с W2-ПОВГ, 30 с W3-ПОВГ), обследованных в 2020–2024 гг. Всем пациентам выполнено МСКТ брюшной полости. Далее аксиальные срезы были сегментированы на онлайн-платформе Roboflow. Полученные маски анализировались по текстурным характеристикам: яркость, контрастность, корреляция, куртоз, асимметрия, стандартное отклонение, LBP, вейвлет- и Габор-анализ. Для статистической обработки использованы ANOVA, критерий Крускала–Уоллиса и post–hoc анализ Тьюки. *Результаты и обсуждение.* Текстурный анализ мышечно–апоневротического слоя передней брюшной стенки выявил значимые различия между группами по Вейвлет- и Габор-анализу ($p < 0,0001$). Пациенты группы 2 существенно отличались от групп 1 и 3, тогда как группы 1 и 3 демонстрировали схожие характеристики тканей ($p > 0,05$), что может свидетельствовать об адаптационных изменениях у пациентов с наиболее выраженными грыжевыми дефектами. У пациентов группы 2 наблюдаются выраженные изменения структуры мышц, что подтверждается значимыми различиями по контрастности ($p < 0,0001$), корреляции ($p < 0,0001$) и куртозису ($p = 0,001$). При этом средняя яркость и однородность не показали статистически значимых различий между группами ($p > 0,05$), что указывает на схожесть общего распределения интенсивностей сигнала. Выводы. Наиболее выраженные признаки структурной дезорганизации мышечно-апоневротического слоя выявлены у пациентов с W2–ПОВГ, что указывает на морфофункциональную нестабильность. В группе W3–ПОВГ преобладают адаптационные процессы. Выявленные закономерности подтверждают этапность морфологических изменений при ПОВГ и подчеркивают значимость текстурного анализа для персонализированного хирургического планирования.

Ключевые слова: текстурный анализ, послеоперационная вентральная грыжа, мышечно-апоневротический слой, структурные изменения, адаптационные изменения, фиброз, хирургическая тактика.

Информация о финансировании: работа выполнена без финансовой поддержки.

Информация о конфликте интересов. Авторы заявляют об отсутствии конфликтов интересов.

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CLINICAL CASE REPORT
КЛИНИЧЕСКИЙ СЛУЧАЙ

Application of monoclonal antibodies in primary chronic osteomyelitis of the mandible in children

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Abstract. *Relevance*. Primary chronic osteomyelitis (PCO) is a rare condition that poses diagnostic challenges, primarily affecting children between the ages of 5 and 17. It can occur in various bones, including the mandible in the maxillofacial region. The complexity of distinguishing PCO from infections, tumors, metabolic disorders, and other inflammatory conditions has led to misdiagnoses, resulting in inappropriate treatment strategies and recurrent episodes. Currently, there is no standardized treatment protocol for PCO, with most therapies starting with non-steroidal anti-inflammatory drugs (NSAIDs) to manage symptoms. The purpose of this case report is to find a new treatment approach by using monoclonal antibodies such as Denosumab in the treatment protocol. Monoclonal antibodies like Denosumab have shown promising results by targeting the RANKL-RANK interaction, inhibiting osteoclast activity, and reducing inflammatory bone resorption. *Materials and Methods:* In the Department of Maxillofacial Surgery of the Russian Children's Clinical Hospital — a branch of the Federal State Autonomous Educational Institution of Higher Education Russian National Research Medical University named after. N.I. Pirogov of the Ministry of Health of the Russian Federation of Moscow from 2015 to 2023, 45 children underwent inpatient treatment for primary chronic osteomyelitis (PCO). Of these, 17 children received combination therapy, which included decortication with removal of all granulomatous tissue and administration of the drug Denosumab, and that is after receiving negative culture results which conforms the diagnose of PCO. From these 17 patients, a 9-year-old girl with a persistently relapsing course was selected for this article. *Results*: The treatment methods employed in this clinical case successfully increased the density of the affected area. However, if small cystic components were retained and the sanitation of the granulated tissues was incomplete, a relapse occurred, necessitating repeated surgical treatment. *Conclusion:* By using this approach, we found that the intervals between collapses have been prolonged; leaving no doubt that the addition of Denosumab to the treatment protocol has played a significant role in achieving this optimal result by maintaining remission stability, even after the symptoms disappeared.

Key words: primary chronic osteomyelitis, rare diseases, auto inflammatory bone diseases, denosumab, antiresorptive treatment

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Ethics approval — not applicable due to the retrospective nature of the study.

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Consent for publication: Voluntary written consent was obtained from the patients participate in the study in accordance with the World Medical Association Declaration of Helsinki (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013) and the processing of personal data.

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Introduction

Primary Chronic Osteomyelitis (PCO) is a rare autoinflammatory disorder mostly affecting children and adolescents and lacks a bacterial origin. The term «Chronic Non-bacterial Osteomyelitis» was first introduced by Bjorksten et al. in 1980 to describe a clinical state marked by the persistent occurrence of chronic sterile osteomyelitis [1–3].

This disease, along with any other autoimmune disease, is characterized by the spontaneous activation of the innate immune system, which results in bone inflammation [4–7]. This phenomenon is evident through recurrent cycles of remission and exacerbation, manifesting as episodes of pain and fever accompanied by sterile cultures that do not respond to antibiotic treatment [8, 9].

The suspicion of PCO arises in the absence of clear indicators of bone infection, such as pus, fistula formation, or sequestrum. Consequently, the diagnostic process is challenging and typically involves the exclusion of other bone pathologies through radiographic imaging and, when necessary, biopsy [10, 11].

In the absence of placebo-controlled trials, treatment of PCO relies on personal experience, case collections, and expert opinion. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen and Naproxen, are regarded as the first-line treatment, demonstrating efficacy in pain management and inducing remission in approximately 43% to 83% of patients. In patients who are refractory to NSAID or in individuals with vertebral lesions, more aggressive treatment is commonly applied, including corticosteroids, sulfasalazine (SSZ), methotrexate (MTX), or TNF-α inhibitors [12, 13].

Due to the pivotal involvement of RANK and its ligand RANKL in the primary pathophysiological mechanisms associated PCO, Denosumab as a monoclonal antibody that specifically targets RANKL, an acronym for Receptor Activator of Nuclear Factor-Kappa B Ligand [14, 15], has recently been employed as a therapeutic intervention. By inhibiting the activation of RANKL on the surface of osteoclasts, Denosumab subsequently influences the RANK receptor. This blockade of the interaction between RANKL and

RANK effectively hinders osteoclast differentiation, functionality, and longevity, thereby leading to a reduction in bone resorption [16–20].

Material and methods

At the Department of Maxillofacial Surgery of the Russian Children's Clinical Hospital (RDKB), a branch of the Federal State Autonomous Educational Institution of Higher Education at the Russian National Research Medical University named after N.I. Pirogov, under the Ministry of Health of the Russian Federation in Moscow, 45 children received inpatient treatment for primary chronic osteomyelitis (PCO) from 2015 to 2023.

Among these patients, a 9-year-old girl with a persistently relapsing course was selected for this article. In her clinical case, debridement and decortication were performed, involving the resection of granulomatous fibro-osseous tissue from the affected area. Subsequent culture and morphological analysis verified the aseptic characteristics of the inflammatory condition. Following this, a single administration of the monoclonal antibody Denosumab was performed. Prior to the administration of the monoclonal antibodies, the patient underwent standard biochemical assessments of blood and urine to exclude the possibility of renal dysfunction, and informed consent was secured for the off-label application of the medication.

The patient's parents provided informed voluntary consent to participate in the study according to the Helsinki Declaration of the World Medical Association (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013) and personal data processing.

Clinical case description

Description of the clinical case: A 9-year-old female patient had been ill since February 2020, when she first exhibited facial asymmetry accompanied by pain in the lower jaw. A lower jaw anomaly was identified through multi-slice computed tomography (MSCT) conducted at her place of residence. Subsequently, a surgical procedure was performed, during which a biopsy was obtained, leading to a diagnosis of fibrous dysplasia of the left half of the lower jaw.

Over the following year, the patient experienced recurrent episodes of her condition, necessitating her admission to RDKB hospital in January 2021 for further evaluation and treatment. Upon her admission, notable asymmetry of the lower jaw was observed, attributed to bone deformation in the left body of the lower jaw (Figure 1).

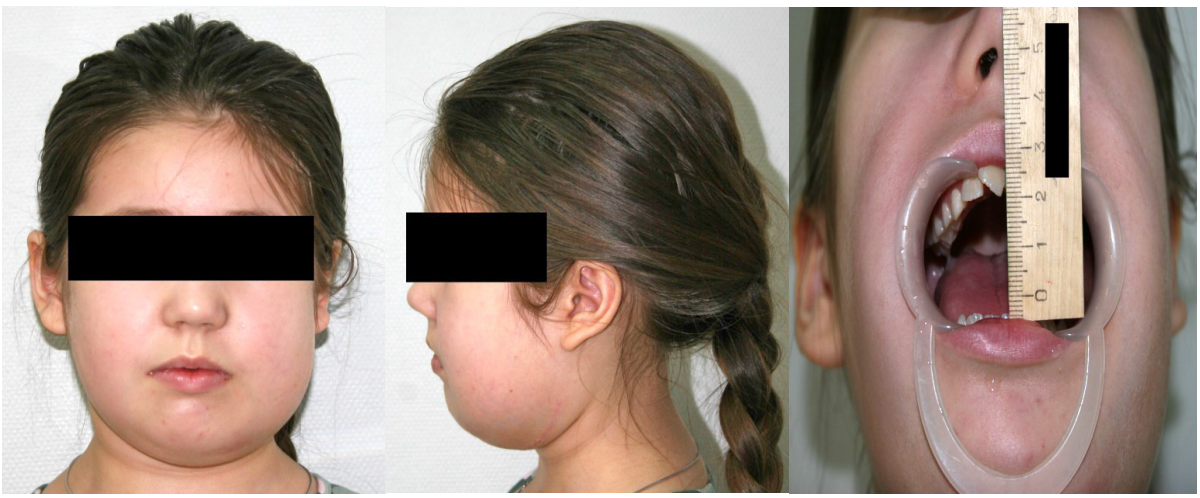

Fig 1. Patient's visual evaluation when admitted to the hospital for the first time

Diagnosis

The MSCT imaging reveals edema and deformity in the left segment of the mandible. The affected osseous structure exhibits uneven compaction resembling a «ground glass» appearance, accompanied by localized areas of softening and disruption of the cortical layer. Notably, there is a periosteal thickening along the anterior surface of the altered bone, measuring up to 2.5 mm. Additionally, the mandibular canal demonstrates widening, and the compaction of bone extends into the right segment over a distance of 10 mm. The left masseter muscle appears slightly hypertrophied, and the surrounding soft tissues exhibit edema, with linear compaction extending to the skin (Figure 2).

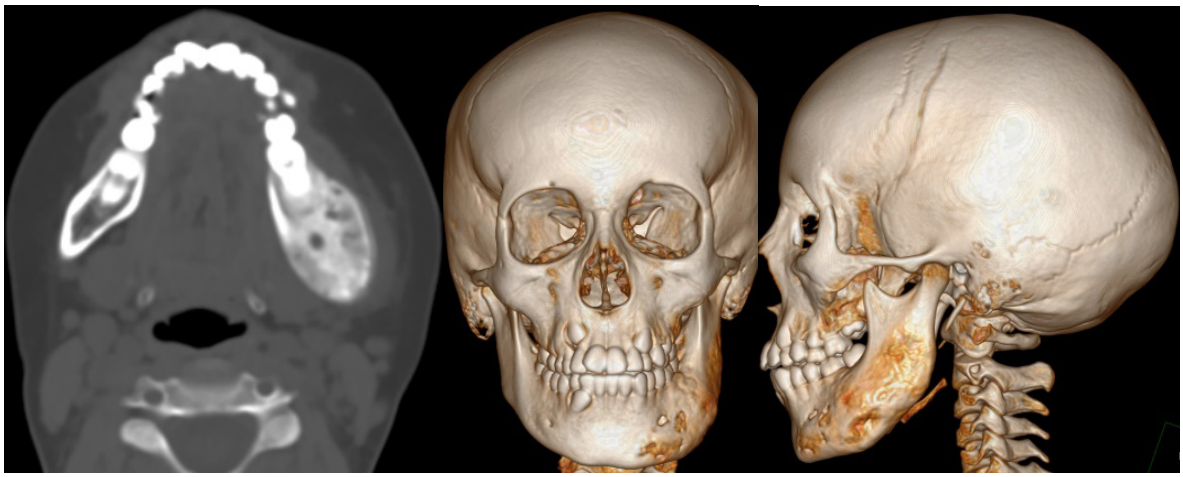

Fig. 2. MSCT scan in January 2021 shows the affected area that includes the body, angle and the ramus of the left half of the mandible. It can also be noted the widening of the mandibular canal on the left side

Treatment

In light of the clinical and radiographic findings, a surgical intervention was conducted involving the excision of fibrously altered tissues using Volkmann spoon and a bur until the sclerotic margins of the cavity were palpated. In the area corresponding to tooth 3.8, the cortical layer was excised, and the rudimentary structure of tooth 3.8 was extracted. The excised tissue was subsequently sent for culture and histopathological analysis. The postoperative course was uneventful, during which antibacterial and symptomatic therapies were administered, along with a single dose of 60 mg of the monoclonal antibody Denosumab.

Histological analysis of the provided bone material revealed fragments of spongy bone with areas of osteolysis and reactive bone formation. The intertrabecular spaces were occupied by loose fibrous connective tissue, which contained minimal foci of productive, non-granulomatous inflammation. The results from the culture did not demonstrate any microbial growth, thereby conforming the sterilized status of the PCO. Following an improvement in the patient's condition, the child was discharged under the care of specialists at their place of residence.

Observation

Throughout the subsequent year, no relapses were observed; however, in the month prior to the second admission which was in April 2022, the patient experienced mild pain on the right side of the lower jaw, necessitating readmission to the RDKB. A MSCT scan conducted upon admission revealed a softening focus measuring up to 5 mm in depth and 1 cm in diameter located at the angle of the right half of the lower jaw, accompanied by a cystic cavity in the vicinity of the roots of tooth 3.5. Additionally, an irregular structure of the body of the left half of the lower jaw was noted (Figure 3).

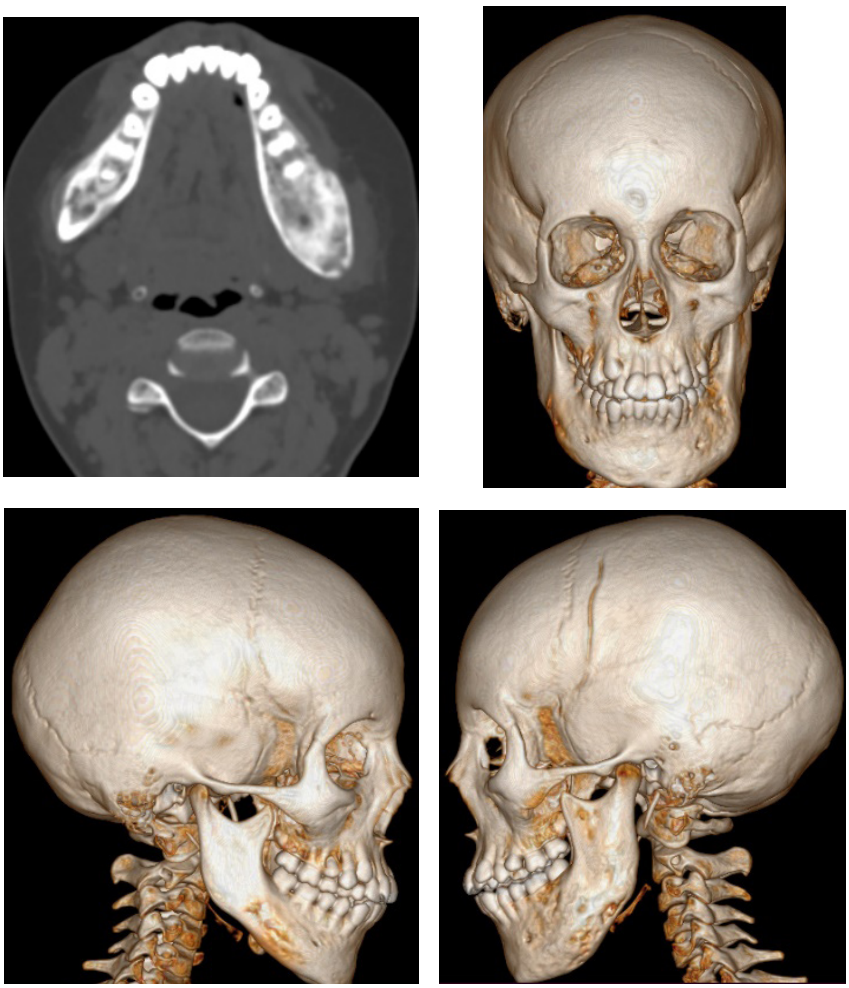

Fig. 3. MSCT scan in April 2022 exhibits the extension of the bone destruction on both halves of the mandible

Consequently, a decision was made to perform decortication on both sides and to excise the fibrous-altered tissues utilizing Volkmann spoons until the sclerotic margins of the cavity were palpated. Since the patient's general condition and radiological findings before the second admission were not as serious as her condition when she was first admitted, and since we had already given the patient a dose of 60 mg of denosumab, which is considered a rather high dose, and for fear of complications of this drug such as osteonecrosis of drug use, it was decided not to repeat the dose in the postoperative period, which was uneventful, and the patient received antibacterial treatment (Medaxone, Metrogyl) along with symptomatic therapy.

Discussion

Monitoring the patient's condition in the year following reveals that the regions of bone destruction were filled, despite the retention of the irregular morphology of the external contour of the mandible. Notably, the child remained pain free throughout this period (Figure 4).

Similarly, a MSCT scan conducted in June 2024, one year later, revealed evidence of bone regeneration, with the external contour of the mandible returning to its typical dimensions and morphology (Figure 5).

Although Denosumab is most commonly used to treat osteoporosis in the elderly and postmenopausal women, it is now being considered as a first-line treatment for primary chronic osteomyelitis. We can see the added benefit of using Denosumab in the treatment plan in achieving stable remission, extending the time period between relapses and consolidating resorption zones. This is illustrated by comparing the patient's condition prior to hospitalization, marked by frequent relapses within a single year, to the following year, during which the patient experienced no pain.

Conclusion

The therapeutic interventions used in this clinical case effectively enhanced the density of the impacted region. Nevertheless, in instances where minor cystic elements were not completely removed and the decontamination of the granulated tissues was inadequate, a recurrence ensued, prompting the need for additional surgical intervention. The utilization of Denosumab postoperatively contributed to the maintenance of disease remission. The most commonly used doses among adult patients are 120 or 60 mg. However, since our patients are children and their anthropometric parameters differ from adults, it was decided to adjust the dose based on the weight and height of the children. This decision was made to choose smaller doses to prevent the risk

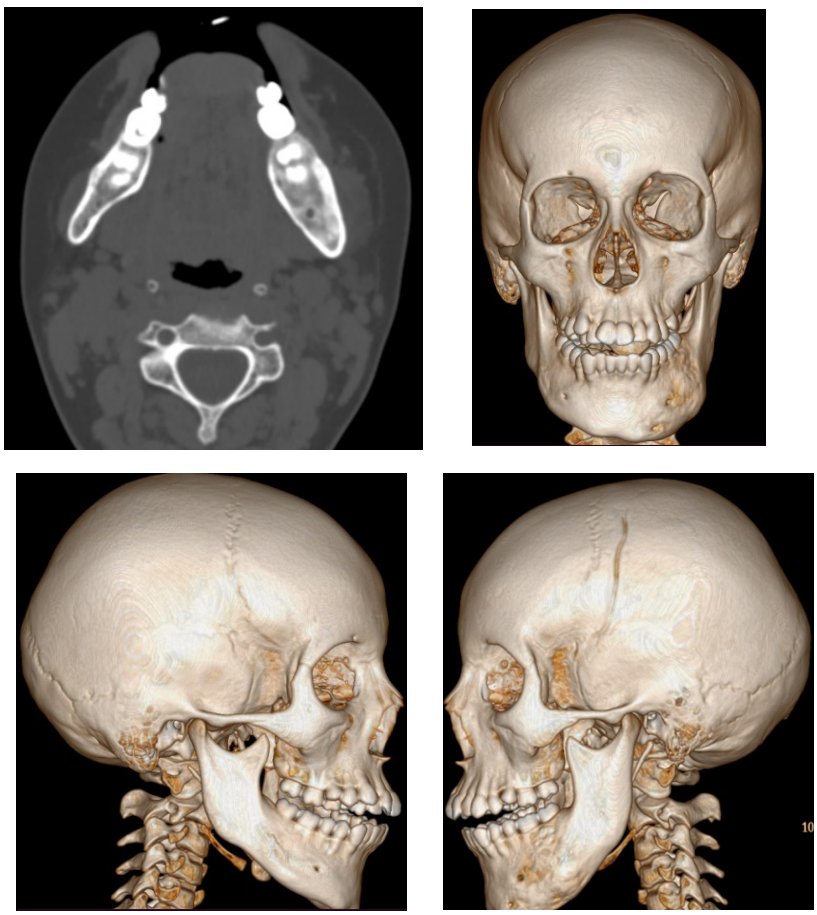

Fig. 4. MSCT scan in May 2023 showing the recovering process of the mandible with the remaining of uneven contour of the left half of the mandible

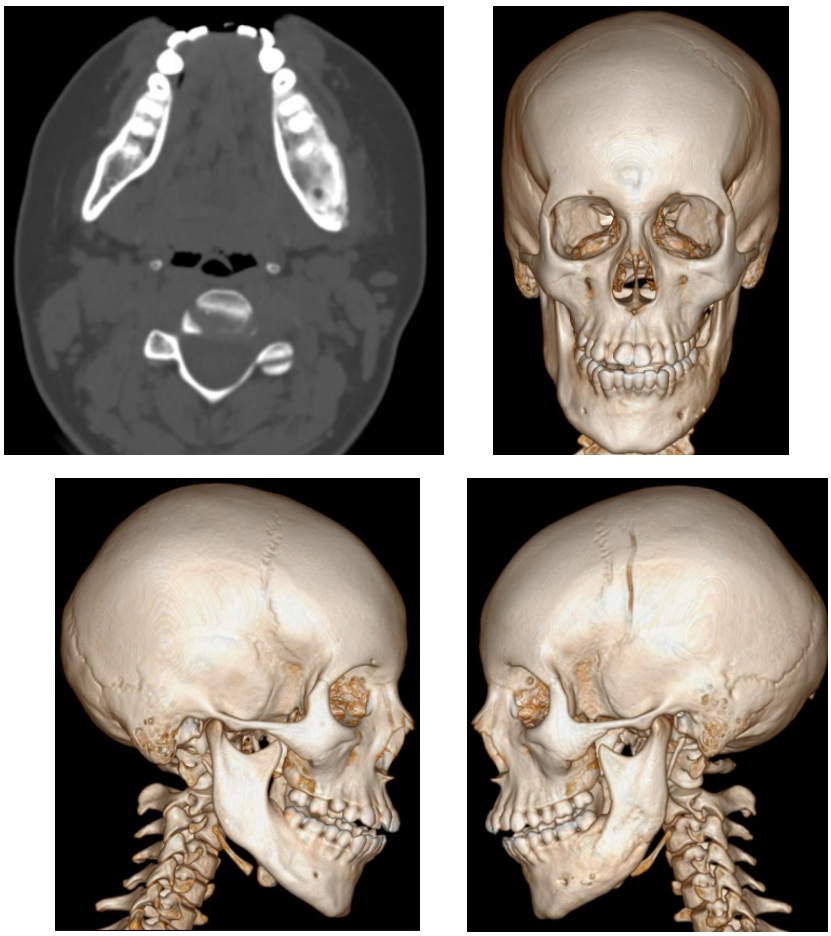

Fig. 5. MSCT scan in June 2024 exhibiting the evidence of bone regeneration and positive dynamic of the treatment protocol. It can be clearly seen the positive effect of adding Denosumab to the treatment protocol in keeping the good outcome of the operation

of osteonecrosis as it is known as the most common complication after using the Anti-resorptive drugs, while ensuring effective rehabilitation and prolonging the periods between relapses.

The inquiry regarding the differential response to Denosumab treatment among patients persists as a topic for future discussion and scientific investigation. Specifically, it remains unclear why certain individuals achieve satisfactory outcomes with a single dose, while others require multiple doses to attain the desired therapeutic effect.

It is essential to determine the correct dosage, treatment duration, and administration frequency of these medications to achieve optimal results and minimize the risk of postoperative complications typically associated with this class of drugs. Consequently, a comprehensive strategy for managing PCO should include antiresorptive therapy. The incorporation of monoclonal antibodies represents an innovative approach to PCO management, aimed at enhancing treatment efficacy.

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Применение моноклональных антител при первичном хроническом остеомиелите нижней челюсти у детей

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Аннотация. *Актуальность.* Первично-хронический остеомиелит (ПХО) — редкое заболевание, которое представляет диагностические трудности, в основном поражая детей в возрасте от 5 до 17 лет. Оно может возникать в различных костях, включая нижнюю челюсть в челюстно-лицевой области. Сложность различения ПХО от инфекций, опухолей,

метаболических нарушений и других воспалительных состояний привела к ошибочным диагнозам, что привело к неадекватным стратегиям лечения и рецидивирующим эпизодам. В настоящее время не существует стандартизированный протокол лечения ПХО, при этом большинство терапий начинаются с нестероидных противовоспалительных препаратов (НПВП) для лечения симптомов. Целью данного отчета о случае является поиск нового подхода к лечению с использованием моноклональных антител, таких как деносумаб, в протоколе лечения. Моноклональные антитела, такие как деносумаб, показали многообещающие результаты, воздействуя на взаимодействие RANKL-RANK, ингибируя активность остеокластов и уменьшая воспалительную резорбцию кости. *Материалы и методы:* В отделении челюстно-лицевой хирургии Российской детской клинической больницы — филиала ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России по г. Москве с 2015 по 2023 г. 45 детей проходили стационарное лечение по поводу первичного хронического остеомиелита (ПХО). Из них 17 детям проводилась комплексная терапия, включавшая декортикацию с удалением всей гранулематозной ткани и назначение препарата деносумаб, и это после получения отрицательных результатов посева, что подтверждает диагноз ПХО. Из этих 17 пациентов для данной статьи была выбрана девочка 9 лет с упорно рецидивирующим течением. *Результаты и обсуждение.* Примененный в данном клиническом случае метод лечения позволил успешно увеличить плотность пораженной зоны. Однако при сохранении мелких кистозных очаги и неполной санации гранулематозных тканей возникал рецидив, требующий повторного хирургического лечения. *Выводы.* При использовании данного подхода мы обнаружили, что периоды между рецидивами удлиняются, что не оставляет сомнений в том, что включение деносумаба в протокол лечения сыграло значительную роль в достижении стойкой ремиссии за счет поддержания стабильности результатов даже после исчезновения симптомов.

Ключевые слова: первично-хронический остеомиелит, редкие заболевания, аутовоспалительные заболевания костей, деносумаб, антирезорбтивное лечение

Информация о финансировании. Исследование не получало гранта от финансирующих агентств в государственном, коммерческом или некоммерческом секторах.

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ORIGINAL RESEARCH
ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Non-invasive diagnostics of monomorphic maculopapular cutaneous mastocytosis

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Abstract. *Relevance*. Monomorphic maculopapular cutaneous mastocytosis (mMPCM) is a rare and diagnostically challenging form of cutaneous mastocytosis, often mimicking other pigmentary and papular dermatoses. The increasing incidence of mMPCM and the complexity of its differential diagnosis underscore the need for effective, non-invasive diagnostic methods. The aim of the study was to evaluate the dermoscopic features of mMPCM and compare them with findings from optical coherence tomography (OCT) and histopathological criteria, aiming to establish a non-invasive diagnostic algorithm. *Materials and Methods.* The study included 30 patients aged 14–30 years with mMPCM, observed at the Moscow Scientific and Practical Center of Dermatovenereology and Cosmetology, Russia from 2022 to 2024. All patients underwent clinical examination, dermoscopy, and, in selected cases, OCT imaging. Dermoscopic and OCT findings were systematically compared with histopathological results from skin biopsies. *Results and Discussion.* Dermoscopic examination of mMPCM lesions revealed increased yellow-brown pigmentation, preservation of skin appendages, unchanged vellus hairs, pigment pseudonetwork, and a weakly expressed asymmetric vascular pattern. Darier's sign was more frequently detected under dermoscopy than on clinical examination. OCT imaging visualized clusters of mast cells as round or oval low-intensity signal zones, most often located in the reticular dermis,

corresponding to histological mast cell infiltrates. The combination of dermoscopy and OCT allowed differentiation of mMPCM from other subtypes of cutaneous mastocytosis based on the depth and distribution of infiltrates. Notably, non-invasive methods provided valuable information for diagnosis and monitoring, reducing the need for routine biopsies. *Conclusion.* Integrating dermoscopy and OCT into the diagnostic workflow for mMPCM offers informative, non-invasive alternative to traditional histopathology, facilitating early and accurate diagnosis as well as monitoring of disease dynamics and therapeutic efficacy. This study is among the first to systematically compare dermoscopic and OCT findings with histopathological features in mMPCM, highlighting the unique diagnostic potential of these non-invasive techniques for rare forms of cutaneous mastocytosis.

Keywords: Non-invasive diagnostics, dermoscopy, OCT, optical coherence tomography, monomorphic maculopapular cutaneous mastocytosis, Lumen Stratis, MosDerma

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Author contributions. E.I. Kasikhina — design of the study, conducting non-invasive examination, data analysis, text writing, editing the manuscript. M.N. Ostretsova — design of the study, text writing, editing the manuscript. V. Yu. Udhukhu — design of the study, editing the manuscript. K.S. Petrova — design of the study, conducting non-invasive. examination, data analysis, text writing, editing the manuscript. O.N. Goeva — design of the study, conducting non-invasive examination, data analysis. E.K. Sukhina — literature review. A.A. Korobova — literature review. All authors made significant contributions to the conception, conduct of the study and preparation of the article, and read and approved the final version before publication.
Conflicts of interest statement. Authors declare no conflict of interest.

Ethics approval. The study was approved by the Local Ethics Committee at the Moscow Scientific and Practical Center of Dermatovenereology and Cosmetology № 58 dated March 31, 2022.

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Introduction

Mastocytosis is a complex heterogeneous multisystem disease associated with pathological activation or accumulation of neoplastic mast cells (MCs) in one or more organs [1, 2]. It has been demonstrated that abnormal activation of clonal MCs is characteristic of all clinical forms (subtypes) of mastocytosis [3]. Hartmann K. et al. in 2016 published a consensus report that proposed a classification of cutaneous mastocytosis [4]. Skin lesions in adults with mastocytosis are defined as a monomorphic type of maculopapular cutaneous mastocytosis (MPCM), whereas in children several subtypes are distinguished: single and multiple mastocytomas, diffuse (DCM), polymorphic MPCM (pMPCM) and monomorphic MRCM (mMPCM) [5]. The monomorphic type of MPCM is usually diagnosed in adults, less often in the pediatric population. In most patients, the onset of the disease occurs after 2 years of age, closer to puberty. mMPCM is characterized by small, brown, maculopapular lesions of uniform shape and size, located primarily on the trunk and thighs (Figure 1).

In adolescents and adults, lesions may look like melanocytic nevi, making differential diagnosis difficult (Figure 2).

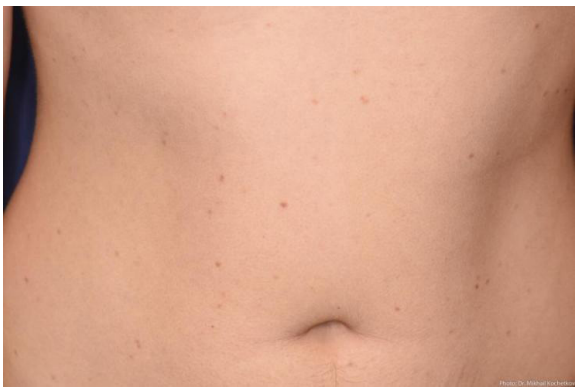


Fig. 1. Typical lesions in monomorphic MPCM

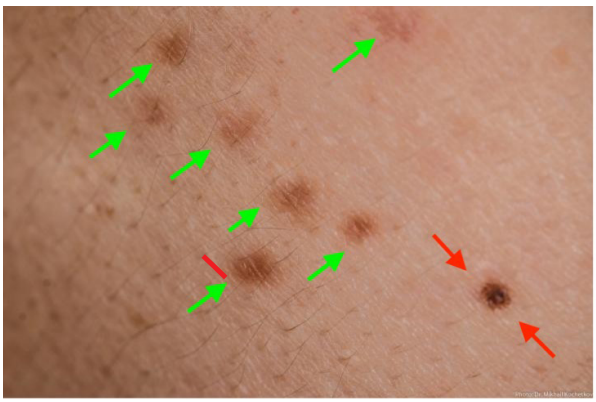


Fig. 2. mMPCM lesions (green arrows) and melanocytic nevus (red arrows)

In mMPCM, blister formation is rare. Blisters in mMPCM are rare. This is explained by the pathomorphological features of mMPCM, in which mast cell infiltration is mainly located in the reticular dermis with preservation of the papillary dermis, whereas in polymorphic MPCM and DCM, dense mast cell infiltration is observed in the papillary dermis [5]. In children with mMPCM, the rash has a lower tendency to spontaneous regression and persists into adulthood. Serum tryptase levels vary from normal to significantly elevated values [4].

The increase in the incidence of cutaneous mastocytosis [6, 7], the increase in the number of patients with monomorphic ("adult") type of maculopapular cutaneous mastocytosis (mMPCM) and diffuse cutaneous mastocytosis (DCM), and the complex process of differential diagnosis dictate the need for more widespread implementation of non-invasive diagnostic methods. In recent years, new papers describing the dermoscopic features of mastocytosis have been published [8]. At the same time, publications describing the capabilities of optical coherence tomography (OCT) in mastocytosis are insufficient [9, 10].

Objective

To evaluate dermatoscopic semiotic signs of monomorphic type of maculopapular cutaneous mastocytosis and compare them with the results of optical coherence tomography and histopathologic criteria.

Material and methods

The study included 30 patients aged 14 to 30 years diagnosed with maculopapular cutaneous mastocytosis, who were observed at the Moscow Scientific and Practical Center of Dermatovenereology

and Cosmetology, Russia from 2022 to 2024. The classification of clinical forms and types of cutaneous mastocytosis was carried out in accordance with the current WHO classification [2]. The clinical examination included anamnesis and physical examination of the study participants. The diagnosis was confirmed by histological examination.

Dermoscopy of rashes was performed on all patients using a device for dynamic clinical and instrumental monitoring of patients with skin lesions "MosDerma" (Patent for Utility Model No. 177110 dated 17.04.2017). Immersion and polarization dermoscopy with 20-fold magnification was performed. To avoid capillary collapse, the pressure on the rash was minimized. In patients with a widespread skin process, at least two elements were assessed to consider all possible dermoscopic patterns. Subsequently, the identified dermoscopic patterns were compared with clinical signs and the severity of mediator symptoms in various forms of mastocytosis for each patient.

Optical coherence tomography was performed in 3 patients. An optical coherence tomograph for non-invasive examination of the internal structure of human superficial tissues "OKT-1300-E" (high-speed modification (92000 A-scans per second), developed by BioMedTech LLC (Russia) was used. The device is equipped with a specialized probe for examining external biotissues with 3D modeling of optical "sections". Technical characteristics of the device: radiation wavelength — 1300 nm, radiation power at the object 0.75 mW (below the level permissible by the AMSI standard), spatial resolution — 8–20 μm, scanning depth — up to 2 mm, scanning area 5×5 mm, image acquisition time — 20 seconds.

The Lumen Stratis software developed at Lobachevsky University was used for image processing and analysis (certificate of state registration of the software "Visual statistical analysis of skin structure images obtained by non-invasive methods (Lumen stratis)" No. 2024615567 dated 03/11/2024). The software is written in the Python 3.10 programming language in the open-source development environment PyCharm Community Edition 2023.2.3. Required type and version of the operating system: Windows 7/8/10/11. The Lumen Stratis software performs the following tasks: fast loading (without a converter) of OCT images; visualization of statistical analysis of images, carried out in a dialogue with the user; saving the results of the study in the formats.bmp,.JPG,.tmg,.dat,.png and txt.

Results and discussion

Dermoscopy

The frequency of detection of dermatoscopic patterns in patients with mMPCM is presented in Table 1.

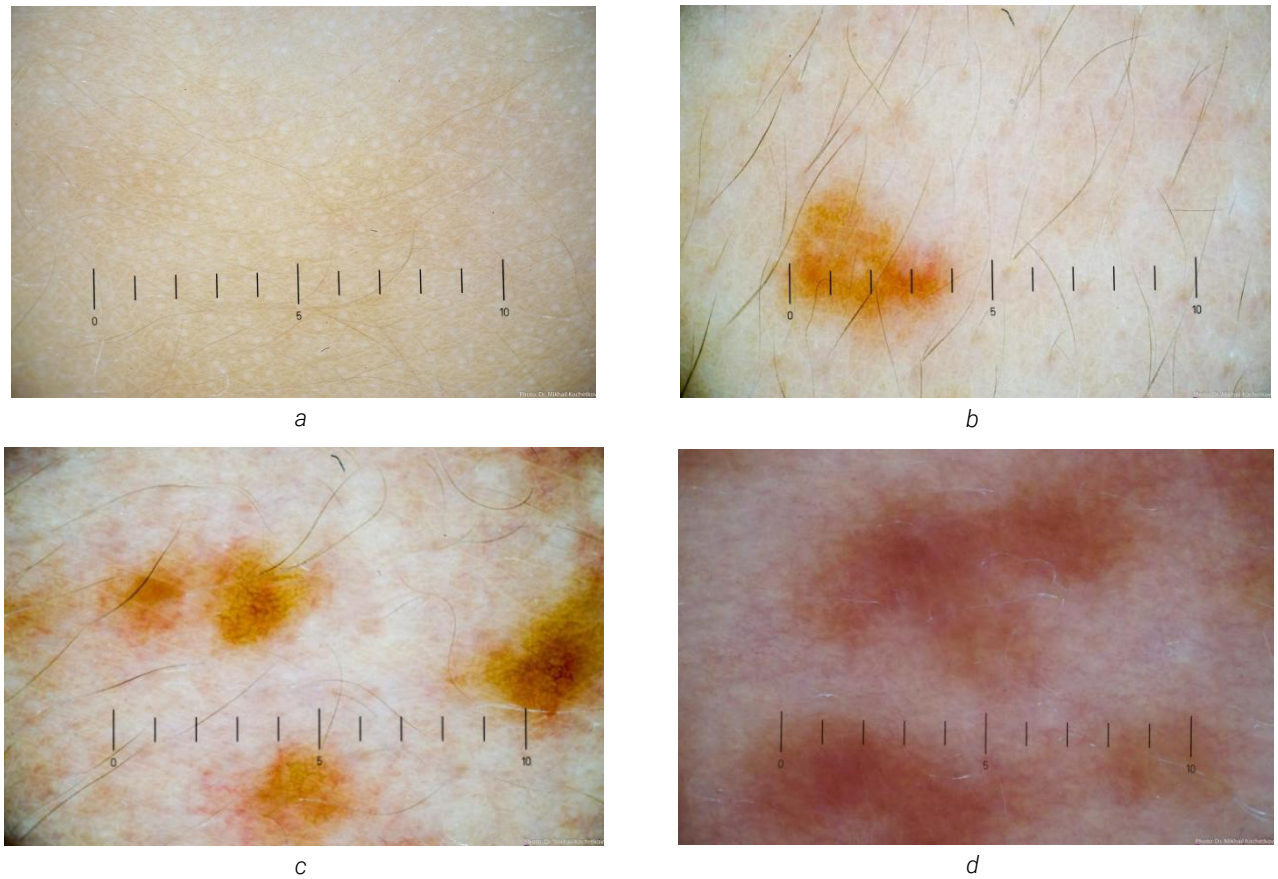
Darier's sign with wheal formation was detected in 10 patients (7 men and 3 women). Darier's sign was detected only by dermatoscopic examination in 20 patients (14 men and 6 women).

Dermoscopy of monomorphic macular lesions reveals an increase in yellow-brown color, preservation of skin appendages, unchanged vellus hair shafts, pseudonetwork pigmentation (Figure 3*a*), a weakly expressed asymmetric vascular pattern, and moderate erythema in adjacent areas (Figure 3*b*). When defining Darier's sign, a more pronounced vascular pattern is determined, but with a predominance of the pigment component, which is associated with a deeper location of the mast cell infiltrate in the reticular dermis (Figure 3*c*). In pMPCM, predominant localization of the mast cell infiltrate is observed in the papillary dermis.

Table 1

Frequency of detection of dermatoscopic signs in patients with mMPCM (*n*=30)

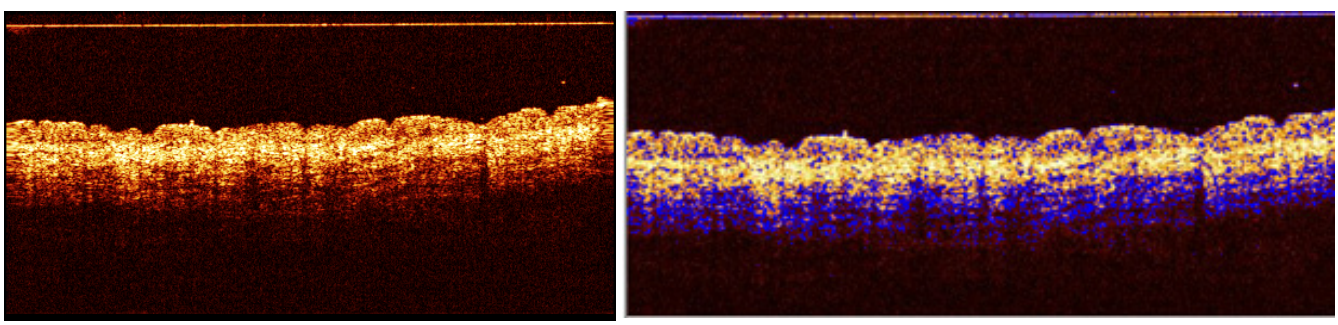
Gender	Yellow-brown coloration	Pigment pattern, pseudonetwork	Peripheral erythema	Pronounced vascular pattern
Male (n=21)	21 (100,0%)	19 (90,5%)	19 (90,5%)	4 (19,1%)
Female (n=9)	9 (100,0%)	4 (44,4%)	3 (33,3%)	3 (33,3%)



a *b*

c *d*

Fig. 3. Dermoscopy of mMPCM lesions: *a* — mild manifestations; *b* — pronounced manifestations of mMPCM; *c, d* — positive Darier's sign (description in text)



a *b*

Fig. 4. OCT images of healthy skin: *a* — made using "OKT-1300-E"; *b* — processed by the Lumen Stratis software

Optical coherence tomography

The images of healthy skin of various anatomical locations showed a typical five-layer structure of skin images without pathological inclusions (Figure 4).

The same changes in varying degrees of severity were observed in the images of all foci of mastocytosis, regardless of the location and age of the patient. Within the optical equivalents of the lower part of the epidermis, the papillary layer of the dermis and, in some cases, the reticular layer of the dermis, round, oval and elongated dark zones of low signal intensity were clearly defined. The zones were of different

sizes, with relatively clear boundaries (Figure 5), and corresponded to the histological description of mastocyte clusters (Figure 6) in shape, size (from 100 microns and more), characteristics and location (marked with red circles).

When identifying clusters of mast cells, these zones were differentiated from skin vessels, also represented by zones of low signal intensity. According to the available data, the resolution of this modification of the OCT device allows for the detection of pathologically dilated vessels within the papillary layer of the dermis only in patients with pathology of the main vessels (varicose veins, malformations) [11]. There were no such pathologies in the examined patients.

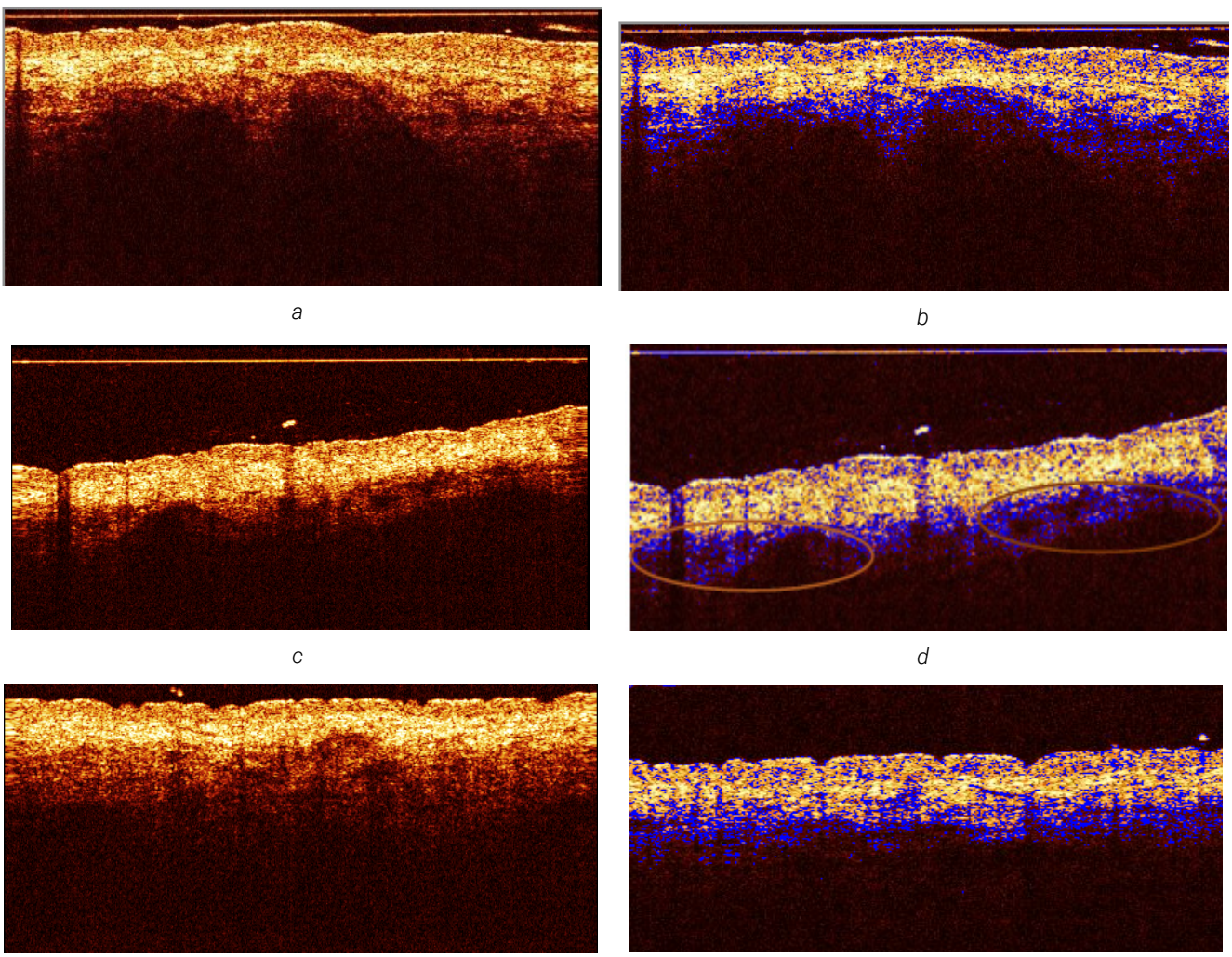


Fig. 5. OCT images of the skin of the lateral part of the trunk of a patient with mastocytosis in the area of a wheal (Darier's sign +) (*a*) and inflammatory macule (*c*), non-inflammatory macule (*e*) and OCT images of similar areas processed by the Lumen Stratis software (*b, d, f*)

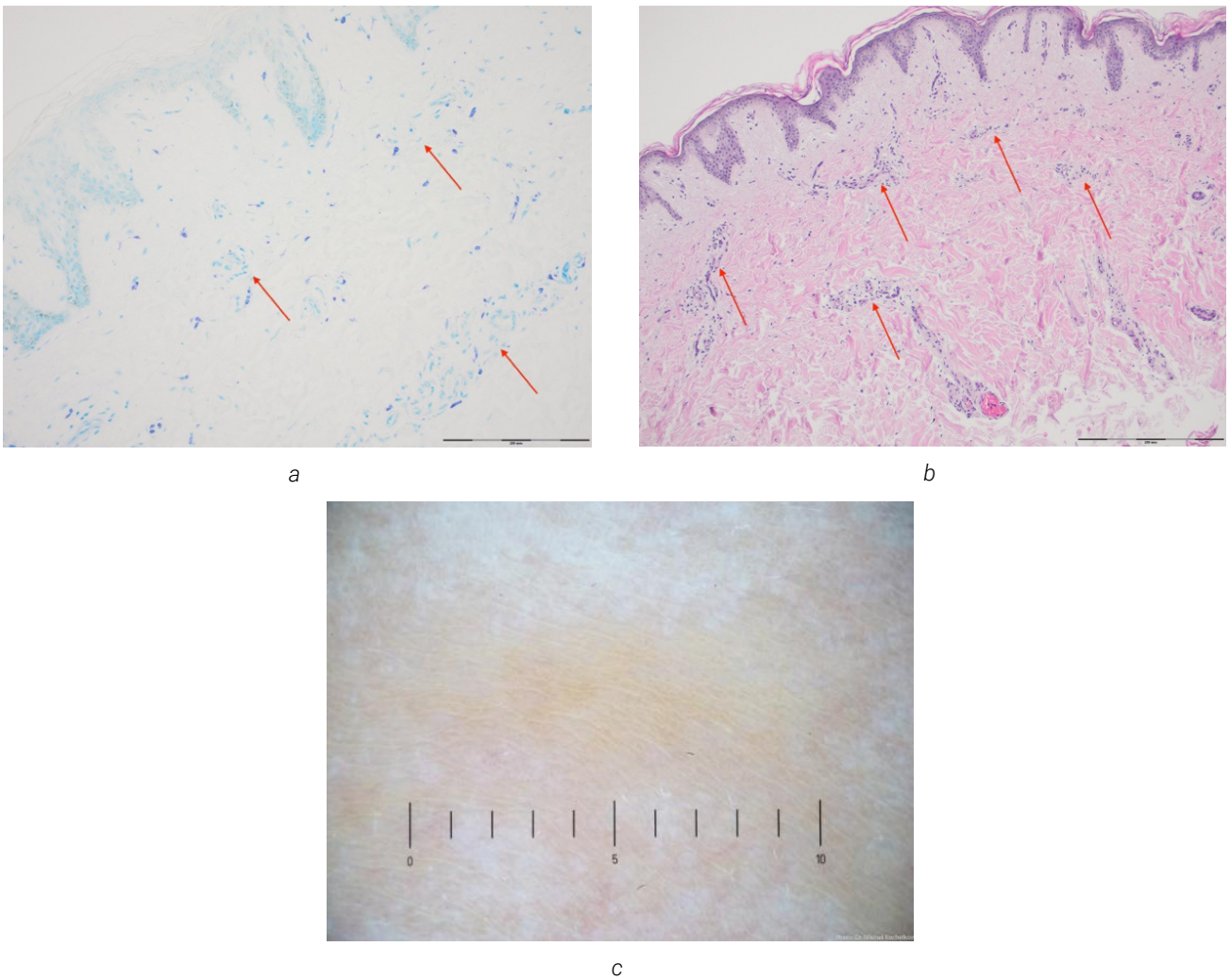


Fig. 6. Male-patient, 14 years old. Non-inflammatory macules of mMPCM: *a* — toluidine blue staining, magnification x 200; *b* — hematoxylin-eosin staining, magnification x 200; Mastocyte clusters — red arrows; *c* — dermosopy of the lesion

In addition, it has been previously shown that vessels in OCT images of vertical skin sections are represented by slit-shaped, oval and tree-shaped areas of low signal with clear boundaries, without a contour in the case of visualization of venules or with a light contour in the case of visualization of arterioles [11]. When analyzing OCT images of pathomorphological elements in patients with mastocytosis, the absence of clear boundaries was noted in areas of low intensity, defined as clusters of mast cells (Figure 5).

Thus, the OCT images within the epidermis and upper dermis visualized the desired clusters of mast cells. Attempts to visualize these objects using high-frequency ultrasound were unsuccessful. This was primarily due to the low resolution of the method, as well as the lack of the ability to clearly and in detail visualize the epidermis and dermo-epidermal junction zones of most interest to us, which are practically inseparable from the “sensor-gel-skin” interface in high-frequency ultrasound images.

Clinical examination is the first line in the diagnosis and treatment approach of cutaneous mastocytosis. However, dermoscopy and OCT are complementary tools that can improve the diagnosis of CM, monitor treatment, and provide pathophysiological characterization of the lesions.

To date, there are few studies regarding non-invasive methods of visualizing the lesions in CM. Dermoscopy is a simple method of assessing the lesions, useful as a first approach to many dermatoses associated with pigmentary disorders, and is commonly used in addition to clinical assessment [12]. OCT was first used for skin imaging in 1997 and has undergone significant technological advances since then. The high resolution and moderate penetration depth of OCT allows the method to fill the imaging gap between high-frequency ultrasound and reflectance confocal microscopy [13, 14]. The ability to visualize skin morphology and dermal blood flow using OCT allows for the evaluation of the functional and structural characteristics of inflammatory lesions in CM. Table 2 shows the correspondence of dermoscopic, OCT and histopathological features of lesions in mMPCM.

Table 2

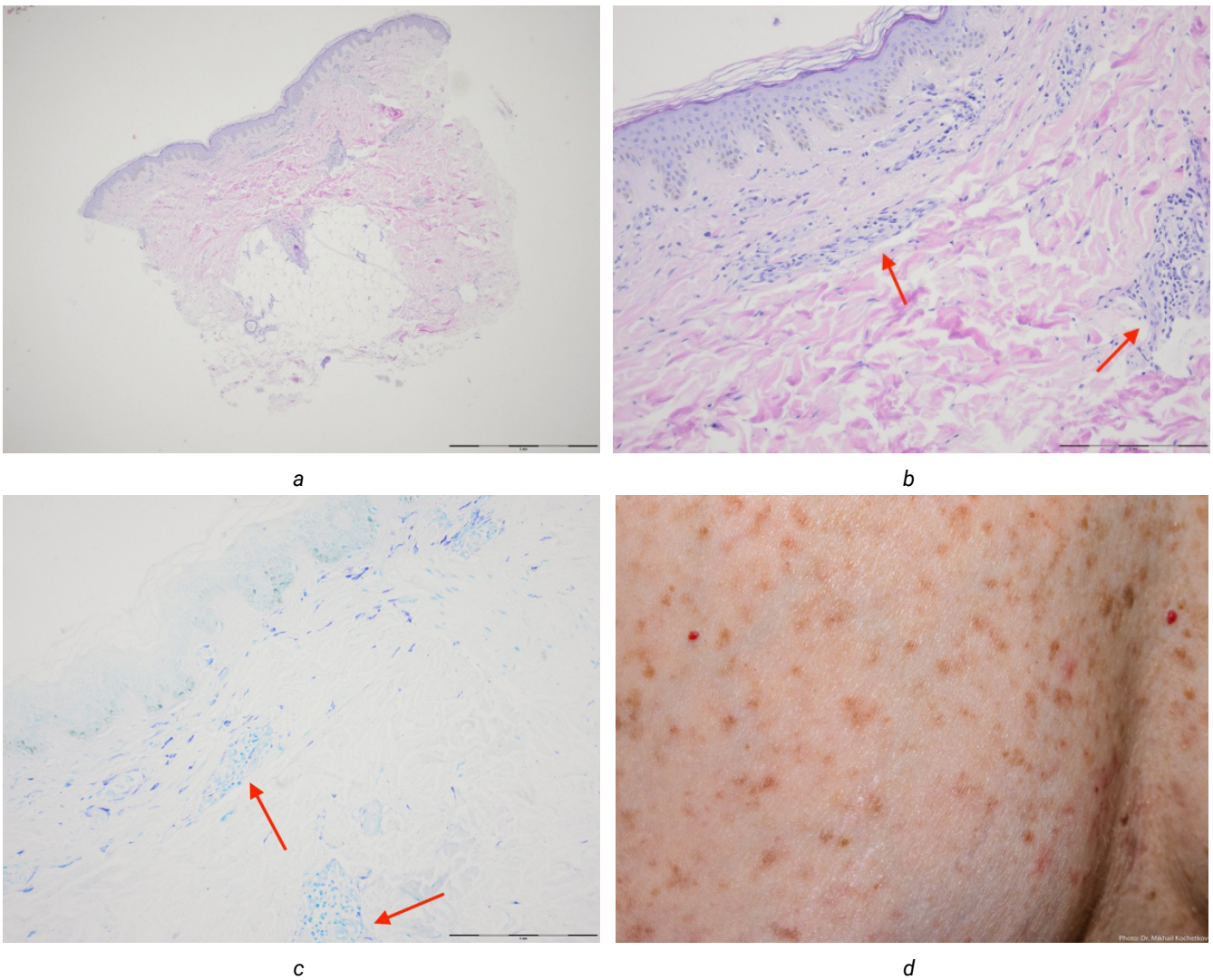
Correspondence of dermatoscopic, OCT and histopathological features of lesions in mMPCM

Type of lesions	Dermoscopy	OCT	Histopathology
Non-inflammatory macules	Yellow-brown coloration, pigment pseudonetwork (Figure 6*a, b*)	Rounded and elongated dark zones of low signal intensity of various sizes with relatively clear boundaries (Figure 5*e, f*)	The epidermis of normal thickness with hyperpigmentation of basal keratinocytes without pigment loss, infiltrates in the reticular dermis (Figure 6*c*)
Inflammatory macules, papules	Peripheral erythema, punctate vessels, pigment pseudonetwork (Figu-re 3*b, c*)	The above signs in combination with optical signs of edema (decrease in signal intensity and increase in the height of the optical layers) within the optical equivalents of the epidermis and dermis (Figure 5*c, d*)	Superficial perivascular mast cell infiltrates in the papillary and reticular dermis (Figure 7)
Wheals (Darier's sign)	Erythema and linear dilated vessels (Figure 3*c*), intense redness with barely discernible pigment pseudonetwork (Figure 3*d*)	Pronounced optical signs of edema in the form of a decrease in signal intensity within all visualized layers, an increase in the depth of the useful signal, a decrease in the clarity of the boundaries, an increase in the visualization of the optical equivalents of vessels within the reticular layer of the dermis (Figure 5*a, b*)	The dermis is somewhat edematous, the vascular pattern is enhanced, the endothelium is swollen, the vascular lumens are dilated, there are scattered perivascular infiltrates of mast cells, fibroblasts, histiocytes and eosinophils (Figure 8*a, b*)

In the clinical diagnosis of mMPCM, the most difficult are non-inflammatory spots, which are caused by mast cell infiltrates, histologically determined in the reticular dermis. On OCT images, they can look like apparently healthy skin (Figure 5*e*). Dermoscopy at the onset can observe a pale yellow-brown coloration with a gradual formation of a pigment pseudonetwork, which is associated with hyperpigmentation of the basal layer of the epidermis (Figure 6).

When the infiltrates are located in the papillary dermis, both macules and papules can be observed in patients (Figure 7). Dermoscopic examination demonstrates a bright yellow-brown staining of the lesion with a peripheral vascular pattern (Figure 3b, c). OCT visualizes a bright pattern of vascular reaction to mast cell infiltration of the papillary dermis (Figure 5*c*, *d*).

A prominent Darier's sign in systemic mastocytosis may be an indicator of massive mast cell degranulation and serve as a marker for anaphylaxis. Dermoscopy shows a predominantly vascular pattern (Figure 8). Histologically, both deep and superficial perivascular mast cell infiltrates can be identified.



a *b*

c *d*

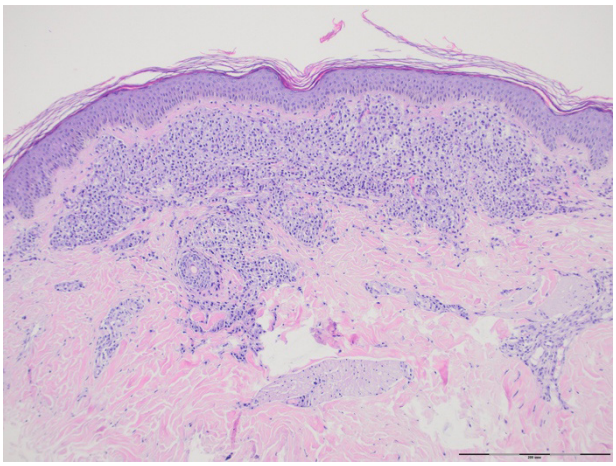
Fig. 7. Monomorphic type of MPCM, patient T., 27 years old.

a — a skin fragment with a subcutaneous adipose tissue area, lined with an epidermis of normal thickness with hyperpigmentation of basal keratinocytes. Hematoxylin-eosin staining, magnification x 40; ***b*** — superficial perivascular infiltrates in the dermis (red arrows). Hematoxylin-eosin staining, magnification x 200; ***c*** — an admixture of tissue mast cells of an elongated shape is detected in the infiltrate (red arrows). Some mast cells spread interstitially. Toluidine blue staining, magnification x 200; ***d*** — inflammatory macules, papules of mMPCM

Conclusion

Clinical and histopathological examinations play an important role in the diagnosis of inflammatory skin diseases. Rare diseases, including mastocytosis, tend to debut in children and adults, imitating various skin diseases. Non-invasive skin diagnostic methods, such as dermoscopy and OCT, can be useful in disease identification and differential diagnosis. Histopathological examination is useful as a clarifying diagnosis. Non-invasive methods can be used in routine practice to monitor the effectiveness of drug therapy and the dynamics of clinical manifestations.

Although the role of dermoscopy and OCT in routine clinical practice is not fully defined, non-invasive skin visualization shows promising results in cutaneous mastocytosis due to the correlation with histopathological features.



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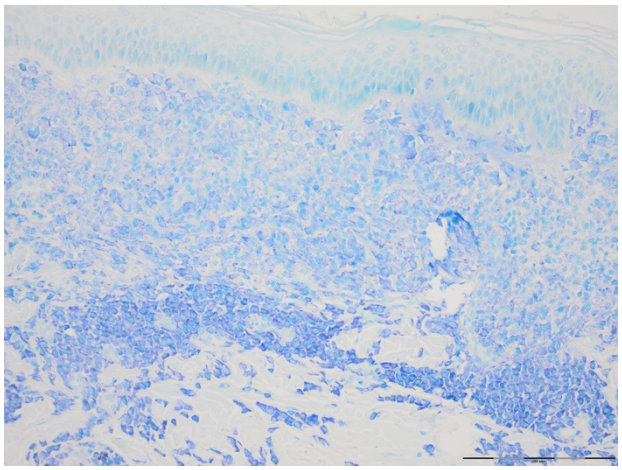

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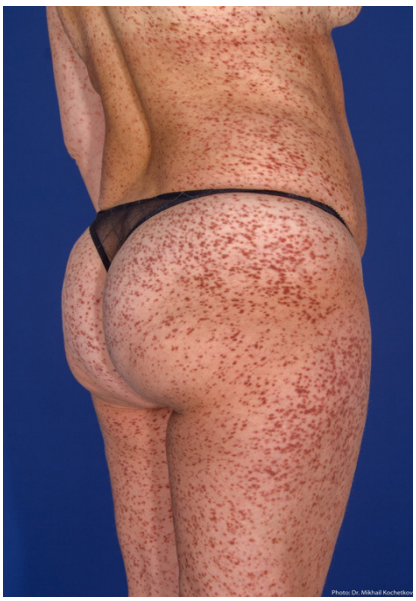

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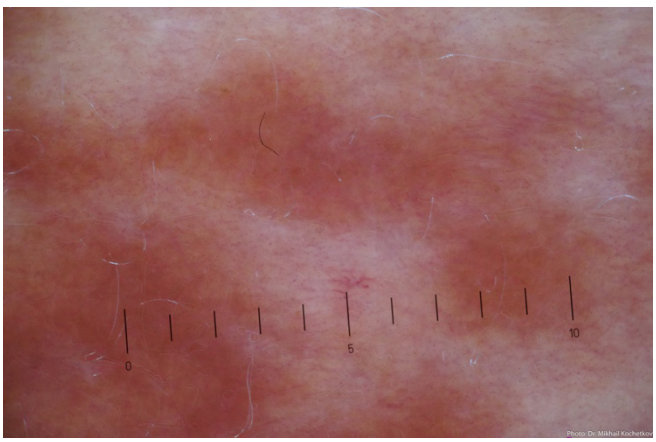

d

Fig. 8. Systemic mastocytosis. ***a*** — hyperpigmentation of keratinocytes of the basal layer, superficial perivascular infiltrates in the dermis. Hematoxylin-eosin staining, magnification x 200; ***b*** — an admixture of mast cells is detected in the infiltrate. Toluidine blue staining, magnification x 200; ***c*** — cutaneous manifestation of indolent systemic mastocytosis; ***d*** — dermoscopy of the lesions

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Неинвазивная диагностика мономорфного типа пятнисто-папулезного кожного мастоцитоза

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Аннотация. *Актуальность*. Мономорфный тип пятнисто-папулезного кожного мастоцитоза (мППКМ) — это редкая и диагностически сложная форма кожного мастоцитоза, часто требующая дифференциальной диагностики с другие пигментными и папулезными дерматозами, что подчеркивает необходимость поиска эффективных неинвазивных диагностических методов. *Цель*. Оценить дерматоскопические признаки мППКМ и сопоставить их с результатами оптической когерентной томографии (ОКТ) и гистопатологическими критериями с целью разработки неинвазивного диагностического алгоритма. *Материал и методы*. В исследование были включены 30 пациентов в возрасте от 14 до 30 лет с диагнозом мППКМ, наблюдавшихся в ГБУЗ «Московский Центр дерматовенерологии и косметологии в период с 2022 по 2024 год. Всем пациентам проводились клинический осмотр, дерматоскопия, а в отдельных случаях — ОКТ. Дерматоскопические и ОКТ-признаки систематически сравнивались с гистопатологическими результатами кожных биопсий. Результаты и обсуждение. Дерматоскопическое исследование очагов мППКМ выявило усиление желто-коричневой пигментации, сохранность придатков кожи, неизмененные пушковые волосы, псевдопигментную сеть и слабо выраженный асимметричный сосудистый рисунок. Симптом Дарье чаще определялся при дерматоскопии, чем при клиническом осмотре. ОКТ визуализировала скопления тучных клеток в виде округлых или овальных зон низкой интенсивности сигнала, преимущественно в ретикулярной дерме, что соответствовало гистологическим инфильтратам тучных клеток. Совмещение дерматоскопии и ОКТ позволило дифференцировать мППКМ от других подтипов кожного мастоцитоза на основании глубины и распределения инфильтратов. Важно отметить, что неинвазивные методы предоставили ценную информацию для диагностики и мониторинга, снизив необходимость рутинных биопсий. Выводы. Включение дерматоскопии и ОКТ в диагностический алгоритм мППКМ обеспечивает информативную, неинвазивную

альтернативу традиционной гистопатологии, способствуя ранней и точной диагностике, а также мониторингу динамики заболевания и эффективности терапии. Данное исследование является одним из первых, где системно сопоставляются дерматоскопические и ОКТ-признаки с гистологическими особенностями мППКМ, что подчеркивает уникальный диагностический потенциал этих неинвазивных методов для редких форм кожного мастоцитоза.

Ключевые слова: неинвазивная диагностика, дерматоскопия, ОКТ, оптическая когерентная томография, мономорфный макулопапулезный мастоцитоз кожи, «МосДерма», Lumen Stratis

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Effect of polydeoxyribonucleotide therapy on the regeneration of long-term non-healing postoperative skin defects

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Abstract. *Relevance.* Chronic wound healing currently remains a serious problem due to its frequency and associated complications. Polydeoxyribonucleotide therapy, which promotes angiogenesis and tissue regeneration, offers a promising treatment. *Aim:* to analyze the proliferative and apoptotic activity of regenerative wound surface cells in biopsy samples of long-term non-healing postoperative skin defects at the stages of its healing during polydeoxyribonucleotide therapy. *Materials and Methods*. We used 24 C57/B1 white mice aged 4–6 months weight 32 ± 0.01g, divided into control (n = 12) and main (n = 12) groups. In the main group 0,38 ml of polydeoxyribonucleotide solution was injected into the bottom and around the surgical ischemic skin defect. On days 4, 7, 10, and 12 after wound modeling, biopsies were embedded in paraffin, stained with hematoxylin and eosin. Biopsy cells in a state of mitotic division, proapoptosis, and with expression of the anti-apoptotic *Bcl-2* gene were identified immunohistochemically using primary antibodies *Ki-67* (Monoclonal rabbit [SP6] Cell Marque, USA), *p53* (Polyclonal rabbit, (GTX50438) GeneTex Inc, USA) and *Bcl-2* ([N1N2), (GTX100064) GeneTex Inc, USA), respectively. Secondary antibodies (HiDef Detection™ HRP Polymer system, Cell Marque, USA) conjugated with horseradish peroxidase, were used as secondary antibodies. To adequately represent the structure of the regeneration, the biopsy sections were additionally stained with Mayer's hematoxylin. The index of antigen-positive cells was determined by counting their number per 100 cells at a microscope magnification ×1350, followed by calculation of the index as a percentage. Statistical analysis included testing for normal distribution using the Shapiro-Wilk test, the Mann-Whitney test for pairwise comparisons, and group data were described using the median, first and third quartiles (interquartile range). *Results and Discussion.* By day 12 in the main group, the granulation tissue of the biopsy specimens was at the beginning of the third stage of the wound process, while in the control group the second stage of the wound process continued. A stable cell population was formed in the main group 2 days earlier than in the control group. *Conclusion.* Polydeoxyribonucleotide therapy turned out to be safe and tolerable and accelerated the

healing of long-term non-healing postoperative skin defects by 16,67±0,01% by stimulating the proliferative activity of dermal fibroblasts, regulating the expression of the anti-apoptotic gene *Bcl-2* and the proapoptotic gene *p53* in fibroblast differon cells.

Keywords: polynucleotides, long-term non-healing postoperative skin defects, wound process, proliferation, apoptosis

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Conflict of interest statement. The authors declare no conflict of interest.

Ethics approval. All manipulations were performed in accordance with the "International Guidelines for Biomedical Research Using Animals" (EEC, Strasbourg, 1985) and the Declaration of Helsinki of the World Medical Association. The study was approved by the Local Ethics Committee of the V.I. Vernadsky Crimean Federal University (protocol No. 11 of 12/05/22).

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Introduction

One of the priority tasks of modern medicine is the development of medical science and innovations in the healthcare sector. It involves the development and implementation of new effective technologies for the treatment of socially significant diseases [1]. Chronic wound healing currently remains a serious problem due to its frequency and associated complications [2]. Chronic wounds, including long-term non-healing postoperative skin defects, are also a severe complication of many diseases associated with a local decrease in blood flow in venous and arterial vessels and microcirculation [2].

Advances in understanding the biology of chronic ischemic wounds have led to the development of small molecule nucleic acid nucleotide therapies that stimulate angiogenic activity and modulate the repair process with exciting potential for clinical application [3]. Many literatures data report that nucleotides secreted by cells into the extracellular space in response to damage take part in all stages of wound healing. They activate the corresponding nucleotide receptors [4].

On this basis a new class of medicinal substances has now emerged — polydeoxyribonucleotides (PDRN). PDRN can be extracted from the sperm of salmon fish. PDRN contains deoxyribonucleotide polymers with 50–2000 nitrogen base pairs [5].

It is known that PDRN is a combination of purine and phosphodiester bonds forming a monometric unit of pyrimidine nucleotides, which selectively bind the A2 purinergic receptor. This complex promotes cell growth of fibroblasts and epidermocytes, as well as neogenesis [6]. Experimental study indicates an increase in the mobility and proliferation of human fibroblasts at the wound site, depending on the concentration of PDRN [7].

In the available literature, there is practically no information about the proliferation of regenerative wound surface cells and proapoptosis of the same cells in the wound healing process of long-term non-healing postoperative skin defects against the background of PDRN therapy. In this regard, the purpose of the study was to analyze the proliferative and apoptotic activity of regenerative wound surface cells in biopsy samples of long-term non-healing postoperative skin wound at the stages of its healing against the background of PDRN administration.

The aim of this study: to analyze the proliferative and apoptotic activity of regenerative wound surface cells in biopsy samples of long-term non-healing postoperative skin defects at the stages of its healing during PDRN therapy.

Materials and methods

Animals for in vivo study

The study used 24 white male laboratory mice of the C57/B1 line, 4–6 months old. The sample size (n = 72) was calculated using the on-line Sample Size Calculator at a given confidence level of 95% and a permissible error of 4% by the formula

$$n = z2 \times p \times (1 — p) / e2,$$

where: z = 1.96 at a confidence level (α) of 95%, p = proportion (expressed as a decimal fraction), e = error. All animals were divided into control and main groups (three mice for each studied day in each studied group).

The experiments were carried out in compliance with all principles of humanity contained in the European Community Directive (86/609/EC) and the Declaration of Helsinki. The method of forming a model wound is described in the work of Baranovsky Yu. G. et al., 2016 [8]. In the MG, the model wound was injected immediately after surgery with 0.38 ml of PDRN "Plenhyage Medium" from I.R.A. Istituto Ricerche Applicate Sri (Italy).

Morphological study

After 4, 7, 10 and 12 days, the recovering ischemic skin defect was excised during repeated surgery under anesthesia of a 2.5% avertin solution 0.3–0.4 ml intraperitoneal injection. The biopsy specimen was placed in a 10% solution of buffered neutral formalin. The surgical wound was sutured and the mice were returned to the vivarium after healing.

According to the generally accepted method, the material was impregnated with paraffin. Survey staining of the sections was carried out with Mayer's hematoxylin and eosin.

Immunohistochemical study

Regenerative tissue cells in a state of mitotic division were identified immunohistochemically using primary monoclonal antibodies *Ki-67* (Monoclonal rabbit [SP6] "Cell Marque", USA), which bind to the nuclear antigen that functions in cells in a state of proliferation. Cells in a state of proapoptosis were identified based on the expression of the tumor suppressor gene *p53* in their nuclei using monoclonal antibodies to *p53* (Polyclonal rabbit, (GTX50438) GeneTex Inc, USA). The anti-apoptotic protein *Bcl-2*, which blocks apoptosis and prolongs cell life, was identified by monoclonal antibodies to *Bcl-2* [N1N2], (GTX100064) GeneTex Inc, USA). This protein is involved in maintaining the balance between cell proliferation and differentiation.

Universal antibodies (HiDef Detection™ HRP Polymer system, Cell Marque, USA) were used as secondary antibodies, allowing the detection of rabbit primary antibodies conjugated to an enzyme complex based on horseradish peroxidase. Visualization was carried out in the diaminobenzidine — hydrogen peroxide system. To adequately represent the structure of tissue and cell nuclei, biopsy sections of a healing ischemic skin wound of mice were additionally stained with Mayer's hematoxylin for 3 minutes. For each marker, control studies were performed to exclude pseudopositive and pseudonegative results.

Quantitative analysis

The index of antigen-positive cells was determined by counting their number per 100 cells at a magnification of an Olympus ×1350 light microscope. The percentage of antibody positive cells were calculated as an average

based on the results of 30 studied visual fields of each biopsy in the CG and MG.

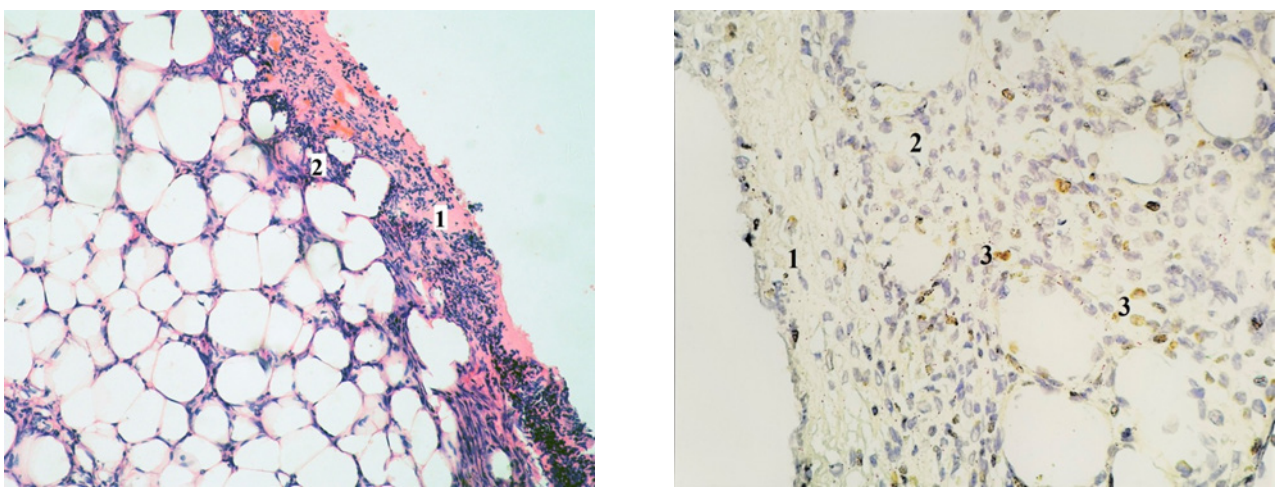
Statistical analysis

The normality of data distribution was checked using the Shapiro-Wilk test [9]. Pairwise comparisons were made between the control and main groups of mice after 4, 7, 10 and 12 days from the start of the model wound healing. Because the distribution of the data was not normal, the Mann-Whitney test was used for pairwise comparisons, and group data were described using the median, first and third quartiles (interquartile range) [9, 10]. All calculations were carried out in the statistical environment R version 4.2.3 [11]. The data obtained were visualized using the Ggplot2 package [12]. Significance of differences was accepted at a significance level of $P < 0.05$.

Results and discussion

On day 4 after the wound modeling, the epidermis in CG and MG mice is not determined, and the skin defect is covered with a voluminous scab (Figure 1*a*). The edges of the wound were limited by a stitched silicone ring. Histological examination revealed that the scab is formed by fibrin, which contains mostly dead and destructured inflammatory cells. The scab is more voluminous in the CG [13]. Directly under the scab lies a thin layer of granulation tissue in the second proliferative stage of the wound process with collagen fibers and rare blood vessels. The rest of the defect is filled with white adipocytes rising from the hypodermis.

In CG and MG cells in a state of proliferation (Figure 1*b*) are scattered throughout the granulation tissue and the interquartile range of the index of these cells is 9.42–11.52 and 17.28–21.12, respectively (Table). Cells expressing the anti-apoptotic gene *Bcl-2* are more numerous and have the same localization in the granulation tissue of both groups. The interquartile range of their index is 18.1–22.4 for the CG and 35.5–43.4 after the introduction of PDRN. The numerical value of the median index of cells with expression of the anti-apoptotic gene *Bcl-2* in the MG is 48.99±0.01% greater than that in the CG. Cells in a state of proapoptosis are not detected. This ratio of the numerical value of the median of proliferating cells and cells in a state of proapoptosis in the regeneration of the CG and OG allows us to classify this cell population as a growing cell population [14].



a *b*

Fig. 1. Biopsy section of the MG on the day 4 after surgery to simulate an ischemic skin defect. Scab (1) and granulation tissue (2). ***a*** — Hematoxylin and eosin staining. Magnification: x200. ***b*** — cells in a state of proliferation (3). Staining with monoclonal antibodies to *Ki-67*. Visualization in the diaminobenzidine–hydrogen peroxide system, magn. ×400

Table

Comparison of statistical samples of cell indices in the state of proliferation (*Ki-67*), proapoptosis (*p53*) and arrest of apoptosis (*Bcl-2*) in biopsy samples of regenerating wounds of the control and main groups

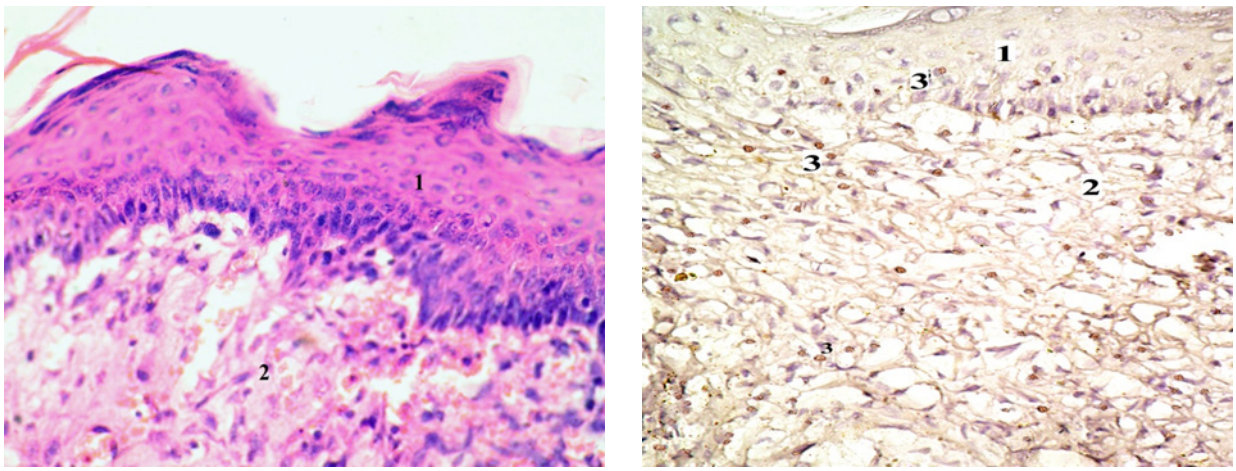
Day	Main groupmedian (1–3 quartiles), interquartile range	Control group median (1–3 quartiles), interquartile range	P-value	Studied indices
4	19.20 (17.28–21.12)	10.47 (9.42–11.52)	<0.01	*Ki-67*
7	50.06 (45.05–55.07)	20.93(18.84–23.02)	<0.01	*Ki-67*
10	63.34 (57.01–69.67)	51.95 (48.76–53.15)	<0.01	*Ki-67*
12	71.27 (68.58–78.40)	64.22 (57.80–65.64)	<0.05	*Ki-67*
4	39.42 (35.5–43.4)	20.11 (18.1–22.4)	<0.01	*Bcl-2*
7	53.41 (48.1–58.8)	27.17 (24.4–29.9)	<0.01	*Bcl-2*
10	30.55 (27.5–33.6)	57.73 (52.0–63.5)	<0.01	*Bcl-2*
12	22.05 (19.8–24.3)	60.27 (54.2–66.3)	<0.01	*Bcl-2*
4	0.00	0.00	-	*p53*
7	7.97 (7.17–9.71)	0.00	-	*p53*
10	42.19 (37.97–46.41)	0.00	-	*p53*
12	69.52 (62.57–76.47)	3.3 (2.97–3.63)	-	*p53*

On day 7, the position of the restrictive silicone ring around the wound did not change in both groups. The surface of the wound is a scab. On microscopic examinations the scab contains fibrin and a small amount of cellular debris. At the studied stage of regenerative tissue histogenesis, complete epithelization of the skin defect in the MG was recorded, while in the CG the central areas of the defect did not achieve this result. After PDRN administration, the epidermis is significantly thicker due to the appearance of an additional third row of epidermocytes [13]. The thickness of granulation tissue of biopsy specimens also increased statistically significantly in both groups. Active healing of an ischemic skin defect is accompanied by an increase in the index of fibroblast proliferating cells.

In the CG and MG, the interquartile range of the index of *Ki-67*-positive cells was 20.93 (18.84–23.02) and 50.06 (45.05–55.07) respectively (Table). As a percentage, the numerical value of the median of dividing cells in MG biopsy samples is 51.18% greater than those in CG biopsies.

The interquartile range of the index of cells with expression of the anti-apoptotic gene *Bcl-2* is 27.17 (24.4–29.9) in the CG and 53.41 (48.1–58.8) in the MG. As a percentage, the numerical value of the median of cells with the active *Bcl-2* gene is 48.99% greater during the administration of PDRN compared to that in the CG (Table). At the same time among the cellular elements of the MG regenerative tissue present cells positive for apoptosis marker *p53*. The interquartile range of the index of cells in a state of proapoptosis is 7.97 (7.17–9.71). The cell population of both groups can still be classified as a growing cell population due to the high numerical value of the median index of proliferating cells, which is facilitated by the high numerical value of the median index of cells expressing the anti-apoptotic gene *Bcl-2*.

On the day 10.4 ± 0.01 of the postoperative period, spontaneous separation of the silicone ring from the wound was observed in MG mice, while it was present in CG mice. On day 10, the entire surface of the wound in both groups is covered with regenerated epidermis. After puncturing the PDRN wound (MG) epidermis is noticeably thicker and has more pronounced differentiation into layers of the forming stratified squamous partially keratinized epithelium [13]. Fragmented scab remains above the epidermis in MG (Figure 2*a*). The basis of biopsy specimens at this stage of wound healing is granulation tissue, which appears more differentiated in the MG.



a *b*

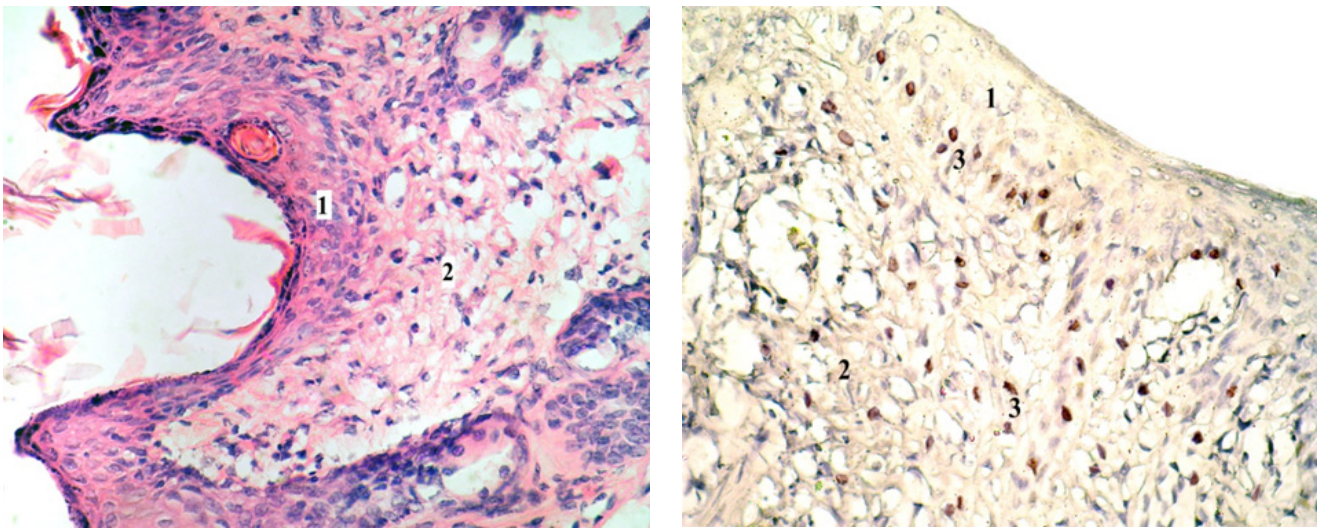
Fig.2. Biopsy section of the MG on day 10 after surgery to simulate an ischemic skin defect. Epidermis (1) and granulation tissue (2). ***a*** — Hematoxylin and eosin staining. Magnification: 400. ***b*** — cells in a state of proapoptosis (3). Staining with monoclonal antibodies to p-53. Visualization in the diaminobenzidine–hydrogen peroxide system, magn. × 200

Numerical value of the median of regenerative tissue cells of all studied biopsy samples in a state of proliferation continue to actively increase. In the CG and MG, it increased compared to the previously described period of wound healing by 59.71% and 20.97%, respectively (Table). In the MG, the median of cells with the *Ki-67* marker is 17.98 ± 0.01% higher compared to that in the CG. Against the background of PDRN-puncture, the numerical value of the median of apoptotic cells from days 7 to 10 increased by 81.51% (Figure 2*b*). In the CG there are no cells with expression of the proapoptosis gene *p53* (Table).

The numerical value of the median index of cells with expression of the anti-apoptotic gene *Bcl-2* among the population of biopsy cells from the CG increased by 52.95% compared to the 7th day of regeneration. At the same time in the MG the numerical value of median *Bcl-2*-positive cells decreased by 42.80%, which likely the regenerated cells actively participate in the process of eliminating excess cellular elements. In the CG, the numerical value of the median index of cells with the *Bcl-2* marker is 47.08% higher. Based on the fact that the numerical value of the median index of proliferating cells reliably exceeds the numerical value of the median index of cells in a state of proapoptosis (Table), the cell population in both groups on the day 10 of regenerative tissue histogenesis can be assessed as a growing cell population.

On day 12, the ring around the model wound was absent in mice of both groups. In biopsy sections in the stratified squamous partially keratinized epithelium of the epidermis the number of rows of epidermocytes increased and differentiated into four layers: basal, spinosum, granulosum and cornium. The epidermis is widest and looks more differentiated after PDRN- therapy (Figure 3*a*). Among the cells of the stratum basale and stratum spinousum *Ki-67*-positive proliferating cells, are well contoured. Under the epidermis in the expanding, fibrosing and differentiating granulation tissue, cellular elements with a positive reaction to the *Ki-67* marker are also present.

The numerical value of the median index of *Ki-67*-positive cells increased by 11.13% compared to day 10 of wound healing. In CG biopsies the numerical median index value of proliferating epidermis cells is noticeably thinner than in the MG [13]. In granulation tissue it increased statistically significantly by 19.11 ± 0.01% over day 7 to day 10 (Figure 3*b*). However, when comparing the numerical value of the median index of *Ki-67*-positive cells in the structures of biopsy specimens from the CG and MG, it statistically significantly 9.89 ± 0.01% higher in mice



a *b*

Fig.3. Biopsy section of the MG on day 12 after surgery to simulate an ischemic skin defect. Epidermis (1) and granulation tissue (2). ***a*** — Hematoxylin and eosin staining. Magnification: x200. ***b*** — cells in a state of proliferation (3). Staining with monoclonal antibodies to *Ki-67*. Visualization in the diaminobenzidine–hydrogen peroxide system, magn. ×200

of the MG. The numerical value of the median index of cells with arrested apoptosis after PDRN therapy decreased by 37.08% compared to the day 10 of the model wound regeneration, allowing the elimination of cells from the composition of the regenerative tissue. Thus, the numerical value of the median index of *p53*-positive cells over the same period increased by 37.87%. The depletion of granulation tissue in cellular elements indicates the beginning of the process of fibrosis [14].

In the CG, the numerical value of the median index of cells with *Bcl-2* gene expression continued to increase, but the increase was 4.21%, which is statistically insignificant. In this regard, on day 12 of the model skin defect healing cells with an active apoptosis gene *p53* were detected for the first time. Their interquartile range is 3.3 (2.97–3.63) (Table). A comparison of biopsy samples from the CG and MG at this stage of regenerative tissue histogenesis revealed that among the cellular elements, the numerical value of the median index of cells with expression of the *Bcl-2* gene is 63.40% higher in the CG than in the MG. The numerical value of the median index of cells in the state of proapoptosis — 95.25% higher in the MG (Table). Based on the fact that in the cell population of MG biopsies, the numerical value of the median index of cells in a state of proliferation statistically does not differ from numerical values of the median index of cells in a state of proapoptosis, such a cell population can be classified as a stable cell population. The cell population of CG biopsies continues to grow.

The stated research topic is practically not covered in the domestic literature, probably due to the need for a specialized sterile laboratory, highly qualified scientific and support personnel who have undergone specialized training, and the high cost of the pharmacological preparation of polydeoxyribonucleotides, which is not produced in the Russian Federation and is distributed by network marketing as pharmacological preparation for cosmetic correction of facial skin. A few works by foreign authors [6, 15] reflect successful attempts to use pharmacological preparations of PDRN (the range of which is quite wide in the European and North American pharmacological industry) in the clinical practice of surgeons in the treatment of long-term non-healing ischemic skin defects, which occur in 1–2% of the elderly population and seriously worsening the working capacity and quality of life of the population. At the same time, the cellular mechanisms of healing of ischemic skin defects after PDRN therapy remain unclear.

During all the days of healing of the ischemic model wound we studied, the difference between the

indicators of the MG and CG was significant. On days 4 and 7 the difference between the CG and MG was most pronounced. Subsequently, the difference decreases, nevertheless remaining statistically significant (Table). The proliferative activity of regenerative tissue cells is higher after PDRN therapy.

By the 12th day of healing of an ischemic model wound, mice of both groups observed the absence of a silicone ring limiting the wound and complete epithelization of the wound. After puncturing an ischemic skin defect with polydeoxyribonucleotides, it accelerates the healing of the defect by 16.67 ± 0.01%, which is ensured by the active proliferation of fibroblast differon cells, predominantly differentiated specialized fibroblasts (Table). However, on day 12 of regenerative tissue histogenesis in the MG granulation tissue is at the beginning of the third stage of the wound process, while in the CG the second stage of the wound process continues. A stable cell population is formed in MG 2 days earlier than in the CG.

Our findings align with the results reported by Azhikova et al. [16, 17], who demonstrated that tissue repair stimulators (such as panthenol) enhance granulation and epithelization without extensive scarring. This supports the efficacy of the regenerative agents used in our study in significantly reducing healing time.

The index of cells with expression of the anti-apoptotic gene *Bcl-2* in the CG is statistically significant and increases up to day 12 of wound healing. In the MG it statistically significantly decreases by day 12, which leads to a sharp increase in the index of cells with *p53* gene expression and their elimination from the population by apoptosis. This elimination is necessary for fibrosis of granulation tissue in the third stage of wound healing process.

Conclusion

An injection of a PDRN solution into the edges and bottom long-term non-healing ischemic skin defects appears to be a strong candidate for the innovative treatment of chronic ischemic skin defects and the prevention of excessive scarring. PDRN therapy turned out to be safe and tolerable and accelerates the healing of long-term non-healing ischemic skin defects by 16.67±0.01% by stimulating the proliferative activity of dermal differentiated specialized fibroblasts and regulating the expression of the anti-apoptotic gene *Bcl-2* and the apoptosis gene *p53* in the nuclei of fibroblast differentiated cells.

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Влияние терапии полидезоксирибонуклеотидами на регенерацию длительно незаживающих послеоперационных дефектов кожи

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Аннотация. *Актуальность*. Лечение хронических ран на сегодняшний день остается серьезной проблемой ввиду их распространенности и сопутствующих осложнений. Терапия полидезоксирибонуклеотидами, способствующая ангиогенезу и регенерации тканей, является перспективным методом лечения. Цель: анализ пролиферативной и апоптотической активности клеток регенераторного гистиона в биоптатах длительно незаживающих послеоперационных дефектов кожи на этапах заживления на фоне терапии полидезоксирибонуклеотидами. Материалы и методы. В работе использовали 24 белых мыши линии C57/Bl в возрасте 4–6 месяцев и весом 32 ± 0,01 г, разделенных на контрольную (n = 12) и основную (n = 12) группы. В основной группе 0,38 мл раствора полидезоксирибонуклеотидов вводили в дно и края хирургического ишемизированного дефекта кожи. На 4, 7, 10 и 12-е сутки после моделирования раны биоптаты заливали в парафин и окрашивали гематоксилином и эозином. Клетки биоптатов в состоянии митотического деления, проапоптоза и с экспрессией антиапоптотического гена Bcl-2 выявляли иммуногистохимически с использованием первичных антител Ki-67 (моноклональные кроличьи [SP6] Cell Marque, США), p53 (поликлональные кроличьи [GTX50438] GeneTex Inc, США) и Bcl-2 ([N1N2], [GTX100064] GeneTex Inc, США) соответственно. В качестве вторичных антител использовали систему HiDef Detection™ HRP Polymer (Cell Marque, США), конъюгированную с пероксидазой хрена. Для адекватной визуализации структуры регенерата срезы биоптатов дополнительно докрашивали гематоксилином Майера. Индекс антиген-положительных клеток определяли путем их подсчета на 100 клеток при увеличении микроскопа ×1350 с последующим расчетом индекса в процентах. Статистический анализ включал проверку на нормальность распределения с помощью теста Шапиро–Уилка и использование критерия Манна–Уитни для попарных сравнений; данные групп описывали с помощью медианы, первого и третьего квартилей (межквартильный размах). Результаты и обсуждение. К 12-м суткам в основной группе грануляционная ткань биоптатов находилась в начале третьей фазы раневого процесса, тогда как в контрольной группе продолжалась вторая фаза раневого процесса. Стабильная клеточная популяция в основной группе сформировалась на 2 дня раньше, чем в контрольной. *Выводы*. Терапия полидезоксирибонуклеотидами оказалась безопасной и хорошо переносимой; она ускорила заживление длительно незаживающих послеоперационных дефектов кожи на 16,67 ± 0,01% за счет стимуляции пролиферативной активности фибробластов дермы, регуляции экспрессии антиапоптотического гена Bcl-2 и проапоптотического гена *p53* в клетках фибробластического дифферона.

Ключевые слова: полинуклеотиды, длительно незаживающие послеоперационные дефекты кожи, раневой процесс, пролиферация, апоптоз

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ORIGINAL RESEARCH
ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Virus-induced changes in peroxisomal markers among HIV-infected patients

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Abstract. *Relevance.* It is been currently known that viruses rewire the metabolic machinery host's cell to promote successful viral replication via reprogramming host energy flows, resource, metabolic tools and further, the reorganization of cellular structures. Recent studies indicate that the human immunodeficiency virus significantly reduces the number of peroxisomes in infected cells. However, there is still no clear understanding of the reasons for this apparent HIV intervention. The aim of the study was to confirm the hypothesis about the causes of the decrease in the number of peroxisomes in HIV infection. In this study, changes in several hematological markers of peroxisomal metabolism were assessed in connection with data on the unique role of these organelles in the catabolism of the amino acid L-lysine, the level of which correlates with the level of viral RNA in the blood plasma of HIV-infected individuals. *Materials and Methods.* A study was conducted on the levels of total cholesterol, catalase, L-lysine, and its derivative L-carnitine among HIV-infected individuals (controllers and patients with rapidly progressive disease) in comparison with similar indicators in cohorts of HIV-infected patients and healthy individuals. *Results and Discussion.* The study confirms the presence of significant differences in plasma levels of markers associated with peroxisomal metabolism, such as catalase, cholesterol, and the amino acid L-lysine, in the compared groups of HIV controllers and patients with rapidly progressing disease. The most negative changes in peroxisomal markers were detected among patients with accelerated HIV disease progression and, to a lesser extent, in individuals from the overall cohort. *Conclusion.* The results of this study indicate that HIV interference with host peroxisome biogenesis is accompanied by a concomitant dysregulation of peroxisomal enzyme systems and L-lysine-related substrates. Virus-induced reprogramming of the catabolism of this essential

amino acid indirectly confirms the hypothesis of a key role of L-lysine in the HIV life cycle and is a factor in the successful implementation of the reproductive strategy of the human immunodeficiency virus.

Keywords: HIV, peroxisomes, L-lysine amino acid, cholesterol, catalase, HIV controllers, HIV rapid progressors

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Introduction

Viruses do not possess their own metabolic tools. Therefore, they use and alter the metabolism of infected cells to ensure an optimal environment for their life cycle. The main goal of any virus is effective replication in a suitable host cell type and production of progeny for new infections. Reproductive strategies involve reprogramming cellular metabolic pathways to provide an increasing number of pools consisting of free nucleotides and amino acids. This is necessary for energy-intensive processes of viral genome synthesis and virions assembly[1–6].

The available data indicate common metabolic changes induced by most viruses studied, such as changes in central carbon utilization pathways, induction of aerobic glycolysis, also known as the Warburg effect, upregulation of fatty acid synthesis and glutaminolysis, manipulation of host protein metabolism, and related aminogram abnormalities [7–15]. Simultaneously, each virus species implements its own highly specific alterations in cellular metabolism that mirror the needs of the respective pathogen for certain molecular compounds.

It is also widely known that viral intervention and related metabolic changes are accompanied by the induction and development of oxidative stress and inflammation through mitochondrial and peroxisomal dysfunctions in cells. There is no doubt that the profound functional alterations in these important organelles of cellular metabolism are associated with their involvement in the antiviral signaling system and in the further implementation of the antiviral response by the host organism, which allows infected cells to survive and eliminate an infectious process [16–20].

On the other hand, reprogramming peroxisomes' functional activity and their significant quantitative variability may be an important part of viral strategy. It is also a supporting factor for the effective reproduction of viruses that cause long-lasting chronic infections. In particular, human cytomegalovirus (HCMV), herpes simplex virus type 1 (HSV-1), and Kaposi's sarcoma-associated herpesvirus induce biogenesis and

morphological changes in peroxisomes and support their replication [3, 18, 21, 22]. In contrast, hepatitis C virus (HCV) [23]and some flaviviruses, such as West Nile, Dengue, and Zika, are known for their active inhibition of peroxisomal antiviral functions. They significantly decrease peroxisome number by sequestering and degrading a critical biogenesis factor [23–25].

It has recently become apparent that human immunodeficiency virus (HIV) has also been associated with the inhibition of peroxisome biogenesis factors. On average, HIV-infected cells contained 30–65% less peroxisomes compared to uninfected ones [26–28]. However, the reasons for multidirectional changes in the number of these organelles remain unclear. According to our assumption, the reasons are primarily associated with cellular metabolic reprogramming: to meet the energy and building needs of viruses, and not only to evade the host's antiviral response. Accordingly, the aim of our study was to answer the question: Why does HIV need to reduce the number of peroxisomes? To achieve this goal, we tried to assess the alterations in some hematological markers of peroxisome metabolism among HIV-positive patients in relation to the intensity of the infectious process, taking into account the data of our earlier studies [29, 30].

Previously, it was shown that there is an inverse correlation between HIV-1 ribonucleic acid (RNA) and L-lysine amino acid levels. Excess intake of this essential substrate causes an increased viral load, and vice versa. We assumed that viral load-dependent plasma fluctuations in the levels of L-lysine in HIV-infected persons are associated with viral intervention in peroxisomal activity, because the initiation of L-lysine catabolism occurs only in these organelles.

Materials and methods

We conducted a case-control cohort study among HIV-infected patients followed up at the Surgut Municipal Center for HIV/AIDS prophylaxis, Russian Federation. Samples were obtained from forty-six individuals, classified into two groups: a group of two elite controllers and 18 viremic controllers, hereafter referred to as HIV controllers (n = 20), and a group of patients with fulminant disease progression as HIV rapid progressors (n = 26).

According to the accepted classification [31], patients with undetectable charge or less than 50 copies/ml and CD4 cells counted as more than 800 cells/μL for more than 20 years of follow-up in the absence of antiretroviral therapy (ART) were considered elite controllers. The subgroup of viremic controllers included HIV-infected persons with a mean viral load less than 50 copies/ml, rare blips up to 2000 copies/ml, and CD4 cell counts > 500 cells/μL for more than 18 years of follow-up, also without ART. The key criterion for identifying patients with rapid progression of the disease was the period from the onset of verified HIV infection to death from AIDS, the average duration of which was, unfortunately, only 2.5 years. Therefore, with the mean number of viral particles of more than 500.000 in ml of plasma and CD4 cell counts less than 350 cells/μL for the entire observation period.

Viral load and hematological, immunological, and peroxisomal markers were measured at the start of the study and every subsequent 3 months among HIV controllers (166 samples) and HIV rapid progressors (139 samples). The patients' baseline characteristics and targeted hematological parameters were compared with those of HIV-infected individual and healthy donors as controls. The HIV-positive cohort included 250 individuals with analogical age, sex, and an average verified disease duration of 7.4 years. Patients on ART were excluded from the comparison groups and controls, with the exception of HIV rapid progressors, about 50% of whom received therapy in the last months of their lives in the AIDS stage. Reference values for the analyzed parameters were established in an HIV-negative cohort of 85 regional donors.

The ethics committee of the Surgut Municipal Center for HIV/AIDS prophylaxis approved of the study, and blood samples were obtained after informed consent from all participants. All methods were performed in accordance with the relevant guidelines and regulations of the ethics committee of the Surgut Municipal Center for HIV/AIDS prophylaxis. Detailed characteristics of the groups and controls are presented in Table 1.

Overnight fasting venous blood samples for measurement of hematological and immunological parameters, HIV-1 RNA levels and amino-acid profiles were collected in 5 ml tubes containing 1.6 mg/ml K^2 EDTA (BD Vacutainer®, USA). For targeted l-lysine analysis, venous blood was deproteinized with 3% sulfosalicylic acid, carefully mixed, and immediately centrifuged at 3500 rpm; 10 min to remove plasma proteins. Aliquots (200 μL) were pipetted into Eppendorf tubes, stored, –40 °C and analyzed within the following fortnight. Each metabolite was detected spectrophotometrically after a post-column reaction with the ninhydrin reagent using an automatic amino acid analyzer (L-8800, Hitachi, Japan). Blood samples for measurement of HIV-1 RNA levels were centrifuged (3500 rpm; 10 min), and aliquots plasma of 1.0 ml were pipetted into Eppendorf tubes and stored at –40 °C til ready for use.

Quantification of HIV-1 RNA was performed by quantitative competitive reverse-transcriptase polymerase chain reaction (RT-PCR) using the commercially available Amplisens® HIV-monitor-FRT kit (Amplisens®, Russian Federation) with a sensitivity limit of 50 HIV-1 RNA copies/ml and a real-time PCR cycler (Rotor-Gene Q, QIAGEN, Germany). A laboratory survey of immune function was conducted using a flow cytometer according to the method of defining CD3, CD4, and CD8 lymphocyte counts (Coulter Epics XL, Beckman Coulter, USA).

Plasma total L-carnitine levels were measured using an enzymatic UV test kit (Roche Diagnostics GmbH, Germany). Serum catalase activity was determined spectrophotometrically at 240 nm using the method described by Abei H. [32].

The Student's t-test with a 95% confidence interval was applied to compare the hematological, immunological, and virological parameters and peroxisomal markers among HIV controllers, HIV rapid progressors, and controls. The correlation between HIV-1 RNA and CD4 and cholesterol levels was estimated using Pearson's correlation coefficient. Data are reported as mean ± standard deviation (SD), and *P* values 0.05 were considered to indicate statistical significance. Statistical analyses were performed using the statistical software package.

Results and discussion

Baseline clinical characteristics of comparison groups

We ascertained patients' general attributes among HIV controllers and HIV rapid progressors: age (40.9 ± 2.3 and 40.8 ± 5.4 years, respectively), sex (only males), co-infection HCV (100% and 92%) and drug use (95% and 84%). However, HIV-infected patients from compared groups have obvious differences in such criteria as, duration of HIV infection (18.7 ± 3.1 and 2.5 ± 1.4 years), the presence of progressive stages [B, C] of the disease (15 and 84%, respectively) and purpose of HAART (only in 50% of HIV rapid progressors). In the control group 1 (HIV-positive cohort) were included only men (mean age 42.4 ± 5.8 years), average duration of the disease was 7.4 ± 3.2 years, without HAART, 94% of patients had experience of drug use, HCV co-infection was detected in 90% of cases, at stages A (90%) and B (10) of HIV infection (according CDC guidelines, 1993). Control group 2 (HIV-negative cohort) consisted of healthy male donors with an average age of 38.3 ± 6.2 years.

Baseline clinical characteristics of comparison groups and controls are summarized in Table 1.

Immunological and virological parameters of HIV-infected patients in comparison groups

The obtained data showed obvious differences in basic immunological and virological disease markers between HIV controllers and HIV progressors (Table 2). In the combined group of controllers and slow progressors, the average viral load was 2.707 ± 197 copies/ml over the next 18 years. At the same time, the average number of HIV-1 RNA copies in rapid progressors was 607.600 ± 82.440 copies/ml over 2.5 years of observation from the moment of infection to death due to HIV ($P<0.001$). The mean level of viral load in samples of the HIV-positive cohort was 136.000 ± 9.614 copies/ml ($P<0.001$ for all comparison groups).

Table 1

Clinical data of HIV-infected patients in comparison groups and healthy control subjects

Clinical data	HIV controllers and slow progressors (*n*=20)	HIV rapid progressors (*n*=26)	Control 1	Control 2
			HIV-positive cohort (random sampling) (*n*=250)	HIV-negative cohort (donors) (*n*=85)
Age (years)	40.9 ± 2.3	40.8 ± 5.4	42.4 ± 5.8	38.3 ± 6.2
Sex (male/female)	20/0	26/0	250/0	85/0
Duration of the disease (years)	18.7 ± 3.1	2.5 ± 1.4	7.4 ± 3.2	–
CDC stages of HIV infection A (1, 2, 3)/B (1, 2, 3)/C (1, 2, 3)	17/ 3/0	4/2/20	226/24/0	–
Prescribing highly active antiretroviral therapy (without/under HAART)	20/0	12/14	250/0	–
Drug use (yes/no)	19/1	22/4	235/15	0/85
HBV/HCV	0/20	2/24	26/224	0/0
BMI (kg/m^2)	24.65 ± 3.72[1, 2, 5]	22.23 ± 2.46[3, 4]	23.31 ± 2.34	23.96 ± 2.67

Note:
[1] HIV controllers *versus* controls 1, *P*<0.05 or less;
[2] HIV controllers *versus* controls 2, *P*<0.05 or less;
[3] HIV progressors *versus* controls 1, *P*<0.05 or less;
[4] HIV progressors *versus* controls 2, *P*<0.05 or less;
[5] HIV controllers *versus* HIV progressors, *P*<0.05 or less.

We found significant differences in absolute CD4 cell counts among patients in the compared groups. The plasma average value of this immunological parameter in HIV controllers (931 ± 307 cells/μL) was considerably higher than that in rapid progressors (329 ± 187 cells/μL, $P < 0.001$), HIV entire cohort (481 ± 199 cells/μL, $P < 0.001$), and lower than our reference values (1231 ± 389 cells/μL, $P < 0.01$). The present study shows that the mean absolute CD4 cell counts markedly decreased in HIV rapid progressors (329 ± 187 cells/μL) compared with controls 1 (481 ± 199 cells/μL, $P < 0.001$) and 2 (1231 ± 389 cells/μL, $P < 0.001$).

The plasma average levels of CD8 lymphocytes were higher in the group of HIV controllers (1164 ± 450 cells/μL) than in rapid progressors (1048 ± 434 cells/μL, $P < 0.05$) and healthy controls (813 ± 310 cells/μL, $P < 0.05$). Hence, we detected that the mean values of CD8 lymphocytes in HIV rapid progressors were evidently lower than those in donors ($P < 0.05$). At the same time, no significant differences were found between the average absolute CD8 cell counts in controllers and rapid progressors compared to HIV-positive cohort ($P > 0.05$).

The lowest CD4/CD8 ratio was detected in HIV-infected males from the group of rapid progressors (0.31 ± 0.19) compared with the same parameters in HIV controllers (0.90 ± 0.39, $P < 0.001$), the control group 1 (0.50 ± 0.24, $P < 0.01$), and healthy controls (1.58 ± 0.51, $P<0.001$). We retrospectively observed

Table 2

Virological and immunological parameters of HIV-infected patients in comparison groups and healthy control subjects

Immunological parameters	HIV controllers and slow progressors(*n* = 20) (number of samples = 166)	HIV rapid progressors(*n* = 26) (number of samples = 139)	Control 1	Control 2
			HIV-positive cohort (random sampling) (*n* = 250) (number of samples = 250)	HIV-negative cohort(donors) (*n* = 85) (number of samples = 85)
Viral charge (copies/ml)	2.707 ± 197[1, 5]	607.600 ± 82.440[3]	136.000 ± 9.614	–
CD4 (cells/μl)	931 ± 307[1, 2, 5]	329 ± 187[3, 4]	481 ± 199	1231 ± 389
CD8 (cells/μl)	1164 ± 450[2, 5]	1048 ± 434[4]	1075 ± 463	813 ± 310
CD4/CD8 ratio	0.90 ± 0.39[1, 2, 5]	0.31 ± 0.19[3, 4]	0.50 ± 0.24	1.58 ± 0.51

Note:
[1] HIV controllers *versus* controls 1, *P*<0.05 or less;
[2] HIV controllers *versus* controls 2, *P*<0.05 or less;
[3] HIV progressors *versus* controls 1, *P*<0.05 or less;
[4] HIV progressors *versus* controls 2, *P*<0.05 or less;
[5] HIV controllers *versus* HIV progressors, *P*<0.05 or less.

that the mean CD4/CD8 ratio was mildly decreased among HIV controllers and slow progressors, with the exception of two elite controllers with constant immunological parameters.

Hematological markers related to the functional activity of peroxisomes in compared groups of HIV-infected patients and controls

The concentrations of total cholesterol, catalase, L-lysine (Lys), and its derivative (L-carnitine), as hematological peroxisome-related markers, were evaluated between HIV controllers and HIV rapid progressors in comparison with the entire patient cohort and healthy donors.

The present survey showed that the average levels of total cholesterol (Chl) in rapid progressors were significantly lower than those in HIV controllers ($P < 0.01$), control 1 ($P < 0.01$), and control 2 ($P < 0.01$). At the same time, the mean Chl values in the controllers were higher than those in the control group 1 ($P < 0.05$) and lower than those in the control group 2 ($P < 0.05$).

We found that the mean L-lysine amino acid levels were significantly decreased in both HIV controllers ($P < 0.001$ for all controls) and rapid progressors ($P < 0.001$ for all controls) compared to the controls. The lowest concentrations of Lys were detected among patients with accelerated progression of HIV infection (118.5 ± 111.7 μmol/L). The same tendencies were observed for the average plasma levels of L-lysine derivative (total L-carnitine (TC)) in HIV rapid progressors.

Our data revealed that the average concentrations of TC were evidently decreased compared to those in controls 1 and 2 ($P < 0.001$ for all parameters). At the same time, the mean L-carnitine level was markedly higher in the controllers than in the entire HIV cohort ($P < 0.05$) and lower than that in healthy donors ($P < 0.05$).

The average level of serum catalase (CAT) was significantly lower in the HIV rapid progressors' study group (1.72 ± 1.15 specific activity in U/mg of protein) than in HIV controllers ($P < 0.001$) and controls 1 and 2 ($P < 0.001$ and $P < 0.001$, respectively). At the same time, the mean level of CAT in the HIV controllers group (2.97 ± 1.32) was evidently higher than that in the control group 1 ($P < 0.05$) and did not differ from the level of our reference values ($P > 0.05$).

In the present study, we observed a weak negative correlation between serum cholesterol and HIV-1 RNA levels and, conversely, a positive correlation between Chl and absolute CD4 cell counts in the HIV-positive cohort ($r = -0.13$, $P < 0.036$ and $r = 0.11$, $P < 0.047$, respectively). A comparison of peroxisomal markers in HIV-infected patients and healthy control subjects is shown in Table 3.

Table 3

Hematological markers related with peroxisomes' functional activity

Peroxisomal markers	HIV controllers and slow progressors (*n* = 20) (166 samples)	HIV rapid progressors (*n* = 26) (139 samples)	Control 1	Control 2
			HIV-positive cohort (random sampling) (*n* = 250) (number of samples = 250)	HIV-negative cohort(donors) (*n* = 85) (number of samples = 85)
Total cholesterol (Chl) (mmol/l)	4.26 ± 0.79[1, 2, 5]	3.44 ± 0.49[3, 4]	3.91 ± 0.96	4.90 ± 0.48
L-lysine amino acid (μmol/L) (Lys)	146.0±117.2[1, 2, 5]	118.5±111.7[3, 4]	236.1 ± 148.7	265.6 ± 143.2
Total L-carnitine (TC) (μmol/l)	39.1 ± 5.6	19.5 ± 5.4	32.4 ± 6.7	44.8 ± 6.3
Catalase (CAT) (IU/L)U/mg of protein	2.97±1.32[1, 5]	1.72±1.15[3, 4]	2.57±1.94	3.21±1.46

Note:
[1] HIV controllers ***versus*** controls 1, *P*<0.05 or less;
[2] HIV controllers ***versus*** controls 2, *P*<0.05 or less;
[3] HIV progressors ***versus*** controls 1, *P*<0.05 or less;
[4] HIV progressors ***versus*** controls 2, *P*<0.05 or less;
[5] HIV controllers ***versus*** HIV progressors, *P*<0.05 or less.

Despite substantial progress in HIV science and antiretroviral therapy (ART) in the past years, HIV infection is the leading cause of morbidity and mortality worldwide, and the goal of eradicating the disease remains elusive. Many links between the virus replication cycle, the mechanisms of chronic immune inflammation, and the formation and reactivation of latent viral reservoirs that sustain HIV persistence remain relatively obscure. Arguably, the key to these tasks is a thorough understanding of the metabolic interactions between the human immunodeficiency virus and host target cells with respect to HIV infection pathogenesis.

There is no doubt that an increase in HIV comorbidities, including changes in brain tissue [33–35], dyslipidemia, insulin resistance, cardiovascular, liver, kidney, bone, and nonalcoholic fatty liver diseases in both naïve and HIV-infected persons under ART [36–38]is the result of final metabolic alterations at the organism level due to the unknown biochemical details of virus-host relationships at the molecular level.

Similar to all viruses, HIV is an obligate intracellular parasite that relies entirely on the energy, nucleotides, amino acids, or lipids of the host to copy its own genetic material, synthesize viral proteins, and assemble new virions. Pathogenic changes in infected cells ultimately reflect the implementation of a reproduction virus strategy via reprogramming host resources, metabolic tools, and reorganization of cellular structures. Recent studies have shown that some viruses actively alter peroxisomal biogenesis.

Peroxisomes are essential subcellular and highly dynamic metabolic hubs that contain over 50 different enzymes and perform variety cellular functions [3, 39–41]. It is also known that in humans, catabolism of the essential amino acid L-lysine is initiated only in peroxisomes containing unique L-lysine oxidase. While the precise role of peroxisomes in the life cycle of most viruses is unclear, recent data suggest their critical importance in the host antiviral defense system.

At the same time, it is unlikely that these multifunctional cellular hubs are involved only in the host innate immune response and antiviral signaling system. The plastic nature of peroxisomes allows them to play dual roles in the progression of human viral infections. Peroxisomes rewire their metabolism, structure, and biogenesis.

Both the host and pathogen may leverage the functions of these multifunctional organelles to achieve antiviral defense or support cellular processes for virus replication and spread [42–43]. In connection with this, the roles of peroxisomes in HIV biology are diverse.

Virus-induced dysfunction and loss of these organelles are fundamental aspects of the viral reproductive strategy and HIV infection pathogenesis.

To answer the goal of our research, we tried to connect the available data on the unique importance of peroxisomes in the metabolism of L-lysine amino acids and the results of previous findings that showed an inverse correlation between plasma Lys and HIV-1 RNA levels. We assumed that a decrease in the number of peroxisomes and their functional activity are associated with targeted viral intervention in L-lysine amino acid catabolism.

The priority of the present study was to analyze certain peroxisomal markers among HIV-infected individuals in relation to the intensity of the infectious process. To accomplish the assigned task, we formed two contrasting groups of patients according to the criteria for disease progression. We enrolled in the first group the so-called HIV controllers (n=20), with an average duration of HIV infection 18.7 years. The second group included patients (n=26) with fulminant disease progression within 2.5 years from the moment of infection to AIDS-related death.

The obtained data showed significant differences in immunological and virological parameters between the compared groups of HIV controllers and progressors. We also observed that the average levels of peroxisomal markers, such as total cholesterol (Chl) and catalase (CAT), were evidently decreased among patients with fulminant progression of HIV infection compared to those capable of controlling virus replication.

Cholesterol plays a key role in the pathogenesis of many infectious agents that modify their metabolism to meet their needs at different stages of the life cycle and weaken the host's immune response. Although the participation of peroxisomes in the pathogenesis of cholesterol remains unclear, the mevalonate pathway or pre-squalene segment of this multistep process is localized in these organelles [44–47]. In addition, recent findings indicate that the peroxisome proliferator-activated receptor (PPARs) system is involved in cholesterol metabolism and the maintenance of homeostasis in humans [48].

Available data indicate that HIV relies on cholesterol at many stages of its replication cycle including entry, assembly, and release. It is clear that membrane-associated Chl in target cells is critical for HIV infection and syncytium formation [49–52]. Inhibition of Chl synthesis by lovastatin was followed by a decrease in the number of HIV particles. This confirms the importance of intracellular cholesterol in viral assembly [55, 54]. Undoubtedly the active use of this substrate's resources by HIV leads to the development of hypocholesterolemia, which correlates with a high viral load in infected patients.

It is assumed that the depletion of cholesterol resources is associated with demyelination processes and the development of HIV-associated neurocognitive disorders, severity of the inflammatory response, metabolic dysregulation, organ dysfunction, and disease prognosis [55]. In regard to this, the worst Chl levels correspond to the terminal stages of HIV infection and to the group of patients with a rapid disease progression.

The next step of our study was to assess the plasma changes of a unique peroxisomal marker, L-lysine amino acid (Lys), the catabolism of which is triggered only in peroxisomes. The mean concentrations of this substrate were evaluated in groups of HIV controllers and rapid progressors versus HIV-positive and HIV-negative cohorts. We found that the average levels of Lys were significantly reduced in both patient groups that were able to control HIV replication and those with accelerated progression of the infection compared to the two controls. However, the mean concentration of this amino acid among HIV controllers was markedly higher than that among HIV rapid progressors.

The low plasma levels of Lys and its derivatives in HIV-infected patients [58] can be explained by consider the available data on the limiting function of host amino acids in the replicative cycle of viral systems. It is well known that deficiency of these host substrates leads to a fundamental changes in infected cells' metabolism, especially in the control of successful viral reproduction. Based on this reliable information, we hypothesized that the host's essential L-lysine amino acid plays a key role in the HIV life cycle.

In this regard, a decrease in Lys levels among HIV rapid progressors is the result of the endless huge production of viral particles, which requires sufficient resources for this amino acid. In fact, the human immunodeficiency virus interferes with the biogenesis of peroxisomes to reduce their number and enzymatic activity, in particular L-lysine oxidase [58, 59], and redirect the flow of L-lysine amino acids for their own needs.

Based on the obtained data, it is possible to answer the question about the reasons for the impact of HIV on peroxisome biogenesis with the following statement: a targeted reduction in the number of peroxisomes and their metabolic activity is associated with viral intervention in the catabolism of L-lysine amino acid for its intracellular accumulation and subsequent use in the virus life cycle.

In the context of this hypothesis, some topics and open questions concerning the biology of HIV and the pathogenesis of the disease acquire completeness or other interpretations.

In particular:

• The effects of reducing the viral load and preventing HIV-associated brain inflammation in infected persons after treatment with thiazolidinediones, in particular rosiglitazone, etc. [18, 60–68]. These antidiabetic drugs are known to enhance peroxisomal activity through peroxisome proliferator-activated receptors-γ (PPARs-γ), which are also involved in the control of systemic inflammation and is suppressed by the HIV-1 accessory protein R (Vpr) [69]. The relative recovery of the pool of these organelles' and their enzymatic activity contributes to the redirection of L-lysine to the needs of the infected organism and the limitation of its use by the virus, followed by a noticeable decrease in HIV-1 RNA blood levels.

• Negative changes in L-carnitine plasma concentrations in HIV-infected patients [18, 70–72]. Arguably, the reason for this imbalance also lies in the active consumption of L-lysine resources by the human immunodeficiency virus, which reduces the synthesis of LC, despite their partial intake from food. The role of this Lys derivative in the processes of cellular apoptosis and metabolism is well known, and its deficiency may be related to premature age-related changes in HIV-infected persons.

• The recurrence of varicella-zoster virus (VZV) is associated with high HIV-1 RNA and low L-lysine plasma levels [73–76]. Undoubtedly, the infectious processes trigger a large-scale reprogramming of cellular metabolic pathways that are accompanied by noticeable alterations, including the amino acid profile. The concentration of L-arginine (Arg) is important in the life cycle of VZV, and it is likely that a change in the Lys/Arg ratio may cause disease relapse. In this regard, data on the effectiveness of restricting dietary L-arginine and prescribing high doses of L-lysine amino acids in the treatment of recurrent herpes zoster are becoming more convincing.

• HIV tropism towards certain body tissues. The gray matter in the brain, Peyer's patches, and lymph are very attractive for the human immunodeficiency virus [18, 62–84, 77]. We assume that this phenomenon is associated with the access of immune target cells to Lys located in these lysine-rich tissues or their participation in the assimilation and transportation of this essential amino acid after its intake with food. For this reason, macrophages and long-lived infected cells form potential reservoirs of HIV, primarily in the brain and lymph nodes, where the necessary resources are available for virus replication [78–82].

• High levels of HIV-associated neurocognitive disorders (HAND) [18, 27, 83–90]. It was recently established that virus-induced loss of peroxisomes is associated with the development of HAND in HIV-infected patients. The proposed mechanism of these disorders includes the altered expression of miRNAs in infected cells, subsequent depletion of the pool of peroxisomes responsible for myelin formation, and functioning of the central nervous system. Therefore, it is not surprising that the most pronounced consequences of HIV intervention in the biogenesis of these cellular metabolic hubs are manifested in a large percentage of brain tissues sensitive to both virus-induced Lys deficiency and concomitant peroxisomal dysregulation of plasmalogen and cholesterol synthesis.

• Antiviral effects of L-lysine-α-oxidase (LysOx) in vitro and in vivo. It is well known that this enzyme is

highly selective for L-lysine amino acids, in addition to antitumor, antimetastatic, and antibacterial properties, and has unique antiviral activity, particularly against herpes simplex virus 1 and 2 (HSV-1 and HSV-2), tick-borne encephalitis virus (TBEV), and HIV [58, 91, 92]. An in vitro study showed that the production of viral particles and the level of Lys in HIV-infected cells are significantly reduced when LysOx is added to the medium [93, 94]. Similar results were obtained in an in vivo experiment. It is assumed that the cytotoxic and antiviral effects of this enzyme are associated with its attachment to the cellular surface, local accumulation of hydrogen peroxide, and development of apoptosis and necrosis of the affected cells. In our opinion, L-lysine play an important role in HIV biology, and the depletion of Lys is the main reason for the decrease in viral load, taking into account the fact that H_2O_2 activates the processes of HIV transcription.

- To date, unanswered questions remain regarding the role of uncharged tRNALys packed in the HIV capsid [95–97]. It is well known that the human immunodeficiency virus requires cellular tRNALys as a primer to initiate reverse transcription on entry into a target cell. Undoubtedly, the start of this process will be successful after the activation of this highly specific primer with free covalent L-lysine. In this regard, the presence of a sufficient concentration of this amino acid in the cytosol facilitates initiation of the HIV reproductive cycle. Moreover, several uncharged primers are packaged in a capsid to increase the chances of survival of virus progeny during the formation of new virions.

Overall, our results indicate that HIV intervention in the biogenesis of host' peroxisomes is accompanied by the concomitant dysregulation of peroxisomal enzyme systems and substrates. The most pronounced negative changes were found in catalase, cholesterol, and L-lysine amino acid levels in HIV rapid progressors and, to a lesser extent, among persons from the total HIV-positive cohort.

There is also no doubt that the so-called disease' controllers have certain mechanisms that prevent viral reprogramming of these organelles, which is confirmed by CD4 cell counts within reference values, undetectable viremia, and unchanged concentrations of the analyzed markers, with the exception of Lys. It is likely that the decrease in L-lysine levels among HIV controllers is a genetically determined process that makes it difficult to use this essential amino acid for the virus's needs. At the same time, among HIV rapid progressors, this mechanism seems to be lost, which allows the virus to redirect Lys flux for the production of viral particles.

In connection with this, there is evidence that excessive Lys consumption may increase the risk of high HIV replication and vice versa [29]. Limited dietary L-lysine intake is also a metabolic factor that determines the non-pathogenic course of simian immunodeficiency virus (SIV) infection and the absence of AIDS-like symptoms [98–105] in its natural hosts.

Conclusion

In summary, the results of this study confirmed significant differences in the plasma levels of certain hematological markers related to peroxisomes, such as catalase, cholesterol, L-lysine amino acid, and its derivatives [L-carnitine] in compared groups of HIV controllers, rapid progressors, and controls. The most negative changes in these peroxisomal substrates were observed in patients with accelerated disease progression. We tried to connect the results of the present study with the data on the unique role of peroxisomes in catabolism of L-lysine, the recent findings on a significant reduction in the pool of cellular peroxisomes due to HIV infection, and the evidence of an inverse correlation between the plasma concentrations of this amino acid and viral load. It is obvious that virus-induced metabolic reprogramming of peroxisomes occurs to create an excess of L-lysine in the cell cytosol for the successful implementation of the HIV reproductive strategy. Thus, our current findings support the hypothesis that L-lysine definitely plays a limiting role in the human immunodeficiency virus life cycle, and its access to the resources of this essential amino acid increases the risk of high levels of HIV-1 RNA, immunosuppression, and AIDS development. A better understanding of this fact may

contribute to the development of novel approaches for the therapy and regulation of HIV infection through metabolic intervention.

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Вирусиндуцированные изменения пероксисомальных маркеров при ВИЧ-инфекции

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Аннотация. *Актуальность*. Общеизвестно, что для успешной реализации своего жизненного цикла вирусы перестраивают метаболический аппарат клетки хозяина посредством перепрограммирования потоков энергии, ресурсов и метаболических инструментов клетки с последующей реорганизацией клеточных структур. Результаты недавних исследований свидетельствуют, что вирус иммунодефицита человека значительно снижает количество пероксисом в инфицированных клетках. Однако до сих пор нет четкого понимания очевидного вмешательства ВИЧ в этот процесс. Цель нашего исследования — подтвердить предположение о причинах снижения количества пероксисом при ВИЧ-инфекции. В настоящем исследовании проведена оценка изменений некоторых гематологических маркеров метаболизма пероксисом в связи с данными об уникальной роли этих органелл в катаболизме аминокислоты L-лизина, уровень которого коррелирует с уровнем РНК вируса в плазме крови ВИЧ-инфицированных лиц. *Материалы и методы*. Проведено исследование уровней общего холестерина, каталазы, L-лизина и его производного L-карнитина среди ВИЧ-инфицированных (контролеры и пациенты с быстро прогрессирующим заболеванием) в сравнении с аналогичными показателями когорт ВИЧ-инфицированных пациентов и здоровых лиц. *Результаты и обсуждение*. Исследование подтверждает наличие существенных различий в плазменных уровнях маркеров, связанных с метаболизмом пероксисом, таких как каталаза, холестерин и аминокислота L-лизин в сравниваемых группах ВИЧ-контроллеров и пациентов с быстро прогрессирующим заболеванием. Наиболее негативные изменения пероксисомальных маркеров были выявлены среди пациентов с ускоренным прогрессированием ВИЧ-инфекции и, в меньшей степени, у лиц из общей когорты. *Выводы.* Результаты настоящего исследования свидетельствуют о том, что вмешательство ВИЧ в биогенез пероксисом хозяина сопровождается сопутствующим нарушением регуляции систем пероксисомальных ферментов и субстратов, связанных с L-лизином. Вирусиндуцированное перепрограммирование катаболизма данной эссенциальной аминокислоты косвенно подтверждает гипотезу о ключевой роли L-лизина в жизненном цикле ВИЧ и является фактором успешной реализации репродуктивной стратегии вируса иммунодефицита человека.

Ключевые слова: ВИЧ, пероксисомы, аминокислота L-лизин, холестерин, каталаза, ВИЧ-контроллеры, ВИЧ-прогрессоры

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REVIEW
ОБЗОР

Bacteriophages: an alternative to antibiotics in the era of antimicrobial resistance

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Abstract. *Relevance.* Antibiotic resistance is one of the most urgent global health challenges, caused by the widespread and often inappropriate use of antibiotics and by evolutionarily entrenched bacterial adaptation mechanisms. By 2050, antimicrobial resistance is projected to cause up to 10 million deaths annually, underscoring the urgent need for novel therapeutic strategies. In this context, bacteriophages — viruses that specifically infect bacteria — emerge as a promising alternative to antibiotics. This review analyzes the primary mechanisms by which bacteria develop resistance, including β-lactamase–mediated drug inactivation, efflux pump activity, target modification, and horizontal gene transfer, as well as the clinical significance of the ESKAPE pathogen group. We discuss phage classification into lytic and lysogenic types, their morphological characteristics, and life cycles. Special attention is given to modern methods of phage delivery (oral, topical, parenteral, and inhalational) and to phage–host immune interactions, including antibody production and immunomodulatory effects on macrophages, neutrophils, and lymphocytes. A dedicated section addresses the clinical applications of phage therapy in surgery and chronic wound management. We summarize outcomes from cardiothoracic, abdominal, and orthopedic surgical settings, combined phage–antibiotic regimens, and the implementation of vacuum-assisted wound therapy with phage instillation, all of which demonstrate accelerated healing, reduced microbial burden, and fewer postoperative complications. *Conclusion.* Phage therapy offers several advantages — high specificity, efficacy against multidrug-resistant strains, compatibility with antibiotics, and minimal side effects. On the other hand, its broad clinical implementation requires addressing challenges such as standardizing phage preparation manufacturing, establishing centralized phage banks, developing algorithms for strain selection in personalized therapy, and addressing regulatory barriers. Further randomized clinical trials and the creation of an appropriate legal and regulatory framework are essential for the full utilization of phages as an effective tool in the fight against antibiotic resistance.

Keywords: antimicrobial resistance, bacteriophages, alternative to antibiotics, chronic wound treatment, surgery, purulent surgery, phage therapy, multidrug-resistant infections

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Introduction

Antibiotic resistance has become one of the main threats to modern medicine, calling into question the effectiveness of traditional methods for treating bacterial infections. The constant increase in the number of antibiotic-resistant strains of bacteria is forcing the search for alternative approaches to therapy. One of the research areas in this direction is the study of bacteriophages — viruses that selectively infect bacteria without harming the human body. The use of bacteriophages in medicine, known as phage therapy, was successful in the last century, but interest in it temporarily waned with the advent of antibiotics. Today, in the context of the growing crisis of antibiotic resistance, phage therapy is being revisited as a potential solution.

Antibiotic resistance

Antibiotic resistance is a complex biological phenomenon that reflects the ability of bacteria to adapt to the effects of antibiotics through evolutionarily established mechanisms and genetic variability [1]. This phenomenon is seen not only as a result of modern human activities, including the irrational use of antibiotics, but also as a natural adaptation of bacteria that formed long before humans existed. After the introduction of new antibiotics, the emergence of resistant strains of bacteria that were previously sensitive to these drugs is inevitable. The variety of resistance mechanisms contributes to the development of resistant phenotypes in bacterial pathogens, rendering the treatment of human infections caused by them extremely difficult [2, 3].

Antibiotics are the primary means for preventing and treating bacterial infections. However, their widespread and often irrational use contributes to the development of antibiotic resistance — the ability of bacteria to adapt and resist the action of antimicrobial drugs. This complicates the treatment of infections,

increases their spread, and raises the level of morbidity and mortality [4].

Between 2000 and 2018, global consumption of antibacterial drugs increased by 46% [5]. This increase is particularly noticeable in low- and middle-income countries, where access to antibiotics is growing [6]. According to experts, by 2050, antimicrobial resistance could cause up to 10 million deaths worldwide each year [7].

Antibiotic resistance is one of the leading global health challenges. It threatens the effectiveness of treatment for diseases such as pneumonia, tuberculosis, sepsis, and gonorrhea. The World Health Organization warns that new resistance mechanisms are spreading rapidly, reducing the clinical value of antibiotics [8].

Without the implementation of comprehensive measures to control and prevent resistance, there is a real risk of entering a post-antibiotic era, when even routine infections and minor injuries could become fatal.

Strategies to combat antibiotic resistance include surveillance, reducing the use of antibiotics in livestock, improving access to quality medicines, and developing new therapeutic alternatives such as nanoparticles and bacteriophages [5, 9].

Mechanisms of antibiotic resistance development

Bacteria are constantly competing for resources, which leads to the evolution of chemicals that can inhibit or eliminate other microorganisms [10].

Bacteria develop resistance mechanisms very quickly due to selective pressure. Defensive mechanisms against antibacterial drugs include the following [10–12]:

1. Destruction or modification of antibiotics. Certain bacteria produce enzymes that can eliminate or modify antibiotics, rendering them inactive against microorganisms, such as several classes of beta-lactamases and the like.
2. Efflux pumps. Bacteria can use special proteins to pump antibiotics out of their cells, reducing their concentration to an ineffective level.
3. Alteration of cell wall permeability. Bacteria can change the permeability of their cell walls to prevent antibiotics from entering the cell.
4. Antibiotic target modification. Bacteria can alter the structure of the molecules to which antibiotics bind, rendering the antibiotics ineffective.
5. Metabolic changes or auxotrophy. Bacteria can modify their metabolic pathways to reduce the effectiveness of antibiotics.
6. Target protection proteins. Bacteria can synthesize proteins that protect the targets of antibiotics.
7. Cell morphology changes. Bacteria can change their cell shape to reduce the impact of antibiotics.
8. Cooperative resistance in a colony. Bacteria can interact within a colony to enhance overall resistance to antibiotics.
9. Horizontal gene transfer. This mechanism enables bacteria to acquire new genetic material from external sources, facilitating the exchange of a diverse array of genes that encode traits advantageous for adaptation to their local environment [13, 14]. This is achieved through conjugation, transduction, and natural transformation, which allows resistance genes to spread rapidly among different species of bacteria [15].

The ESKAPE pathogen group and their characteristics

The ESKAPE group is a collection of six nosocomial pathogens known for their ability to "evade" the effects of antimicrobial drugs. These pathogens include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter spp* [12]. They have natural resistance to a number of antibiotics due to various resistance mechanisms, including the exchange of plasmid-encoded resistance genes through horizontal gene transfer, which leads to an increase in the level of antimicrobial resistance in these microorganisms [16].

1. *Enterococcus spp***.** These are gram-positive cocci, facultative anaerobes, and gastrointestinal commensals that can survive in various conditions [17]. They can cause infectious diseases in humans,

particularly in patients with weakened immune systems. More than 50 species of this microorganism have been described, yet enterococcal infections are most often caused by two species: *E. faecalis* and *E. faecium*. *E. faecalis* is the most pathogenic species, although *E. faecium* is more resistant to various antimicrobial drugs [18].

2. *Staphylococcus aureus.* These are gram-positive cocci that can cause a wide range of diseases in humans, as well as various infectious complications, particularly in surgery. They are facultative anaerobes and are catalase- and coagulase-positive cocci [19]. This microorganism poses a significant threat due to its ability to quickly adapt and develop resistance to antibiotics. Staphylococcus aureus can cause systemic and deep infections (endocarditis, osteomyelitis, pneumonia), hospital-acquired infections (surgical wound infections, catheter-associated infections), skin and soft tissue infections (boils, abscesses, cellulitis, phlegmon), and others.

The literature describes three antibiotic-resistant forms of *S. aureus*: methicillin-resistant Staphylococcus aureus (MRSA), which is resistant to methicillin and other beta-lactam antibiotics [20]; vancomycin-intermediate Staphylococcus aureus (VISA); and vancomycin-resistant *Staphylococcus aureus* (VRSA). The latter two forms are resistant to vancomycin, one of the last effective antibiotics against *S. aureus* [21].

3. *Klebsiella pneumoniae.* This is a gram-negative bacterium of the Enterobacteriaceae family. This microorganism is opportunistic — it lives in the intestines of humans and animals and under certain conditions can cause serious infections. *K. pneumoniae* is one of the leading etiological agents of nosocomial pneumonia, especially among immunocompromised patients. It also causes infections of the urinary tract, including cystitis and pyelonephritis. *K. pneumoniae* is involved in the pathogenesis of intra-abdominal inflammatory processes, such as peritonitis and abdominal abscesses, especially after surgery or traumatic injuries. Additionally, it can cause postoperative wound infections [22,23]. Numerous strains of K. pneumoniae exhibit high resistance to antibacterial drugs, including beta-lactam antibiotics (penicillins, cephalosporins) and carbapenems. Certain strains of *K. pneumoniae* produce enzymes called carbapenemases, which can inactivate carbapenems — the last line of antibiotics effective against a number of multidrug-resistant microorganisms [24]. Strains demonstrating carbapenem resistance are classified as CRKP (carbapenem-resistant *Klebsiella pneumoniae*) [25].

4. *Acinetobacter baumannii.* This is an aerobic gram-negative bacterium, which is a common causative agent of nosocomial infections [26]. *A. baumannii* contributes to infectious complications such as pneumonia (especially in patients on mechanical ventilation), urinary tract infections (common in patients with catheters or other medical devices), wound infections (often occur in patients with open wounds), as well as sepsis and bacteraemia. There are mechanisms of resistance, including the production of β-lactamases, efflux, and modification of the antibiotic target [27,28].

5. *Pseudomonas aeruginosa*. This is a gram-negative opportunistic pathogen that is widespread in the environment and frequently found in hospitals. It exhibits natural resistance to a number of antibiotics and can cause serious infections, especially in patients with weakened immune systems [29, 30]. The pathologies associated with this microorganism include pneumonia (especially common among patients on mechanical ventilation and can be associated with the development of lung abscesses), urinary tract infections, and skin and soft tissue infections. The mechanisms of resistance in P. aeruginosa are related to the production of β-lactamases, efflux, and mutation of antibiotic targets [31].

6. *Enterobacter spp*. This is a genus of gram-negative bacteria of the Enterobacteriaceae family. The most common pathogens are Enterobacter cloacae and Enterobacter aerogenes [32]. They form part of the commensal intestinal microbiota in both humans and animals, but can also cause a number of serious infectious diseases, including urinary tract infections; pneumonia (especially in patients on mechanical ventilation); bacteremia and sepsis; intra-abdominal infections (peritonitis and abdominal abscesses can occur due to the spread of infection from the gastrointestinal tract). They employ the following resistance mechanisms: production of extended-spectrum beta-lactamases (ESBL); certain strains of

Enterobacter spp. produce enzymes that eliminate carbapenems; presence of mechanisms for developing antibiotic resistance through efflux pumps; mutation of antibiotic targets [33].

Pathogens from the ESKAPE group pose a serious threat to public health due to their ability to adapt to existing antibiotics and quickly develop resistance to new drugs. Therefore, addressing these pathogens necessitates the development of new treatment strategies, including combination therapy, new classes of antibiotics, and improved methods of infection prevention.

In response to the widespread threat of antibiotic resistance, the World Health Organization has developed a Global Action Plan aimed at minimizing the impact of antibiotic resistance on the health of humans and animals. The "One Health" concept unites the efforts of various international organizations, such as the Food and Agriculture Organization of the United Nations and the World Organization for Animal Health, to provide an integrated approach to ensure a coordinated response to this threat, considering the integrated nature of human, animal, and environmental health [34, 35]. At the national level, a number of countries, including Japan, Tanzania, and China, have developed their own action plans to combat antibiotic resistance, aimed at monitoring and reducing the spread of antibiotic resistance. An important element in the fight against antibiotic resistance is raising public awareness about the causes and consequences of this threat, which helps to form the right attitude towards the use of antibiotics [7].

In the face of the growing global threat of antibiotic resistance, there is an increasing need to develop new effective methods for treating bacterial infections that are resistant to antibiotics. In this context, experts are increasingly viewing bacteriophage therapy as a promising alternative. Although interest in using bacteriophages to treat infectious diseases was rekindled in recent years, current research has confirmed their significant therapeutic potential. Whether used alone or in combination with antibiotics, bacteriophages remain a promising replacement for traditional antibacterial agents [2, 36, 37].

Tables 1 and 2 present the most critical dangerous antibiotic-resistant pathogens according to the World Health Organization (WHO). This challenge requires the development of alternative treatment methods, which is stimulating renewed interest in the use of bacteriophages in medical practice [38].

Table 1

List of priorities for the development of new antibiotics according to the World Health Organization [39]

Priority	Types of pathogens	Resistance to antimicrobials
Critical	Acinetobacter baumannii	Carbapenem-resistant
	Pseudomonas aeruginosa	Carbapenem-resistant
	Enterobacteriaceae* (*Enterobacteria include: *Klebsiella pneumonia, Escherichia coli, Enterobacter spp., Serratia spp., Proteus spp.* и *Providencia spp., Morganella spp.*)	Carbapenem-resistant, third-generation cephalosporin-resistant
High	*Enterococcus faecium*	Vancomycin-resistant
	Staphylococcus aureus	Methicillin-resistant, vancomycin-intermediate and vancomycin-resistant
	Helicobacter pylori	Clarithromycin-resistant
	Campylobacter	Fluoroquinolone-resistant
	Salmonella spp.	Fluoroquinolone-resistant
	Neisseria gonorrhoeae	Third-generation cephalosporin-resistant, fluoroquinolone-resistant
Medium	*Streptococcus pneumoniae*	Penicillin-resistant
	Haemophilus influenzae	Ampicillin-resistant
	Shigella spp.	Fluoroquinolone-resistant

Table 2

Comparative overview of bacterial pathogen priority tiers, 2017 versus 2024. According to Sati H. et al., 2025 [40]

Priority tier	2017	2024
Critical	*Acinetobacter baumannii*, carbapenem-resistant; *Pseudomonas aeruginosa*, carbapenem-resistant; *Enterobacteriaceae*, carbapenem-resistant, third-generation cephalosporin-resistant	*A.baumannii*, carbapenem-resistant; *Enterobacterales*, third-generation cephalosporin-resistant; *Enterobacterales*, carbapenem-resistant; *Mycobacterium tuberculosis*, rifampicin-resistant
High	*Enterococcus faecium*, vancomycin-resistant; *Staphylococcus aureus*, meticillin-resistant, vancomycin intermediate and-resistant; *Helicobacter pylori*, clarithromycin-resistant; *Campylobacter spp*, fluoroquinolone-resistant; *salmonellae*, fluoroquinolone-resistant; *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant	*Salmonella enterica* serotype Typhi, fluoroquinolone-resistant; *Shigella spp*, fluoroquinolone-resistant; *E. faecium*, vancomycin-resistant; *P. aeruginosa*, carbapenem-resistant; non-typhoidal *Salmonella*, fluoroquinolone-resistant; *N. gonorrhoeae*, third-generation cephalosporin-resistant, fluoroquinolone-resistant; *S. aureus*, meticillin-resistant
Medium	*streptococcus pneumoniae*, penicillin non-susceptible; *Haemophilus influenzae*, ampicillin-resistant; *Shigella spp*, fluoroquinolone-resistant	*Group A streptococci*, macrolide-resistant; *S. pneumoniae*, macrolide-resistant; *H. influenzae*, ampicillin-resistant; *group B streptococci*, penicillin-resistant

Bacteriophages

On September 10, 1917, F. J. d'Herelle published a brief note in the journal "Comptes rendus de l'Académie des sciences", describing a new type of microbe, which he characterized as an "obligate intracellular parasite" of bacteria [41]. This discovery became a turning point in d'Herelle's career, earning him international recognition, honorary academic degrees, a Nobel Prize nomination, and a long-lasting yet controversial scientific reputation. D'Herelle's work, published in 1917, includes the first clear and experimentally grounded description of a bacteriophage. Although in 1915 F.W. Twort provided observations of phenomena that he called "glassy transformation" and "transmissible lysis", he did not offer an explanation for the viral nature, intracellular parasitism, or the ability of the infectious agent to reproduce serially [42]. On September 15, 1917, Dr. Emile Roux presented d'Herelle's note to the Academy of Sciences, introducing the medical community to an invisible microbial antagonist of the dysentery bacillus; this antagonist was named a bacteriophage [43, 44].

In the USSR, as well as in the rest of the world, research was conducted on the use of bacteriophages in the treatment of infectious diseases and the search for other effective means to solve this problem. For instance, prior to the advent of antibiotics, Z.V. Ermolyeva was investigating bacteriophages and lysozyme, which is mentioned in an article by Yu.V. Belchich (a review of the monograph by A.V. Gorshenin "History of scientific activities by the Soviet microbiologist Z.V. Ermolyeva on the study and use of antibacterial agents in the 1930s"). The article describes the significance of Ermolyeva's contribution to science, namely the creation of a new direction in medical bacterial biochemistry, the development of antibacterial drugs based on lysozyme and bacteriophages, active training of personnel in the field of microbiology, and the fight against infectious diseases [45]. This significantly increased the effectiveness of medical practice and improved the health of the USSR population, and her work received international recognition.

In the modern medical community, a significant number of specialists remain skeptical about the potential of phage therapy for treating severe bacterial infections. The first successful attempts to use virulent bacteriophages to treat several infectious diseases in the first quarter of the 20th century did not receive further active development, as antibiotics appeared on the historical scene and demonstrated high effectiveness in combating bacterial infections [46].

Phages are small viral particles that are sensitive to certain strains of bacteria and can specifically infect bacteria, effectively eliminating the bacterial cells [47]. Currently, phage therapy is experiencing a resurgence of interest as an alternative to antibiotics in the fight against resistant bacterial infections [48–50].

The interest in phage therapy is driven by a number of primary factors. Firstly, the increasing number of antibiotic-resistant bacteria poses a serious health threat,

necessitating development of alternative treatment methods. Phage therapy, due to the high specificity of bacteriophages, can effectively combat bacterial infections while minimizing the impact on beneficial microbial flora and reducing the risk of side effects.

Scientific and technological advances, such as progress in molecular biology and biotechnological production, allow for a deeper understanding of the mechanisms of interaction between bacteriophages and bacteria, and the development of more effective therapeutic strategies. Additionally, phage therapy is being explored as a potential strategy to address multidrug-resistant infections and can be combined with antibiotics to enhance the therapeutic effect. These factors, along with economic and social aspects, stimulate interest in phage therapy from both the scientific community and potential funders. Structural model of bacteriophage is presented on Figure 1.

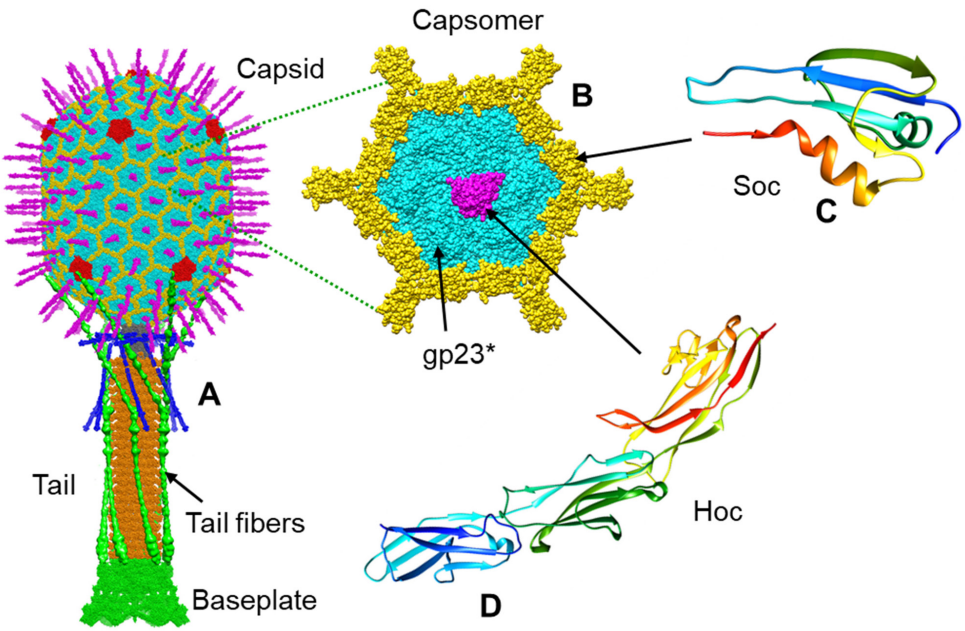

Fig. 1. Structural model of bacteriophage T4 virion. According to Rao V.B. et al., 2023 [51]

Advantages and disadvantages of using phage therapy

The use of bacteriophages (phages) to treat infections, including chronic wounds, demonstrates several advantages that render them a promising alternative or addition to traditional antibiotic therapy [52]. The main advantages of using bacteriophages include:

1. High specificity: bacteriophages selectively target specific strains of bacteria without disrupting the beneficial microbiota of the host. This reduces the risk of dysbiosis and other side effects associated with the elimination of beneficial bacteria. Bacteriophages are highly specific viruses that can effectively target pathogenic bacteria and eliminate them, rendering them a promising alternative to antibiotics in the treatment of infections [50]. In N.S. Kuptsov's study, it is shown that commercial bacteriophage preparations effectively eliminate strains of Staphylococcus aureus, Klebsiella pneumoniae, and Pseudomonas aeruginosa, but their effectiveness remains low against Enterococcus faecium [53]. Although certain monoisolates of bacteriophages also showed activity against these pathogens, commercial preparations have shown enhanced effectiveness.

2. Effectiveness against multidrug-resistant bacteria: phage therapy can be effective even against antibiotic-resistant bacteria. This is of great importance given the growing challenge of antibiotic resistance. Bacteriophages are highly specific viruses that can effectively target and eliminate pathogenic bacteria, rendering them a promising alternative to antibiotics in the treatment of infections [50]. Phage therapy has demonstrated its effectiveness in combating outbreaks of healthcare-associated infections caused by antibiotic-resistant bacteria such as *S. aureus* and *K. pneumoniae* [54].

3. Compatibility with other treatment methods: bacteriophages can be used in combination with antibiotics and other standard treatment methods, enhancing the overall effectiveness of therapy [55].

4. Minimal side effects: since bacteriophages are natural components of the ecosystem, they demonstrate a favorable safety profile in clinical use and exhibit a low level of toxicity [56, 57].

5. The ability to adapt: due to their nature, bacteriophages can quickly adapt to changing conditions and bacterial mutations, remaining effective despite resistant bacterial mutants [58, 59].

6. Convenience of use: modern research allows for development of convenient forms of bacteriophage-based preparations, such as ointments, creams, and gels, which are easy to use in clinical practice.

However, there are also disadvantages to using phage therapy [60]:

1. Specificity to bacteria. Phages have high specificity for certain strains of bacteria, which requires identifying and selecting the appropriate phage for each specific case of infection. This can complicate the treatment process, as different patients may require different phage preparations.

2. Development of bacterial resistance. Bacteria can develop resistance to phages, analogous to their development of antibiotic resistance. Although it happens less frequently than the development of resistance to antibiotics, this challenge still requires attention.

3. Immune response. The use of phages can stimulate the human immune system to produce neutralizing antibodies, which may reduce the effectiveness of therapy. It is especially critical when therapy extends over a prolonged period.

4. The need for extensive libraries of diverse bacteriophages. Successful phage therapy requires well-characterized libraries of phages ready for use. Developing and maintaining such libraries requires significant resources and effort.

5. Regulatory restrictions. In numerous countries, there are strict regulatory barriers to the approval of phage therapy, which slows down its implementation in medical practice.

Separately, the debatable issue of the possibility of the participation of bacteriophages in the transfer of antibiotic resistance genes should be noted. Modern research shows that phages can have various effects on bacteria, contributing to both the development of sensitivity and the formation of antibiotic resistance. One of the possible mechanisms is the horizontal transfer of genetic material containing antibiotic resistance genes (ARGs) by transduction [61]. The use of cocktails containing lytic phages, their clinical efficacy, confirmed by cytomorphological analysis, the administration of bacteriophage drugs after receiving phagogram results, and the certification of phages with their sequencing, make it possible to minimize the possibility of this phenomenon. At the same time, the availability of data in the literature indicating the potential role of phages in the spread of antibiotic resistance requires further research.

Despite these promising results and advantages, as well as the disadvantages of using bacteriophages (the need for refrigerated storage, frequent dosing), additional randomized clinical trials are needed to fully establish the effectiveness and safety of phage therapy [56].

Classification and morphology of bacteriophages

Based on their life cycle bacteriophages can be classified as either lytic or lysogenic. Lytic (virulent) phages: after infecting a bacterium, these phages multiply rapidly and eliminate (lyse) the host cell, releasing new phage particles [60]. This process is called the lytic cycle.

Lysogenic (temperate) phages — these phage particles integrate their genetic material into the genome of the host bacterium and remain there in a latent state until conditions become favorable for transitioning to the lytic cycle [62]. Unlike lytic phages, lysogenic phages integrate their nucleic acid into the genome of the bacterial host. The phage genome can consist of DNA (double-stranded or single-stranded) or RNA (also double-stranded or single-stranded) [63].

In the review article by Liang Huang and Ye Xiang bacteriophages that infect gram-positive bacteria exhibit various morphological characteristics depending on their tail appendages type: podoviruses have short non-contractile tails, siphoviruses have long non-contractile tails, and myoviruses have long contractile tails [64]. These differences in morphology are associated with adaptation to specific conditions for infecting and penetrating host cells. The main structural components of bacteriophages include the capsid, which protects the genetic material, and the tail apparatus, which plays a primary role in the infection process by allowing the virus to attach to the cell wall and membrane of the host and deliver its genetic material into the cell. An important element is also the connector, which joins the head of the capsid to the tail and performs several functions, including initiating capsid assembly, holding the packaged genome, and mediating tail assembly. The process of infecting a cell with a bacteriophage occurs with the virus recognizing and attaching to the surface of the host cell via special receptors. The virus then injects its genetic material into the cytoplasm of the cell, leaving the empty capsid outside. Inside the cell, the viral genetic material is used to synthesize viral proteins and replicate the viral genome. The assembled viral components merge to form new viral particles. In the final stage, the progeny virions exit by lysing the cell or by budding from its membrane, preserving cell viability and perpetuating infection

Phage delivery methods

There are several main methods for delivering bacteriophages [65]:

1. *Oral administration*

Oral administration is one of the most common methods for delivering bacteriophages. This method is used to treat gastrointestinal infections and various systemic diseases. A major challenge is that the acidity of the stomach can eliminate the phages, therefore it is necessary to develop special protective coatings or capsules to increase their stability [66].

2. *Topical administration*

Topical use of bacteriophages includes the application of ointments, creams, gels, or sprays to treat skin infections, wounds, ulcers, and other superficial lesions [67]. This method allows phages to be delivered directly to the site of infection, bypassing the gastrointestinal tract.

3. *Parenteral administration*

Systemic delivery involves intravenous, intramuscular, or subcutaneous administration of bacteriophages [52]. This method is used to treat more severe infections, when rapid distribution of phages throughout the body is required. However, it necessitates a high degree of purification of the preparations and consideration of possible immune reactions of the organism.

4. *Inhalation*

Inhalation is used to deliver phages to the respiratory tract, especially in the treatment of respiratory infections [68]. This method allows for quick delivery of phages to the site of infection, but it requires special equipment and preparation of the phage solution.

Immune response to phage therapy

When a foreign agent (antigen) enters the body, the immune system of humans and animals initiates the process of synthesizing specific protective proteins — antibodies (immunoglobulins). This adaptive response plays a primary role in protecting the body from pathogenic microorganisms and toxic substances. However, the high variability of potential threats determines the ability of the immune system to respond not only to pathogens, but also to other agents, including non-pathogenic microorganisms such as bacteriophages [69].

In the book section "Phage as a Modulator of Immune Responses: Practical Implications for Phage Therapy", Andrzej Górski describes fundamental research on the interaction between bacteriophages and immune system cells and their potential applications, particularly in the field of phage therapy [70]. Two main aspects of these interactions are considered:

1. The immunogenicity of bacteriophages. The ability of bacteriophages to elicit specific immune responses, including the production of antibodies against viral antigens. The mechanisms of this process and its potential consequences for the effectiveness of phage therapy are being investigated;
2. The immunomodulatory activity of bacteriophages. The indirect effects of bacteriophages on the functions of immune system cells, such as phagocytosis, cytokine production, and the proliferation of T and B cells. These studies provide a valuable insight on how bacteriophages can influence the course of infections and the effectiveness of treatment.

The leading aspects of immunogenicity include antibody production and cellular immune response. Regarding the former, bacteriophages can stimulate the body to produce antibodies that specifically recognize and neutralize phage particles. This can significantly limit the effectiveness of phage therapy, as antibodies can bind to phages and interfere with their interaction with bacteria. As for the cellular immune response, there is less data on the cellular response to bacteriophages, but there is evidence that phages can trigger cellular reactions similar to those observed during viral infections. For instance, they can stimulate the proliferation of T lymphocytes and other immune system cells. Bacteriophages can also affect immune system cells by altering their functions. Phages can influence the ability of macrophages and neutrophils to ingest and eliminate pathogens. Various studies show that phages can either enhance or suppress phagocytosis depending on the experimental conditions. Bacteriophages can affect the synthesis of various cytokines, such as interferons and interleukins, which can influence the overall course of infection and inflammation.

There is evidence that phages can modulate the proliferation and function of lymphocytes, which can have both positive and negative effects on the immune response. Thus, bacteriophages assume dual immunomodulatory functions in interactions with the mammalian immune system. On the one hand, they elicit specific immune responses, including the production of antibodies and cellular reactions, which can limit their therapeutic effectiveness. On the other hand, bacteriophages can modulate the functions of immune cells, such as macrophages and lymphocytes, influencing phagocytosis, cytokine production, and cell proliferation, which exhibits the potential to create new therapeutic strategies. However, when using phages therapeutically in patients, the expected formation of antibodies was not always observed, or proved to not enhance the effectiveness of the phages in combating bacterial infection [71–73].

Bacteriophages, as viruses that infect bacteria, can be used for creating vaccines and therapy due to their ability to interact with the immune system [74]. Phage-based vaccines use phage display technology, which allows antigens to be attached to phage capsids, stimulating an immune response. Additionally, bacteriophages can serve as carriers of epitopes, which are small antigen fragments recognized by the immune system. In a therapeutic context, bacteriophages are used to eliminate pathogenic bacteria in phage therapy, particularly effective against antibiotic-resistant infections. Moreover, bacteriophages can enhance the immune response by stimulating phagocytosis and the activation of T lymphocytes. Despite the advantages of high specificity and low toxicity, there are risks associated with possible allergic reactions and the development of resistance in bacteria. This requires further research and optimization for safe and effective use.

Chronic wounds

Chronic wounds are tissue injuries in which the healing process is disrupted, and they do not achieve complete anatomical and functional integrity [52]. Such wounds are often associated with vascular, endocrine disorders, or prolonged mechanical pressure. The challenge related to chronic wounds is relevant for global healthcare, as it affects significant segments of

the population. According to various estimates, 1 to 2% of the population in developed countries experience chronic wounds at certain point in their lives [75]. The incidence of chronic wounds is increasing, which is due to the ageing population, the rise in obesity and the associated risk of developing diabetes mellitus. Chronic wounds negatively affect the quality of life of the patient and their environment, leading to pain, reduced functional activity, psychoemotional disorders such as stress, anxiety and depression, as well as social isolation.

Wound healing

Wound healing is a complex and carefully regulated process that plays a leading role in maintaining the barrier function of the skin and its other functions. This process can be influenced by various factors, both modifiable and non-modifiable, and includes several phases, each with its own characteristics and potential complications. The skin is the largest organ in the human body; it acts as a waterproof mechanical barrier between the organism and the environment, thereby preventing the loss of various biological components of the organism and providing protection against external aggressive factors [76]. The skin is often subjected to various injuries of chemical, physical, or mechanical origin. After any such impact, the wound healing process occurs immediately, consisting of four consecutive phases and lasting a certain amount of time.

The wound healing process includes the following phases: hemostasis, inflammation, proliferation, and remodeling. These phases can overlap and occur simultaneously, requiring a comprehensive approach to treatment to ensure that the healing process is not interrupted and proceeds without complications [77–79].

1. Hemostasis. During hemostasis, vasoconstriction occurs, platelets aggregate, and a thrombus (fibrin clot) is formed, which restores the protective properties of the skin and maintains its structural integrity. Fibrin also promotes cell migration to the site of injury and stimulates the proliferative activity of fibroblasts [80, 81].

2. Inflammation. The inflammation phase occurs immediately after the skin is injured, initiating healing processes. The inflammation phase lasts approximately 4–6 days, during which neutrophils, monocytes, and lymphocytes migrate to the damaged area. Monocytes differentiate into macrophages, which engage in phagocytosis and secrete reactive oxygen species, cytokines, and a spectrum of mediators that drive angiogenesis, inflammation, and fibrosis [52, 81–83].

3. Proliferation. During the proliferation phase, primary processes such as angiogenesis, synthesis of connective tissue (fibroplasia), and re-epithelialization occur [52, 77, 84, 85]. During this stage, granulation tissue forms, filling the wound cavity. Fibroblasts are activated and acquire the ability to contract, thereby promoting the approximation of the wound edges. Simultaneously, migration and proliferation of keratinocytes surrounding the wound edges occur, leading to the closure of the affected area.

4. Tissue remodeling. This is the final stage of the healing process, which occurs several weeks after the injury and can last up to one year [86]. During this period, the newly formed tissue undergoes restructuring and strengthening, which ultimately leads to the formation of a scar. Scar tissue generally exhibits greater thickness and lower elasticity compared to the original skin [76].

Impaired wound healing

Wound healing disorders are a complex issue associated with numerous factors, both local and systemic. The main factors affecting wound healing include: infectious agents, occurrence of biofilms in the wound, systemic diseases, and the impact of medications.

- Infections: bacterial agents, especially bacteria of the genera *Proteus* and *Pseudomonas*, significantly slows down the wound healing process [87].
- Hypoxia and inflammation: chronic wounds are characterized by persistent inflammation and, as a rule, bacterial biofilms, which complicate healing and prolong the transition to the proliferation phase of the wound process [88];

- Wound size: greater depth, complex topography, and larger wound dimensions correlate with an increase in the duration of the healing process [87];
- Type I and II diabetes mellitus: impaired wound healing in patients with diabetes mellitus is a significant clinical complication associated with complex pathophysiological mechanisms. Hyperglycemia, characterized by elevated plasma glucose levels, promotes the formation of bacterial biofilms and impedes the effectiveness of treatment measures. Chronic inflammation and polymicrobial infections also significantly impede normal tissue regeneration. Additionally, reduced angiogenesis activity, expressed as decreased formation of new blood vessels, impairs the recovery processes. Dysfunction of fibroblasts, which play a primary role in healing, exacerbates these impairments. The combination of these factors leads to significant difficulties in wound healing in diabetic patients [89–92].
- Clinically significant atherosclerosis is a major systemic factor affecting wound healing [87]. Atherosclerotic changes in blood vessels impede the wound healing process due to impaired vascular function and a chronic inflammatory response. These factors contribute to reduced angiogenesis and cell proliferation, which impairs the regeneration processes [93–95];
- Medications: numerous drugs, such as chemotherapy agents and immunosuppressants, non-steroidal anti-inflammatory drugs, as well as certain antibacterial drugs, can have a negative impact on wound healing [96].

Other factors contributing to impaired wound healing include age, poor nutrition, chronic diseases, immune dysregulation, and genetic aberrations [88,97–99].

Microorganisms in wounds

Microorganisms present in chronic wounds significantly impact the delay in the healing process. The spread of bacterial infection in a wound can impede the immune response. Evidence of bacteria in a wound goes through various stages, from initial contamination to colonization by microorganisms. With prolonged presence of bacterial agents, bacterial biofilms form, leading to critical colonization. This stage is often accompanied by an unpleasant odor. Surrounding tissues may also become infected, leading to deep or systemic infections [86].

Exposed subcutaneous fat, necrotic tissue within wounds of diverse etiology, and a weakened immune system of the patient provide optimal conditions for the colonization and growth of microorganisms in the wound [100]. Contamination by bacterial agents occurs through endogenous pathways and directly from the surrounding skin [101].

The most common bacteria found in chronic wounds are *Staphylococcus aureus*, *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, and Klebsiella pneumoniae*. These microorganisms can cause both mono-infections and polymicrobial infections, which complicates treatment [102–104].

Bacteriophages in surgery

Bacteriophages have found application in various fields of surgery: cardiothoracic, abdominal, purulent, traumatology, and orthopaedics. Phage therapy has shown its effectiveness in treating infections associated with cardiothoracic surgery, especially in cases where traditional antibiotic therapy is unsuccessful. According to a study by E. Rubalskii et al., eight patients with infections caused by antibiotic-resistant bacteria were successfully treated with phages. It was noted that the target bacteria were eliminated in seven out of eight patients without serious side effects [105]. In cardiosurgical practice, infections of vascular grafts are one of the significant problems due to the difficulties in therapy and the high mortality rate. Bacteriophages can be used both for the prevention and treatment of these infections, and both monotherapy and a combined approach with antibiotics are possible. However, the successful phage therapy implementation requires standardization of methods for delivering bacteriophages to the site of infection, which will allow achieving the necessary local concentration and minimize the systemic spread of phage agents [106]. The use of combined therapy with bacteriophages and antibacterial drugs during surgical treatment of affected tissue areas is also

of interest. For instance, in a clinical observation by K. Racenis et al., a positive clinical effect was achieved using a combined therapeutic approach, specifically the use of the synergy between a bacteriophage and an antibiotic along with surgical intervention in a patient with a left ventricular assist device (LVAD) and recurrent infection with multidrug-resistant *P. aeruginosa* [107]. A systematic review demonstrated the safety and effectiveness of phage therapy in treating infectious complications in cardiac surgery. In the analyzed clinical studies involving 40 patients, 70.3% achieved complete resolution of the infectious process, while 10.8% showed significant improvement. Adverse events associated with the use of phages were minimal and had no direct connection with the therapeutic agent itself [108].

Data demonstrate that the use of polyvalent bacteriophages in the treatment of postoperative purulent-inflammatory complications in emergency abdominal surgery can reduce the development of antibiotic-resistant strains and the risk of nosocomial microbial associations, as well as reduce the number of postoperative complications [109]. In his dissertation research, A.N. Morozov's describes that the use of bacteriophages in the perioperative period during laparoscopic appendectomy leads to a significant reduction in the number of postoperative complications and an improvement in the quality of life for patients [110]. Animal experiments and clinical trials have demonstrated that bacteriophages contribute to faster tissue recovery and a reduction in inflammatory processes compared to traditional antibiotic therapy. Additionally, patients treated with bacteriophages exhibited lower levels of leukocytes and C-reactive protein, as well as more stable temperature readings in the surgical area, indicating the benefits of their use in surgical practice.

Bacteriophages are also becoming a promising tool in the treatment of infections in traumatology, especially in cases of antibiotic resistance. A clinical observation by T. Ferry et al. describes a case of successful use of personalized phage therapy in a patient with a recurrent infection of a knee joint prosthesis caused by a multidrug-resistant strain of *P. aeruginosa* is described [111]. In E.A. Fedorov's dissertation research phage therapy is considered a primary element in improving the outcomes of treatment for deep periprosthetic infection [112]. The study showed that phage therapy offers several potential advantages compared to traditional antibiotic treatment methods. Bacteriophages are able to penetrate the exopolysaccharide matrix of biofilms, destroying bacteria within the biofilm, which makes them effective against antibiotic-resistant bacteria. Additionally, bacteriophages can be successfully impregnated into polymethyl methacrylate (bone cement) used in endoprosthetics.

The author concluded that the use of bacteriophages in combination with antibiotics led to a significant improvement in the treatment outcomes for deep periprosthetic infections of staphylococcal etiology. In the group where phage therapy was used, the treatment effectiveness was 95.5%, while in the comparison group it was only 69.0%.

Surgical treatment of purulent wounds. Bacteriophages in the treatment of wounds and wound infections

In the fundamental work Wounds and Wound Infections by M.I. Kuzin and B.M. Kostyuchenok, a method of active surgical treatment of wounds and wound infection is described which remains relevant to this day [113]. The most important method and the gold standard for treating purulent wounds of various etiologies and locations is the surgical treatment of the purulent focus, aimed at removing all necrotic and non-viable tissues and preparing the wound bed for healing. This is confirmed by numerous articles and literature reviews of recent years [114–117].

The goal of surgical treatment of a purulent-necrotic focus is to ensure wide access, its adequate drainage, removal of nonviable tissue that harbors infection, and prevention of its further spread. The main surgical technique is the radical excision of necrotic tissue. Effective surgical management requires halting infection spread along the anatomical planes of subcutaneous tissue, fascial layers, tendon sheaths, and intermuscular compartments. The approach should be anatomical and

low-traumatic, providing a good view of the wound and freedom for surgical manipulations [113]. The preferred surgical corridor follows the most direct route to the infection focus. However, in various situations, utilization of a minimally invasive (remote) approach is essential to preserve critical neurovascular bundles, internal organs, joint capsules, and serous membranes.

Surgical intervention should be performed promptly upon confirmed diagnosis. In cases of extensive areas of damage, staged surgical treatments and necrectomy procedures may be required.

Currently, alternative and additional methods of influencing the wound process are being introduced and widely used, such as the use of biological antibacterial drugs (phage therapy), as well as physical methods of treatment, for instance, ultrasonic cavitation, local negative pressure wound therapy (NPWT), plasma flows, ozone therapy, etc [118].

NPWT is used to treat various types of acute and chronic wounds, including ulcers, surgical infections, and complex injuries. It facilitates wound repair via multiple fundamental mechanisms: improving blood circulation by opening the capillary segment of the microcirculatory bed, which subsequently enhances redox processes in the wound [119]. Additionally, it involves macrodeformation of tissues, drainage of extracellular inflammatory fluids, stabilization of the wound environment, and microdeformation of the wound bed [120].

Research on the use of bacteriophages in surgery has been conducted for an extensive period of time, indicating increased effectiveness when applied in surgical practice. In his dissertation, R.N. Islamov concluded that a polyvalent bacteriophage is effective in vitro, suppressing the growth of the most relevant microorganisms causing nosocomial purulent-septic complications [121]. The introduction of bacteriophages into the preoperative prevention regimen for surgical infections contributes to a significant reduction in the number of suppurations of the surgical wound and extrawound complications.

In R.S. Sufiyarov's dissertation, it is primarily noted that complex surgical treatment using enzyme preparations and a polyvalent pyobacteriophage shows better results compared to traditional methods [122]. The use of the proposed methods leads to a reduction in the average length of stay of patients in the hospital and a decrease in the number of postoperative complications.

We have presented our experience with treating wounds using negative pressure therapy with instillation of a polyvalent bacteriophage after radical surgical treatment of the purulent focus. The advantages of vacuum therapy have been described above. Recent studies demonstrate that instillation-enhanced NPWT achieves superior healing outcomes compared with standard NPWT. In an observational study, H. Duan et al. describe that a vacuum system with instillation effectively removes remnants of necrotic tissue, promotes wound healing, and controls infection in patients with necrotizing soft tissue infection [123]. In a clinical observation, J. Kilo et al. describe a patient with a severe purulent complication after implantation of a left ventricular assist device (LVAD) is described [124]. For local wound treatment, the local negative pressure therapy with instillation method was successfully applied, showing durable therapeutic success. In a large clinical study, V.A. Potapov describes a method for using a combined vacuum-assisted dressing with oral administration and local irrigation with bacteriophage solutions in patients with deep sternal infection [125]. The authors of the article obtained better results compared to traditional methods, especially in the presence of multidrug-resistant microorganisms.

The first publication documenting successful use of negative pressure therapy with bacteriophage instillation was a clinical observation by V.A. Mitish et al [126]. The article presents a clinical observation of complex surgical treatment of a patient with rheumatoid arthritis and a long-term non-healing wound in the right gluteal region, which formed after surgical treatment of a post-injection abscess. The successful use of a domestic negative pressure device with the ability to instill is noted, indicating sustained clinical benefits. In this clinical observation, all the advantages of using vacuum wound therapy were demonstrated, confirmed by cytological and microbiological examinations at all stages of treatment.

Conclusion

Antibiotic resistance represents one of the most urgent threats to public health, requiring an immediate search for alternative treatments for bacterial infections. Bacteriophages represent a promising alternative to antibiotics due to their unique properties.

Bacteriophages exhibit high specificity, allowing them to effectively eliminate pathogenic bacteria while minimizing the impact on beneficial microbial flora. Their ability to adapt to changes in bacterial structure and resistance to antibiotics offers broad opportunities for combating multidrug-resistant infections. Modern advances in molecular biology and biotechnology significantly improve the understanding of the mechanisms of interaction between bacteriophages and bacteria, paving the way for next-generation therapeutic strategies.

However, despite significant advantages, the use of bacteriophages faces certain challenges, including the requirement for personalized phage selection on a per-patient basis for each patient, the possible development of resistance in bacteria, and regulatory barriers. To integrate phage therapy into routine clinical care, further research is required to confirm the safety and effectiveness of this method, as well as to streamline regulatory pathways for its authorization.

In conclusion, bacteriophages represent an important tool in the fight against antibiotic resistance, and their potential deserves close attention from the scientific and medical communities.

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Бактериофаги: альтернатива антибиотикам в эпоху антибиотикорезистентности

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Аннотация. Антибиотикорезистентность представляет собой одну из наиболее острых глобальных проблем здравоохранения, обусловленную широким и часто нерациональным применением антибиотиков, а также эволюционно закрепленными механизмами адаптации бактерий. По оценкам, к 2050 г. ежегодно из-за устойчивости к противомикробным препаратам будет умирать до 10 млн человек, что требует срочного поиска новых терапевтических стратегий. В этом контексте бактериофаги — вирусы, специфически инфицирующие бактерии — выступают многообещающей альтернативой антибиотикам. В обзоре анализируются ключевые механизмы развития антибиотикорезистентности, включая инактивацию препаратов β-лактамазами, работу эффлюксных насосов, модификацию мишеней и горизонтальный перенос генов, а также особое значение группы ESKAPE патогенов в клинической практике. Рассмотрены классификация фагов на литические и лизогенные, их морфологические особенности и жизненные циклы. Особое внимание уделено современным методам доставки фагов (перорально, местно, парентерально, ингаляционно) и взаимодействию фаговой терапии с иммунной системой хозяина, включая продуцирование антител и иммуномодулирующие эффекты на макрофаги, нейтрофилы и лимфоциты. Отдельный раздел посвящен практическому применению фаготерапии в хирургии и лечении хронических ран: описаны результаты клинических наблюдений в кардиоторакальной, абдоминальной и ортопедической хирургии, применения фагов в сочетании с антибиотиками, а также внедрение вакуум-ассистированной терапии с инстилляцией бактериофагов, что демонстрирует ускорение заживления, снижение микробной обсемененности и количества послеоперационных осложнений. *Выводы.* Таким образом, терапия бактриофагами обладает рядом преимуществ — высокой специфичностью, эффективностью против мультирезистентных штаммов, возможностью сочетания с антибиотиками и минимальным уровнем побочных эффектов. Вместе с тем ее широкое клиническое внедрение требует решения задач по стандартизации производства фаговых препаратов, созданию централизованных фагобанков, отработке алгоритмов подбора штаммов для персонализированной терапии и преодолению регуляторных барьеров. Дальнейшие рандомизированные клинические исследования и разработка нормативно-правовой базы необходимы для полноценного использования фагов как эффективного инструмента в борьбе с антибиотикорезистентностью.

Ключевые слова: Антибиотикорезистентность, бактериофаги, альтернатива антибиотикам, лечение хронических ран, хирургия, гнойная хирургия, фаготерапия, мультирезистентные инфекции

Информация о финансировании. Авторы заявляют об отсутствии финансовой поддержки и спонсорской помощи при проведении данного исследования.

Вклад авторов. Г.В. Хамидулин — формулировка целей, разработка исследования, обзор литературы, критический анализ научных источников, написание, редактирование и утверждение окончательной версии рукописи. Ю.С. Пасхалова — сбор и систематизация научных данных, анализ современных подходов к использованию бактериофагов, подготовка разделов по классификации фагов и механизмам действия; критическая доработка рукописи. В.А. Митиш — анализ современных методов диагностики и лечения хронических ран, оценка эффективности фаготерапии при гнойных ранах, обзор клинических исследований по применению бактериофагов. А.А. Ушаков — поиск литературы, отбор соответствующих научных публикаций, подготовка раздела о механизмах развития антибиотикорезистентности и их клинических последствиях. С.А. Оруджева — анализ микробиологических данных, систематизация информации о классификации и морфологии бактериофагов. С.Д. Магомедова — оценка научной достоверности представленных данных и проверка соответствия стандартам научной публикации. В.К. Бораненков — редактирование рукописи. Все авторы внесли значительный вклад в подготовку рукописи, прочитали и утвердили окончательную версию перед публикацией.

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ORIGINAL RESEARCH
ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Antibiotic use density in trauma intensive care unit at a tertiary care hospital in Western Rajasthan

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Abstract. *Relevance*. The excessive use of antibiotics is a public health issue that has hampered poor and middle-income nations and is linked to rising healthcare expenses and antimicrobial resistance, which is regarded as an important risk to world health. In addition, resistance raises expenses, prolongs hospital stays for patients, and causes mortality. Defined daily dose (DDD) represents the average adult daily maintenance dose of a specific drug applied according to its primary indication. Antibiotic use density is expressed as defined daily doses/ 100 patient- days. *Aim*. The aim of this study is to evaluate the pattern of usage of antibiotics and to find out antibiotic use density in trauma intensive care unit (ICU). *Materials and Methods*. In this prospective observational study prescription data of 100 consecutive patients at admission into the trauma ICU was audited. Patients of all age of either gender admitted in the trauma ICU during the study period, which have been prescribed with antibiotics. The study was conducted over a period of eight months from August 2022 March 2023. During this period, all the included patients were followed up for their entire duration of stay in trauma ICU. *Results and Discussion*. The prescriptions of 100 consecutive patients admitted into the ICU were analyzed. On analyzing co- morbidities it was noted that 79% were affected with contusions in brain/ intracerebral hemorrhage/ subdural hematoma followed by 5% with pnumothorax. According to DDD/100 bed days in our study piperacillin+tazobactam (10.64), cefoperazone+sulbactam (5.21), amikacin (7.5), vancomycin (3.2) and linezolid (3.2) were most consumed drugs in trauma ICU patients. *Conclusion*. Present study results conclude that overuse of antibiotics can cause antibiotic resistance, increased duration of stay in hospitals and reason of mortality.

Key words: antibiotics use density, trauma ICU, antibiotics resistance

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Ethics approval. Prior to starting the study institutional ethical committee clearance (EC/P-132/2022) was taken.

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Introduction

Increasing healthcare costs and antimicrobial resistance, which is considered a major threat to global health, are associated with the overuse of antibiotics, a public health problem that has plagued low- and middle-income countries [1]. Antibiotic resistance is partly caused by hospitals' overuse of antibiotics [2]. Furthermore, resistance results in increased costs, longer hospital stays for patients, and increased mortality [3]. By using evidence-based strategies, antibiotic resistance can be decreased [4]. Over time, the pattern of antimicrobial resistance (AMR) shifts, differing between nations and even within hospitals in the same nation [5]. The intensive care unit (ICU) consumes much more antibiotics overall than ordinary hospital wards, despite the fact that antibiotics are one of the most often given medication classes among all hospitalized patients [6]. There is ample evidence that up to 50% of antibiotic prescriptions are given incorrectly, despite several recommendations from governmental and professional organizations [7]. Monitoring and assessing the use of antibiotics in the intensive care unit on a regular basis is crucial. The defined daily dose (DDD) and the anatomical therapeutic chemical (ATC) categorization system are highly recommended by the World Health Organization (WHO) as a measuring unit for medication usage research [8]. The average adult daily maintenance dose of a particular medication administered in accordance with its principal indication is known as the defined daily dose, or DDD. The formula for density is defined daily dosages per 100 patient days. The aim of this study is to evaluate the pattern of usage of antibiotics and to find out antibiotic use Density in trauma ICU.

Materials and methods

This prospective observational research was conducted using the Case Sheets of patients who were admitted to the trauma intensive care unit between August 2022 and March 2023. This study was carried out in the Dr. S.N. Medical College and Hospital's pharmacology department in Jodhpur. When 100 consecutive patients were admitted to the trauma intensive care unit, their prescription data was audited. The study comprised patients of any age, male or

female, who were admitted to the trauma intensive care unit during the study period, had been administered antibiotics, and were willing to participate. Patients who were not provided antibiotics and who did not meet the WHO's definition of a medication usage study were not included.

All of the enrolled patients were monitored throughout this time for the length of their trauma intensive care unit stay. All patients' initial demographic information, including name, age, gender, hospital number, and clinical diagnosis, was documented. Additional factors were recorded, including the total number of medications administered during the hospital stay, the ailment for which the patient was hospitalized, the length of the intensive care unit stay, mortality, and the total number of antibiotics provided. The medications that were prescribed while the patient was in the intensive care unit were recorded. The Anatomical Therapeutic Chemical (ATC) categorization method (ATC/DDD version 2010) was used to categorize the medications [8].

Prescribing Indicators:

1) The average number of medications per prescription was calculated by dividing the total number of prescriptions written for the various medicines under study.

2) The proportion of pharmaceuticals supplied under the generic name was determined by dividing the number of prescriptions for generic drugs by the total number of medications administered, and then multiplying the result by 100.

3) The percentage of prescriptions that contained an injection was calculated by dividing the number of patient interactions during which an injection or antibiotic would be given by the total number of surveys. The result was then multiplied by 100.

4) The percentage of drugs provided from the National List of Essential Medicines (NLEM) 2022 was calculated by dividing the number of medications from the hospital's essential medicine list.

The following formula was used to compute the antibiotic use density (AD), which was given as DDD/100 patient-days (DDD100) [9].

AD = drug consumption in the study period (Gm)× × 100 / DDD (Gm) x study period x bed strength× × avg. occupancy

Statistical analysis: Mean ± SD was used to express the data. A Microsoft Excel sheet was used to enter all of the data into a master chart, after which it was statistically analyzed. SPSS software was used for all of the analyses. P-values less than 0.05 were regarded as statistically significant.

Results and discussion

One hundred consecutive patients who were hospitalized to the trauma intensive care unit had their prescriptions examined. There were 25 female patients and 75 male patients. The majority of patients admitted to the trauma intensive care unit were between the ages of 35 and 65 (Table 1). Antimicrobial resistance may be driven differently in rural regions. Because fewer healthcare facilities are available, there may be less access to antibiotics overall, yet abuse can still happen because people are unaware of how to use them properly. Antibiotics are frequently sold over-the-counter in India without a prescription; this practice may be especially prevalent in rural regions with inadequate access to healthcare [10].

The number of antibiotics prescribed was compared with gender, age, and length of treatment in the study. It was discovered that the majority of patients received three prescriptions for each antibiotic, which was statistically significant ($P<0.05$) when compared to all groups that received one, two, or more than three prescriptions. In a similar vein, Priyadharsini et al. discovered that 57% of the population was male and the majority of the patients were between the ages of 40 and 60 [11].

According to the analysis of the research population's co-morbidities, 79% of the participants had head contusions, intracerebral hemorrhages, or subdural hematomas, while 5% had pneumothorax (Table 2). According to the analysis of the research population's co-morbidities, 79% of the participants had brain contusions, intracerebral hemorrhages, or subdural hematomas, while 5% had pnumothorax.

According to earlier research, the other reasons for admission in a study were head damage (32.39%), difficult instances of acute abdomen (25.35%), and cardiovascular problems (21.94%) [12]. Information about trauma due to factors including poverty, education, political and religious beliefs, and a nation's geographic and economic trends, ICU admissions vary from one center to another [13].

Table 1

Demographical distribution of patients according to the number of antibiotics prescribed in trauma ICU

Demographic Data		N	No. of Antibiotics				p-value
			1 Antibiotics	2 Antibiotics	3 Antibiotics	> 3 Antibiotics	
Gender	Male	75	13	14	45*	3	P<0.05
	Female	25	1	6	16*	2	
Age	< 35	32	6	6	19*	1	P<0.05
	35–65	54	6	11	33*	4	
	> 66	14	2	3	9	0	
Duration of stay	< 6 days	41	6	7	24*	4	P<0.05
	6–10 days	28	5	7	16*	0	
	> 10 days	31	3	6	21*	1	

Note: P<0.05 (Z test) is considered significant.

Table 2

Co-morbid conditions of patients on admission in trauma ICU

№	Disease Condition	No. Of patients (%), *n* = 100
1	Acute febrile illness	1
2	Anti- nuclear antibody	1
3	Biliary tract cancer	1
4	Contusion in Brain/ICH /SDH	79
5	Cardiac arrest	1
6	Cervical injury	1
7	Cranioplasty	1
8	Facial nerve palsy	1
9	Gall bladder surgery	1
10	GI obstruction	1
11	Intestinal obstruction	1
12	Nephrolethotomy	1
13	Peritionities	1
14	Pneumothorax	5
15	Postpartum hemorrhage	1
16	Septic arthritis	1
17	Seizure	1
18	Superior orbital fissure	1

Note: ICH — intracerebral hemorrhage; SDH- subdural hematoma; GI- gastrointestinal.

The mortality rate was 54% in trauma intensive care unit. 46% patients were transferred to different wards of the hospital (Table 3). The average duration of stay in trauma ICU was 8.58 days and average number of drugs prescribed was 8.98. The average duration of antimicrobials including all prescribed antibiotics to 100 traumas ICU patients was 5.91. The average length of stay for patients in a U.S. research was 5.2 ± 9.8 days, and the overall death rate was 33% [14]. 8.58 days was the average length of stay in the trauma intensive care unit, and 8.98 medications were provided on average. For 100 trauma ICU patients, the average duration of antimicrobials, including all given medicines, was 5.91. In a study reported from a trauma ICU, mean ± SD number of drugs was 9.1 ± 6.5 [15]. In another study the number was 12.1 ± 7.6 [14]. The average number of drugs should be kept as low as possible to minimize the risk of drug interactions, development of bacterial resistance and hospital costs [16].

Table 3

Patients characteristics and drugs prescription

Patients Characteristics	TICU (*n* = 100)
Mortality	54
Mortality before 07 days	29
Mortality after 07 days	25
Transfer to ward	46
Average duration of stay in ICU (Mean ± SD)	8.58±6.21
Average no. of drugs prescribed (Mean ± SD)	8.98±2.80
Average duration of antimicrobial agents (Mean ± SD)	5.91±1.66

Note: TICU- trauma intensive care unit; ICU- intensive care unit; SD- standard deviation.

We have expressed the frequency of medication prescriptions using the DDD/100 bed-days technique and the ATC categorization. We have determined DDDs for the medications given to trauma intensive care unit patients. The medication use metric that we have employed is the DDD per 100 bed days (Table 4). Because of the 100% occupancy rate during the trial, the occupancy index in the DDD/100 bed-days computation was 01. In grams, the DDD dosage and ATC code of each antibiotic or combination were obtained from the WHO ATC/DDD Toolkit, which is accessible on the authorized website www.atcddd.fhi.no. Except for cotrimoxazole, every antibiotic was administered intravenously. The sum of all prescribed units times the antibiotic's potency in grams was used to determine each antibiotic's total dosage.

In our analysis, the most often used medications among trauma intensive care unit patients were piperacillin+tazobactam (10.64), cefoperazone+sulbactam (5.21), amikacin (7.5), vancomycin (3.2), and linezolid (3.2) based on DDD/100 bed days. However, according to a research, penicillins with beta-lactamase inhibitors were the most often utilized class of antibiotics, followed by quinolones and second-generation cephalosporins [17, 18]. meropenem, ceftriaxone, and amoxicillin clavulanate consumption in ddd / 100 Bed days were 61.41, 24.24, and 10.91 in another investigation [19]. With their ever-increasing use and misuse, microorganisms have developed antimicrobial resistance in India and worldwide. *Klebsiella pneumoniae's* imipenem susceptibility dropped from 65% in 2016 to 43% in 2021, according to the Indian Council of Medical Research's (ICMR) 2021 annual report in India, while *Escherichia coli's* imipenem susceptibility dropped from 86% in 2016 to 64% in 2021 [20]. A study done by Sharma et al. also found that the sensitivity of *Klebsiella pneumoniae* to meropenem decreased from 15% in 2018 to 2.5% in 2022, while the sensitivity of *Klebsiella* to colistin decreased from 96% in 2018 to 28% in 2022 [21]. The

incidence and prevalence of antimicrobial-resistant-bacterial infections has attained incongruous levels during 21st century and threatens global public health as a silent pandemic, necessitating urgent interventions [22, 23]. One significant factor affecting patient mortality and morbidity is bacterial resistance to medications. A number of variables, such as the severity of the disease, the requirement for extended hospitalization, and the frequent use of broad-spectrum antibiotics, are linked to the formation and spread of bacterial resistance in intensive care units.

Table 4

Antibiotic use density according to DDD/100 patient-days along with ATC code in trauma ICU

S.N.	Antibiotics	ROA	ATC CODE	DDD (gm)	DDD/100 Bed Days
A.	**Group-Beta lactamase**				
i.	Cephalosporin				
1	Cefixime	IV	J01DD08	0.4	0
2	Ceftazidime	IV	J01DD02	4	0.32
3	Cefotaxime	IV	J01DD01	4	0.57
4	Ceftriaxone	IV	J01DD04	2	2.10
5	Cefepime+Tazobactam	IV	J01DE01	4	0.48
6	Cefoperazone+Sulbactam	IV	J01DD62	4	5.21#
ii.	Penicillin				
1	Amoxicillin+clavulanic acid	IV	J01CR02	3	0.72
2	Piperacillin+Tazobactam	IV	J01CR05	14	10.64#
3	Ticarcillin+ Clavulanicn Acid	IV	J01CR03	15	0.25
iii.	Carbapenems				
1	Meropenem	IV	J01DH02	3	2.42
2	Imipenem+Cilastatin	IV	J01DH51	2	1.76
iv.	Monobactam				
1	Aztreonam	IV	J01DF01	4	1.14
v.	Sulfonamides				
1	Cotrimoxazole	IV	J01EE01	4	0.17
B.	**Group- Macrolide**				
1	Azithromycin	Oral	J01FA10	0.3	0
i.	Fluro- Quinolone				
1	Levofloxacin	IV	J01MA12	0.5	1.05
2	Ciprofloxacin	IV	J01MA02	0.8	0.24
C.	**Group-Aminoglycoside**				
1	Amikacin	IV	J01GB06	1	7.5#
2	Clindamycin	IV	J01FF01	1.8	6.17
D.	**Group-Nitroimidazole**				
1	Metronidazole	IV	J01XD01	1.5	1.30

Ending tabl. 4

S.N.	Antibiotics	ROA	ATC CODE	DDD (gm)	DDD/100 Bed Days
E.	**Anti-Viral**				
1	Remedsvir	IV	J05AB16	0.1	0
F.	**Group- Others**				
1	Vancomycin	IV	J01XA01	2	3.22#
2	Teicoplanin	IV	J01XA02	0.4	1.63
3	Rifampicin	IV	J04AB03	0.6	0
4	Linezolid	IV	J01XX08	2	3.29
5	Polymyxin B	IV	J01XB02	0.15	2.93

Note: ROA – root of administration; ATC – anatomical therapeutic chemical; DDD- defined daily dose.

Conclusion

The current study's findings indicate that excessive antibiotic usage can lead to antibiotic resistance, longer hospital stays, and higher death. The institution's antimicrobial policy should be rigorously applied on a regular basis, with a committee participating to ensure the availability of standard treatment regimens and to monitor prescription trends.

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Частота использования антибиотиков в отделении интенсивной терапии травматологического профиля в многопрофильной больнице в Западном Раджастане

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Аннотация. *Актуальность*. Чрезмерное использование антибиотиков является проблемой общественного здравоохранения, которая наносит ущерб бедным и средним странам и связана с ростом расходов на здравоохранение и антимикробной резистентностью, которая рассматривается как важный риск для здоровья населения во всем мире. Кроме того, резистентность увеличивает расходы, продлевает пребывание пациентов в больнице и приводит к смертности. Определенная суточная доза (ОСД) представляет собой среднюю суточную поддерживающую дозу конкретного препарата для взрослых, применяемую в соответствии с его основным показанием. Плотность использования антибиотиков выражается как определенные суточные дозы/100 пациенто-дней. *Цель*. Цель данного исследования — оценить характер использования антибиотиков и определить частоту их применения в отделении интенсивной терапии травматологических больных (ОИТТ). *Материалы и методы*. В этом проспективном обсервационном исследовании были проанализированы данные о назначениях антибиотиков 100 пациентам, последовательно поступившим в ОИТТ травматологических больных. В исследование были включены пациенты всех возрастов и обоих полов, поступившие в ОИТТ в течение периода исследования, которым были назначены антибиотики. Исследование проводилось в течение восьми месяцев, с августа 2022 по март 2023 года. В течение этого периода все включенные пациенты наблюдались на протяжении всего периода пребывания в ОИТТ. *Результаты и обсуждение*. При анализе сопутствующих заболеваний было отмечено, что у 79% пациентов наблюдались ушибы головного мозга/внутримозговое кровоизлияние/субдуральная гематома, а у 5% — пневмоторакс. Согласно данным ОСД/100 койко-дней, в нашем исследовании наиболее часто используемыми препаратами у пациентов травматологического отделения интенсивной терапии были пиперациллин+тазобактам (10,64), цефоперазон+сульбактам (5,21), амикацин (7,5), ванкомицин (3,2) и линезолид (3,2). *Выводы*. Результаты настоящего исследования показывают, что чрезмерное использование антибиотиков может привести к развитию антибиотикорезистентности, увеличению продолжительности пребывания в больнице и повышению смертности.

Ключевые слова: плотность использования антибиотиков, травматологическое отделение интенсивной терапии, антибиотикорезистентность

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