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Anatomy of the ileum-intestinal tract of the human fetus at 16–22 weeks of ontogenesis

Tatyana A. Vasileva, Elvira N. Galeeva, Victoriya A. Galiakbarova, Anastasiya A. Grigoreva
Orenburg State Medical University (Orenburg, Russian Federation)

Abstract

Aim – to obtain new data on the quantitative macromicroscopic anatomy of the iliac-intestinal region in the intermediate fetal period of human ontogenesis from the 16th to the 22nd week of development.

Material and methods. The study was performed on 30 subjects of both sexes (18 female and 12 male fetuses) using the following methods: macro- and microscopic preparation, N.I. Pirogov sawing, histotopographic method, morphometry, and variation-statistical methods. All the morphometric data obtained were subjected to variation-statistical processing in Windows XP-based Excel 2010 and Statistics 13.0 application software packages. When testing statistical hypotheses in this study, the critical level of statistical significance (p) was assumed to be 0.05. The Student's t-test was used to assess the reliability. A set of tools for macromicroscopic preparation of the fetus was used.

Results. During the period of development in question, the position of the ileum has slight vertical deviations, which affects the formation and magnitude of the angle between the ileum and the cecum, as well as between the ileum and the ascending colon. The predominant shape of the cecum is cylindrical (80%), less often conical (20%). There is an uneven growth of the walls of the cecum, where the lateral wall prevails over the medial one, which is associated with the formation of flap structures. The ileo-intestinal opening is oval in shape, the frenules are weakly pronounced, with a more pronounced ileo-colon lip. Semilunar folds are differentiated on the mucous membrane of the cecum from 16-17 weeks, and a free muscle band is also determined. The omental and mesenteric bands are not pronounced. There is no morphological boundary between the appendix and the cecum. From 19-20 weeks, the presence of 1-2 gausters is noted. The quantitative parameters of the iliac-intestinal region are characterized by a gradual twofold increase in values.

Keywords: ileocephalic intestine, cecum, human fetus, intermediate period, ileocecal angle, vermiform process.

Conflict of interest: nothing to disclose.

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Анатомия подвздошно-слепокишечного отдела кишечника плода человека на 16–22 неделе онтогенеза

Т.А. Васильева, Э.Н. Галеева, В.А. Галиакбарова, А.А. Григорьева
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Аннотация

Цель – получить новые данные по количественной макромикроскопической анатомии подвздошно-слепокишечного отдела в промежуточном плодном периоде онтогенеза человека с 16 по 22 неделю развития.

Материал и методы. Исследование выполнено на 30 объектах обоего пола (18 плодов женского пола, 12 – мужского) с использованием методов: макро- и микроскопического препарирования, распилов по Н.И. Пирогову, гистотопографического, морфометрии, вариационно-статистических методов. Полученные морфометрические данные были подвергнуты вариационно-статистической обработке в среде Windows-XP с использованием пакета прикладных программ Excel 2010 и «Статистика 13.0». Критический уровень статистической значимости (p) при проверке статистических гипотез в данном исследовании принимали равным 0,05. Для оценки достоверности был использован критерий Стьюдента. Применен набор инструментов для макромикроскопического препарирования плода.

Результаты. В указанный период развития положение подвздошно-слепокишечного отдела имеет незначительное отклонение по вертикали, что оказывает влияние на формирование и величину угла между подвздошной кишкой и слепой, а также между подвздошной кишкой и восходящей ободочной. Преобладающей формой слепой кишки является цилиндрическая (80%), реже – конусовидная (20%). Отмечается неравномерный рост стенок слепой кишки, где латеральная стенка преобладает над медиальной, что связано с формированием структур заслонки. Определены подвздошно-кишечное отверстие овальной формы, слабо выраженные уздечки, с более выраженной подвздошно-ободочно-кишечной губой. На слизистой оболочке слепой кишки с 16–17 недели дифференцируются полулунные складки, а также определяется свободная мышечная лента. Сальниковые и брыжеечный ленты не выражены. Морфологическая граница между червеобразным отростком и слепой кишкой отсутствует. На 19–20 неделе отмечается наличие 1–2 гаустр. Количественные параметры подвздошно-слепокишечного отдела характеризуются постепенным двукратным нарастанием значений.

Ключевые слова: подвздошно-слепокишечный отдел кишечника, слепая кишка, плод человека, промежуточной период, илеоцекальный угол, червеобразный отросток.

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INTRODUCTION

The morphological basis for many pathologies of the ileocecal intestinal region is established during prenatal ontogenesis [1, 2]. Congenital intestinal malformations (malrotation, intestinal volvulus, cecocolic intussusception, intestinal obstruction, and atresias) account for 3–6% of cases, with malformations of the colon being predominant. Modern diagnostic techniques enable clear visualization of the human fetal intestine and allow for early endoscopic diagnosis in newborns and young children [3, 4].

The current scientific data mainly concern the formation of components of the ileocecal intestinal region individually, anatomy and morphometry of the cecum and the vermiform appendix in the fetal period of development, as well as the anatomy of the ileocecal angle in newborns, children, and persons of advanced age. Studies comprehensively addressing the anatomical features of the ileocecal intestinal region during the fetal period of human ontogenesis are virtually absent in scientific literature. Meanwhile, the processes of its formation and migration, with the small intestine moving (from right to left, behind the superior mesenteric artery) and the large intestine moving (from left to right relative to the same artery), collectively termed intestinal rotation, are completed during the intermediate fetal period of ontogenesis [5]. The gastrointestinal tract of the fetus, as the digestive organ, starts functioning from 16th-20th week [6], which opens an opportunity of prevention of many of its congenital damages. It is known that the ileocecal region of the intestine represents a transitional zone between the small and large intestines, connecting the terminal segment of the ileum, the cecum with its vermiform appendix, and the ileocecal valve (Bauhin's valve), as well as the initial portion of the ascending colon [7]. This region is frequently associated with congenital developmental anomalies.

AIM

To obtain new data on the quantitative macromicroscopic anatomy of the iliac-intestinal region in the intermediate fetal period of human ontogenesis from the 16th to the 22nd week of development.

MATERIAL AND METHODS

This study was conducted at the Department of Human Anatomy, Orenburg State Medical University, from 2019 to 2024. An approval (No. 237, dated 16.10.2019) was obtained from the Local Ethics Committee of OSMU. The research utilized cadaveric material (human fetal torsos from the fetal collection of the Department of Human Anatomy, OSMU) obtained following termination of normally progressing physiological pregnancies for social reasons, with full compliance with all relevant deontological, ethical, and legal standards.

The study was conducted on 30 specimens of both sexes (18 female and 12 male fetuses). The specimens were divided into 3 age groups: 16-17 weeks (n=10), 18-19 weeks (n=10), and 20-22 weeks (n=10). The selected age range virtually fully corresponds to the second trimester of pregnancy and the intermediate fetal period of human ontogenesis.

The study utilized the following research methods: macro- and microscopic dissection method, N.I. Pirogov's sectioning method in three mutually perpendicular planes, histotopographic method, morphometric method, and variational-statistical methods of data processing (mean value (X), standard error of the mean (Sx), standard deviation (σ), minimum parameter value (min), maximum parameter value (max), growth rate (GR), growth increment rate (GIR), and growth intensity (GI)).

The obtained morphometric data were processed in Windows XP using the Excel 2010 and Statistica 13.3 software suites. Given the obtained normal distribution of sample data, parametric methods were used for statistical analysis. The critical level of statistical significance (p) when testing statistical hypotheses in this study was set at 0.05. Student's t-test was used to assess reliability. The study employed a set of tools and devices for macromicroscopic dissection of fetal torsos (fetal torso dissection stand, magnifying loupe and illuminated eyepieces, digital caliper, set of microscopic instruments (microscissors, forceps, scalpel, and bayonet medical probe)).

RESULTS

During macroscopic examination of the ileocecal intestinal region in fetuses with opened anterior abdominal wall, the transition zone between the terminal ileum and cecum, the cecum with its vermiform appendix, and the ileocecal orifice were clearly identifiable (**Fig. 1**).

The position of the ileocecal region shows a slight vertical deviation (with some lateral inclination). The area of the ileocecal (cecocolic) angle is clearly identifiable for macroscopic examination and measurements.

In most cases (80%), the ileum enters the cecal lumen obliquely in a craniomedial direction, while in 20% of observations the entry orientation is horizontal, forming a 90° angle. At the fundus region, the cecum continues into the vermiform appendix either medially (75% of cases) or laterally (15%), without a distinct demarcation boundary.

A firm contact is observed between the medial wall of the cecum and the lateral wall of the ileum, forming the so-called

ileocecal angle. This angle varies depending on the entry pattern of the terminal ileum into the cecum. The cecum and ascending colon follow a unidirectional axis deviated medially from the vertical plane. In this configuration, the ileum predominantly enters the medial wall of the cecum in a horizontal orientation, forming a 90-115° angle between the ileum and ascending colon, and a 27-40° ileocecal angle between the ileum and cecum.

The cecum and ascending colon follow a shared axis with slight lateral deviation from the vertical plane (the cecum deviates laterally), while the terminal ileum enters the cecum in a craniomedial oblique orientation through the posteromedial wall of the cecal body. This configuration forms a 70-80° angle between the ileum and ascending colon, and a 30-60° angle between the cecum and ileum.

In the fetuses of 16-17 weeks, the cecum appears as an outpouching of the intestinal tube with a cylindrical shape. It is located in the right iliac region of the fetus, between the iliopsoas muscle and anterior abdominal wall. The cecal axis continues the axis of the ascending colon. Between 16-22 weeks, the cecum adjoins the anterior surface of the ileum with its medial or posterior wall. In most observations, it shares a common mesentery with the ileum. The cecum is positioned slightly below the right fetal kidney, with its lateral or posterior wall contacting the medial portion of the anterior surface of the kidney.

During these ontogenetic periods, the shape of the cecum holds particular significance. At 16-22 weeks of the study period, the cecum appears as a moderately distended segment of the proximal colon, featuring a formed fundus and a small-sized body. By mid and late observations, the cecum becomes a well-defined structure, predominantly cylindrical in shape (80%), less commonly conical (20%) with a slightly expanded sac-like fundus. It is located in the right iliac fossa of the fetus. From 16-22 weeks of development, the cecum demonstrates a body with medial, lateral, anterior and posterior walls, along with a fundus (dome). During the study period, the cecal fundus was positioned cranially (ventrolaterally and ventromedially) in most cases (75%), or caudally (15%) (ventrolaterally and ventromedially).

The length of the cecum (from the end of the ascending colon to the orifice of the vermiform appendix) changes during the observation period from 1.0-1.50 mm (mean values 1.16±0.25 mm) to 3.0-3.60 mm (mean values 3.24±0.27 mm), with a growth rate of 2.1 times and GI of 82%. The width of the cecum changes accordingly from 0.50-0.70 mm (mean values 0.62±0.09 mm) to 2.0-2.60 mm (mean values 2.35±0.24 mm) with a growth rate of 2.1 times and GI of 135%. The conducted morphometric studies and compared parameters are statistically significant at $p<0.05$. No gender differences were identified.

During the observation period, as the fetus grows, uneven growth of the cecal walls is observed, with the lateral wall predominating over the medial wall. This is due to the medial wall being occupied by the upper and lower lips of the Bauhin's valve. It should be noted that from 16-17 weeks, semilunar folds begin to differentiate on the cecal mucosa, and a free taenia is identified on the posteromedial wall of the cecum. The omental and mesenteric taeniae are not pronounced. In the cecal wall at 19-20 weeks of development,

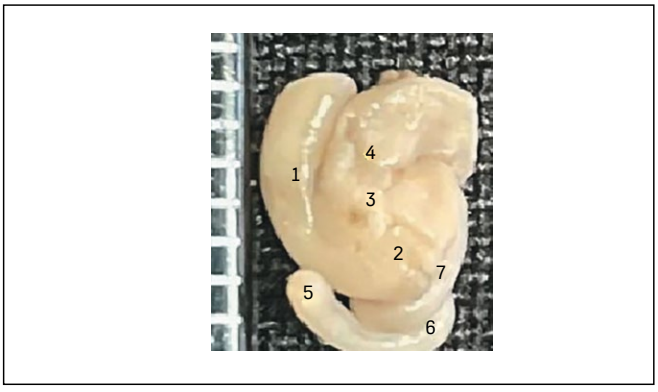

Figure 1. *Photo of a macro-preparation of the ileum-intestinal tract of the human fetus. Front view. ×7 magnification. Fetal age: 18–19 weeks, sex: male. 1 – ascending colon; 2 – dome of the cecum; 3 – ileocecal angle; 4 – ileum; 5 – tip of the appendix; 6 – third curl of the appendix; 7 – first curl of the appendix.*

Рисунок 1. *Фото макропрепарата подвздошно-слепокишечного отдела кишечника плода человека. Вид спереди. Увеличено в 7 раз. Возраст плода 18–19 недель, пол мужской. 1 – восходящая ободочная кишка; 2 – купол слепой кишки; 3 – илеоцекальный угол; 4 – подвздошная кишка; 5 – верхушка червеобразного отростка; 6 – третий завиток червеобразного отростка; 7 – первый завиток червеобразного отростка.*

1-2 haustra are observed. During the studied developmental period, the zone where the terminal ileum enters the cecum is identified slightly above the origin (orifice) of the vermiform appendix.

Dissection of the anterior surface of the cecum reveals its weakly folded wall, ileocolic lip (superior lip), and ileocecal lip (inferior lip), which occupy approximately two-thirds of the cecal body cavity volume and are located 3.0-5.0 mm from its fundus. The wall thickness in the cecal dome region measures 0.30-0.40 mm at 16-17 weeks, 0.4-0.60 mm at 18-19 weeks, and 0.50-0.60 mm at 20-22 weeks. The cecal wall thickness in the region of the Bauhin's valve measures 0.10-0.15 mm at 16-17 weeks, 0.15-0.17 mm at 18-19 weeks, and 0.17-0.20 mm at 20-22 weeks. The conducted morphometric studies and compared parameters are statistically significant at $p<0.05$.

On the medial wall of the cecal body lies the zone of shared ileal and cecal wall. This connection is located within the cecal wall and is not detectable upon dissection since it does not protrude into the lumen. The shared ileal-cecal wall zone forms through the union of the terminal lateral wall of the ileum with the medial wall of the cecum, visualized macroscopically as an extension of the ileocecal (inferior) lip of Bauhin's valve.

The ileum enters either the medial or anterior wall of the cecum. At the beginning of the study period, the ileum primarily enters the posterior wall of the cecum, while in later observation periods it is found to enter either the medial wall or a posteromedial portion of the cecal wall.

The structural feature of the ileocecal angle is the presence of: the ileal orifice, frenula of the ileal orifice, ileocolic lip (superior lip), and ileocecal lip (inferior lip) - collectively termed the ileocecal valve or Bauhin's valve (**Figure 2**).

Upon dissection of the anterior wall of the cecum, the terminal portion of the ileum is identified, protruding into the cecal lumen. The oval shape of the valve is characterized by the longer dimension of the ileocolic lip (superior lip).

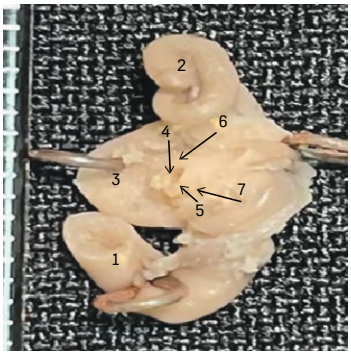

Figure 2. *Photo of the macro-preparation of the iliac-intestinal valve (bauhin's valve) of the fetus. ×5 magnification. Front view (the anterior wall of the cecum is opened). Fetal age: 18–19 weeks, sex: male. 1 – ileum; 2 – vermiform appendix; 3 – mucous membrane of the cecum; 4 – upper lip of the ileocecal valve (bauhin's valve); 5 – lower lip of the ileocecal valve (bauhin's valve); 6 – frenulum of the upper lip of the ileocecal valve; 7 – frenulum of the lower lip of the ileocecal valve.*

Рисунок 2. *Фото макропрепарата подвздошно-слепокишечного клапана (баугиниевой заслонки) плода. Вид спереди (вскрыта передняя стенка слепой кишки). Увеличено в 5 раз. Возраст плода 18–19 недель, пол мужской. 1 – подвздошная кишка; 2 – червеобразный отросток; 3 – слизистая оболочка слепой кишки; 4 – верхняя губа илеоцекального клапана (баугиниевой заслонки); 5 – нижняя губа илеоцекального клапана (баугиниевой заслонки); 6 – уздечка верхней губы илеоцекального клапана; 7 – уздечка нижней губы илеоцекального клапана.*

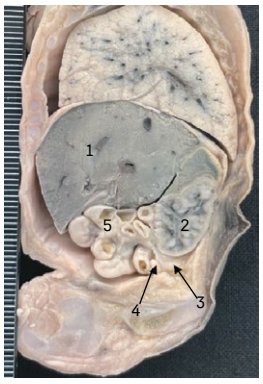

Figure 3. *Anatomy of the ileocecal intestine on the sagittal sections of the fetal torso. Sagittal sawing of the fetal torso, right view. ×2 magnification. Photos from the macro preparation. Protocol No. 143, fetal age: 18–19 weeks, sex: female. 1 – right lobe of the liver; 2 – right kidney; 3 – dome of the cecum; 4 – tip of the appendix; 5 – loops of the small intestine.*

Рисунок 3. *Анатомия подвздошно-слепокишечного отдела кишечника на сагиттальных распилах торса плода. Сагиттальный распил торса плода, вид справа. Увеличено в 2 раза. Фото с макропрепарата. Протокол №143, возраст плода 18–19 недель, пол женский. 1 – правая доля печени; 2 – правая почка; 3 – купол слепой кишки; 4 – верхушка червеобразного отростка; 5 – петли тонкой кишки.*

Between the two lips lies an oval-shaped orifice. The frenula are visualized but weakly developed.

The quantitative characteristics of the ileocecal valve structural elements are as follows: the length of the superior lip ranges from 0.50-1.10 mm to 1.50-2.0 mm. The length of the inferior lip ranges from 0.50-0.90 mm to 1.30-1.60 mm. The length of the superior lip frenulum ranges from 0.30-0.50 mm to 0.70-1.0 mm. The length of the inferior lip frenulum ranges from 0.30-0.50 mm to 0.70-1.0 mm. The conducted morphometric studies and compared parameters are statistically significant at $p<0.05$.

The lateral (right) frenulum is narrower and extends from the ileocecal valve along the inner surface of the right wall of the large intestine. The medial (left) frenulum (fold of the large intestine) extends leftward from Bauhin's valve and is somewhat wider than the lateral one. The frenula are integral components of Bauhin's valve and connect it to the wall of the large intestine. The two lips and two frenula constitute a unified anatomical structure - the ileocecal valve. Both the wall of the small intestine and the wall of the large intestine participate in the formation of the ileocecal valve lips, with each lip having both small and large intestinal aspects that transition into one another along the free edge of the lip. The superior lip of the ileocecal valve serves as a direct continuation of the lateral frenulum, while the inferior lip represents an extension of the shared ileal-cecal wall zone. Thus, a portion of the ileum resides within the cecum. The lateral cecal wall is free-standing, constituting the terminal segment of the small intestine that continues into the superior lip of the Bauhin's valve. The medial cecal wall forms the shared ileal-cecal wall zone, transitioning directly into the inferior lip of the ileocecal valve. The morphological boundary between the cecum and ascending colon is demarcated by the zone of the superior and inferior lips of the Bauhin's valve of the fetus.

At 16-22 weeks of gestation, the cecal cavity reveals a relatively wide orifice of the vermiform appendix leading into its lumen, with no apparent appendiceal valve detected. During this ontogenetic period, the vermiform appendix is already a well-formed organ possessing a rounded lumen. It is located in the right iliac fossa and along the iliac crest, extending continuously without external demarcation from the posteromedial surface of the cecal fundus (**Figure 3**).

Macroscopic examination of the fetal vermiform appendix reveals distinct proximal and distal ends. In the vast majority of cases (87%), the elongated appendix exhibits a tubular shape with variable diameter along its length (**Figure 4**).

The proximal end of the appendix originates as a continuation of the cecum, featuring a broad base, while the apical portion of the distal end is rounded and club-shaped. During weeks 16-22 of intermediate fetal development, the vermiform appendix demonstrates a tendency for spiral coiling and three-tiered folding, typically forming no more than three loops/sections of varying length and width.

The proximal, middle, and distal loops of the vermiform appendix initially occupy a more medial position and are anteriorly covered by small intestinal loops. By mid and late observation periods, the boundaries extend somewhat laterally and leftward, where the middle and distal appendiceal loops are found directly posterior to the anterior abdominal wall.

Throughout the observation period, various positions of the vermiform appendix are observed. At the beginning of the observation period (16-17 weeks of ontogenesis), ascending (cranial) position is typically found in 50% of cases, descending (caudal) position in 25%, medial position in 17%, and lateral position in 8%. Anterior position of the vermiform appendix was classified as a variant of lateral position. By

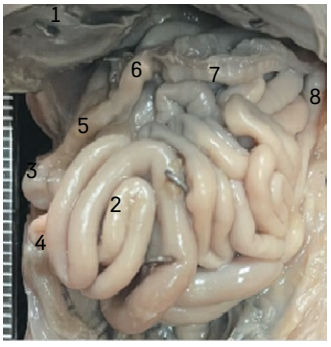

Figure 4. *Photo of a macro-preparation of the position of the ileum-intestinal tract in the abdominal cavity of a human fetus. Photos from the macro preparation. ×3 magnification. Protocol No. 186, fetal age: 18–19 weeks, sex: female. 1 – right lobe of the liver; 2 – loops of the small intestine; 3 – dome of the cecum; 4 – appendix; 5 – ascending colon; 6 – hepatic bend of the colon; 7 – transverse colon; 8 – descending colon.*

Рисунок 4. *Фото макропрепарата положения подвздошно-слепокишечного отдела кишечника в брюшной полости плода человека. Фото с макропрепарата. Увлечено в 3 раза. Протокол №186, возраст плода 18–19 недель, пол женский. 1 – правая доля печени; 2 – петли тонкой кишки; 3 – купол слепой кишки; 4 – червеобразный отросток; 5 – восходящая ободочная кишка; 6 – печеночный изгиб ободочной кишки; 7 – поперечная ободочная кишка; 8 – нисходящая ободочная кишка.*

Figure 5. *Anatomy of the ileocecal angle of the human fetus. Photo histotopogram for MBS-10 (sagittal section). Van Gieson staining. 2×14 magnification. Protocol No. 200, fetal age: 22 weeks, sex: female. 1 – ileocecal angle; 2 – right kidney; 3 – right adrenal gland; 4 – liver; 5 – transverse colon; 6 – descending colon; 7 – loop of the small intestine.*

Рисунок 5. *Анатомия илеоцекального угла плода человека. Фото гистотопограммы под МБС-10 (сагиттальный срез). Окраска по Ван Гизону. Увеличение об. 2, ок. 14. Протокол №200, возраст плода 22 недели, пол женский. 1 – илеоцекальный угол; 2 – правая почка; 3 – правый надпочечник; 4 – печень; 5 – поперечная ободочная кишка; 6 – нисходящая ободочная кишка; 7 – петля тонкой кишки.*

mid-observation (18-19 weeks of intermediate ontogenesis), medial position is observed in 45% of cases, ascending (cranial) position in 36%, descending (caudal) position in 25%, anterolateral position in 10%, and descending (caudal) orientation in 9%. At the end of the observation period (20-22 weeks of ontogenesis), we identified the following positional variations of the vermiform appendix: anterolateral position was observed in 38% of cases, ascending and descending positions were equally represented in 25%, and medial position of the fetal vermiform appendix was found in 12.5%.

The first (proximal) loop constitutes the segment extending from the cecal wall to the first bend, the second (middle) loop spans between the first and second bends of the appendix, while the third (distal/terminal/end) loop represents the section from the second bend to the apex of the vermiform appendix.

In the majority of observations (88%), the loops were compactly folded in a ring-like configuration and positioned in the space between the cecal segment and the terminal portion of the ileum. The second and third loops are most readily visualized. In 12% of observations, an unfolded form of the vermiform appendix occurs, where the loop segments align linearly.

It was observed that the loops of the human fetal vermiform appendix vary in length throughout their course. By week 22, the third loop shows a slight predominance in length compared to the first. The longitudinal growth of the appendix occurs primarily through elongation of the middle and terminal loops. At the beginning of the observation period (16-17 weeks), the third loop is shorter than the first and second. By the end of the study period (20-22 weeks), the third loop demonstrates a modest length advantage over the first. The loop dimensions change dynamically during the observation period, increasing to the following ranges: first loop 5.16-6.09 mm, second loop 4.56-8.60 mm, and third loop 4.05-7.82 mm. No gender differences were identified.

The transverse dimensions of the appendix coils at 16–22 weeks of intermediate ontogenesis exhibit uneven values throughout their length. The dimensions of the third coil are smaller than those of the first and second. The transverse dimensions of the coils range from 1.62 mm to 3.26 mm for the first, 1.17 mm to 1.87 mm for the second, and 1.23 mm to 1.72 mm for the third. No sex differences were identified.

Histotopograms of different section planes (sagittal, frontal, and horizontal) allow for clear detailing of the anatomical features of the cecum and vermiform appendix in the human fetus (**Figure 5**).

The weakly folded wall, smooth mucosa of the cecum, and occasional semilunar folds are identified, along with the protruding ileocecal valve. The wall thickness can be measured both at the dome of the cecum and at the Bauhin's valve.

DISCUSSION

The study provides a morphological description and details the anatomy of the ileocecal region of the human fetus at 16–22 weeks of ontogenesis. It presents quantitative and morphofunctional characteristics of each structural component, which represents a novel contribution, as this topic is scarcely covered in the scientific literature. Only fragmentary data exist regarding the development of this specific region [8–10].

The differences in the macro-microscopic anatomy of the fetal ileocecal region are manifested in the shape of the cecum, the junction of the terminal ileum with the cecum, the morphology of the Bauhin's valve, and the quantitative parameters of the distance from the superior lip of the Bauhin's valve to the orifice of the vermiform appendix. The establishment of definitive anatomy and the transition to postnatal structural features of the ileocecal region

occur after 24 weeks of ontogenesis. This is crucial for understanding the pathogenesis of congenital malformations in this area [11].

Current literature indicates that the formation of the ileocecal angle occurs during midgut transformation through a 270° rotation, with differentiation of the ileocecal valve culminating in angle stabilization and reflux prevention by 13-20 weeks. During the studied period, the angle of ileal entry into the cecum is acute. Our findings differ from some researchers' conclusions. Specifically, P.L. Moore (2013) reports final angle stabilization by week 16 [12], whereas our results indicate a later timeframe - week 24. We also observed a wider range of ileocecal angle variations compared to classical studies.

The study by M.A. Malas *et al*. (2004) reported that between 13-16 weeks the angle measures 60° (range 50-70°), increases to 85-95° by 17-24 weeks, and the cecum becomes fixed in the iliac fossa [13]. By 25-38 weeks, the angle stabilizes (90-100°) and vascularization of the area is completed. In our study, during 16-22 weeks of ontogenesis, we observed an increase in the ileocecal angle from 27° to 60°, reflecting dynamic changes and the establishment of colonic anatomy. These findings should be considered during endoscopic evaluation of the colon in newborns, as F.F. Antonenko *et al*. (2022) suggest that one contributing factor to cecocolic intussusception in infants may be an obtuse ileocecal angle, along with an elongated, downward-projecting cecal dome and lack of fixation in the iliac fossa [1]. Meanwhile, it is known that abnormalities of the ileocecal angle (angle <60°) can lead to intestinal obstruction in newborns. Early diagnosis of such conditions is possible through ultrasound screening at 16-22 weeks of development. In our study, we determined the range of angle variation between the ileum and ascending colon in fetuses at 16-22 weeks of development (ranging from 70° to 115°), which represents a novel finding not previously reported in the scientific literature.

We established that at 16-17 weeks of fetal development, the cecum exhibits a cylindrical shape with its length exceeding its width. Throughout the study period, both length and width of the cecum demonstrate a uniform two-fold increase, with more intensive growth observed in width. During fetal development, we noted asymmetrical growth of the cecal walls - the lateral wall develops more prominently than the medial wall. This pattern can be explained by the fact that the medial wall is occupied by the superior and inferior lips of the ileocecal valve. Our findings are consistent with the data reported by Yu.T. Akhtemiychuk *et al*. (2006) [2].

It was determined that even in the early stages of the study period, the semilunar folds of the cecal mucosa are clearly differentiated, and the free taenia is present. The omental and mesocolic taeniae remain undeveloped, as their differentiation begins later, at approximately 21-22 weeks of development. According to literature sources, this process is associated with the embryogenesis of the small and large intestine, where the proximal segments of the large intestine (cecum, ascending colon) develop more slowly than the distal segments, as well as with fetal liver characteristics, as it occupies most of the abdominal cavity during this period. With the expansion of the abdominal cavity and closure of the physiological umbilical hernia, intestinal rotation occurs, after which the ileocecal angle becomes localized in the right iliac fossa and begins its intensive growth.

Our findings demonstrate that haustration begins at 19-20 weeks of prenatal ontogenesis, with approximately 1-2 haustra present throughout the entire cecal surface. In contrast, haustration of the descending colon and sigmoid colon begins earlier, with 7-15 haustra developing in these segments. M.A. Malas et al. observed that haustra and taeniae coli development initiates in the ascending colon and progresses toward the sigmoid colon [13]. According to these authors, the development of haustra and muscular bands progresses slowly during the first trimester of pregnancy, becoming more intensive during the second trimester. The mucosal thickness in both ascending and descending colon shows significant increase by mid-second trimester. C. Bardwell *et al*. (2022) reported that the length of both small and large intestine increases linearly with fetal age [14].

Our investigations revealed that during this developmental period, the following structures are clearly identifiable: the ileal orifice, the frenula of the ileal orifice, the ileocolic lip (superior lip), and the ileocecal lip (inferior lip). Both lips correspond to mucosal folds that traverse the walls of the cecum. The oval-shaped orifice is situated between the superior and inferior lips.

The fetal vermiform appendix represents a relatively long structure characterized by variable shape and position. During the studied developmental period, various anatomical positions of the appendix are being established [15-19]. Literature indicates that the ascending or descending position of the appendix in fetuses is not related to its topographic proximity to the terminal ileum. Spiralization of the appendix occurs when positioned posterior to the ileocecal junction [19-23]. We established that the vermiform appendix tends to spiralize, displaying three well-defined coils and transitioning into the cecum without a distinct boundary. Dissection specimens reveal its orifice and the absence of a valve. Valve formation occurs at later developmental stages, which aligns with data from A.A. Pujari *et al*., who report that in most newborns, a mucosal fold (appendiceal valve, Gerlach's valve) is observed near the appendiceal orifice [11].

CONCLUSION

The study yielded new data on the anatomy of the fetal ileocecal region at 16-22 weeks of development.

Since the ileocecal angle forms through complex interactions during embryonic intestinal loop rotation, its anatomical and morphological characteristics approach postnatal features by week 22. This finding has significant implications for understanding the pathogenesis of congenital malformations and their correction. The obtained data may prove valuable for endoscopic specialists, neonatologists, and pediatric surgeons [24].

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Compliance with Ethical Standards. This study was conducted on the basis of the Department of Human Anatomy from 2019 to 2024. A positive conclusion of the LEK OrGMU dated 16.10.2019 No. 237 was received.	***Соответствие нормам этики.*** Исследование проведено на базе кафедры анатомии человека с 2019 г. по 2024 г. Было получено положительное заключение ЛЭК ОрГМУ от 16.10.2019 №237.
Contribution of individual authors. Vasileva T.A., Grigoreva A.A.: data analysis, writing of the text of the article. Galeeva E.N., Galiakbarova V.A.: study design, interpretation of results, editing of the article. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Васильева Т.А., Григорьева А.А. – анализ данных, написание текста статьи. Галеева Э.Н., Галиакбарова В.А. – дизайн исследования, интерпретация результатов, редактирование статьи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Review | Научный обзор
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Role of membrane components in the initiation and progression of tumour growth in endometrial cancer

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Abstract

This review discusses the role of membrane components in the initiation and progression of endometrial cancer. Cancer cells that are the substrate of the tumor growth are subject to multiple interactions both among themselves and with the tumor microenvironment.The cell membrane of tumor cells undergoes changes, resulting in simplified antigenic structure and the expression of molecules found in embryonic tissues, changes in the intercellular contacts that maintain epithelial homeostasis. Dense contacts form the basis for the preservation of normal endometrial histological organization. These changes also affect intercellular contacts, leading to the alteration of mechanical properties and invasive growth of tumor cells. In addition, components of dense contacts are participants of intracellular signal transduction pathways. The review highlights the potential role of claudin proteins, specifically in tight junctions and intracellular signaling, as promising targets for further study. Epithelial-mesenchymal transformation (EMT) represented in normal tissues in processes of reparation, plays a significant role in endometrial cancer progression, and the altered characterization of E-cadherin and β-catenin is important in understanding EMT's role in the disease. Researchers are focusing on the E-cadherin as a component of oncogene activation pathways. Hyperestrogenemia (high serum estrogen levels) is known to underlie Type I endometrial adenocarcinoma. Additionally, estrogen receptors and claudins are implicated in intracellular signaling activating cell proliferation both in the norm and in the course of disease. Recent research also involved other molecules serving as targets for estrogens, e.g. claudin proteins. Change of clausin expression profiles mediated by sex hormones manifest both in suppression and replacement of one protein with another. Further study of cell membrane-associated markers has the potential to provide insights into tumor biology and aid in the development of new therapeutic approaches for endometrial cancer.

Keywords: endometrial cancer, cell membrane structures, cancer initiation, cancer progression, cell junction, claudins, E-cadherin, β-catenin, intracellular signalling, hyperestrogenemia.
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Роль мембранных компонентов в инициации и прогрессии опухолевого роста при раке эндометрия

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Аннотация

В настоящем обзоре мы предприняли попытку систематизировать значение мембранных компонентов в инициации и прогрессии опухолевого роста при раке эндометрия. Клетки, составляющие субстрат опухолевого роста, подвержены множеству взаимодействий как между собой, так и с опухолевым микроокружением. Наблюдается упрощение антигенной структуры клеточной мембраны опухолевых клеток, экспрессия молекул, характерных в том числе для эмбриональных тканей, изменение свойств межклеточных контактов, поддерживающих эпителиальный гомеостаз. Плотные контакты составляют основу сохранения нормальной гистоархитектоники. Изменения их свойств, выраженные в замене одних компонентов другими, определяют механические свойства опухолевых клеток, для которых характерны инвазивный рост и метастазирование. Помимо этого, компоненты плотных контактов являются участниками внутриклеточных путей передачи сигнала. Перспективными, на наш взгляд, выглядят исследования роли белков-клаудинов, являющихся компонентами плотных соединений. В этом обзоре мы собрали имеющиеся сведения о клаудинах как о компонентах клеточных контактов и участниках внутриклеточной сигнализации. В патогенезе эндометриального рака немаловажной характеристикой является эпителиально-мезенхимальная трансформация (ЭМТ), широко представленная в

нормальных тканях в процессах, связанных с репарацией. Изменение характеристик Е-кадгерина и β-катенина не могло быть не рассмотрено в рамках обсуждения роли ЭМТ в прогрессии рака эндометрия. Кроме того, исследователи все больше обращают внимание на Е-кадгерин как компонент путей активации онкогенов. Известно, что в основе эндометриального рака I типа лежит гиперэстрогенемия (высокие сывороточные урови эстрогенов). Рецепторы эстрогена, бесспорно, включены во внутриклеточную сигнализацию, активирующую пролиферацию клеток в норме и патологии. Кроме того, недавние исследования указывают на другие таргетные для эстрогенов молекулы. Таковыми являются клаудины. Изменение профилей экспрессии клаудинов под влиянием половых гормонов выражаются как в снижении, так и в замещении одного белка другим. Несомненно, дальнейшее изучение маркеров, ассоциированных с клеточной мембраной, может уточнить биологические свойства опухоли и служить основой поиска таргетных молекул для разработки новых путей терапии рака эндометрия.

Ключевые слова: рак эндометрия; мембранные компоненты; инициация; прогрессия; клеточные контакты; клаудины; Е-кадгерин; β-катенин; пути внутриклеточной сигнализации; гиперэстрогенемия.

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Список сокращений
ЗНО – злокачественное новообразование; ЭК – эндометриальная карцинома; ЭМТ – эпителиально-мезенхимальная трансформация.

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BACKGROUND

In 2023, in the Russian Federation there were 29,233 registered cases of endometrial cancer. According to the evaluation of the P.A. Herzen Moscow Scientific and Research Oncological Institute, it amounts to 8.0% of the total malignant tumor rate in Russian women. Endometrial cancer accounts for 37.34 cases per 100,000 population, and the average annual increase rate is 1.89%. Mortality from uterine malignant neoplasms, excluding cervical cancer, increases with age, starting from the age group of 25-29 years and reaching its maximum in the age group of 65-69 years at 6.59% [1]. In recent years, there has been some decrease in the overall mortality rate from endometrial carcinoma (EC) [2].

Following the pathogenetic criteria, there are two types of EC. Type I EC develops against a background of hyperestrogenemia (approx. 80% cases). It is preceded by atypical glandular hyperplasia of the endometrium / endometriosis intra-epithelial neoplasia. Type II EC develops against a background of endometrial atrophy in the absence of hyperestrogenemia, includes serous-papillary and clear cell types, and is more aggressive and estrogen-independent. Surgery remains the main method of treatment of uterine malignant neoplasms. In addition to hysterectomy, neoadjuvant chemotherapy is used, and approaches to targeted therapy based on tumor heterogeneity are being developed. There is evidence, based on tumor genome analysis (The Cancer Genome Atlas, TCGA), indicating heterogeneity in the genetic characteristics of endometrial carcinoma. The analysis identified the following molecular and genetic subtypes of EC: Group 1, *POLE*-ultramutated EC, associated with a favorable prognosis; Group 2, EC with microsatellite instability (MSI), showing intermediate prognosis; Group 3, EC with low copy-number alterations, also associated with intermediate prognosis; Group 4, EC with high copy-number alterations and TP53 mutations, associated with poor prognosis [3].

Considering the foregoing, there is practical interest in looking for targets to develop targeted therapy of endometrial adenocarcinoma.

The tumor consists of several key components, including the tumor parenchyma itself, its microenvironment (the stroma, immune system cells, and tissues providing trophic support and drainage for the tumor substrate, blood and lymphatic vessels). Most targeted therapy drugs under development focus on direct and/or indirect effects on tumor-specific biomarkers.

The cells comprising the substrate of the tumor growth are subject to a multitude of interactions between one another and their microenvironment. Such interactions are often corrupt making the tissue differentiation go back to the early stages of ontogenesis. Along with a simplification of the antigen structure of the cell membrane of the tumor cells, molecules are expressed that are characteristic for embryonal tissue. Interactions of cells with one another are also of importance, since they support the epithelial homeostasis.

This review is an attempt at systematizing the existing data on the changes in the structure of intercellular interaction (junctions) and cell interaction with their environment matrix, and their role in the pathogenesis of the endometrial carcinoma.

STRUCTURE AND FUNCTION OF MEMBRANE COMPONENTS IN NORMAL ENDOMETRIUM AND DURING PHYSIOLOGICAL REGENERATION

Cell Junctions

The primary participants in cellular interactions within tissues are intercellular junctions. These consist of protein molecules with distinct characteristics, each performing a specific function. Intercellular junctions connect cells to one another to maintain cellular polarity, stability, and the integrity of glandular structures. By preserving the polarity of the cell layer, intercellular junctions play a crucial role in regulating their mobility relative to the basement membrane.

Tight junctions, hemidesmosoma

Tight junctions are located in the uppermost part of the lateral cell membrane of two adjacent cells, thereby

regulating intercellular transport between cells (gate function) and maintaining apicobasal polarity (fence function). Tricellular tight junctions (tTJs) are formed in the intercellular contacts of three neighboring cells near their apical surfaces and are seen in polarized epithelia [4]. Tight junctions consist of three main membrane proteins: occludins, claudins, and adherens junctions molecules. The claudins are likely crucial in the protective and barrier functions of the junctions, intercellular differentiation, and support of epithelial polarity.

The hemidemosoma connect the intracellular filaments with the basal plate. Tricellulin (TRIC) was the first identified molecular component of tricellular tight junctions, and the Angulin-1/LSR, the novel integral membrane protein localized at tricellular tight junctions (tTJs).

Claudin proteins

Claudins (claudin-1, -2, -3, -4, -5, -7) are synthesized in endometrial epithelial cells and serve as components of tight junctions. Their secretion normally increases during the secretory phase of the endometrium.

E-cadherin and β-catenin are synthesized on the lateral membrane of glandular epithelial cells during the proliferative and early secretory phases, with protein synthesis decreasing during the secretory phase. E-cadherin represents one of the key epithelial adhesion molecules that plays a critical role in maintaining both cellular polarity and suppression of epithelial-mesenchymal transition (EMT) processes.

Adherens junctions

Adherens junctions and desmosomes interconnect adjacent cells. While adherens junctions are associated with intracellular actin bundles, desmosomes are linked to intermediate filaments.

Gap junctions

Gap junctions are intercellular membrane channels that directly connect the cytoplasm of adjacent cells, enabling the exchange of ions, second messengers, and small metabolites. Each gap junction channel consists of two hemichannels (connexons), with each hemichannel composed of six protein subunits (connexins).

The proteins of gap junctions are connexins Cx26, Cx32, Cx43. The increase of connexin Cx26 synthesis is seen in the epithelial cells of the endometrium during the proliferative phase, but the synthesis stops in the secretory phase [5]. Unlike tight and adherens junctions, the gap junctions are present in the stromal cells of the endometrium. These channels consist of the Cx43 protein. Similar to other connexins of the endometrium, the level of the Cx43 in the stromal cells of the endometrium also decreases during the secretory phase [6].

Normal EMT

The epithelial-mesenchymal transition (EMT) process is an important property of a healthy endometrium securing its physiological function. The EMT processes are well studies in the embryonal development, at the same time, there appear numerous proof of importance of these processes for the phenotypical and functional flexibility of the endometrium vital for the successful decidualization, regeneration and reepithelization, and embryo implantation [7].

Contact inhibition

Epithelial homeostasis is maintained through cellular polarity and cell density. Disruptions of these processes lead to malignant transformation of normal epithelia. Epithelial cells exhibit contact inhibition, a mechanism that arrests cell division and motility. Here, “cell motility” refers to the ability of individual cells to lose apicobasal polarity, undergo genetic rearrangements that drive cytoskeletal reorganization, and acquire an invasive phenotype [8]. It ensures tissue reparation in the process of normal physiological processes and in the response to damage.

ENDOMETRIUM FUNCTION IN MALIGNANT TRANSFORMATIONS

Molecular mechanisms of malignant transformation of epithelia include the PAR3 (partitioning defective), TGF-β (tumor-growth factor) and Hippo-signal pathways. The mutations of the *KRAS* protooncogene are found in almost 25% of adenocarcinomas including the endometrial carcinoma and endometriosis (adenomyosis).

Alterations in tumor cell motility in endometrial carcinoma have been extensively studied using the Sawano cell line. This line was established from uterine endometrial adenocarcinoma and carries a heterozygous KRAS G13D mutation with wild-type *BRaf*. Sawano cells exhibit high horizontal motility at low cell density, while at high cell density, their growth and motility are temporarily arrested due to contact inhibition. Under high-density conditions, this cell line initiated multilayered growth. Furthermore, in the presence of MAPK (mitogen-activated protein kinase) inhibitors, the cells maintained a highly differentiated state [9].

It is worthwhile focusing on these factors and analyze the structure of tricellular junctions. We have identified claudin proteins, occluding and adherens junctions as the main contributors to tight junctions. The transmembrane protein Angulin-1, a component of tTJs, is to be focused on.

Tricellular tight junctions, macropinocytosis, Angulin-1/LSR

Current evidence indicates tumor progression in colorectal cancer, pancreatic cancer, and lung adenocarcinoma cell lines, mediated through EGF-dependent claudin-2 and TGF-β-dependent angulin-1/LSR pathways [10, 11].

In the tissues of the endometrioid endometrial carcinoma, as well as in the endometriosis tissues, the angulin-1/LSR is located not only in the subapical zone but on the lateral surface of the membrane as well. There is evidence as to simultaneous decrease of expression of this protein with the growth of malignancy potential of endometrial carcinoma. The decreased expression of the angulin-1/LSR is seen in phases G2 and G3 of the cellular cycle in the cells of the endometrioid endometrial carcinoma, and the TRiC (T-complex protein Ring Complex) decreases as early as in G1 phase.

The apoptosis-stimulating protein of p53-2 (ASPP2) is an inducer of apoptosis that functions through binding with p53 and the epithelial polarity factor PAR3. ASPP2 suppression

promotes cell migration and invasion, downregulates LSR expression, and upregulates phosphorylated YAP as well as claudin-1, -4, and -7 expression with comparable efficiency to LSR loss [12].

The *PARD3* gene belongs to the par-3 family acting as regulators of cell polarity. The adaptor protein plays a crucial role in regulating asymmetric cell division and polarization processes in epithelial cells. Evidence suggests it serves as a key component of epithelial tight junctions [13]. In a study utilizing small interfering RNAs (siRNAs), J. Peng et al. (2021) demonstrated that transfection of HEC-1A cells with si-Par3 resulted in tight junction shortening, which enhanced tumor cell migration and invasion.

Using the Sawano EEC cell line, the authors also demonstrated impaired epithelial barrier function along with increased tumor cell proliferation, migration, and invasion [14].

T. Kohno, T. Kojima (2022) performed studies demonstrating the LSR ligand role in the regulation of cellular motility through atypical macropinocytosys [9]. Macropinocytosis is an actin-driven process of nonspecific uptake of micrometer-sized (visible by light microscopy) extracellular droplets. This process has been described in mammalian cells, among others [16]. Macropinocytosis serves as an important mechanism for nonspecific internalization of extracellular components [17]. In the recent years, additional functions of macropinocytosys were identified, such as intracellular drug introduction pathway, bacterial and viral infection, and nutrient consumption pathway by tumor cells. The LSR ligand is a fragment of the C-terminal peptide of the β-subunit of the Clostridium perfringens ι-toxin. In the Sawano and HPAC cell lines, the LSR downregulates the expression on of the latter and causes the barrier function to decrease resulting in an increased malignant transformation of the cells. In a monolayer of Sawano cells with a preserved mechanism of contact inhibition in the conditions of high cell density, the introduction of the LSR ligand leads to a transient fast enhancement of the horizontal motility of the cells. This process requires micropinocytosis initiated by the emergence of a gap between neighboring cells. LSR-ligand-driven pinocytosis does not occur neither in the apical nor in the basal membranes. Besides, in the course of accumulation of the macropinosomas there was not observed a significant accumulation of actine filaments. In the presence of the quinolinic inhibitor Rac1 (NSC23766) or in the cells expressing the dominant-suppressed Rac1, LSR-ligand-driven macropinocytosis is suppressed. The activity of Rac is required to activate the JNK (c-Jun N-terminal kinase) and instrumental in the subsequent enhancement of cell motility. In the Sawano cells, stimulation with the LSR ligand enhances cell motility through JNK activation. The JNK inhibitors, or silencing of the JNK gene not only suppresses the cell motility but also inhibits macropinocytosis [15].

EMT, loss of E-cadhedrin

Transforming growth factor (TGF)-β is a pleiotropic cytokine regulating the growth, differentiation, apoptosis, migration, cell adhesion and immune response. TGF-β activates the Smad-signal pathway through two its receptors on the cell membrane (TβRII and ALK5/TβRI), resulting in the Smad-mediated transcription regulation [18]. The analysis of potential candidates of prognostic factors of clinical outcomes demonstrates a correlation between the expression of TGF-β and its receptor and survivability in endometrial cancer. It was shown that the high expression of TGF-β and its receptor TGFβ1 correlates with a low overall survival [19]. K. Horiguchi *et al*. (2009) showed that TGF-β induces transcription of Snail through KRas-signaling, which results in the epithelial-mesenchymal transformation in the pancreatic carcinoma cells Panc-1 and HeLa cells [20]. This indicates, in the first place, a correlation of the Ras-signal pathway, Hedhehog-pathway and EMT; in the second place, it sheds some light on the dual role of TGF-β in the carcinogenesis.

LEF-1 is a component of the TCF/LEF-1, the factor associated with some types of malignant neoplasms, specifically, colorectal cancer [21]. In the endometrium, the LEF-1 is expressed in the norm[1]. In mouse experiments, D.N. Shelton *et al*. (2012) demonstrated that the expression profiles of LEF-1 and Cyclin D1—a known proliferation marker and target of the Wnt/β-catenin/LEF-1 signaling pathway—coincided and peaked during proestrus (equivalent to the human endometrial proliferative phase and ovarian follicular phase), corresponding to conditions of elevated estradiol (E2) levels [22].

Epithelial cell adhesion molecule (EpCAM) is a membrane protein known to function as an mediator in the intercellular interaction and cell and intercellular matrix interaction. The current data as to the role of EpCAM hyperexpression are contradictory: on the one hand, EpCAM is supporting the normal histoarchitecture of epithelia, on the other hand, the adherens molecule might activate the intracellular pathways promoting cell invasion [23, 24]. Y.T. Hsu *et al*. (2016) report that the EpCAM integral protein is split into the extra- and intracellular domains (EpEX and EpICD, respectively) when induced by activated EGFR. The EpICD, subjected to nuclear translocation, together with the LEF-1 acts as activator of transcription of target genes responsible for epithelial-mesenchymal transformation [25].

G-protein-coupled receptor 64 (GPR64) is a member of the GPCR family. *GPR64* was identified as the target gene of the β-catenin/T-cell factor (TCF) in the ovarian endometrioid adenocarcinoma. It was shown that the downregulated expression of *GPR64* together with the deletion of the GPR64 gene increases the malignant potential of the tumor and upregulates the processes of cell proliferation, migration and invasion; GPR64 regulates expression of Cx43 and activity of AMP-activated protein kinase (AMPK) in the endometrium cancer cells [26].

The Hippo-signal pathway is an important contributor to the maintenance of cellular polarity and density of the cell layer; the inactivation of the pathway may result in the increase of cell proliferation and decrease of apoptosis this leading to the tumor genesis and progression [27].

[1] The Human Protein Atlas [Internet]. Tissue expression of LEF1. Staining in endometrium. 2000 [cited 2025 Feb 12]; [about 2 p.]. Available from https://www.proteinatlas.org/ENSG00000138795-LEF1/tissue/endometrium

The nuclear component of this signaling pathway is also regulated by multiple other pathways. Inactivation of the Hippo signaling pathway triggers activation of its primary effector oncogenes, YAP/TAZ, which in turn promote tumor invasion, migration, and proliferation in endometrial cancer [28]. YAP/TAZ are transcriptional coactivators that move between the cytoplasm and the nucleus, where they recognize the cis-regulatory elements and interact with other transcription factors, specifically, with members of the TEA domain family (TEAD). Emerging evidence clarifies the crosstalk between the Wnt-signaling pathway that governs β-catenin accumulation and activity (canonical pathway) and the transcriptional coactivator TAZ [29, 30].

Various signaling pathways, including Wnt/β-catenin- and Notch-pathways, induce the EMT and downregulate the expression of E-cadhedrin. The experiment on the HEC-1A, HEC-1B, KLE cell lines of the endometrial carcinoma showed that the knockdown of the fibulin-4 gene may bring about the activation of the Wnt-pathway and promote the EMT. Upregulation of the fibulin-4 expression may suppress the Wnt-pathway and prevent the EMT, but this question calls for further research [31, 32]. In the HeLa cervical cancer cells, the overexpression of EFEMP1 (EGF-containing fibulin-like extracellular matrix protein 1), also known as fibulin-3, results in the enhancement of angiogenesis and progression of tumor growth through the VEGF-pathway [33]. Besides, EMP undergoes regression under the influence of other inhibitors of the Wnt-signaling pathway.

The Hedhehog-signaling pathway ensures the proper cell differentiation in the embryo. Its disruptions in the embryogenesis account for the teratogenic effect. Its role in the adult organism however is completely opposite: the activation of the Hedhehog-pathway has proven relation with the development of malignant neoplasms of the brain, lungs, mammary glands, prostate, and skin. The activation of the Hedgehog-signaling pathway results in the upregulation of expression of the Snail protein and downregulation of E-cadhedrin and tight junctions [34].

Claudin proteins

The family of claudin proteins is an integral part of tight junctions. Claudins are considered to be instrumental in the processes of maintenance of cell polarity, cell monolayer and EMT regulation, since their loss promotes destruction of cell junctions. Abnormal expression of claudin proteins affects cancer progression in several ways: firstly, changes in claudin expression lead to disruption and leakage of tight junctions, which promotes tumor metastasis and invasion; secondly, loss of cell polarity increases the delivery of nutrients and growth factors to the tumor and enhances the invasive potential of tumor cells; thirdly, reduced intercellular adhesion increases the risk of metastasis and promotes tumor invasion [35].

In endometrial adenocarcinoma, overexpression of claudins-3 and -4 directly correlates with tumor grade. A significant increase in levels of claudins-1, -3, -4, and -7 compared to normal endometrial cells is observed in serous-papillary endometrial carcinoma, the most aggressive variant of type II estrogen-independent endometrial carcinoma. These tumor cells show decreased synthesis of claudins-2 and -5 [36].

The abnormal expression of the claudin-6 protein may result in disruption of integrity of tight junctions through various mechanisms; it is a factor in the tumor genesis and progression [37]. Available data indicate that claudin-6 is normally expressed in embryonic tissues of the stomach, lungs, and kidneys, but is not detected in healthy adult human tissues. [38, 39]. Other research, however, does not prove this thesis, and the mechanisms of claudin-6 expression regulation remain understudies and contradictory [40].

Claudin-6 is known to be expressed in various tumors and to play an important role in the tumor growth genesis and progression. Increased expression of claudin-6 has been demonstrated in endometrial carcinoma. Knockdown of the CLDN6 gene may suppress proliferation and migration of the HEC-1-B endometrial carcinoma cell line through the PI3K/Akt/mTOR signaling pathway [41].

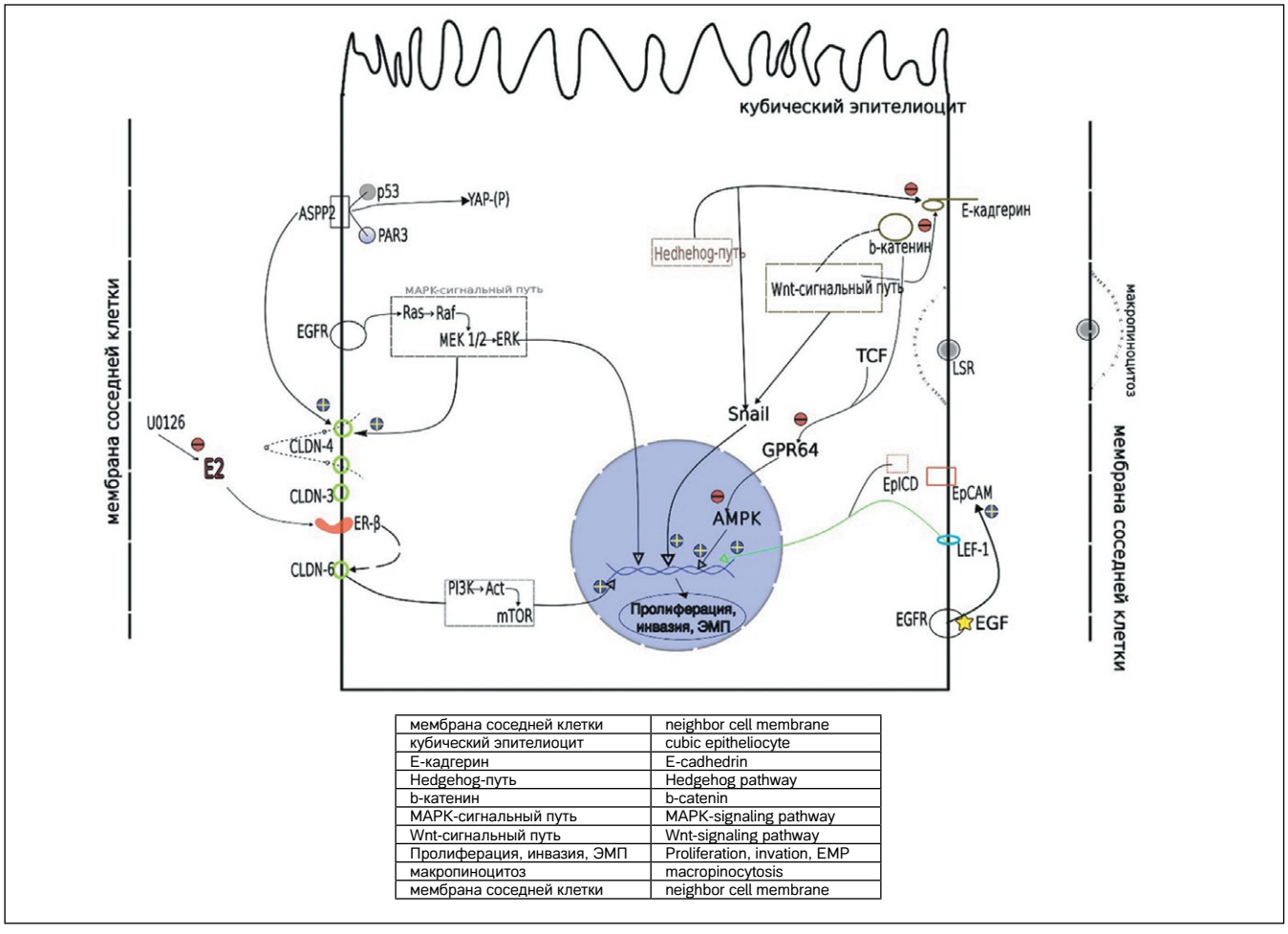
In epidemiological studies, C. Zhang *et al*. (2021) demonstrated that high claudin-6 expression serves as an independent prognostic factor for worse recurrence-free survival in endometrial cancer within the following clinical subgroups: age over 60 years; body weight over 80 kg; body mass index above 30; FIGO Grade IB or higher; postmenopausal status; large residual tumor after neoadjuvant chemoradiotherapy [42].

The influence of sex hormones on the expression of tight junction proteins, including claudins, is of interest. Thus, M. Someya *et al*. (2013) report that estradiol (E2) induces overexpression of claudin-3 and -4. Effects opposite to those described, i.e., a decrease in conditional 'pro-oncogenic' claudins, are mediated by progesterone (P4) stimulation. Barrier and fence functions in Sawano endometrial cancer cells were reduced under high-dose E2 exposure. These results indicate an increase in claudin-3 and -4 that do not fulfill tight junction functions under E2 influence in the pathogenesis of endometrial adenocarcinoma [41]. The question of biphasic effect of estradiol on claudin-4 expression remains debated [43, 44]. The biphasic effect of estradiol, within the scope of influence on the expression of tight junction proteins under consideration, is manifested in the increased expression of claudin-4 mediated by low doses of E2 and its suppression by high doses of estradiol.

It is necessary to explain the differences between the barrier and fence functions of tight junctions. The barrier function is defined by the ability of tight junctions to regulate the diffusion of soluble substances through intercellular spaces. Examples include hormones such as the aforementioned E2 and P4. The fence function of tight junctions consists in their ability to prevent mixing of molecules from the apical membrane domain with molecules of the lateral cell membrane surface.

The increased expression of claudin-3 induced by E2 is suppressed by the MAPK pathway inhibitor U0126. A decrease in claudin-4 expression is also observed under conditions of inhibited intracellular signaling through both the MAPK pathway and Hedgehog pathway (inhibitor: cyclopamine).

It has been established that estrogens regulate claudin-6 expression at the transcriptional level through estrogen receptor beta (ER-β). ER-β activation can trigger tumor cell autophagy via claudin-6 overexpression and inhibit migration



мембрана соседней клетки	neighbor cell membrane
кубический эпителиоцит	cubic epitheliocyte
E-кадгерин	E-cadhedrin
Hedgehog-путь	Hedgehog pathway
b-катенин	b-catenin
МАРК-сигнальный путь	MAPK-signaling pathway
Wnt-сигнальный путь	Wnt-signaling pathway
Пролиферация, инвазия, ЭМП	Proliferation, invation, EMP
макропиноцитоз	macropinocytosis
мембрана соседней клетки	neighbor cell membrane

Figure 1. *Relation of membrane structures to intracellular signaling pathways complicit in the malignant transformation of endometrial glands.*
Рисунок 1. *Связь мембранных структур с путями внутриклеточной сигнализации, опосредующими злокачественную трансформацию желез эндометрия.*

and invasion in breast cancer cells. There are other claudin family proteins whose expression is altered by sex hormones (**Fig. 1**).

Connexin proteins

Disruption of gap junction contacts, or aberrant connexin expression, represents one of the key mechanisms in carcinogenesis. In endometrial carcinoma cells with hyperplasia, the synthesis of Cx26 and Cx32 proteins, as well as Cx43 in endometrial stromal cells, is reduced, leading to impaired gap junction intercellular communication. Studies indicate that dysregulation of gap junction intercellular communication may occur at relatively early stages of endometrial carcinogenesis. The correlation between reduced connexin synthesis and cancer progression is supported by the fact that estrogen receptor-alpha activation, a major etiological factor in endometrial hyperplasia and adenocarcinoma development, disrupts gap junction communication and downregulates expression of connexins Cx26 and Cx32 in endometrial carcinoma cells [45].

CONCLUSION

The classical understanding of endometrial cancer pathogenesis describes it as a condition arising from abnormally high proliferative activity of glandular structures under the influence of external and internal factors. The primary contributing factors include sex hormones, directly affecting cellular metabolism in cells expressing nuclear estrogen and progesterone receptors. Another significant factor of excessive proliferation is local hypoxia. It occurs in various pathological processes, such as inflammation, local and systemic circulatory disorders, and impaired nutrient utilization, which force cells to switch to anaerobic glycolysis and beta-oxidation of lipids, which in turn become major sources of free radicals in cells.

In addition to the aforementioned factors, attention should be paid to the intrinsic properties of epithelial cells that contribute to maintaining normal histoarchitecture. We have attempted to compile data on the relationship between widely expressed molecular components supporting homeostasis, such as EGFR, and minor specialized components involved in maintaining cellular polarity and monolayer organization.

Identification of molecular disorders occurring in the tumor cells allows clarification of biological properties of the tumor, their role and place in the tumor growth pathogenesis and prognostic significance. While some molecules acts as potential malignancy markers, others may indicate degree of malignity, serve as outcome predictors or as direct targets for targeted treatment with drug.

For the diagnosis of endometrial cancer, the following markers are clinically significant in practice: tumor suppression markers (p53), differential diagnostic markers for determining histogenesis (p16), tumor receptor profile

markers, tumor proliferative potential markers, and specific antigen markers.

Intercellular contacts mediate interactions between tumor cells and their microenvironment. We have attempted to summarize available data on tumor cell interactions with the external environment and metabolic changes that enhance proliferation, invasion, and metastatic potential.

Development of classification of endometrial carcinoma based on the alteration of cellular junction protein alterations might be an interesting task in the study of this pathology. There exist epidemiological data, albeit unsystematized, that indicate differences in the survival of patients with endometrial cancer and various profiles of claudim cadhedrin proteins and other cellular adhesion molecule expression.

We believe that an association exists between altered E-cadherin expression patterns in tumor cells in EEC and increased cellular motility. In our opinion, such patterns are to include loss of E-cadhedrin expression near the apical membrane and its preservation only along the basolateral surface of the cells undergoing malignant transformation. Considering the important role of EMT in carcinogenesis in EEC it might be allowed that the combination of E-cadhedrin loss near the apical membrane and the aberrations in claudin expression (replacement of one claudin type with another, loss of claudins normal for the type of tissue) are to be considered molecular pattern of a risk of malignant transformation. It is suggested that data on alterations in the structure and function of intercellular junctions will have the highest clinical relevance when examining diagnostic specimens (scrapings). Further detailed investigation of the clinicopathological role of intercellular junction molecules will help clarify the biological properties of tumors and facilitate the development of drugs targeting this aspect of tumor growth.

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Conflict of Interest. The authors have no relationships, activities or interests for the last three years related with for-profit or not-for-profit third parties whose interests may be affected by the content of the article.	***Конфликт интересов.*** Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.
Generative AI. Generative AI technologies were not used for this article creation.	***Генеративный искусственный интеллект.*** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Statement of originality. The authors did not use previously published information (text, illustrations, data) to create this paper.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
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Microscopic features of chronic cheilitis

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Abstract

Aim – to evaluate morphological changes of the lip mucosa in chronic cheilitis: the condition of the epithelium, the microcirculation and the inflammatory infiltration of the intrinsic lamina of the mucosa.

Material and methods. A retrospective analysis was performed of medical records, biopsy specimens and archive histological material after lip resection in patients with the diagnosis of chronic cheilitis (Tver Regional Clinical Oncological Dispensary). The sample consisted of 46 patients aged 34–72 years (19 women and 27 men). After the microscopic examination, two groups have been formed: Group A, instances of chronic inflammation of the lip without signs of epithelial dysplasia (n=24), Group B, instances with low- and high-grade dysplasia in the squamous epithelium (n=22). Changes in the epithelium, severity of hyperplasia, stratification, degree of epithelial cells maturation, karyopycnotic index, and character of inflammatory infiltrate and vascularization of intrinsic lamina of the mucosa were evaluated. Microscopic examination was performed using an Olympus CX-41 light microscope with a digital camera. Specialized software suite Video Test-Morphology 5.2 was used to study 10 fields of view of the microscope (×40 lens magnification, ×10 eyepiece) in every specimen: diameter, number of blood vessels and stromal and angiomatous components ratio measured per 1 mm2. The data was statistically processed using SPSS 22.0 suite.

Results. Elderly men predominated in both groups. A comparative analysis of changes in the squamous epithelium, inflammatory reaction, and the nature of vascularization of the proper mucosa plate was performed. According to the results of morphometry, it was found that in patients of Group B the number of vessels per unit area was significantly higher than in Group A. Microscopic features of reactive changes in the epithelium and proper plate of the mucous membrane of the red border of the lips predisposing to malignant transformation were found. In chronic cheilitis with epithelial dysplasia, an uneven arrangement of vascular loops with alternating sections of hypovascularized stroma and foci of increased vascularization of the proper mucosa plate due to the accumulation of small capillaries was noted, which can be recommended as a morphological sign of an unfavorable prognosis of the inflammatory process of the red lip rim.

Conclusion. In the differential diagnosis of lip diseases, pathologists should note the nature and severity of microcirculatory changes and inflammatory infiltration in the mucous membrane at the conclusion of the pathology study, along with the characteristics of squamous epithelium dysplasia, and clinicians should consider these morphological data when choosing treatment tactics for patients.

Keywords: red lip border, potentially malignant lip diseases, dysplasia, microcirculation, cheilitis.

Conflict of interest: nothing to disclose.

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Микроскопические особенности хронических хейлитов

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Аннотация

Цель – оценить морфологические изменения слизистой оболочки губы при хронических хейлитах: состояние покровного эпителия, особенности васкуляризации и воспалительной реакции собственной пластинки слизистой.

Материал и методы. Проведено ретроспективное исследование с анализом историй болезни, протоколов прижизненного патологоанатомического исследования и архивного гистологического материала пациентов Тверского областного клинического онкологического диспансера после резекции губы с диагнозом «хронический хейлит». Выборку составили 46 пациентов в возрасте 34–72 лет (19 женщин и 27 мужчин). Клинические наблюдения после микроскопического исследования разделили на две группы: А – клинические наблюдения хронического воспаления губы без признаков дисплазии покровного эпителия (n=24), Б – с диспластическими изменениями многослойного плоского эпителия низкой и высокой степени (n=22). Оценивали изменения эпителиального пласта, выраженность гиперплазии, клеточный состав, степень созревания эпи-

телиоцитов, кариопикнотический индекс, особенности воспалительного инфильтрата и васкуляризации собственной пластинки слизистой. Микроскопическое исследование проводили с помощью светового микроскопа Olympus CX-41 с цифровой фотокамерой. В специализированном программном обеспечении «Видео Тест-Морфология 5.2» в каждом препарате изучали 10 полей зрения микроскопа (об. 40, ок. 10): измеряли диаметр, количество, численную плотность сосудов и соотношение стромального и ангиоматозного компонентов с пересчетом на 1 мкм^2 площади. Данные статистически обработаны с применением программы SPSS, версия 22,0.
Результаты. В обеих выделенных группах преобладали пожилые мужчины. Проведен сравнительный анализ изменений покровного многослойного плоского эпителия, воспалительной реакции и характера васкуляризации собственной пластинки слизистой. По результатам морфометрии установлено, что у пациентов группы Б число сосудов в единице площади было достоверно больше, чем в группе А. Выявлены микроскопические особенности реактивных изменений эпителия и собственной пластинки слизистой красной каймы губ, предрасполагающие к злокачественной трансформации. При хронических хейлитах с дисплазией покровного эпителия отмечено неравномерное расположение сосудистых петель с чередованием участков гиповаскуляризованной стромы и очагов усиления васкуляризации собственной пластинки слизистой за счет скопления мелких капилляров, что можно рекомендовать в качестве морфологического признака неблагоприятного прогноза течения воспалительного процесса красной каймы губ.
Заключение. При дифференциальной диагностике заболеваний губ врачам-патологоанатомам в заключении патологоанатомического исследования наряду с указанием характеристики дисплазии многослойного плоского эпителия следует отмечать характер и степень выраженности микроциркуляторных изменений и воспалительной инфильтрации в слизистой оболочке, а врачам-клиницистам учитывать эти морфологические данные при выборе тактики лечения больных.
Ключевые слова: красная кайма губ, потенциально злокачественные заболевания губ, дисплазия, микроциркуляция, хейлиты.
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Список сокращений
ККГ – красная кайма губ; СПС – собственная пластинка слизистой; ШИК – Шифф-йодная кислота.

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INTRODUCTION

Cheilitis is a significant issue in modern dentistry that encompasses not only medical but also social aspects. There are few studies dedicated to cheilitis in the scientific literature, and the data presented in them are contradictory. According to medical periodicals, the prevalence of specific types of cheilitis among various population groups varies widely, ranging from 6.8% to 25.0%. The incidence of cheilitis ranges from 6 to 15 cases per 10,000 population. The prevalence of inflammatory diseases of the lip vermilion border among the adult population is notably high. Thus, atopic cheilitis is seen mostly in women (54.05%) aged 20–44, angular cheilitis in 7.8% of elderly women; in men of advanced age, meteorological cheilitis is seen in 6.4% cases, and angular cheilitis, in 9.6% cases [1].

The vermilion border of the lips is constantly exposed to external and internal factors and frequently undergoes inflammatory processes (cheilitis), experiencing various morphological transformations. Any tissue damage is accompanied by an inflammatory response manifested as a complex of vascular-stromal and intracellular changes aimed at forming a new cellular microenvironment for repair purposes. This process initiates a cascade of molecular events that, under unfavorable conditions, may lead to oncogenesis [2–5].

An important feature of epithelial structural organization is the arrangement of its cells on the basement membrane. Any damage to the basement membrane, particularly chronic damage, increases the likelihood of dysregenerative changes and the potential risk of neoplastic transformation of epithelial cells [6]. The mechanisms controlling the heterogeneous differentiation pattern of the regenerating epithelium of the lip vermilion border remain insufficiently studied. It is suggested that the maturation degree of epithelial cells is regulated by humoral factors secreted by cells of the underlying connective tissue lamina propria. When considering factors modulating intercellular interactions, the characteristics of hemocirculation should be taken into account.

Cheilites do not have specific clinical manifestations but demonstrate variable morphological changes, often with different neoplastic potential. Therefore, the diagnosis of ‘cheilitis’ is to be seen as a clinical and anatomical one. This results in substantial complications in the clinical diagnosis. The basis of the clinical diagnostics of the vermilion border of the lip lies in the visual and instrumental examination. The final verification of the pathological process is only possible by antemortem pathology study (biopsy).

The lack of clinical guidelines for the diagnosis and treatment of chronic cheilitis, coupled with the limited diagnostic value of cytological examination, often leads clinicians to opt for surgical treatment. This approach aims to completely remove the pathologically altered tissue area followed by histological examination [7]. Thus, the morphologist’s conclusion is decisive for the clinician (dentist, maxillofacial surgeon, oncologist) in the diagnosis and treatment of diseases, particularly oncological ones.

Professional medical literature describes angular, contact (allergic), actinic, atopic, abrasive, glandular, granulomatous, exfoliative, and plasma cell cheilitis, some of which are classified as obligate or facultative precancerous conditions [8, 9]. Thus, abrasive cheilitis (Manganotti’s type) is classified as an obligate precancerous condition, while actinic cheilitis is considered a facultative precancerous condition [10, 11]. The diversity of clinical and morphological forms, the lack of a unified

clinicopathological classification, and prognostic criteria regarding cheilitis malignancy reflect insufficient synthesis of accumulated data, a disconnect between clinicians and pathologists, and underscore the importance of clinicopathological correlation and systematic analysis of clinical observations.

Manganotti's cheilitis usually localizes on the lower lip [9]. On morphological examination, the epithelial layer is thinned and atrophic, with erosion. At margins of the erosion, stratified squamous epithelium forms wide acanthotic epithelial projections deeply penetrating the underlying stroma. Within the proliferating epithelial projections, against a background of disrupted stratification, there is nuclear hyperchromasia in spinous layer cells with varying degrees of atypia manifested by increased size and number of nucleoli. The stroma contains a diffuse infiltrate composed of lymphocytes, plasma cells, and histiocytes.

Actinic cheilitis most commonly affects the lower lip and is characterized by acanthosis, the presence of 'empty' cells in the spinous layer, parakeratosis and hyperkeratosis with loss of connection between spinous and horny layer cells, and features of cellular atypia [9]. The connective tissue layer shows increased glycogen content with accumulation of abnormal elastic fibers that impart a disorganized appearance to the tissue, along with infiltration by lymphocytes and plasma cells. An elevated number of mast cells (labrocytes) is also observed.

Among modern trends in oncomorphology, particularly for head and neck tumors, special attention is focused on studying signaling pathways in neoplastic epithelial transformation, tumor cell metabolism features, and the search for informative molecular-genetic and immunohistochemical differential diagnostic criteria [12, 13]. The role of hypoxia as a factor stimulating dysplastic and neoplastic processes in epithelial tissue has been proven. According to literature data, dysplastic changes in stratified squamous epithelium, as well as the progression rate of dysplasia into epithelial tumors, are often associated with alterations in subepithelial tissue vascularization. Moreover, high expression of angiogenesis factors is accompanied by early malignancy and active invasion of atypical cells [14, 15]. However, morphological descriptions of vascularization features in the subepithelial stroma in chronic cheilitis are lacking in the medical literature.

AIM

To evaluate morphological changes of the lip mucosa in chronic cheilitis: the condition of the epithelium, the microcirculation and the inflammatory infiltration of the intrinsic lamina of the mucosa.

MATERIAL AND METHODS

A retrospective study was conducted analyzing medical records, antemortem pathological examination reports, and archival histological specimens from patients of the Tver Regional Clinical Oncology Center who underwent lip resection with a diagnosis of "chronic cheilitis". The study was conducted in compliance with the "Regulations of Clinical Practices in the Russian Federation" approved by the Order of the Ministry of Health of the Russian Federation No. 266 dated 19.06.2003. The study was approved by the resolution of the Ethics Committee of the Tver State Medical University of the Ministry of Health of Russia on 28.01.2025.

The sample was 46 patients aged 34–72 including 19 women and 27 men. The disease history varied from 4 to 12 months. Morphological assessment of the surgical material was performed according to the 5th Edition of the World Health Organization Classification of Head and Neck Tumors (2022) [16,17]. Following microscopic examination of hematoxylin and eosin-stained histological specimens, clinical cases were divided into two groups. Group A comprised cases of chronic lip inflammation without signs of covering epithelial dysplasia (24 cases), while Group B included cases with low- and high-grade dysplastic changes in the stratified squamous epithelium (22 cases). To verify dystrophic changes in the covering epithelium and visualize the basement membrane, additional sections were prepared from paraffin blocks and stained with periodic acid-Schiff (PAS). During morphological examination, the following were evaluated: alterations in the epithelial layer, characteristics of the inflammatory infiltrate, and vascularization of the lamina propria; in the covering epithelium - the degree of hyperplasia, cellular composition, maturation stage of epithelial cells, and karyopyknotic index. Microscopic examination was performed using an Olympus CX-41 light microscope equipped with a digital camera. Using the specialized software "Video Test Morphology 5.2", each specimen was examined in 10 fields of vision of the microscope (×40 lens, ×10 eyepiece) with measurements of diameter, quantity, numeric density of vessels and ratio of stromal and angiomatous components calculated for 1 μm^2 of area. The data were statistically processed using SPSS software, version 22.0. Descriptive statistics, the Shapiro-Wilk test, and Wilks' lambda criterion ($n<50$) were used to determine the distribution type of quantitative data. The data are presented as arithmetic mean (Sx) and standard deviation (σ). Student's t-test and one-way ANOVA were applied to compare means between independent groups. The critical level of statistical significance was set at 0.05 (p).

RESULTS AND DISCUSSION

The results of light microscopic evaluation revealed focal hyperplasia of stratified squamous keratinized epithelium with signs of acanthosis, parakeratosis, and hyperkeratosis of varying degrees in all cases (**Fig. 1**).

The severity of reactive changes decreased toward the resection line. In the epithelium of the affected lip area in Group A patients, alterations predominantly involved the spinous and granular layers. Some specimens contained balloon-shaped cells resembling koilocytes, with excessive optically clear cytoplasm due to glycogen accumulation. The submucosa exhibited uniformly distributed capillaries with ectatic loops; mild perivascular edema of the interstitium with either no inflammation or focal lymphocytic infiltration of minimal severity.

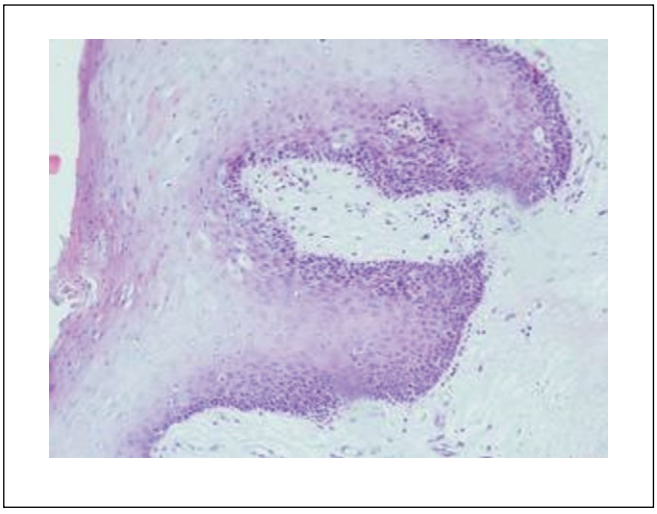

Figure 1. *Changes of the lip mucosa in a patient of Group A. Focal hyperplasia with acanthosis and hyperorthoceratosis of the squamous epithelium. Staining with hematoxylin and eosin, ×100.*

Рисунок 1. *Изменения слизистой оболочки губы в очаге повреждения у пациента группы А. Очаговая гиперплазия многослойного плоского эпителия с акантозом и гиперортокератозом. Окраска гематоксилином и эозином, ×100.*

In Group B patients, the hyperplastic epithelium demonstrated focal proliferation of epithelial cells with hyperchromatic polymorphic nuclei against a background of acanthotic, papillomatous, and dystrophic features. These changes included loss of polarity, partial disruption of epithelial stratification starting from the basal layer and extending to upper layers, involving areas of varying size and epithelial thickness. Low-grade dysplasia was diagnosed in 6 patients, high-grade dysplasia in 16 patients, among which 5 cases (31.3%) showed combined foci of low- and high-grade dysplasia, and 6 cases (37.5%) revealed areas of covering epithelium ulceration with marked reactive inflammation in the subepithelial stroma manifested by diffuse infiltration of segmented leukocytes, lymphocytes, and histiocytes along with occasional eosinophilic granulocytes and macrophages. In specimens with intact epithelial lining, mixed inflammatory cell infiltration of the lamina propria was also observed, varying in intensity and cellular composition. The epithelial changes characteristic of Group B patients are illustrated in **Figures 2** and **3**.

The comparative analysis data of microscopic changes in the covering epithelium in histological specimens from patients of Groups A and B are presented in **Table 1**.

When assessing vascularization features in lip lesion areas, the density of blood vessels per unit area in the submucosa was higher in Group B patients than in Group A patients (**Table 2**). Vascular structures were unevenly distributed across the affected area and varied in size and morphology. Small capillaries with thickened, partially hyalinized walls predominated. Some capillaries showed signs of basement membrane sclerosis. The endothelial lining appeared either normal or flattened. In the peripheral zone of the lesion, vascularization was significantly reduced. Small-caliber capillaries were surrounded by clusters of spindle-shaped histiocytic cells and bundles of collagen fibers. In some vessels, the lumen was absent due to endothelial cell proliferation. The stroma exhibited unevenly distributed diffuse polymorphous inflammatory infiltration, consisting of lymphocytes, histiocytes, segmented leukocytes, occasional eosinophilic granulocytes, and macrophages.

A comparative morphometric analysis revealed a statistically significant increase in vessel density per unit area of the lamina propria in Group B patients compared to Group A patients.

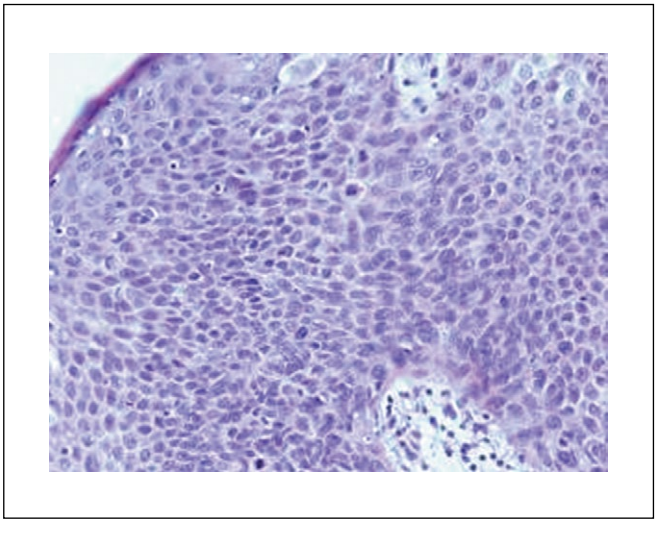

Figure 2. *Changes in the lip mucosa at the lesion site in Group B patients. Hyperplasic squamous epithelium has high-grade dysplasia with intra- and subepithelial lymphocytic infiltration. Staining with hematoxylin and eosin. ×200.*

Рисунок 2. *Изменения слизистой оболочки губы в очаге повреждения у пациентов группы Б. В гиперплазированном многослойном плоском эпителии дисплазия высокой степени тяжести с интра- и субэпителиальной лимфоцитарной инфильтрацией. Окраска гематоксилином и эозином. ×200.*

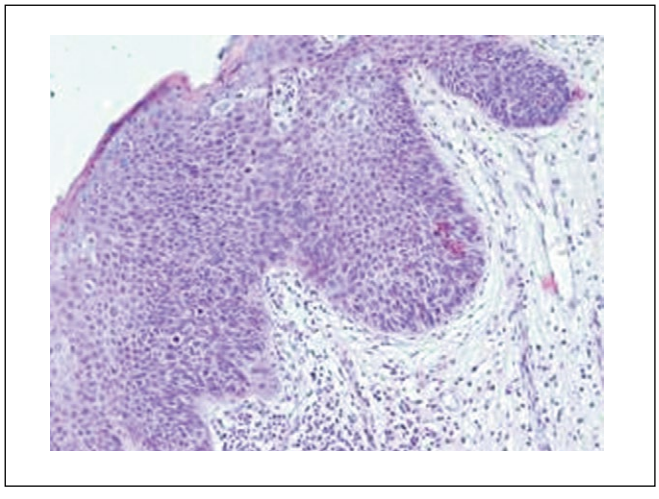

Figure 3. *Changes in the submucosa in the lesions of the lip in patients of Group B. There is a high degree of dysplasia in the stratified squamous epithelium. In the proper plate of the mucosa, capillaries of various sizes with ectatized free lumens, pronounced diffuse lymphoplasmocytic infiltration. Staining with hematoxylin and eosin. ×100.*

Рисунок 3. *Изменения подслизистой основы в очагах повреждения губы у пациентов группы Б. В многослойном плоском эпителии дисплазия высокой степени. В собственной пластинке слизистой разнокалиберные капилляры с эктазированными свободными просветами, выраженная диффузная лимфоплазмоцитарная инфильтрация. Окраска гематоксилином и эозином. ×100.*

Criteria	Values	
	Group A (n=24)	Group B (n=22)
Hyperkeratosis	Severe	Moderate
Parakeratosis	Severe	Severe
Acanthosis	Mild	Moderate / severe
Balloon-shaped cells	+	++/+++
Epithelial maturation index, % (average)	0/86/10,5/3,5	8/76/14/2
Kariopicnotic index (%)	1	4

Table 1. *Morphometric and semi-quantitative indices of microscopic changes in the integumentary epithelium in chronic cheilitis*

Таблица 1. *Морфометрические и полуколичественные показатели микроскопических изменений покровного эпителия при хронических хейлитах*

Comparison groups / Parameter	A (n=24)	Б (n=22)
Number of vessels per 1 mm² *	14 ± 1	16 ± 3
Average vessel diameter, μm*	7,0 ± 1,6	9,8 ± 3,2
Max vessel diameter, μm	11,1 ± 1,6	14,0 ± 3,2
Min vessel diameter, μm	5,6 ± 1,2	4,2 ± 1,6
Number of monocyte cells per 1 mm²	32 ± 9	48 ± 17

*Note: - Student's t-test was used; * - differences significant at p=0.05.*
*Примечания: – использовали t -тест Стьюдента; * – различия значимы при p = 0,05.*

Table 2. *Morphometric parameters in comparison groups, (Sx± σ)*

Таблица 2. *Морфометрические параметры в группах сравнения, (Sx± σ)*

The results of discriminant function statistical analysis using Wilks' lambda criterion (λ = 0.0000011, approximate F(15.254) = 2157.1, p < 0.00001) are graphically presented in **Figure 4**.

In ulcerated areas of stratified squamous epithelium within pathological foci, the subepithelial stroma exhibited ectatic congested capillaries and polymorphous inflammatory infiltration of varying intensity. In regions of lip vermilion border mucosa with epithelial dysplastic changes, vascular distribution demonstrated marked variability, alternating between hypovascularized zones of the lamina propria and angiomatosis fields characterized by clusters of tightly packed small capillaries surrounded by pericytes and fibroblast-like cells.

The uneven density of the angiomatosis component indicates the presence of stromal hypovascularization foci, which causes relative or absolute tissue hypoxia. Microcirculatory impairment in cheilitis is accompanied by shifts in vascular-platelet and coagulation hemostasis parameters mediated by local tissue coagulation factors. Microcirculatory hemostasis disturbances are not specifically isolated but rather reflect to some extent the nature of inflammatory and destructive tissue processes. The chronic course of the inflammatory process is accompanied by dysregenerative disorders of stromal and epithelial compartments forming a mutually modulating system and represents the key pathogenetic factor in the development of basal epithelial dysplastic changes.

During regeneration, the epithelial layer and underlying tissue structures act as mutual short-range modulators of cell differentiation, as well as fibrillogenesis and angiogenesis processes. Consequently, there is impaired production of inflammatory mediators and dysregulation of inflammatory signaling cascades; moreover, a spectrum of molecular processes is initiated that under unfavorable conditions may lead to proliferative, hyperplastic, and oncoplastic processes. This occurs because many biologically active molecules possess both pro-inflammatory (mitogenic) and anti-inflammatory (anti-mitogenic) properties simultaneously, resulting in mutagenic potential.

Thus, microscopic examination of biopsy material from patients clinically diagnosed with chronic cheilitis, as the severity of dysplasia of the epithelium progresses in the mucosa of the lip vermilion border, the microstructural changes become more manifested as well as the inflammatory infiltration in the lamina propria of the mucosa.

CONCLUSION

It should be acknowledged that cheilitis conditions are diverse in their morphological manifestations, require thorough differential diagnosis, and present challenges

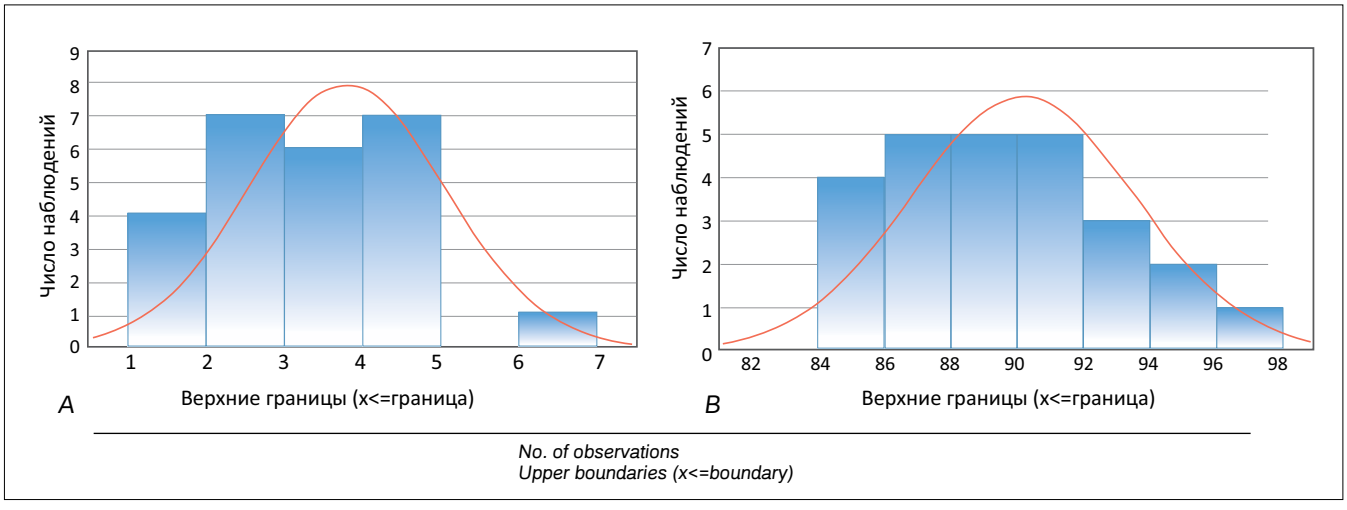

Figure 4. *Histograms of the results of the analysis of discriminant functions of vascularization features in histological samples of Groups A (a) and B (b).*

Рисунок 4. *Гистограммы результатов анализа дискриминантных функций особенностей васкуляризации в гистологических образцах групп А (а) и Б (б).*

in histopathological verification. Each pathological variant is characterized by distinct structural features and varying predisposition to dysplasia development and malignant transformation. During human ontogeny, the regenerative capacity of epithelium significantly declines. The results of this study demonstrate a predominance of elderly male patients among those with chronic cheilitis exhibiting dysplastic changes in the covering epithelium.

In their everyday work, clinical practitioners take into account the morphological signs of pre-tumor pathology of the examined biopsy material that might justify the subsequent tactics and amount of treatment in each specific case. In the differential diagnosis of lip diseases, pathologists must document in histological reports the presence and degree of stratified squamous epithelial dysplasia, the nature and severity of microcirculatory changes, and inflammatory infiltration in the mucosa. Clinicians should consider these morphological findings when determining treatment strategies. Dentists, in turn, should maintain oncological vigilance when managing elderly male patients. Studies of microhemodynamics and blood flow velocity in various chronic inflammatory processes, such as lip diseases (cheilitis), hold diagnostic and prognostic value for clinical practice.

In chronic cheilitis with epithelial dysplasia, focal increased vascularization of the lamina propria is observed due to increased numbers of small capillaries (as reactive changes to hypoxia), along with uneven distribution of vascular loops alternating with hypovascularized stromal areas. These features may serve as morphological indicators of an unfavorable prognosis for the inflammatory process in the lip vermilion border.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
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Conflict of Interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Compliance with Ethical Standards. The study was approved by the decision of the Ethics Committee of the Tver State Medical University dated 01/28/2025.	***Соответствие нормам этики.*** Исследование было одобрено решением этического комитета ФГБОУ ВО Тверской ГМУ Минзрава России от 28.01.2025 г.
Contribution of individual authors. S.N. Lebedev, Yu.V. Lebedeva: study design. D.V. Marku, I.S. Lebedev: literature search and analysis. O.N. Skaryakina: statistical data processing. O.N. Guskova, A.F. Solnyshkina: concept and writing of the article, editing of the article.	***Участие авторов.*** С.Н. Лебедев, Ю.В. Лебедева – дизайн исследования. Д.В. Марку, И.С. Лебедев – поиск и анализ литературы. О.Н. Скарякина – статистическая обработка данных. О.Н. Гуськова, А.Ф. Солнышкина – концепция и написание текста статьи, редактирование статьи.

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Original research | Оригинальное исследование
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Multifactorial prediction of adverse outcome of acute coronary syndrome combined with post-COVID syndrome

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Abstract

Aim – to build a multivariate model for predicting adverse outcomes of acute coronary syndrome with and without ST segment elevation in patients with post-COVID syndrome.

Material and methods. The study included 118 patients (61 men and 57 women) with acute coronary syndrome and post-COVID syndrome. All patients underwent medical history review, clinical examination, laboratory tests, coronary angiography, echocardiography, electrocardiography, and molecular genetic marker testing. The influence of each factor on the probability of developing a combined endpoint, including the total number of cardiovascular complications and fatal outcomes, was assessed using logistic regression analysis. The statistical significance of the model was determined by the χ^2 test. The sensitivity and specificity of the model were assessed using ROC analysis.

Results. The constructed multivariate regression model showed that the development of an unfavorable outcome in patients with acute coronary syndrome in combination with PCS is associated with the presence of chronic heart failure, elevated soluble fms-like tyrosine kinase-1, hypokinesis zones on echocardiography, carrier status of the *TT/AA* genotype of the genetic marker rs2285666 of the *ACE2* gene (χ^2 = 38.416, p <0.001). The sensitivity of the model is 93.5%, and the specificity is 21.8%, the accuracy is 76.6%, the area under the curve (AUC) = 0.8.

Conclusion. A multivariate regression model was constructed and tested to predict, with high accuracy, the development of an unfavorable outcome of acute coronary syndrome in combination with post-COVID syndrome.

Keywords: acute coronary syndrome, multivariate regression model, genetic markers, post-COVID syndrome.

Conflict of interest: nothing to disclose.

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Многофакторное прогнозирование неблагоприятного исхода острого коронарного синдрома в сочетании с постковидным синдромом

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Аннотация

Цель – построить многофакторную модель для прогнозирования неблагоприятного исхода острого коронарного синдрома с подъемом и без подъема сегмента ST у пациентов с постковидным синдромом.

Материал и методы. В исследование вошли 118 пациентов, из них 61 мужчина и 57 женщин с острым коронарным синдромом в сочетании с постковидным синдромом. Всем пациентам проводились сбор анамнеза, клинический осмотр, забор лабораторных анализов, коронароангиография, эхокардиография, электрокардиография, диагностика молекулярно-генетических маркеров. Оценивалось влияние каждого из факторов на вероятность развития комбинированной конечной точки, включающей суммарное количество кардиоваскулярных осложнений и летальных исходов, с помощью применения логистического регрессионного анализа. Статистическая значимость модели определялась критерием χ^2. Чувствительность и специфичность модели оценивались с помощью ROC-анализа.

Результаты. Построенная многофакторная регрессионная модель показала, что с развитием неблагоприятного исхода у пациентов с острым коронарным синдромом в сочетании с постковидным синдромом связаны наличие хронической сердечной недостаточности, наличие растворимой fms-подобной тирозинкиназы-1, зоны гипокинеза по эхокардиографии, носительство генотипа *TT/AA* генетического маркера rs2285666 гена *ACE2* (χ^2 = 38,416, p<0,001). Чувствительность модели составила 93,5%, специфичность – 21,8%, точность – 76,6%, площадь под кривой (AUC) = 0,8.

Выводы. Получена и апробирована многофакторная регрессионная модель, прогнозирующая с высокой точностью развитие неблагоприятного исхода острого коронарного синдрома в сочетании с постковидным синдромом.

Ключевые слова: острый коронарный синдром, многофакторная регрессионная модель, генетические маркеры, постковидный синдром.

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ОКС – острый коронарный синдром; ПКС – постковидный синдром; НКИ – новая коронавирусная инфекция; ЭКГ – электрокардиография; ЭхоКГ – эхокардиография; КАГ – коронароангиография; ИБС – ишемическая болезнь сердца; САД – суточное артериальное давление; ЧСС – частота сердечных сокращений; ВНП – вариант нуклеотидной последовательности.

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INTRODUCTION

According to global registries, acute coronary syndrome (ACS), including both ST-segment elevation and non-ST-segment elevation myocardial infarction, represents the leading cause of morbidity and mortality in Russia and worldwide [1]. Various prognostic risk stratification tools for adverse outcomes in ACS are currently available. The GRACE risk model is among the most widely recognized. In addition to predicting in-hospital complications of ACS, it enables assessment of long-term adverse outcomes. Furthermore, the discriminant power of the GRACE model significantly surpasses that of models based on randomized clinical trial data. However, emerging evidence highlights important limitations of the GRACE model, particularly its failure to incorporate biochemical blood markers, electrocardiographic (ECG) and echocardiographic (EchoCG) parameters, and genetic indicators being a significant shortcoming that diminishes its alignment with contemporary scientific and clinical practice standards [2]. In particular, the COVID-19 pandemic has adversely impacted the course and outcomes of cardiovascular diseases [3]. The World Health Organization has classified post-COVID syndrome (PCS) as a distinct clinical entity - a condition characterized by signs and symptoms that emerge during or following COVID-19 infection, persist for over 12 weeks, and cannot be attributed to alternative diagnoses [3]. The development and implementation of a multifactorial risk assessment model is clinically imperative, as even highly experienced practitioners often focus solely on PCS diagnosis. In contrast, a comprehensive risk stratification model incorporates numerous predictive factors and should therefore become an essential clinical tool for all physicians, enabling routine identification of patients at risk for adverse outcomes.

Thus, patients with ACS and concomitant PCS require a comprehensive prognostic model for assessing ACS-related adverse outcomes to guide targeted prevention strategies and personalized rehabilitation programs.

AIM

To build a multivariate model for predicting adverse outcomes of acute coronary syndrome with and without ST segment elevation in patients with post-COVID syndrome.

MATERIAL AND METHODS

The prospective cohort study included 118 patients (61 men, 57 women). The average age of women was 57.5±6.2 years; the average age of men was 53.7±8.3 years. The comparison group included 121 patients (62 men, 59 women) with ACS, without PCS (the history had no diagnosis of the COVID-19 infection confirmed by a PCR test from a swab or identification of A, M, G immunoglobulins (IgA, IgM, IgG) for SARS-CoV-2 by immunochemical assay.

The patients were matched by sex and age. All were emergently transported to the regional vascular center by emergency medical services. Upon admission, all patients were diagnosed with ACS. The diagnosis was established based on current clinical guidelines "Acute coronary syndrome with ECG ST segment elevation"[1] and "Acute coronary syndrome without ECG ST segment elevation"[2], approved by the Scientific Practical Council of the Ministry of Health of the Russian Federation.

Inclusion criteria: history of COVID-19 meeting the criteria of the "Post-COVID syndrome" diagnosis as per the recommendations of the Methodological recommendations "Features of long-COVID infection clinical course. Therapeutic and rehabilitation measures" [4]. According to the updated International Classification of Diseases (ICD-10), post-COVID syndrome (PCS) develops in individuals with confirmed SARS-CoV-2 infection three months after COVID-19 onset. For study participants, prior COVID-19 diagnosis was confirmed using laboratory diagnostic methods specified in the provisional clinical guidelines "Prevention, Diagnosis, and Treatment of COVID-19" (Version 18, 26.10.2023) approved by the Scientific and Practical Council of the Ministry of Health of the Russian Federation[3].

To predict the risk of adverse ACS outcomes, logistic regression analysis was employed. The logistic regression model was constructed using the following equation (1)

$$P = 1 / (1 + e^{-y}), \quad (1)$$

where P is the probability of development of the index event; e is the base of natural logarithms (Euler's number, 2.718), and y represents the standard regression equation.

The standard regression equation is presented as follows (2)

$$y = a + b1X1 + b2X2 + ... + bnXn, \quad (2)$$

where a is the constant; b are regression factors; X are initial variables.

[1] Acute coronary syndrome without ECG ST segment elevation. Clinical guidelines. 2024. Available online: https://scardio.ru/content/Guidelines/2024_09_26.pdf
[2] Acute myocardial infarction with ECG ST segment elevation. Clinical guidelines. 2024. Available online: https://russjcardiol.elpub.ru/jour/article/view/6306
[3] Provisional clinical guidelines "Prevention, Diagnosis, and Treatment of the new coronavirus infection COVID-19" (Version 18, 26.10.2023). Available online: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/064/610/original/%D0%92%D0%9C%D0%A0_COVID-19_V18.pdf

The X value was represented with quantitative or qualitative variables. The qualitative variables were taken as binary values, where 1 means the presence of the factor and 0, its absence.

A prognostic model was developed using stepwise logistic regression analysis incorporating statistically significant factors (variables).

The statistical significance of the model was assessed using the χ^2 test. With $p < 0.05$, the null hypothesis of model insignificance was rejected. A cutoff threshold of 0.5 was established for predicting the index event after model development. The model's sensitivity and specificity were evaluated through ROC analysis. Results were interpreted by constructing ROC curves with calculation of the area under the ROC curve (AUC).

The study was approved by the Local Ethics Committee of Novosibirsk State Medical University (Protocol No. 155 dated November 29, 2023) and by the Problem Commission (Protocol No. 1 "Current Issues in Prevention, Diagnosis and Treatment of Internal Diseases" dated October 25, 2023). All patients provided written informed consent to participate in the study.

RESULTS

The analysis included the following baseline variables: clinical and anamnestic parameters (sex, age, weight, obesity grade (if any), duration, localization and character of pain, presence of arterial hypertension, coronary artery disease, chronic heart failure, presence/absence of prior COVID-19 infection, disease severity, variant wave (Alpha, Delta, Omicron), treatment modality, smoking status, severity of prior cardiovascular events); instrumental parameters: electrocardiogram (ECG), Holter ECG monitoring, 24-hour blood pressure monitoring (BP), findings of coronary angiography (CAG (multi-vessel or single-vessel involvement, post-catheterization complications)), echocardiography (hypokinesis/akinesis areas, left ventricular ejection fraction (quantitative and qualitative assessment); laboratory parameters: cholesterol fractions (total cholesterol, high-density lipoproteins, low-density lipoproteins, triglycerides), endothelial dysfunction factors (Soluble fms-like tyrosine kinase-1 and anti-endothelial antibodies), biochemical markers (C-reactive protein, lactate dehydrogenase, ferritin, blood glucose, high-sensitivity troponin I); molecular-genetic markers (*ACE2* gene variant rs2285666, *ACE* gene variant rs1799752, *TMPRSS2* gene variant rs12329760).

The prognostic model was developed using stepwise logistic regression incorporating statistically significant factors (variables). Model significance was assessed using the χ^2 test, with the null hypothesis of model insignificance rejected at $p < 0.05$. A cutoff threshold of 0.5 was established for predicting the index event following model development.

Based on the Wald criterion, the most statistically significant predictors were the degree of hypokinesis and the combination of ACS with PCS (**Table 1**). These were followed by tyrosine kinase levels, presence of the ACE2 TT/AA genotype, and presence of chronic heart failure in terms of predictive strength.

Thus, the predicted probability of developing the combined endpoint encompassing the total number of cardiovascular complications and fatal outcomes was expressed by the following formula (3):

$$P = 1 / (1 + 2{,}718^{-(13{,}153 - 1{,}689 \times X1 + 0{,}039 \times X2 + 0{,}870 \times X3 + 0{,}082 \times X4 - 1{,}286 \times X5)}), \quad (3)$$

where X1 means belonging to the "ACS with PCS" group, X1 = 0 – patient with ACS without PCS, X1 = 1 – patient having ACS and PCS, X2 – soluble fms-like tyrosine kinase-1 (X2), pg/mL, X3 – belonging to the "CHF" group, X3 = 0 – patient without signs of CHF, X3 = 1 – patient with signs of CHF, X4 – hypokinesis, X5 – presence of ACE2 TT/AA gene polymorphism, X5 = 0 – patient does not have this gene, X5 = 1 – patient has this gene.

For clarity of interpretation, the final result is multiplied by 100%.

The Hosmer-Lemeshow goodness-of-fit test for this predictive model yielded $\chi^2 = 38.416$, $p = 0.0000$, indicating extremely high statistical significance.

Subsequently, a ROC curve was constructed. Based on the ROC curve analysis, the area under the ROC curve was 0.8 (**Figure 1**), indicating good model quality - an acceptable model. The model's sensitivity (proportion of correctly classified patients with adverse ACS outcomes) was 93.5%, while specificity (proportion of correctly classified patients without adverse ACS outcomes) was 21.8%. The overall accuracy for predicting complications was 76.6%. Thus, the developed model demonstrates excellent predictive capability for adverse ACS occurrence but poor performance for predicting its absence.

DISCUSSION

To date, the literature describes only a few prognostic models designed to assess ACS outcomes [5].

One of the earliest prognostic models was a scoring system proposed in 1962 [6]. It was based on calculating a prognostic index using characteristics of the acute phase of ACS. The resulting data predicted the likelihood of adverse disease progression within 28 days of symptom onset.

Predictor	B (regression factor)	MSE (mean square error)	Wald (Wald criterion, X^2)	P (significance level)	Exp (B)
ACS/PCS group (X1)	-1.689	0.48	12.362	0.0004	0.185
Soluble fms-like tyrosine kinase-1 (X2), pg/ml	0.039	0.01	8.237	0.004	1.04
Chronic heart failure (X3)	0.870	0.39	4.894	0.027	2.388
Hypokynesia (X4), damage of segments of myocardium	0.082	0.02	17.983	0.00002	1.085
Polymorphism of the *ACE 2 TT/AA* gene (X5)	-1.286	0.51	6.419	0.011	0.276

Table 1. *Main results of the analysis of binary logistic regression of the prognosis of the development of unfavorable ACS*
Таблица 1. *Основные результаты анализа бинарной логистической регрессии прогноза развития неблагоприятного ОКС*

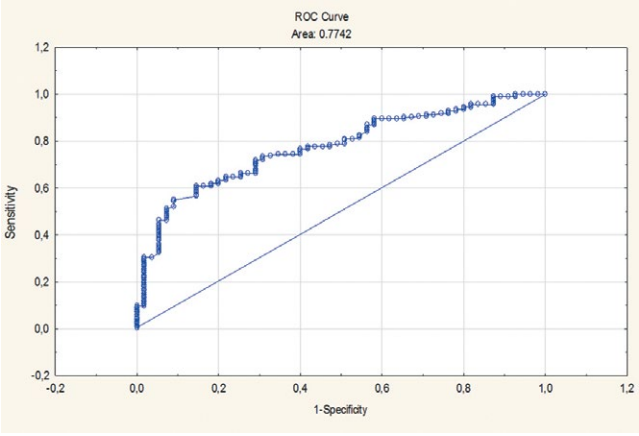

Figure 1. *ROC curve graph for predicting the development of adverse ACS in patients with PCS.*

Рисунок 1. *График ROC-кривой прогнозирования развития неблагоприятного ОКС у пациентов в сочетании с ПКС.*

Modern prognostic models include one developed through regression analysis using data from the GRACE IM registry [6, 7]. This model incorporates eight parameters identified through registry data analysis: patient age, Killip classification of heart failure, systolic blood pressure level, heart rate, creatinine level, diagnostic levels of myocardial necrosis biomarkers, ST-segment changes, and presence of at least one cardiac arrest episode [3].

The TIMI (Thrombolysis In Myocardial Infarction) risk score, developed through clinical trials, incorporates seven variables: age over 65; presence of at least three risk factors of coronary artery disease (CAD) (hypercholesterolemia, family history of CAD, diabetes mellitus, hypertension); previously documented 50%+ stenosis of the coronary artery; ST-segment deviation; at least two angina episodes within 24 hours; aspirin use within the past week; elevated serum cardiac biomarkers. TIMI predicts the 14-day risk of mortality and myocardial infarction [9] and has demonstrated high efficacy in assessing 30-day and 1-year mortality rates in ACS patients.

The PREDICT score (Predicting Risk of Death in Cardiac Disease Tool) is based on a retrospective analysis of MI/unstable angina patients that included the following parameters: age, 24-hour arterial blood pressure (BP), heart rate (HR), ECG data, signs of heart failure, serum urea level, and accounted for comorbidities [10]. This model has demonstrated prognostic efficacy in assessing 6-year mortality post-hospitalization.

The PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) risk model enables assessment of 30-day mortality risk, as well as the likelihood of primary or recurrent myocardial infarction, using the following parameters: age, heart rate, systolic blood pressure, status of ST-segment elevation, heart failure status, and serum cardiac biomarkers [11, 12].

Russian medical literature has also described several prognostic models [13-15]. These models evaluated one-year outcomes in acute coronary syndrome using the following criteria: status of diabetes mellitus in the case history, C-reactive protein level, left ventricular ejection fraction, rs1376251 SNP of the *TAS2R50* gene. The approach demonstrated 82% sensitivity for predicting adverse outcomes, and 80% sensitivity for predicting favorable outcomes.

A prognostic model exists for assessing in-hospital mortality risk in patients with acute coronary syndrome [15]. This model incorporates parameters recorded at hospital admission: urea level, Killip class, age, ST-segment elevation in lateral leads, diagnostic elevation of CK/CK-MB, systolic blood pressure level, and others. Using this model, patients can be stratified into risk groups during hospitalization, from minimal (mortality <1%) to very high (mortality >40%).

Another Russian prognostic model for assessing adverse outcomes in patients with ST-segment elevation myocardial infarction incorporates renal function parameters [8]. According to the authors, renal dysfunction represents one of the key factors determining poor prognosis in myocardial infarction.

Among the first registries established in the Russian Federation were RECORD, RECORD-2, and RECORD-3 [16-18]. These registries served as the foundation for developing a prognostic risk scale assessing adverse ACS outcomes within 6 months post-discharge. The registries enabled evaluation of treatment efficacy and identification of key patient clusters. The 7-point scoring system included hemoglobin levels below 100 g/l, presence of diabetes mellitus, age over 65, Killip class III-IV heart failure, blood pressure below 100 mmHg, ST segment elevation over 1 mm above the baseline. It reliably predicts 6-month mortality following ACS onset [16-18].

At the same time, none of the existing prognostic models for assessing adverse outcomes in ACS account for post-COVID syndrome in patients: a critical limitation that distinguishes our multifactorial regression model.

CONCLUSION

We have developed a multifactorial predictive model for assessing the risk of adverse outcomes in ACS patients (both with and without ST segment elevation) with post-COVID syndrome. The inclusion of the post-COVID syndrome status as a variable significantly differentiates this model from existing risk scores and previously developed prognostic systems.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Compliance with Ethical Standards. The study was approved by the local ethics committee of the Novosibirsk State Medical University (protocol No. 155 dated November 29, 2023), and also approved at a meeting of the problem commission (protocol No. 1 "Current issues of prevention, diagnosis and treatment of internal diseases" dated October 25, 2023).	***Соответствие нормам этики.*** Исследование одобрено локальным этическим комитетом ФГБОУ ВО НГМУ Минздрава России (протокол №155 от 29.11.2023 г.), а также одобрено на заседании проблемной комиссии (протокол №1 «Актуальные вопросы профилактики, диагностики и лечения внутренних болезней» от 25.10.2023 г.).

Contribution of individual authors.

Shpagina L.A.: development of the study concept, text editing. Kozik V.A., Shpagin I.S.: collection and processing of scientific material, writing of the text.

The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.

Участие авторов.

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An increase of the left atrium sphericity index can serve as a marker of paroxysmal atrial fibrillation in patients with hypertension

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Abstract

Aim – to study the possibility of using the left atrium sphericity index (SI), calculated by echocardiography (EchoCG), to identify patients with hypertension with paroxysmal atrial fibrillation (AF).

Material and methods. The study included 298 patients with hypertension, of whom 77 (25.8%) showed paroxysmal AF during 24-hour electrocardiogram monitoring. The control group included 58 patients without cardiovascular diseases. The left atrium volume was determined and the maximum left atrium length was measured. The SI was calculated as the ratio of the left atrium volume to the volume of a sphere whose diameter is equal to the maximum left atrium length.

Results. The average values of SI (presented as the median and 95% confidence interval) increased from the control group to the group of patients with hypertension without AF and to the group of patients with hypertension and AF: 0.68 (0.64–0.72), 0.71 (0.69–0.72) and 0.92 (0.91–0.94), p <0.0001. Multiple linear regression analysis showed that 1-year increase of the age is associated with increase in SI by 0.0015 units, the presence of obesity is accompanied by an increase of SI by 0.0241 units, and the presence of paroxysmal AF leads to an increase in SI by 0.2031 units. All patients included in the study were randomly divided into derivation and validation cohorts (238 and 118 patients). In the derivation cohort, the AUC for SI, as a predictor of AF, was 0.955 (0.920–0.977), and cut-off point was 0.82. In the validation cohort, the 'SI>0.82' criterion, a sign of AF, demonstrated sensitivity of 100 (86.8–100.0) % and specificity of 93.5 (86.3–97.6) %.

Conclusion. The SI calculated by EchoCG has a high discriminating ability in relation to paroxysmal AF in patients with hypertension.

Keywords: arterial hypertension, atrial fibrillation, echocardiography, left atrium, left atrium sphericity index.

Conflict of interest: nothing to disclose.

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Увеличение индекса сферичности левого предсердия может служить маркером пароксизмальной фибрилляции предсердий у больных артериальной гипертензией

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Аннотация

Цель – изучить возможность использования индекса сферичности (ИС) левого предсердия, рассчитанного по данным эхокардиографии (ЭхоКГ), для выявления больных артериальной гипертензией (АГ) с пароксизмальной фибрилляцией предсердий (ФП).

Материал и методы. В исследование включены 298 больных АГ, из которых у 77 (25,8%) при суточном мониторировании электрокардиограммы была выявлена пароксизмальная ФП. Контрольную группу составили 58 пациентов без заболеваний сердечно-сосудистой системы. При ЭхоКГ определялся объем левого предсердия и измерялась его максимальная длина. ИС рассчитывался как отношение объема левого предсердия к объему сферы, диаметр которой равен максимальной длине левого предсердия.

Результаты. Средние значения ИС (представлены в виде медианы и 95% доверительного интервала) возрастали от контрольной группы к группе больных АГ без ФП и далее к группе больных АГ с ФП: 0,68 (0,64–0,72), 0,71 (0,69–0,72) и 0,92 (0,91–0,94), p<0,0001. Анализ множественной линейной регрессии показал, что увеличение возраста пациента

на 1 год ассоциируется с возрастанием ИС на 0,0015 единицы, наличие ожирение сопровождается возрастанием ИС на 0,0241 единицы, а наличие пароксизмальной ФП ведет к возрастанию ИС на 0,2031 единицы. Для изучения дискриминирующей способности ИС в отношении ФП все включенные в исследование пациенты были случайным образом разделены на «обучающую» и «экзаменующую» когорты (238 и 118 пациентов). На «обучающей» когорте площадь под кривой ошибок для ИС, как предиктора ФП, оказалась равна 0,955 (0,920–0,977), а отрезная точка – 0,82. На «экзаменующей» когорте критерий «ИС >0,82», как признак пароксизмальной ФП, продемонстрировал чувствительность 100 (86,8–100,0) % и специфичность 93,5 (86,3–97,6) %.

Заключение. ИС, рассчитанный по данным ЭхоКГ, обладает высокой дискриминирующей способностью в отношении пароксизмальной ФП у больных АГ.

Ключевые слова: артериальная гипертония, фибрилляция предсердий, эхокардиография, левое предсердие, индекс сферичности левого предсердия.

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АГ – артериальная гипертензия; ИММЛЖ – индекс массы миокарда левого желудочка; ИОЛП – индекс объема левого предсердия; ИС – индекс сферичности; ЛП – левое предсердие; МДЛП – механическая дисперсия левого предсердия; ОЛП – объем левого предсердия; ЭхоКГ – эхокардиография; AUC – площадь под кривой; E/e' – отношение скорости трансмитрального кровотока в раннюю фазу диастолического наполнения к скорости смещения кольца митрального клапана.

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INTRODUCTION

Early identification of paroxysmal atrial fibrillation (AF) is crucial for prevention of thromboembolic complications, facilitating timely prescription of anticoagulant treatment to persons with risk factors of cerebral stroke [1, 2]. In the opinion of European experts, predictors of AF may include signs of atrial cardiomyopathy, or a combination of structural, functional and electrophysiological changes of atrial myocardia capable of bringing about the clinically significant symptoms, specifically, atrial fibrillation [3, 4].

One of the early pre-clinical signs of atrial cardiomyopathy is the change of shale of the left atrium, from the relatively elongated (ellipsoid) to globe-shaped (spherical). The sphericity of the left atrium allows evaluation of the Sphericity Index (SI), i.e. the ratio of the actual volume of the left atrium to the volume of the sphere whose diameter is equal to that of the maximum diameter of the left atrium. In their study, S. Nakamori et al. [5] showed that SI over 0.84 might serve as a predictor of late recurrent AF after radio-frequency isolation of pulmonary veins (sensitivity 88%, specificity 59%).

To calculate the SI, magnetic resonance imaging data is used, however, it can be calculated using the transthoracic echocardiography. According to literature data, this approach has not been used before, making a study of its prognostic value especially important.

AIM

To study the possibility of using the left atrium sphericity index, calculated by echocardiography, to identify patients with hypertension with paroxysmal atrial fibrillation.

MATERIAL AND METHODS

Between 01.07.2020 and 30.06.2023, 298 patients with previously diagnosed arterial hypertension were consecutively enrolled in the study. All participants underwent evaluation for palpitations, dyspnea, or chest pain. Exclusion criteria included: confirmed or newly detected coronary artery disease, persistent/permanent atrial fibrillation (AF), valvular pathology, or left ventricular systolic dysfunction (ejection fraction <50%). On 24-hour ECG monitoring, paroxysmal AF was diagnosed in 77 patients (25.8%), with arrhythmia episodes lasting ≥30 seconds serving as the diagnostic criterion.

The control group comprised 58 patients with no prior cardiovascular disease (CVD) diagnosis and no ECG or echocardiographic evidence of CVD. While rhythm monitoring to exclude paroxysmal AF was not performed, patients with historical episodes of palpitations were excluded.

Echocardiography was performed using a Vivid S70 system (GE, USA). Left ventricular (LV) structural-functional assessment included LV myocardial mass index (LVMI), E/e' ratio (early mitral inflow velocity to mitral annular tissue Doppler velocity), reflecting LV filling pressure. Left atrial volume (LAV) was measured by disk summation in apical 4- and 2-chamber views; in the same positions, the length of the left atrium was measured. The greater of the two values (D) was used for sphericity index calculation: $SI = LAV/(\pi D/6)$, where $\pi D/6$ represents the volume of the sphere with diameter D.

Two-dimensional echocardiography with speckle-tracking and subsequent analysis was performed on ultrasonic images with at least 50 frames per second. The curves of deformation of the left atrium were re-created by manual tracking of the endocardial border in the apical 4-chamber view in the end of the diastole according to the R-R algorithm (deformation level zero was aligned with R wave). The global longitudinal deformation of the left atrium (reservoir strain) was calculated as the average of peak values of longitudinal deformation in the six segments of the left atrium [6, 7]. Mechanical dispersion of the left atrium (MDLA) was calculated as percentage ratio of the standard deviation of reservoir strain timing in the longitudinal deformation of the myocardium in segments of the left atrium to cardiac cycle duration [8, 9].

The statistical analysis was performed in the MedCalc® Statistical Software suite, version 20.218 (MedCalc Software

Parameter	Group 1 (n = 58)	Group 2 (n = 221)	Group 3 (n = 77)	p
Age, years	50.5 (45.0–54.0)2. 3	61.0 (60.0–63.0)1. 3	66.0 (64.0–67.0)1. 2	<0.0001
Women, n (%)	32 (55.2)3	147 (66.5)	58 (75.3)1	0.0488
Obesity, n (%)	8 (13.8)2. 3	115 (52.0)1	42 (54.5)1	<0.0001
LVMI, g/m2	86.5 (82.1–90.9)2. 3	117.0 (116.0–120.0)1	120.0 (117.0–126.1)1	<0.0001
E/e'	8.0 (7.1–8.6)2. 3	10.0 (9.6–10.5)1	10.2 (9.5–10.6)1	<0.0001
LAVI, ml/m2	25.0 (24.0–27.0)2. 3	29.0 (27.3 30.0)1. 3	37.0 (34.2–40.0)1. 2	<0.0001
LA strain, %	32.0 (28.0–33.0)2. 3	22.0 (21.0–22.4)1. 3	20.0 (19.0–20.7)1. 2	<0.0001
MDLA, %	0.89 (0.72–1.01)2. 3	1.00 (0.95–1.14)1. 3	3.02 (2.87–3.28)1. 2	<0.0001
SI	0.68 (0.64–0.72)2. 3	0.71 (0.69–0.72)1. 3	0.92 (0.91–0.94)1. 2	<0.0001

Notes: p – statistical significance of the grouping factor's effect on the variable; the upper index means the number of the group, in which the post-hoc analysis revealed statistically significant difference in values (p <0.05). LVMI – left ventricle myocardial mass index, E/e' ratio – the ratio of early mitral inflow velocity (E) to mitral annular tissue Doppler velocity (e'), LAVI – left atrium volume index, LA – left atrium, MDLA – mechanical dispersion of the left atrium, SI – sphericity index.

Table 1. *Characteristics of the examined patients*

Таблица 1. *Характеристика обследованных пациентов*

Ltd, Ostend, Belgium). As most numerical variables deviated from normal distribution, data are presented as medians with 95% confidence intervals (95% CI). The Kruskal-Wallis test assessed groupwise differences, with post-hoc Conover analysis for pairwise comparisons. Median differences are reported with 95% CIs.

Chi-square test assessed the impact of grouping factor on the distribution of categorical variables, Bonferroni-adjusted Chi-square test for post-hoc comparison of groupwise comparisons. Multiple linear regression involving consecutive exclusion of independent variables is used to identify the factors providing independent influence on the structural and functional parameters of the left atrium. The predictive utility of left atrial structural-functional parameters for paroxysmal atrial fibrillation (AF) and hypertension-mediated left ventricular changes was evaluated using receiver operating characteristic (ROC) curve analysis in a training cohort (n=238). Areas under the curve (AUC) and inter-curve differences are reported with 95% CIs. Predictive performance was validated in a testing cohort (n=118). Statistical significance was set at p<0.05 for all analyses with a null hypothesis probability threshold <5%.

RESULTS

The results of examination of 58 patients of the control group (Group 1), 221 patients with hypertension without paroxysmal AF (Group 2) and 77 patients with hypertension and paroxysmal AF (Group 3) are shown in Table 1.

Regardless of atrial fibrillation (AF) status, hypertensive patients were older than controls, had a higher proportion of women and individuals with obesity, and showed significantly higher mean left ventricular mass index (LVMI) and E/e' ratios. No statistically significant differences in left ventricular status were observed between hypertensive patients with and without AF.

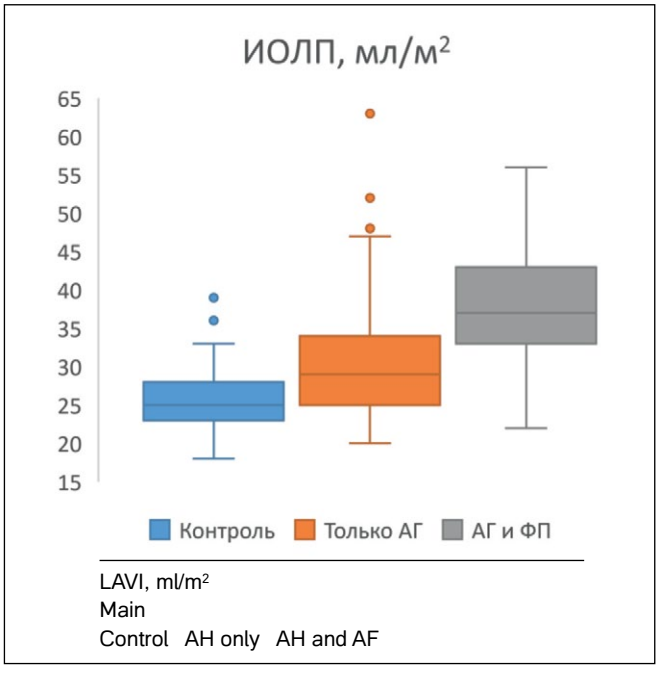

Figure 1. *Left atrium volume index (LAVI) in patients without cardiovascular disease (Control) and patients with arterial hypertension without rhythm disturbances (AH only) and with paroxysmal atrial fibrillation (AH+AF).*

Рисунок 1. *Индекс объема левого предсердия (ИОЛП) у пациентов без заболевания сердечно-сосудистой системы (Контроль) и больных артериальной гипертензией без нарушений ритма (Только АГ) и с пароксизмальной фибрилляцией предсердия (АГ и ФП).*

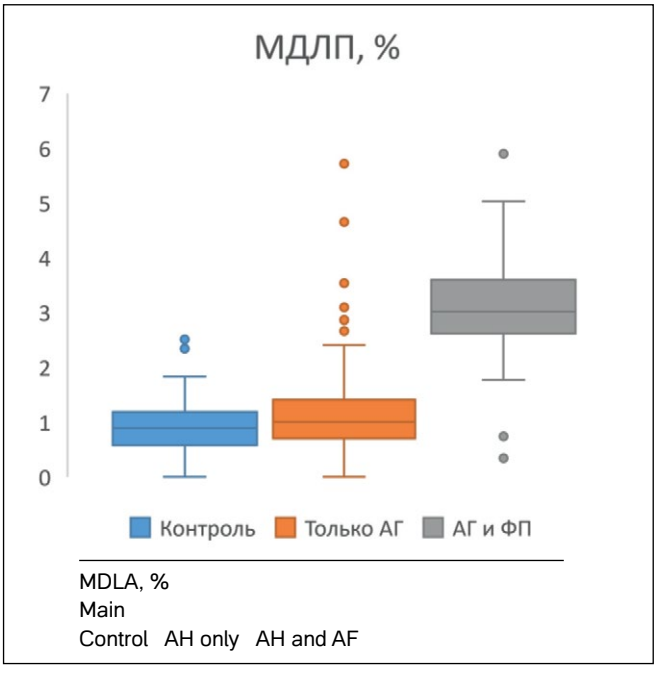

Figure 2. *Mechanical dispersion of the left atrium (MDLA) in patients without cardiovascular disease (Control) and patients with arterial hypertension without rhythm disturbances (AH only) and with paroxysmal atrial fibrillation (AH+AF).*

Рисунок 2. *Механическая дисперсия левого предсердия (МДЛП) у пациентов без заболевания сердечно-сосудистой системы (Контроль) и больных артериальной гипертензией без нарушений ритма (Только АГ) и с пароксизмальной фибрилляцией предсердия (АГ и ФП).*

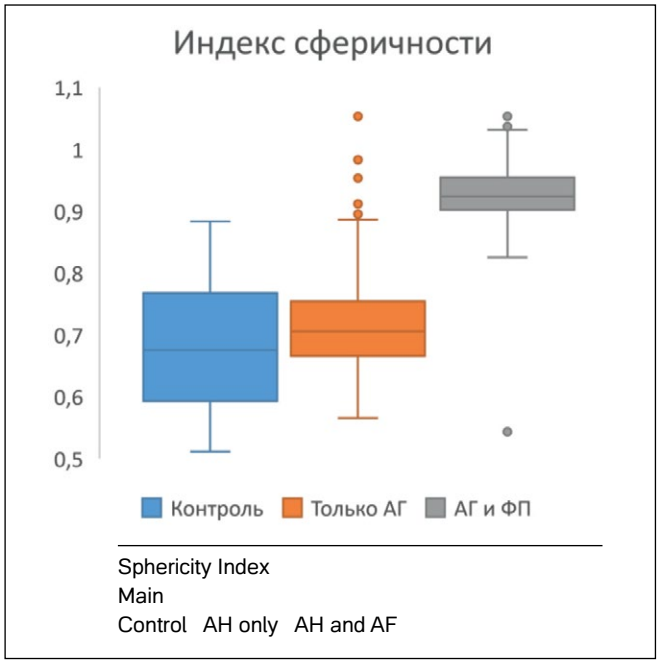

Figure 3. *Left atrium sphericity index in patients without cardiovascular disease (Control) and patients with arterial hypertension without rhythm disturbances (AH only) and with paroxysmal atrial fibrillation (AH+AF).*

Рисунок 3. *Индекс сферичности левого предсердия у пациентов без заболевания сердечно-сосудистой системы (Контроль) и больных артериальной гипертензией без нарушений ритма (Только АГ) и с пароксизмальной фибрилляцией предсердия (АГ и ФП).*

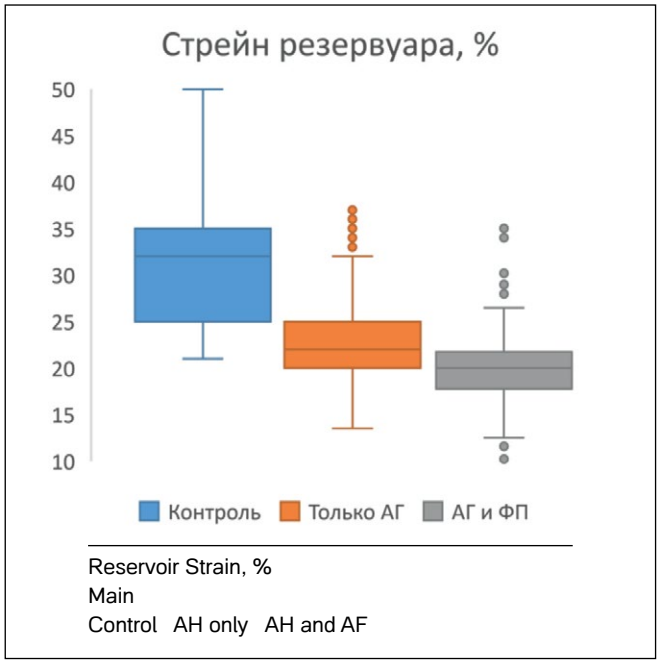

Figure 4. *Strain of the left atrium in the reservoir phase in patients without cardiovascular disease (Control) and patients with arterial hypertension without rhythm disturbances (AH only) and with paroxysmal atrial fibrillation (AH+AF).*

Рисунок 4. *Стрейн левого предсердия в фазу резервуара у пациентов без заболевания сердечно-сосудистой системы (Контроль) и больных артериальной гипертензией без нарушений ритма (Только АГ) и с пароксизмальной фибрилляцией предсердия (АГ и ФП).*

The parameters of the left atrium were statistically different in all the three groups, but the groupwise differences were manifested to various extent. Thus, the difference in the median left atrium volume index (LAVI) between Group 1 and Group 2 was twice as low as that between Group 2 and Group 3: 4.0 (2.0–5.6) and 8.0 (6.0–9.6) ml/m2. The difference in the median mechanical dispersion of the left atrium (MDLA) between Group 1 and Group 2 was by one order of magnitude less than between Group 2 and Group 3: 0.18 (0.02–0.33) and 1.99 (1.80–2.18) percentage points. In the same way, the similar differences of SI medians were varied: 0.04 (0.01–0.06) and 0.22 (0.21–0.24). The reservoir strain in Group 2 was lower, on average, than in Group 1, and in Group 3, lower than in Group 2, at the same time, the difference between Group 1 and Group 2 was 2.5 times lower than the difference between Group 2 and Group 3: 7.0 (9.0–5.0) and 2.9 (4.0–2.0) percentage points.

Dependent variable	Independent variable					Constant
	Age, years	Sex	Obesity	AH	AF	
Strain, %	-0,2018	–	-2,1290	-4,5478	-2,0624	41,254
LAVI, ml/m2	0,1636	–	–	3,0849	6,6060	17,309
MDLA, %	0,0160	–	–	–	1,8193	0,1893
SI	0,0015	–	0,0241	–	0,2031	0,6099

Notes: LAVI – left atrium volume index, MDLA – mechanical dispersion of left atrium, SI – sphericity index, AH – arterial hypertension, AF – atrial fibrillation.

Table 2. *Factors in multiple linear regression equations reflecting the dependence of the characteristics of the left atrium on the clinical characteristics of the patient*

Таблица 2. *Коэффициенты в уравнениях множественной линейной регрессии, отражающих зависимость характеристик левого предсердия от клинических особенностей пациента*

Thus, paroxysmal AF affects LAVI, MDLA and SI in a stronger way than hypertension-mediated structural and functional changes of the left ventricle; the condition of the left ventricle, not the AF, affects the reservoir strain in a stronger way (Fig. 1–4). The same conclusions follow the results of multivariate linear regression that studies the relation between the parameters of the left atrium and the patient's age and sex, obesity, hypertension and paroxysmal AF status (Table 2).

It follows from the table that the patient's age has an independent statistically significant positively manifested effect on all studied parameters of the left atrium. With every decade of life, the reservoir strain decreases by 2 percentage points (on average), the LAVI increases by 1.6 ml/m2, MDLA, by 0.16 percentage points, and the SI by 0.015 units. The patient's sex demonstrated no independent effect on the parameters of the left atrium, and was not included in any of the created models. The obesity status has no significant effect on the LAVI and MDLA, but is associated with decrease of the reservoir strain and increase of sphericity index. Atrial fibrillation affects all studies parameters of the left atrium, and the arterial hypertension, only on the reservoir strain and left atrium volume index. It is to be noted that arterial hypertension affects the reservoir strain more than does the atrial fibrillation, while the latter has a more pronounced effect on the volume index.

To study the possibilities of using the parameters of the left atrium as predictors of paroxysmal atrial fibrillation, all the patients included in the study were randomly divided into the training and testing cohorts by the factor of 2:1 (238 and 118 patients). The training cohort included 39 (16.4%)

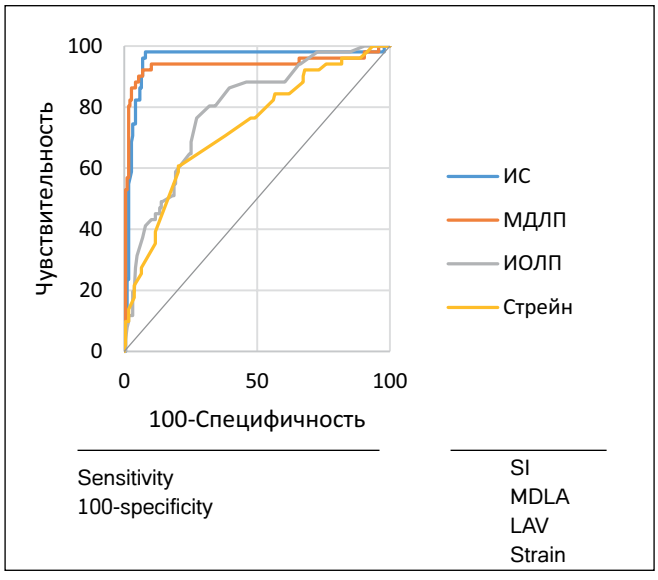

Figure 5. *Receiver operating characteristic curves for the sphericity index (SI), left atrium mechanical dispersion (LAMD), left atrium volume index (LAVI), and reservoir strain as predictors of atrial fibrillation (derivation cohort).*

Рисунок 5. *Кривые ошибок для индекса сферичности (ИС), механической дисперсии левого предсердия (МДЛП), индекса объема левого предсердия (ИОЛП) и стрейна резервуара как предикторов фибрилляции предсердий («обучающая» когорта).*

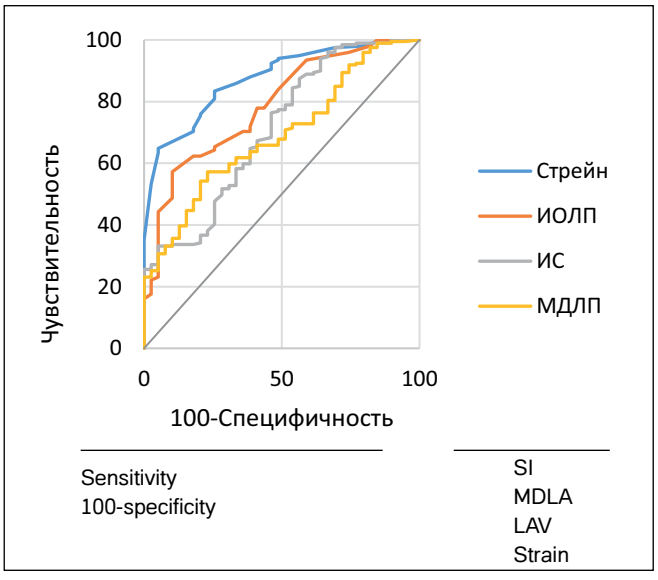

Figure 6. *Receiver operating characteristic curves for the sphericity index (SI), left atrium mechanical dispersion (LAMD), left atrium volume Index (LAVI), and reservoir strain as predictors of hypertension (validation cohorts).*

Рисунок 6. *Кривые ошибок для индекса сферичности (ИС), механической дисперсии левого предсердия (МДЛП), индекса объема левого предсердия (ИОЛП) и стрейна резервуара как предикторов артериальной гипертензии («экзаменующая» когорта).*

patients of the control group, 148 (62.2%) patients with hypertension but without AF, and 51 (21.4%) patients with arterial hypertension and paroxysmal AF. For the testing cohort, the respective numbers were 19 (16.1%), 73 (61.9%) and 26 (22.0%) patients.

The receiver operating curves obtained on the training cohort for the parameters of the left atrium as predictors of paroxysmal AF are shown in Fig. 5.

The areas under curves (AUC) for SI and MDLA were similar, and were significantly more than the AUC for the LAVI and reservoir strain (Table 2). The paroxysmal AF prediction criteria obtained on the training cohort for the SI and MDLA showed a high discriminating performance in the testing cohort (Table 3). At the same time, the discriminating performance of LAVI and reservoir strain with respect to paroxysmal AF was rather low.

The receiver operating curves obtained on the testing cohort for the parameters of the left atrium as hypertension predictors, or hypertension-mediated changes in the structural and functional condition of the left ventricle, are shown in Fig. 6. In this case, the greatest discriminating performance was found in the reservoir strain, and the lowest, in the MDLA (Table 4).

Thus, the SI and MDLA demonstrated considerably high discrimination performance with respect to paroxysmal atrial fibrillation, and low performance with respect to arterial hypertension; therefore, these indicators may be used to identify individuals with high probability of non-diagnosed atrial fibrillation among persons with arterial hypertension and persons without cardiovascular pathologies.

DISCUSSION

This study investigated the utility of echocardiography-derived sphericity index (SI) for detecting paroxysmal atrial fibrillation (AF) in hypertensive patients. The rationale stemmed from prior evidence demonstrating that increased SI measured by computed tomography (CT) or magnetic resonance imaging (MRI) correlates with higher risks of late AF recurrence after ablative pulmonary vein isolation (PVI) [5, 10, 11].

The discriminative performance of SI with respect to AF status in hypertensive patients was compared with the discriminating performance of another three indicators of remodeling of the left atrium: volume index, reservoir strain, and mechanical dispersion. The discriminative performance

Variable	Training cohort (n = 238)		Testing cohort (n = 118)			
	AUC (95% CI)	Criterion	Se	Sp	+LR	-LR
SI, units	0.955 (0.920–0.977)	>0.82	100.0	93.5	15.33	0.00
MDLA, %	0.937 (0.899–0.965)	>1.91	92.3	85.9	6.53	0.090
LAVI, ml/m2	0.791 (0.734–0.841)	>32.0	76.9	71.7	2.72	0.32
Strain, %	0.732 (0.671–0.787)	≤20.3	61.5	80.4	3.15	0.48

Note: AUC – area under the curve, Se – sensitivity, Sp – specificity, +LR – positive likelihood ratio, -LR – negative likelihood ratio, CI – confidence interval, SI – sphericity index, MDLA – mechanical dispersion of the left atrium, LAVI – left atrium volume index.

Table 3. *Characteristics of the structural and functional state of the left atrium as predictors of paroxysmal atrial fibrillation*

Таблица 3. *Характеристики показателей структурно-функционального состояния левого предсердия как предикторов пароксизмальной фибрилляции предсердий*

Variable	Training cohort (n = 238)		Testing cohort (n = 118)			
	AUC (95% CI)	Criterion	Se	Sp	+LR	-LR
SI, units	0.875 (0.826–0.914)	≤22.5	59.6	84.2	3.77	0.48
MDLA, %	0.787 (0.730–0.837)	>29	53.5	89.5	5.09	0.52
LAVI, ml/m^2	0.709 (0.647–0.766)	>0.65	82.8	42.1	1.43	0.41
Strain, %	0.690 (0.627–0.748)	>1.05	63.6	52.6	1.34	0.69

Note: AUC – area under the curve, Se – sensitivity, Sp – specificity, +LR – positive likelihood ratio, -LR – negative likelihood ratio, CI – confidence interval, SI – sphericity index, MDLA – mechanical dispersion of the left atrium, LAVI – left atrium volume index.

Table 4. *Characteristics of indicators of the structural and functional state of the left atrium as predictors of arterial hypertension*

Таблица 4. *Характеристики показателей структурно-функционального состояния левого предсердия как предикторов артериальной гипертензии*

of SI was comparable with that of the MDLA (AUC = 0.955 and 0.937) and was significantly higher than the LAVI and reservoir strain properties (AUC = 0.791 and 0.732). The reason for such manifested differences is that the values of volume index and reservoir strain depend not only on paroxysmal AF, but hypertension-mediated structural and functional changes of the left ventricle. Thus, following the multivariate linear regression analysis, the atrial fibrillation is associated with an increase of volume index by approx. 6.6 ml/m2 and a decrease of reservoir strain by 2.1 percentage points; the hypertensive status is associated with an increase of volume index by 3.1 ml/m^2 and a decrease of the reservoir strain by 4.5 percentage points. The hypertensive status of patients had no statistically significant effect on sphericity index and mechanical dispersion of left atrium, while the atrial fibrillation results in an increase of SI by 0.2 units and an increase of mechanical dispersion by 1.8 percentage points. Thus, SI and MDLA reflect the specific features of remodeling of the left atrium related to atrial fibrillation, whereas the volume index and reservoir strain do not demonstrate such specificity.

The findings of this study find acceptable explanation within the concept of atrial cardiomyopathy, or a combination of structural, functional and electrophysiological changes of the atrial myocardia of different origin [3]. The reasons for the development of atrial cardiomyopathy might lie in the increased load on the atria in the event of disruption of the diastolic function of the ventricles or in the structural heart defects, persistent tachy-arrhythmias, and some extracardiac factors including old age, general and epicardial fat, diabetes mellitus, and genetic predisposition. The most prevalent clinical manifestations of atrial cardiomyopathy are atrial fibrillation [4] and, probably, non-AF-mediated left atrial appendage thrombus [12].

Depending on the prevalent histological changes in the myocardium, four classes of atrial cardiomyopathy are identified. Class I is characterized with changes in the cardiac myocytes (hypertrophy and myocytolysis), Class II, mainly with fibrous changes, Class III, with combined changes in the cardiac myocytes and fibrosis, Class IV, with extracellular infiltration with amyloid (IVa), fat (IVf) or inflammatory cells (IVi) without manifested accumulation of collagen fibers. Classification boundaries remain arbitrary, as cardiomyopathy progression alters histological patterns. Moreover, regional heterogeneity in atrial myocardial histology may simultaneously exhibit features of distinct cardiomyopathy classes [3].

Arterial hypertension leads to left ventricle hypertrophy and disorder of its diastolic function, increasing the strain on the left atrium and promoting development of Class I cardiomyopathy. The findings of this study indicate that a manifestation of such cardiomyopathy is the increase of the volume index and the decrease of the reservoir strain. The morphologic substrate of atrial fibrillation is myocardial fibrosis, i.e. Class II atrial cardiomyopathy. Some studies show that mechanical dispersion of the left atrium allows a more accurate evaluation of the degree of atrial fibrosis than the results of magnetic resonance imaging [13, 14]. We believe that this accounts for the high discriminating performance of MDLA with respect to atrial fibrillation. Sphericity index (SI) demonstrated similarly high discrimination performance in this study, which allows regarding the 'spherification' of the left atrium as a sign of atrial fibrosis.

Unlike mechanical dispersion of the left atrium, a parameter whose calculation requires speckle-tracking echocardiography, the sphericity index is calculated using the findings of regular echo-CG. This facilitates the use of SI in broad clinical practice to identify hypertensive patients with high probability of non-diagnosed paroxysmal AF.

Limitations of this study

In this study, Sphericity Index demonstrated high discrimitating performance with respect to paroxysmal AF in hypertensive patients with left atrial hypertrophy. The possibility of using this parameter to identify isolated AF, as well as AF in individuals with left ventricle systolic dysfunction remains an open question requiring further research [15]. The threshold value of SI, the exceeding of which indicates high probability of paroxysmal AF, needs to be clarified as well. This is all the more important since the SI values depend on the method of measurement of the left atrium volume. The 'area-length' method usually provides higher values of the left atrium volume than the disk method; therefore, the SI values calculated using the 'area-length' method are generally higher than those calculated using the disk method.

CONCLUSION

Sphericity Index calculated using echo-CG data manifests high discriminating performance with respect to paroxysmal AF in hypertensive patients. The sensitivity of the parameter 'SI>0.82' as a predictor of paroxysmal AF reaches 100% (95% CI 86.8–100.0), and its specificity is 93.5% (65% CI 86.3–97.6).

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Compliance with Ethical Standards. The study was approved by the local Ethics Committee of the Tver State Medical University of the Ministry of Health of the Russian Federation, Protocol No. 7 dated 04.20.2019; all patients signed a voluntary informed consent to use the results of their research for scientific purposes.	***Соответствие нормам этики.*** Исследование одобрено локальным этическим комитетом ФГБОУ ВО Тверской ГМУ Минздрава России, протокол №7 от 20.04.2019 г. Все пациенты подписали добровольное информированное согласие на использование результатов выполненных им исследований в научных целях.
Contribution of individual authors. V.V. Mazur: study design, obtaining and interpreting of results. O.V. Nilova: collection of data, interpreting of results and writing of the article. T.O. Nikolaeva: data collection and analysis, writing of the article. N.D. Bazhenov: compilation of results and making of significant edits of the manuscript in order to increase the scientific value of the article. E.S. Mazur: research concept, data analysis and interpretation of results, making of significant edits of the manuscript in order to increase the scientific value of the article. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** В.В. Мазур – дизайн исследования, получение и интерпретация результатов. О.В. Нилова – получение данных, интерпретация результатов и написание статьи. Т.О. Николаева – получение, анализ данных и написание статьи. Н.Д. Баженов – получение результатов и внесение в рукопись существенной правки с целью повышения научной ценности статьи. Е.С. Мазур – концепция исследования, анализ данных и интерпретация результатов, внесение в рукопись существенной важной правки с целью повышения научной ценности статьи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Prediction of adverse outcomes in the long-term follow-up period in patients with chronic heart failure who have suffered a myocardial infarction

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Abstract

Aim – to determine the prognostic significance of global longitudinal strain of the left ventricle (GLS) and soluble stimulating growth factor (sST2) in patients with chronic heart failure (CHF) after myocardial infarction (MI) in the annual follow-up period.

Material and methods. The study included 96 patients with CHF who were hospitalized with acute MI. All subjects underwent speckle-tracking echocardiography and determination of concentrations of sST2, vascular endothelial growth factor (VEGF), N-terminal pro-brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP). After 12 months patients were assessed for cases of stroke, recurrent myocardial infarction, hospitalization for unstable angina or decompensation of CHF, and cardiovascular death, forming a combined endpoint (CEP).

Results. The development of CEP was registered in 44 (45.8%) patients with initially lower left ventricular ejection fraction and GLS, higher left ventricular myocardial mass index, index of impaired local contractility, basal diameter of the excretory tract, as well as a higher score on the Syntax scale and concentrations of CRP, NT-proBNP and sST2. During the ROC-analysis for the development of CEP, optimal thresholds for sST2 and NT proBNP were determined, which were 36.1 ng/ml and 427 pg/ml, respectively. The multifactorial analysis made it possible to develop a mathematical model for predicting adverse outcomes within 12 months after MI, which included such indicators as GLS – odds ratio (OR) 0.51 (0.39; 0.72), the number of points on the Syntax scale – OR 3.05 (2.2; 6.8), concentrations of NTproBNP – OR 2.9 (1.45; 5.1) and sST2 – OR 3.3 (1.65; 7.51).

Conclusion. The developed prognostic model includes factors reflecting various links in the pathogenesis of CHF, which provides an integrated approach to assessing the risks of recurrent cardiovascular events after MI.

Keywords: chronic heart failure, myocardial infarction, global longitudinal strain (GLS), soluble stimulating growth factor (sST2), prognostic model.

Conflict of interest: nothing to disclose.

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Прогнозирование неблагоприятных исходов в отдаленном периоде наблюдения у пациентов с хронической сердечной недостаточностью, перенесших инфаркт миокарда

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Аннотация

Цель – определить прогностическую значимость глобальной продольной деформации левого желудочка (GLS) и растворимого рецептора стимулирующего фактора роста (sST2) у пациентов с хронической сердечной недостаточностью (ХСН), перенесших инфаркт миокарда (ИМ), в годовом периоде наблюдения.

Материал и методы. В исследование включено 96 пациентов с ХСН, госпитализированных с острым ИМ. Всем обследуемым проведена спекл-трекинг эхокардиография и определение концентраций sST2, фактора роста эндотелия сосудов (VEGF), N-концевого предшественника мозгового натрийуретического пептида (NT-proBNP) и С-реактивного белка (СРБ). Через 12 месяцев оценены случаи развития острого нарушения мозгового кровообращения, повторного ИМ, госпитализаций по поводу нестабильной стенокардии или декомпенсации ХСН и сердечно-сосудистой смерти, составивших комбинированную конечную точку (ККТ).

Результаты. Развитие ККТ зарегистрировано у 44 (45,8%) пациентов, имевших исходно более низкие показатели фракции выброса левого желудочка (ЛЖ) и GLS, более высокие показатели индекса массы миокарда ЛЖ, индекса нарушения локальной сократимости, базального диаметра выводного тракта, а также более высокий балл по шкале Syntax и концентраций СРБ, NT-proBNP и sST2. При проведении ROC-анализа в отношении развития комбинированной конечной точки были определены оптимальные пороговые значения для sST2 и NTproBNP, составивших 36,1 нг/мл и 427 пг/мл соответственно. Проведенный многофакторный анализ позволил разработать математическую модель прогнозирования неблагоприятных исходов в течение 12 месяцев после перенесенного ИМ, в которую вошли такие показатели, как величина GLS – отношение рисков (ОР) 0,51 (0,39; 0,72), количество баллов по шкале Syntax – ОР 3,05 (2,2; 6,8), концентрации NTproBNP – 2,9 (1,45; 5,1) и sST2 – ОР 3,3 (1,65; 7,51).
Выводы. Разработанная прогностическая модель включает факторы, отражающие различные звенья патогенеза ХСН, что обеспечивает комплексный подход к оценке рисков развития повторных сердечно-сосудистых событий после перенесенного ИМ.
Ключевые слова: хроническая сердечная недостаточность, инфаркт миокарда, глобальная продольная сократимость, растворимый рецептор стимулирующего фактора роста, прогностическая модель.
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Список сокращений
ХСН – хроническая сердечная недостаточность; СН – сердечная недостаточность; ФВ ЛЖ – фракция выброса левого желудочка; ИБС – ишемическая болезнь сердца; ИМ – инфаркт миокарда; АГ – артериальная гипертензия; БМ – биологический маркер; КАГ – коронароангиография; СД – сахарный диабет; ФП – фибрилляция предсердий; АКШ – аортокоронарное шунтирование; ББА – бета-адреноблокатор; иАПФ – ингибитор ангиотензинпревращающего фермента; АМР – агонист минералкортикоидных рецепторов; БКК – блокатор кальциевых каналов; ЛКА – левая коронарная артерия; ПНА – передняя нисходящая артерия; ОА – огибающая артерия; ПКА – правая коронарная артерия; ЧКВ – чрескожное коронарное вмешательство; ОНМК – острое нарушение мозгового кровообращения; ПИКС – постинфарктный кардиосклероз; ДААТ – двойная антиагрегантная терапия; ЛДФ – лазерная допплеровская флуометрия; ККТ – комбинированная конечная точка; НС – нестабильная стенокардия; ОШ – отношение шансов; ДИ – доверительный интервал; ИММ – индекс массы миокарда; ИНЛС – индекс нарушения локальной сократимости; ШОКС – шкала оценки клинического состояния; ВД – выводной тракт; КДР – конечный диастолический размер; КСР – конечный систолический размер; РКК – резерв капиллярного кровотока; ЛНП – липопротеиды низкой плотности.

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INTRODUCTION

Over the past twenty years, chronic heart failure (CHF) has acquired the character of an “epidemic”. CHF is widespread throughout the world and affects more than 60 million people, and, according to experts, the number of people with this pathology will increase [1]. Despite the impressive body of scientific data on the pathophysiology of heart failure (HF) and the possibilities of surgical and drug treatment and prevention, this pathology is associated with significant morbidity and mortality, especially among older people [2–3].

Left ventricular ejection fraction (LVEF) is a fundamental factor for risk stratification in patients with coronary artery disease (CAD), in particular after myocardial infarction (MI). However, being within the normal range, it does not allow a full recognition of the degree of deformation changes in the myocardium. Today, there is compelling evidence for the prognostic value of LV global longitudinal strain (GLS), which is more valuable than LVEF, in stratifying the risks of adverse clinical outcomes in different groups of patients with cardiovascular diseases. Although GLS is an independent predictor of death, left ventricular remodeling and hospitalization of HF patients with aortic stenosis, acute MI, congestive HF, this indicator is not used in clinical practice widely enough [4–6].

Numerous studies on post-infarction remodeling of the myocardium confirm the close connection between the biological markers (BM) of endothelial dysfunction, fibrosis and inflammation, and development and progression of HF [7–8]. At the same time, despite the processes underlying heart failure being widely known, the studies of prognostic value of biomarkers showing the undergoing structural and functional changes of the cardiovascular system, particularly in the development of MI, with respect to the progression of adverse cardiovascular events both in the short-term and long-term perspective remain a priority in modern cardiology [9].

The most commonly used B-type natriuretic peptides in clinical practice, in particular the N-terminal precursor of brain natriuretic peptide (NT-proBNP), are very useful in diagnosis, risk stratification and determination of optimal treatment; however, they have well-known limitations, since their level is dependent on such factors as renal dysfunction, age, obesity, atrial fibrillation, and some other cardiologic and non-cardiologic diseases [10].

The ST2 growth-stimulating factor is a member of the superfamily of interleukin-1 (IL-1) receptors that exists in two forms: transmembrane receptor (ST2L) and the soluble receptor (sST2). The natural ligand of the ST2 is the IL-33. Due to a complex action that IL-33 causes to tissue damage and inflammation, it is involved in the pathogenesis of some diseases (e.g., allergy, autoimmune diseases, cancer, atherosclerosis, and diabetes). It is most important that IL-33 plays a cardio-protective role preventing fibrosis and hypertrophy of the myocardium as a response to mechanical load with the help of ST2L. The damage of the myocardium or mechanical stress stimulate release of the sST2 that competes with ST2L for binding the IL-33, thus inhibiting the positive effects caused by the interaction of ST2L/IL-33, so, the excess of sST2 may assist development of myocardial fibrosis and ventricular remodeling [11].

It was proven that the sST2 provides important information about the prognosis in heart failure (both acute and chronic), and it is less affected by the renal function, age, body mass index, and disease etiology

than the natriuretic peptides. Although the sST2 is not yet widely used, it can be easily measured multiple times in emergencies and daily clinical practice [11].

AIM

To determine the prognostic significance of GLS and sST2 in patients with CHF after myocardial infarction in the annual follow-up period.

MATERIAL AND METHODS

The study was carried out in the Cardiology Departments No. 1 and No. 2 of the Clinics of the Samara State Medical University in the period from 2021 to 2022. In included 96 patients with CHF urgently hospitalized for in-patient treatment in the acute period of MI not more than 24 hours after the event.

Inclusion criteria: age over 18; signing of voluntary informed consent for participation in the study; previous diagnosis of 'chronic heart failure' of I, II and III functional classes; established diagnosis of 'myocardial infarction' at the moment of signing of the informed consent; availability of coronary angiography (CAG).

Exclusion criteria: decompensated diabetes mellitus; confirmed autoimmune diseases; aggravated oncological history; decompensated renal or hepatic failure; diseases of the blood system; history of coronary artery bypass grafting (CABG); other factors of myocardium geometry change (refractory hypertension, hemodynamically significant congenital and acquired cardiac defects, dilatation and ischemic cardiomyopathy).

Myocardial infarction and CHF were diagnosed in compliance with the effective clinical recommendations [12–14].

The clinical and anamnestic characteristics of patients are shown in Table 1. Among the participants included in the study, male patients prevailed, and the median age was 64.5 (57.0; 72.3) years. In the vast majority of patients, there was a history of arterial hypertension (AH), and CHF of NYHA II functional class. History of previous MI was known in 25 (26%) patients, and that of acute cerebrovascular event, in 7 (7.3%). The diagnosed diabetes mellitus was present in 18 (18.8%) individuals. In most cases (61.6%), nob Q-wave myocardial infarction was found, the incidence rate of the anterior localization of MI was 46.9%. Signs of acute heart failure as per Killip II-III were found in 14.6% patients. In 10 patients, atrial fibrillation (AT) rhythm was found, in eight of those, as a complication of the infarction in progress. The median score of patients with CHF on the Rating scale of clinical state (RSCS) was 5 (3; 6).

In-patient treatment was also compliant with the current clinical recommendations [12–14]. In accordance therewith, the medication therapy as of the moment of patients' inclusion in the study contained antiaggregants, anticoagulants (as needed), beta-blockers (BB), statins, inhibitors of angiotensin converting enzyme (ACEI) or sartans, mineralocorticoid receptor agonists (AMR), loop diuretics, calcium channel blockers (CBB) (**Table 1**). All patients with AF received oral anticoagulants.

Characteristics	Abs. Value	%
Sex		
female	31	32.3
male	65	67.7
PICS	25	26
Smoking	3	3.1
AH	90	93.8
DM	18	18.8
ACVA	7	7.3
AF	10	10.4
CHF, functional class (NYHA)		
II	88	91.7
III	8	8.3
Severity of AHF (Killip)		
I	82	85.4
II	8	8.3
III	6	6.3
IM type		
without Q wave	59	61.5
with Q wave	37	38.5
IM localization		
anterior LV wall	45	46.9
posterior LV wall	51	53.1
Prescribed therapy		
DAAT	94	97.9
Statins	93	96.9
ACEI/sartans	87	90.6
BB	90	93.8
AMR	70	72.9
Loop diuretics	52	54.2
CBB	33	34.4
Results of angiographic investigation		
PCI performed at the hospital	61	63.5
Surgical tactics on discharge		
Indicated for CABG	24	25
Indicated for second-stage PCI	34	35.4
Conservative therapy	38	39.6

Notes: PICS: post-infarction cardiosclerosis; DAAT: double anti-aggregate therapy.

Table 1. *Clinical and anamnestic characteristics of the patients included in the study (n=96)*

Таблица 1. *Клинико-анамнестическая характеристика пациентов, включенных в исследование (n=96)*

Based on CAG data, the current condition of the coronary bed was assessed: lesions of the trunk of the left coronary artery (LCA), left anterior descending artery (ADA), circumflex artery (CX), and right coronary artery (RCA). Afterwards, the severity of coronary bed lesion was evaluated using the Syntax scale. In the event a stenosis over 70% was found, the lesion of the coronary artery was deemed significant. In cases of RCA and trunk of LCA, stenosis over 50% was considered hemodynamically significant. Considering the clinical and angiographic picture, and with the patient's consent, the surgical tactics and time frame of intervention were identified (CABG and/or stenting of the symptom-dependent artery).

Following the results of CAG, in 58 (60.4%) patients triple-vessel disease of the coronary bed was found, in 24 (25%) patients, there was found hemodynamically significant lesion of two coronary arteries, in 20 (20.8%), lesion of the LCA trunk. Percutaneous coronary intervention (PCI) was performed in more than 60% cases. Further surgical tactics (CABG) was identified for 24

Factor	No CEP, n=52	Onset of CEP, n=44	OR (95% CI)	P
Median age, years	61.5 (56.5; 72)	66 (59.5; 73)	1.02 (0.98; 1.07)	0.257
Male sex, n (%)	35 (67.3)	30 (68.2)	1.04 (0.44; 2.46)	0.927
DM, n (%)	10 (19.2)	8 (18.2)	1.08 (0.4; 2.95)	0.881
AF, n (%)	7 (13.5)	3 (6.8)	0.47 (0.11; 1.94)	0.288
History of ACVA, n (%)	3 (5.8)	4 (9.1)	1.63 (0.35; 7.73)	0.533
History of MI, n (%)	12 (23.1)	13 (29.5)	1.4 (0.56; 3.49)	0.472
AH, n (%)	50 (96.2)	40 (90.9)	0.4 (0.07; 2.3)	0.29
MI with Q-wave, n (%)	17 (32.7)	20 (45.5)	1.72 (0.74; 3.93)	0.2
Anterior MI, n (%)	24 (46.2)	21 (47.7)	1.07 (0.48; 2.38)	0.878
Killip II–III, n (%)	5 (9.6)	9 (20.5)	2.42 (0.75; 7.85)	0.134
PCI during hospitalization, n (%)	34 (65.4)	27 (61.4)	0.84 (0.37; 1.94)	0.683

Table 2. *Clinical and anamnestic factors influencing the development of adverse cardiovascular events within 1 year*

Таблица 2. *Клинико-анамнестические факторы, влияющие на развитие неблагоприятных сердечно-сосудистых событий в течение 1 года*

(25%) patients; second-stage PCI for 34 (35.4%) patients; conservative therapy, for 38 (39.6%) patients (**Table 1**).

On the third day of hospitalization, patients' venous blood was sampled to identify concentrations of such biomarkers as sST2 ("Presage ST2 Assay" test system, "Critical Diagnostics", USA), vascular endothelial growth factor (VEGF) ("Human VEGF-A ELISA Kit, Bender MedSystems GmbH", Austria) and NTproBNP ("NT-proBNP" test system, "Biomedica", Austria). The assessments of the total and biochemical blood count, as well as blood coagulation, lipid, and CRP tests were performed within the routine clinical practice.

The ECG was registered on the "CardiovitAT 2" apparatus ("Schiller", Switzerland) in twelve standard leads.

Echocardiography (EchoCG) and 2D mode EchoCG speckle tracking were performed on the "Philips EPIQ 5" ultrasound machine (USA) in accordance with the Guidelines of the American Society of Echocardiography and the European Association for Cardiovascular Imaging [15].

During the hospital period, all patients underwent laser Doppler flowmetry (LDF) in order to determine microcirculation disorders using the general practitioner's laser blood microcirculation analyzer "LAKK-OP" ("Lazma" LLC, Russia).

In the course of the first phase of the study, no cases of hospital death were registered. In the second phase, telephone inquiry was used to assess the disease progress and clinical outcomes within 12 months. The combined end point (CEP) in this study is represented by cases of mortality due to cardiovascular pathology and recurrent cardiovascular events: ACVA, new incidences of IM, unstable angina (UA), and hospitalization for in-patient treatment of CHF decompensation.

Statistical processing of data was performed in the statistical calculation software suite R 4.3.2 (R Foundation for Statistical Computing, Austria). Descriptive statistics are represented as absolute and relative frequencies for qualitative variables, and medians (Me) with interquartile range (Q1; Q3) for quantitative variables. Intergroup differences for quantitative variables were assessed using the Mann–Whitney test between two independent samples; for categorical variables, the Fisher's exact test. The determination of prognostic factors for the occurrence of recurrent events was performed using univariate regression analysis with calculation of the odds ratio (OR) and determination of its 95% confidence interval (CI). The prediction of the study criteria was also assessed by performing ROC (receiver operating characteristics) curve analysis, in which the area under the curve (AUC) values were calculated.

RESULTS

Within the 12 months of observation, the onset of CEP was registered in 44 (45.8%) participants of the study: cardiovascular death took place in 2 (2.1%) cases, 8 (8.3%) patients were hospitalized due to UA and the same number, due to development of recurrent IM, 24 (25%) people were hospitalized due to CHR decompensation, and 2 (2.1%), due to development of ACVA. Based on that, groups of patients were identified with favorable and unfavorable progress in the long term-post-infarction period.

The assessment of effect of clinical and anamnestic characteristics on the probability of development of recurrent cardiovascular events within 12 months from the moment of patients' inclusion in the study revealed no statistically significant associations with sex, age, MI localization, AHF severity as per Killip scale, PCI in the period of hospitalization, history of MI, DM, AH, ACVA, and the presence of AF and NYHA functional class CHF ($p>0.05$ in all cases) (**Table 2**).

At the same time, the patients with an adverse clinical outcome in the year-long follow-up, a statistically significant higher score of RSCS was registered, (5 (4; 7) vs. 4 (3; 5) in patients with a favorable progress of post-MI period, $p<0.001$). The regression analysis revealed that high RSCS scores were significant predictors of development of recurrent cardiovascular events in CHF patients within one year after MI (OR=1.44 (95% CI: 1.17; 1.82), p=0.001).

The comparative analysis of basic EchoCG findings and CAG results (**Table 3**) revealed that in the event of development of adverse cardiovascular events the patients originally had statistically significant lower values of left ventricle ejection fraction (LVEF) and global longitudinal strain (GLS), and statistically significant higher values of end-systolic length (ESL) and end-diastolic length (EDL) of the left ventricle, end-systolic volume of the left ventricle (ESV), myocardial mass index of the left ventricle (LV MMI), wall motion score index (WMSI), basal diameter of the LV outflow tract (LV OT), and higher scores as per Syntax scale. Besides, patients with an adverse long-term outcome demonstrated diastolic dysfunction of the left ventricle (LV DD) significantly more often (70.5%). The groups with favorable and unfavorable clinical prognoses did not differ in the value

Factor	No CEP, n=52	Onset of CEP, n=44	P	OR (95% CI)	p for OR
LV EF*, %	54 (49.5; 57.7)	48 (39; 54)	**<0.001**	0.9 (0.84; 0.95)	**<0.001**
EDR*, mm	48 (44.5; 50)	51 (48; 53.5)	**0.002**	1.11 (1.02; 1.21)	**0.018**
ESR*, mm	33 (30; 37)	36 (32; 42)	**0.004**	1.09 (1.02; 1.17)	**0.013**
ESV*, ml	118.5 (106.5; 139)	129 (114; 151.5)	0.15	1.01 (0.99; 1.02)	0.261
EDV*, ml	55 (45.5; 70.5)	65.5 (56; 86.5)	**0.003**	1.03 (1.01; 1.05)	**0.013**
LV OT dia., mm					
proximal*	28.5 (27; 31)	30 (27; 32)	0.416	1.06 (0.95; 1.19)	0.273
distal*	25 (25; 26.5)	25 (24; 26.5)	0.732	0.98 (0.86; 1.11)	0.748
basal*	35 (32; 38)	38 (35; 40)	**0.01**	1.08 (1; 1.18)	**0.045**
median*	29.5 (27; 31)	30 (27; 32)	0.744	1.02 (0.92; 1.14)	0.699
GLS*, %	19.8 (18.45; 20.3)	16.65 (15.1;17.65)	**<0.001**	0.37 (0.26; 0.54)	**<0.001**
LV MMI*, g/m2	100 (80.5; 110.35)	107 (97.5; 124)	**0.013**	1.02 (1; 1.04)	**0.018**
WMCI*	1.19 (1; 1.4)	1.41 (1.1; 1.8)	**0.008**	4.6 (1.55; 15.4)	**0.009**
LA vol.*, ml	62 (53.5; 68)	65.5 (57; 79.5)	0.089	1.02 (0.99; 1.04)	0.202
PPAsyst.*, Hgmm	30.5 (27; 35.5)	32.5 (27.5; 40.5)	0.145	1.05 (1; 1.1)	0.073
IV LA*, ml/m2	334 (28; 40)	335 (30.75; 42.33)	0.264	1.0 (0.98; 1.01)	0.526
IV RA*, ml/m2	25.2 (22; 28)	26.6 (22.8; 30.55)	0.197	1.01 (0.96; 1.07)	0.639
Vtr*, m/s	2.39 (2.22; 2.6)	2.53 (2.25; 2.8)	0.094	3.27 (1.09; 9.82)	**0.033**
LV DD, n (%)	26 (50)	31 (70.5)	**0.042**	2.39 (1.02; 5.55)	**0.042**
Syntax*, pts.	15.5 (8.5; 21.25)	38 (31; 41)	**<0.001**	1.2 (1.13; 1.29)	**<0.001**
Number of affected coronary arteries					
Single-vessel, n (%)	11 (21.2)	3 (6.8)	0.14	1.58 (0.96; 2.74)	0.081
Two-vessel, n (%)	12 (23.1)	12 (27.3)			
Three-vessel, n (%)	29 (55.8)	29 (65.9)			
LCA trunk disease, n (%)	11 (21.2)	9 (20.5)	0.933	0.96 (0.35; 2.58)	0.933

*Notes: * values are represented as Me (Q1; Q3); IV LA: indexed volume of left atrium; IV RA: indexed volume of right atrium.*

Table 3. *Comparative analysis of echocardiographic parameters and coronary angiography results depending on the development of CEP*

Таблица 3. *Сравнительный анализ эхокардиографических показателей и результатов КАГ в зависимости от развития ККТ*

of the end-diastolic volume of LV (EDV), proximal, distal and median diameter of the LV OT, volumetric values of the left atrium (LA) and right atrium (RA), value of systolic pressure in the pulmonary artery (PPAsyst), and the number of affected coronary arteries and presence of LCA trunk lesion. The statistically significant predictors of development of recurrent cardiovascular events were as follows: LV EF (OR (95% CI) – 0.9 (0.84; 0.95), p<0.001), EDR, ESR, ESV, basal diameter of LV OT (OR (95% CI) – 1.08 (1; 1.18), p=0.045), GLS (OR (95% CI) – 0.37 (0.26; 0.54), p<0.001), LV MMI (OR (95% CI) – 1.02 (1; 1.04), p=0.018), WMCI (OR (95% CI) – 4.6 (1.55; 15.4), p=0.009), triscupid regurgitation velocity (Vtr) (OR (95% CI) – 3.27 (1.09; 9.82), p=0.033), presence of LV DD (OR (95% CI) – 2.39 (1.02; 5.55), p=0.042), and the score on the Syntax scale (OR (95% CI) – 1.2 (1.13; 1.29), p<0.001) (**Table 4**). It is noteworthy that neither the number of affected coronary arteries nor the presence of hemodynamically significant damage to the left coronary artery trunk had a significant impact on the long-term prognosis of patients after MI.

When analyzing the microcirculation parameters obtained during LDF, it was found that patients who developed repeated adverse cardiovascular events during 12 months of follow-up, initially had statistically significantly lower values of the microcirculation index (MI), the amplitudes of blood flow oscillations in the myogenic (Am), neurogenic (An) and endothelial (Ae) frequency ranges, the respiratory test index (RTI) and the Hurst exponent (R/S), as well as statistically significantly higher capillary blood flow reserve (CBFR) (**Table 4**). The groups did not differ in the value of variation coefficient (Kv), values of relative perfusion saturation of blood flow with oxygen (Sm), specific consumption of oxygen in the tissues (I), relative entropy (H0), and correlation dimensions of phase pattern (D2). The obtained data indicate that patients with an unfavorable prognosis had more manifested disturbances of microvascular hemodynamics during the year, as well as a decrease in the amplitude-frequency spectrum of perfusion oscillations.

The odds of development of recurrent cardiovascular events within one year were statistically significantly associated with values of RTI (OR (95% CI) – 0.81 (0.66; 0.97), p=0.025) and CBFR) (OR (95% CI) – 1.15 (1.05; 1.27), p=0.005). Besides, with the Ae value growing by 0.1 the odds ratio of adverse outcome development reached 0.58 (95% CI: 0.37; 0.88), An – 0.32 (95% CI: 0.14; 0.67), Am – 0.52 (95% CI: 0.32; 0.8), R/S – 0.62 (95% CI: 0.39; 0.96) and D2 – 0.68 (95% CI: 0.46; 0.97).

The analysis of levels of general laboratory parameters depending on the development of adverse cardiovascular events within one year after an index MI showed that the patients with adverse outcomes had significantly higher levels of CRP, NTproBNP and sST2, and the calculated glomerular filtration rate (GFR) was significantly lower than the patients with a favorable progression of the remote follow-up period (**Table 5**). The groups did not differ in the levels of troponin, creatine phosphokinase (CPK) and its MB isoform (CPKMB), total cholesterol (TC), low-density lipoproteins (LDL) and VEGF, although there was a tendency towards higher values of glycemia in patients with unfavorable prognosis (p=0.06). The statistically significant predictors of recurrent events were the value of GFR calculated using the CKD-EPI formula

Factor	No CEP, n=52	Onset of CEP, n=44	P	OR (95% CI)	p for OR
MI, pf. u.	15.3 (14.4; 16.3)	14.5 (13.7; 15.9)	**0.042**	0.76 (0.57; 1)	0.055
Kv, %	6.93 (5.06; 8.51)	6.18 (4.73; 7.81)	0.194	0.89 (0.75; 1.06)	0.205
Ae, pf. u.	0.58 (0.52; 0.64)	0.52 (0.44; 0.61)	**0.007**	0.58 (0.37; 0.88)	**0.013**
An, pf. u.	0.57 (0.54; 0.61)	0.54 (0.48; 0.57)	**0.002**	0.32 (0.14; 0.67)	**0.004**
Am, pf. u.	0.51 (0.44; 0.55)	0.42 (0.37; 0.51)	**0.002**	0.52 (0.32; 0.8)	**0.004**
RTI, %	35.5 (34.2; 37)	34.2 (32.6; 38.7)	**0.038**	0.81 (0.66; 0.97)	**0.025**
CBFR, %	127 (124; 129)	130 (125; 133)	**0.008**	1.15 (1.05; 1.27)	**0.005**
Sm, c. u.	4.35 (4.03; 4.6)	4.08 (3.87; 4.65)	0.175	0.58 (0.22; 1.46)	0.249
I, c. u.	33.7 (30.8; 36)	32.1 (29.8; 34.7)	0.229	0.95 (0.85; 1.05)	0.282
R/S	0.47 (0.4; 0.52)	0.4 (0.32; 0.48)	**0.02**	0.62 (0.39; 0.96)	**0.036**
H0	0.34 (0.31; 0.38)	0.34 (0.3; 0.36)	0.197	0.58 (0.24; 1.39)	0.23
D2	1.43 (1.36; 1.5)	1.39 (1.25; 1.49)	0.063	0.68 (0.46; 0.97)	**0.039**

Note: the factor values are gives as medians Me (Q1; Q3).

Table 4. *Comparative analysis of microcirculation parameters depending on the development of CEP*

Таблица 4. Сравнительный *анализ параметров микроциркуляции в зависимости от развития ККТ*

(OR (95% CI) – 0.95 (0.92; 0.98), p=0.006), glucose levels (OR (95% CI) – 1.17 (1.01; 1.36), p=0.029), CRP (OR (95% CI) – 1.06 (1.02; 1.11), p=0.004), NT-proBNP (OR (95% CI) – 1.03 (1.02; 1.08), p<0.001), and sST2 (OR (95% CI) – 1.13 (1.07; 1.2), p<0.001).

Thus, development of adverse cardiovascular events in CHF patients after MI is associated within the following year with decrease of global deformation of the left ventricle, severity of coronary atherosclerosis, disruption of microcirculation, presence of kidney dysfunction, hyperglycemia and elevation of levels of such biomarkers as CRP, NTproBNP and sST2. At the same time, the clinical and anamnestic characteristics as predictors of long-term adverse outcomes become secondary.

To predict the risk of development of recurrent cardiovascular events, a mathematical model was developed with step-by-step selection of predictors that showed their significance in the development of combined endpoint in the single factor analysis, as well as predictors that have wide evidence with respect to riskometry, with exclusions based on the Akaike's information criterion (AIC). The analysis included criteria that showed their prognostic value in a univariate analysis, and the generally accepted risk factors with a vast body of evidence: patient's age and sex, history of DM, history of MI, type of MI and severity of CHF in the Killip class, score on the RSCS and Syntax scales, number of involved coronary arteries, values of LV EF, GLS, LV MMI, RCII, ESL, EDL, ESV, basal diameter of the LV OT and Vtr, presence of LV DD, RTI and CFBR, Hurst exponent, correlation dimensions of the phase pattern and amplitude-frequency spectrum of perfusion oscillations, as well as concentrations of glucose, CRP, NT-proBNP, sST2, TC and LDL, and CKD-EPI calculated GFR.

Following the results of the analysis, the final model (**Table 6**) included such factors as GLS value, points on the Syntax scale, levels of NTproBNP and sST2. The risk ratio (RR) for NTproBNP was 2.9 (1.45; 5.1), for the Syntax scale, 3.05 (2.2; 6.8), for sST2, 3.3 (1.65; 7.51), and for GLS, 0.51 (0.39; 0.72).

The resulting model was characterized by a Nagelkerke pseudo R^2 value of 0.7 (adjusted value – 0.66), Sommers DXY rank correlation of 0.89 (adjusted value – 0.86) and AUC of 0.94 (95% CI: 0.89–0.97) (adjusted value – 0.93) (**Fig. 1**).

Following the results of the multivariate regression analysis, we derived the regression equation using the following mathematical formula:

$P=1/(1+e^{-(Bo + B1*x1 + B2*x2 + B3*x3 + B4*x4)})$, where:

e – base of natural logarithm (2.718); Bo – constant (1.32); B_1 – coefficient for NTproBNP (0.012); B_2 – coefficient for GLS (-0.74); B_3 – coefficient for Syntax scale points (0.13); B_4 – coefficient for sST2 (0,15); x_1 – concentration of NTproBNP, pg/ml; x_2 – GLS value, %; x_3 – number of Syntax scale points; x_4 – concentration of sST2, ng/ml.

Thus, the equation can be written as follows:

$P=1/(1+e^{-(1,32 + 0,012*x1 - 0,74*x2 + 0,13*x3 + 0,15*x4)})$.

Factor	No CEP, n=52	Onset of CEP, n=44	P	OR (95% CI)	p for OR
Glucose, mmol/l	6.0 (5.3; 7.3)	6.6 (5.6; 8.4)	0.06	1.17 (1.01; 1.36)	**0.029**
Troponin, pg/ml	708.5 (174; 2283.1)	616.4 (89.8; 3205.5)	0.953	1.0 (1.0; 1.0)	0.146
CPK, U/l	306.9 (120; 778.2)	315.5 (143.5; 796.8)	0.678	1.0 (1.0; 1.0)	0.707
CPKMB, U/l	31.1 (21.3; 70.6)	47.5 (21.3; 77.8)	0.617	0.99 (0.82; 1.0)	0.439
CKD-EPI GFR, ml/min/1.73m2	77 (74; 80)	67 (61; 77)	**0.003**	0.95 (0.92; 0.98)	**0.006**
TC, mmol/l	5.1 (4.4; 5.65)	5.05 (4.75; 5.4)	0.8	0.86 (0.58; 1.22)	0.396
LDL, mmol/l	3.07 (2.58; 3.9)	3.28 (2.74; 3.32)	0.376	0.94 (0.61; 1.42)	0.759
CRP, mg/l	14.9 (7.9; 21.1)	22.3 (12.5; 31.9)	**0.004**	1.06 (1.02; 1.11)	**0.004**
NT-proBNP, pg/ml	192.4 (111.2; 517.8)	1339.7 (605.4; 1886.9)	**<0.001**	1.03 (1.02; 1.08)	**<0.001**
sST2, ng/ml	27.2 (21.3; 34.8)	45.8 (37; 63.4)	**<0.001**	1.13 (1.07; 1.2)	**<0.001**
VEGF, pg/ml	387 (187.5; 461.6)	249.7 (153.8; 370)	0.116	0.79 (0.53; 1.17)	0.248

Note: the factor values are gives as medians Me (Q1; Q3).

Table 5. *Levels of the main laboratory parameters depending on the development of CEP*

Таблица 5. Уровни *основных лабораторных показателей в зависимости от развития ККТ*

Predictor	β (SE)	RR	95% CI	p	VIF
Constant	1.32	-	-	-	–
NTproBNP, ng/ml	0.012	2.9	1.45; 5.1	0.018	1.34
GLS, %	-0.74	0.51	0.39; 0.72	0.032	1.27
Syntax, points	0.13	3.05	2.2; 6.8	0.002	1.05
sST2, ng/ml	0.15	3.3	1.65; 7.51	0.041	1.08

Table 6. *Coefficients in the model for predicting the risk of recurrent cardiovascular events*

Таблица 6. *Коэффициенты в полученной модели прогнозирования риска развития повторных сердечно-сосудистых событий*

To ensure the ease of use of this formula, a calculator for calculating the probability of development of recurrent cardiovascular events in patients with CHF within a year after a previous MI was designed on its basis. After the required parameters are filled in (NTproBNP and sST2 levels, Syntax scale points and GLS value), the program provides the result of probability of development of recurrent cardiovascular events within 12 months in percent (**Fig. 2**).

Using a predicted event probability of 60% as a threshold, the resulting model had an accuracy of 87.5% (95% CI: 84.2; 91.3), a sensitivity of 81.8% (95% CI: 72.6; 90.8), and a specificity of 92.3% (95% CI: 87.8; 98.1). The positive predictive value was 92.3% (95% CI: 83.9; 96.4).

DISCUSSION

Heart failure is a complex clinical syndrome that occurs in various diseases, including MI, characterized by pathological changes in the structure and/or function of the heart [16].

Currently, there are many studies confirming the prognostic significance of various predictors of adverse outcome in patients with HF. These include EchoCG data, results of effort tests, and levels of such biomarkers as NTproBNP, galectin-3, hs-T-troponin, and CRP. At the same time, despite the identification of many prognostic markers, clinical decision-making in CHF is still based primarily on parameters such as the presence of HF symptoms (NYHA class), LVEF, QRS duration and morphology [17].

Although LVEF is an important indicator in the diagnosis and monitoring of patients with CHF, in some cases, LVEF assessment may not be informative enough and may not reflect the severity of the clinical condition, particularly at the onset of HF. Recent studies suggest that myocardial strain is a more sensitive parameter for assessing cardiac function than LVEF. Thus, P. Janwetchasil *et al*. (2024) studied the prognostic value of GLS using the MRI of the heart in patients with known or suspected coronary heart disease with preserved systolic function of the left ventricle. The multivariate analysis showed that patients with GLS less than 14.4% had a significantly higher risk of adverse cardiovascular events compared with patients with GLS greater than 14.4% [6]. L. Caunite *et al*. (2024) showed that GLS improves stratification of risk based on LVEF in patients after MI with elevation of the ST segment (STEMI). The study included 1909 STEMI patients, the average follow-up

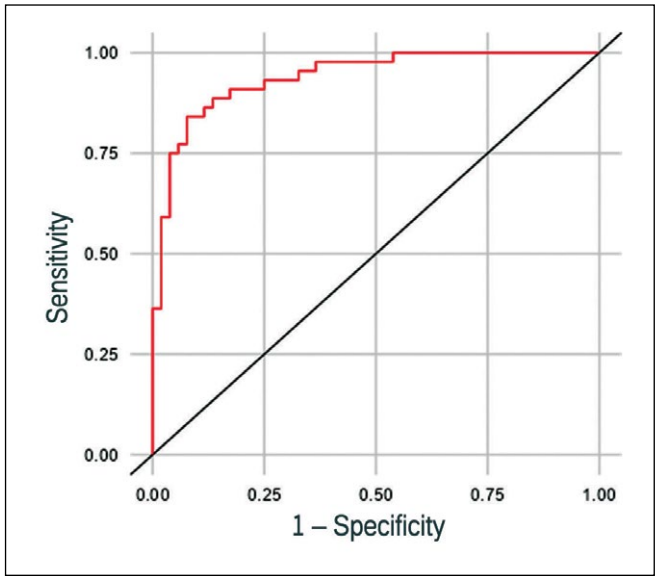

Рисунок 1. *ROC-кривая для предсказаний, полученных с использованием модели.*

Figure 1. *ROC-curve for predictions obtained using the model.*

being 69 months. The cumulative 10-year survival rate was 91% in patients with improvement or slight decline in GLS compared with 85% in patients with a GLS decline of >7% within one year after the index event. In a multivariate regression analysis, a decrease in GLS >7% from baseline remained independently associated with the development of the endpoint after adjustment for clinical and echocardiographic parameters of left and right ventricular function. Thus, speckle tracking strain echocardiography has the potential to improve risk stratification in patients with STEMI, even with preserved or moderately reduced LVEF at baseline and in follow-up [4]. The correlation between the GLS value and level of BNP with the development of pathological remodeling after the MI was demonstrated earlier by V.E. Oleinikov et al. (2022). Patients with pathological LV remodeling on days 7–9 of MI had statistically significantly lower GLS values, and within 6 months the proportion of patients with low and intermediate LVEF was 24.4% and 60%, respectively. A decrease in GLS of less than 11.7% was a

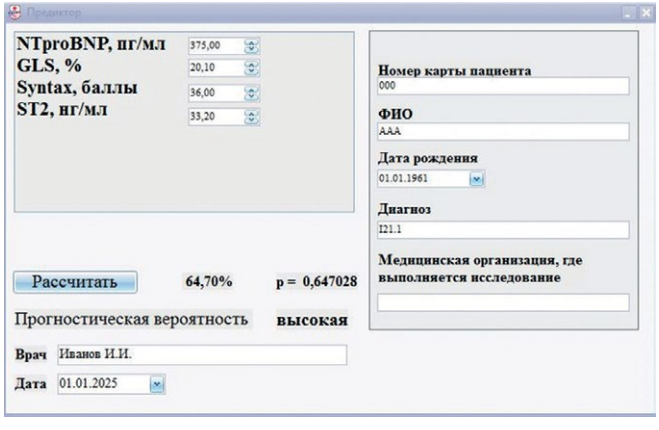

Figure 2. *Example of using a calculator for riskometry in patients with CHF who had MI*

Рисунок 2. *Пример использования калькулятора для рискометрии у пациентов с ХСН, перенесших ИМ.*

highly sensitive and specific predictor of the development of post-infarction pathological LV dilation [18]. In the present study, a dynamic assessment of the GLS value was not performed, but only the effect of GLS on the development of late adverse cardiovascular events was assessed. At the same time, the prognostic significance of GLS was demonstrated by both univariate and multivariate analyses, which makes this indicator a valuable marker for early risk stratification in patients with CHF who have had an MI, regardless of its dynamics.

Recently, the prognostic significance of ST2 and its advantages over natriuretic peptides gained much attention. The clinical effectiveness of assessing the level of sST2 in HF was confirmed by numerous studies conducted over the past 20 years. A meta-analysis of 2016 studied 7 clinical trials with more than 6372 participants and confirmed the prognostic value of sST2 with respect to adverse outcomes in CHF patients [19]. It is known that an increase in sST2 levels after MI has a long-term prognostic value for the development of CHF. According to clinical observations, patients with elevated sST2 levels after MI were more susceptible to subsequent maladaptive myocardial remodeling and progression of HF [20]. sST2 has also been shown to be a powerful predictor of adverse clinical events in AHF. Xue-Qing Guan et al. (2024) increased the predictive value for risk stratification in patients with AHF over a three-year follow-up period by assessing the incidence of major adverse cardiovascular events, defined as re-hospitalization for HF and/or all-cause mortality. The authors found that the optimum threshold value for sST2 was 34 ng/ml. Patients above this threshold had higher rates of re-hospitalization and mortality, which emphasized the prognostic importance of elevated sST2 levels in the study population. The diagnostic value of sST2 varied across different HF patient groups, particularly in patients with a history of MI, indicating the importance of considering prognostic differences between patient groups when monitoring sST2 levels in clinical practice [21].

To assess the risks of developing adverse outcomes within a year for the studied cohort of patients, we proposed a mathematical model for determining the risk of developing recurrent cardiovascular events and death within 12 months in patients with CHF after MI. The multivariate regression analysis established the following as independent predictors of development of adverse clinical outcomes: GLS value, score on the Syntax scale, and concentration of sST2 and NTproBNP identified not later than two days after the development of MI. It is to be noted that in this study, the NTproBNP did not lose its prognostic value. It was proven that the inclusion of new biomarkers in the multi-parametric models, in addition to the widely known natriuretic peptides, significantly improves the risk stratification, and the highly sensitive troponins and the sST2 seem to be more reliable biomarkers for the stratification of risk [22–23].

CONCLUSION

The assessment of levels of GLS and sST2 in patients with IM, along with the assessment of the severity of the coronary atherosclerosis and the level of NTproBNP is a promising tool that can improve early stratification of risk and diagnostic and therapeutic management of patients admitted for emergency care. The increase of sST2 levels in plasma is likely associated with significant activation of both neurohormonal and profibrotic mechanisms, which may help identify patients at high risk of early adverse LV remodeling after MI.

The use of the proposed prognostic model in clinical practice, in particular at the hospital stage, will allow not only to stratify the risk of developing recurrent cardiovascular events in patients with CHF after a previous MI and promptly identify individuals with a high probability of developing adverse clinical events within the next year, but also to provide a more personalized approach to treatment and preventive measures for a specific patient.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Compliance with Ethical Standards. The authors confirm that the rights of the people who participated in the study were respected, including obtaining informed consent.	Соответствие нормам этики. Авторы подтверждают, что соблюдены права людей, принимавших участие в исследовании, включая получение информированного согласия.
Contribution of individual authors. Yu.A. Trusov: conducting of the scientific research and experiment; writing of the article. Yu.V. Shchukin: approval of the research concept, scientific consulting, editing of the manuscript. L.V. Limareva: evaluation of laboratory research methods, development of correlation models based on biomarker data in patients with CHF. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Ю.А. Трусов – проведение научного исследования и эксперимента; написание текста статьи. Ю.В. Щукин – утверждение концепции исследования, научное консультирование, редактирование рукописи. Л.В. Лимарева – оценка лабораторных методов исследования, разработ ка корреляционных моделей на основании данных биомаркеров у пациентов с различными фенотипами ХСН. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Role of mini-invasive technologies in the treatment of colon cancer in the aged patient population

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Abstract

Aim – to evaluate the effectiveness of surgical treatment for colorectal cancer in patients aged 75–90 years (WHO, 2002) in the early postoperative period after laparoscopic and open surgeries. The primary outcome was the total length of hospital stay (bed-days). Secondary outcomes included intraoperative blood loss, C-reactive protein (CRP) levels, postoperative pain (VAS), and the incidence of general and surgical complications.

Material and methods. The study included colorectal cancer (CRC) patients (75–90 years old) who underwent laparoscopic (LS) or laparotomic (LT) surgery. A comparative analysis of demographic, clinical-laboratory, and surgical data was performed.

Results. The LS group demonstrated a shorter hospital stay (10 (3) vs. 10 (7) days, p≤0.001) and lower intraoperative blood loss (50 (20) vs. 150 (150) ml, p≤0.001) compared to the LT group. The LT group had significantly higher CRP levels on days 3 and 5 (p≤0.001) and a higher incidence of complications (pneumonia, anemia, acute urinary retention), 18 (33.9%) vs. 6 (7.2%), p≤0.001. Operative time (p=0.002) and postoperative complications significantly influenced hospital stay duration.

Conclusion. Laparoscopic surgery results in a shorter hospital stay, reduced intraoperative blood loss, lower inflammatory response, and decreased postoperative pain and complication rates. These advantages make it the preferred method for treating elderly patients with colorectal cancer, especially in the presence of comorbidities.

Keywords: colon cancer, laparoscopy, hospital stay duration, blood loss volume, operative time.

Conflict of Interest: nothing to disclose.

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Роль малоинвазивных технологий в лечении рака ободочной кишки у пациентов старческой возрастной группы

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Аннотация

Цель – оценить эффективность хирургического лечения колоректального рака у пациентов 75–90 лет (ВОЗ, 2002) в раннем послеоперационном периоде после лапароскопических и открытых операций. Основной показатель – общая продолжительность госпитализации (койко-дни), которая является первичной конечной точкой исследования. Вторичные показатели: интраоперационная кровопотеря, уровень С-реактивного белка, послеоперационная боль, частота общих и хирургических осложнений.

Материал и методы. В исследование включены пациенты с КРР 75–90 лет, перенесшие лапароскопические (ЛС) и лапаротомные (ЛТ) операции. Проведен сравнительный анализ демографических, клинико-лабораторных и хирургических данных.

Результаты. Группа ЛС показала короткие сроки общей продолжительности госпитализации (10 (3) против 10 (7) дней, p≤0,001) и меньшие цифры интраоперационной кровопотери (50 (20) против 150 (150) мл, p≤0,001) по сравнению с группой ЛТ. В группе ЛТ отмечен более высокий уровень СРБ на 3-и и 5-е сутки (p≤0,001), частые осложнения (пневмония, анемия, острая задержка мочи) в группе ЛТ – 18 (33,9%) против 6 (7,2%), p≤0,001. Существенно влияли на продолжительность госпитализации общая время операции (p=0,002) и послеоперационные осложнения.

Заключение. Лапароскопический доступ обеспечивает более короткую продолжительность госпитализации, снижает интраоперационную кровопотерю, уменьшает выраженность воспалительного ответа и болевого синдрома, а также сокращает частоту ранних послеоперационных осложнений. Эти преимущества делают ее предпочтительным методом в лечении пациентов старческой возрастной группы колоректальным раком, особенно при наличии коморбидного фона.

Ключевые слова: рак ободочной кишки, лапароскопия, продолжительность госпитализации, объем кровопотери, продолжительность операции.

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КРР – колоректальный рак; РОК – рак ободочной кишки; ЛС – лапароскопия; ЛТ – лапаротомия; ИМТ – индекс массы тела; Hb – гемоглобин; СРБ – С-реактивный белок; ASA – Американское общество анестезиологов; ОПГ – общая продолжительность госпитализации; ППГ – постоперационная продолжительность госпитализации.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant neoplasms in the world, ranking third in incidence among both sexes after breast cancer and lung cancer. In terms of mortality, CRC ranks second in the structure of all malignant neoplasms, second only to lung cancer [1, 2]. The main method of radical treatment of CRC remains surgical intervention, while improvements in surgical technologies have significantly improved patient outcomes. Traditionally, open laparotomy (LT) has been and remains the standard surgical procedure for colon resection. However, with the advent of minimally invasive technologies such as laparoscopy (LS), surgical practice has improved significantly over the past few decades.

Laparoscopic surgery offers several potential advantages over LT, including smaller incisions, reduced postoperative pain, faster recovery, and shorter hospital stay [3–5]. A study by Chinese scientists has demonstrated the superiority in efficacy and safety of laparoscopic techniques over open laparotomy operations in the surgical treatment of colorectal cancer in the elderly, namely in terms of accelerated recovery and fewer complications in the early postoperative period [4]. Despite the above advantages, the use of laparoscopic techniques is not yet the method of absolute choice and mainly depends on the patient selection criteria, available surgical skill, and availability of equipment in the medical institution.

An important indicator of postoperative recovery and the effectiveness of healthcare management is the length of a patient's stay in hospital [6]. In addition, reduction of hospital days is one of the effective results noted in LS surgery [7]. Although existing studies show that LS methods reduce the length of hospital stay compared with LT, the extent of this benefit and the factors influencing it continue to be investigated in different populations and real-world clinical practice [7].

AIM

To compare early postoperative outcomes in elderly patients undergoing laparoscopic and open surgery for CRC [8] and to evaluate the recovery benefits of LS surgery within our clinical context.

MATERIAL AND METHODS

Study design and conditions

This retrospective cohort study included 140 patients diagnosed with colon cancer who underwent LS and traditional LT surgeries. The data for the study were retrospectively collected from medical records of patients who underwent surgery at the Oncology Center No. 1 of the S.S. Yudin City Clinical Hospital over a five-year period (from October 2019 to October 2024). Ethical approval for the study was obtained from the local ethics committee of the Sechenov University on 16.11.23, and confidentiality of patient data was respected throughout the study.

Study population and inclusion criteria

The study included 140 patients aged 75–90 years with histologically confirmed colon cancer. Random simple sampling was used to include patients in the study. Inclusion criteria: histologically confirmed CRC, planned surgical

treatment using LS or LT approaches, availability of complete medical records and discharge summaries, including preoperative, intraoperative and early postoperative data (up to 9 days after surgery). Patients undergoing emergency intervention, with primary multiple malignancies and with stage IV disease *were excluded*.

Data collection and characteristics

The patient data was taken from electronic patient records using a standardized data collection form. Demographic characteristics such as age, gender and body mass index (BMI) were recorded as well as the following clinical data: clinical diagnosis, tumor stage, concomitant diseases and perioperative laboratory findings, namely, hemoglobin (Hb) and C-reactive protein (CRP) levels. To determine the tumor stage, the TNM-8 (2017) classification was used [9]. The general functional status of patients was assessed using the Karnofsky score [10]. Perioperative surgical risk was assessed using the American Society of Anesthesiologists scale (ASA) [10].

The anamnesis included preoperative intestinal obstruction, as well as previous surgical operations on the abdominal organs and pelvic organs. Intraoperative data included total operative time in minutes and intraoperative blood loss in milliliters.

Postoperative outcomes included total length of hospital stay and postoperative Hb and CRP levels, general and abdominal postoperative complications. In addition, the total length of hospital stay was chosen as the primary endpoint, while intraoperative blood loss, inflammatory response, severity of postoperative pain and postoperative complications were considered as secondary endpoints.

Statistical analysis

Quantitative variables are presented as mean and standard deviation (M±SD) for normally distributed data. In cases where the normality assumption was violated, the values were described by the median and interquartile range (Me (Q1–Q3)). Normality of distribution was tested using the Shapiro–Wilk test.

For qualitative variables, absolute frequencies and percentages were used (n (%)). The t-test or nonparametric Mann–Whitney test were used to compare baseline demographic, clinical, and perioperative characteristics depending on the data distribution. The categorical variables were compared using the χ^2 test or Fisher's exact test depending on expected frequencies.

Comparison of quantitative variables before and after surgery was performed using the paired t-test or Wilcoxon test, depending on normality. For the analysis of paired categorical data before and after surgery, the McNemar test was used.

To identify the factors related to the total duration of hospitalization and to assess their independent effect, the multivariate linear regression analysis (MLR) was used. Variables that showed statistical significance in the univariate analysis, as well as variables of clinical significance, were included in the model as predictors.

The accuracy of the constructed model was assessed using the model specificity analysis (linktest) and the Nagelkerke's determination coefficient R^2. The criterion of statistical significance were p-values below 0.05 and 95% confidence interval.

The calculations were performed in the Stata software suite, ver. 16.1 (StataCorp, Texac, USA).

RESULTS

Descriptive statistics and comparative analysis of basic demographic and clinical data

The patients were grouped depending on the method of surgical treatment; therefore, the comparative analysis was performed in the LS and LT groups. Due to urgency of the operations and lack of clear histological confirmation, two patients from the LS group and two patients from the LT group were excluded from the study. The final cohort included 53 patients in the LT group and 83 patients in the LS group who met the criteria. The groups were comparable in age (p=0.53) and sex (p=0.85). The median age was 83 (6) years, and women prevailed (61.1%) in the total population. BMI categories were also equally distributed across groups (p=0.91). The majority of patients had a normal BMI value (n=59, 43.7%). The results are shown in **Table 1**.

The classification as per TNM-8 (2017) before the operation showed the prevalence of stage III in the total cohort (64 (47%)), the distribution is comparable in the groups (p=0.26). Despite the prevalence of patients with tumors of the right half of the colon in the overall cohort 71 (52.2%) over patients with tumors of the left half of the colon, 54 (39.7%), no statistical difference was found (p=0.53). According to the Karnofsky's functional performance scale, the groups are comparable (p=0.10), the score of the majority patients being 90…100 points (94 (69%)). The overall baseline status of the patients did not show significant differences between the groups, with the majority of patients being in satisfactory or moderate condition (p=0.24).

Practically all patients had at least one concomitant disease (99.2%). Among the comorbidities, arterial hypertension, coronary heart disease (CHD) and chronic heart failure (CHF) were prevalent (116 (85.9%), 73 (53.6%) and 71 (52.2%), respectively).

As shown in Table 1, most of the comorbidities were related to atherosclerosis and cardiovascular diseases. Comparative analysis of various comorbidities showed that the groups were comparable without statistically significant differences (p>0.05). Only the CHD was more frequent in the LT group than in the LS group ((67.9%) vs. 37 (44.5%) cases, respectively, p=0.009). Mild anemia was found in 89 (65.4%) patients, and severe anemia in 22 (16.1%), with no significant differences (p=0.23). Chronic comorbidities of the gastrointestinal tract were found in 41 (30.1%) patients, the distribution between groups not being different (p=0.70).

Overall, before the operation, 71 (52%) patients were found to have complications of the colon cancer such as toxic anemic syndrome, tumor lysis syndrome, or cachexy, the complications being distributed evenly between the groups (p=0.06). Complications requiring surgical intervention, such as intestinal obstruction, tumor stenosis, or perifocal inflammation, were also found. The surgeries done on the abdominal organs and pelvic organs were performed equally in both groups (p=0.21).

Descriptive statistics and comparative analysis of surgical, laboratory and early postoperative data

Similar to the TNM-8 (2017) classification before surgery, the groups showed no significant differences in the pathological stage of the disease according to the TNM-8

Parameter	Total (n=136)	LS (n=83)	LT (n=53)	p-value
Age, years	83 (79–85)	83 (78–85)	83 (79–85)	0.53
Sex, % Male Female	 53 (38.9) 83 (61.1)	 33 (39.7) 50 (60.3)	 20 (37.7) 33 (62.3)	0.85
BMI, % Norm Excess weight Obesity	 59 (43.7) 47 (34.8) 29 (21.5)	 37 (45.1) 28 (34.1) 17 (20.8)	 22 (41.5) 19 (35.8) 12 (22.7)	0.91
Tumor localization Right half Left half Transverse	 71 (52.2) 54 (39.7) 11 (8.1)	 45 (54.2) 33 (39.7) 5 (6.1)	 26 (49) 21 (39.6) 6 (11.4)	0.53
Stage before operation TNM I II III	 15 (11) 57 (41.9) 64 (47.1)	 12 (14.5) 32 (38.5) 39 (47)	 3 (5.8) 25 (47.1) 25 (47.1)	0.26
Karnofsky's score, % 90–100 70–80 60–70	 94 (69.1) 38 (27.9) 4 (2.9)	 62 (74.7) 20 (24.1) 1 (1.2)	 32 (60.4) 18 (34) 3 (5.6)	0.10
Pre-operative CUD, % IO TAS CAS Cachexy PFI Apostasis Hemorrhage TLS	 31 (22.7) 15 (11) 12 (8.8) 6 (4.4) 3 (2.2) 2 (1.4) 1 (0.7) 1 (0.7)	 15 (18) 7 (8.4) 9 (10.8) 5 (6.0) 1 (1.2) 0 0 1 (1.2)	 16 (30.1) 8 (15) 3 (5.6) 1 (1.9) 2 (3.8) 2 (3.8) 1 (1.9) 0	0.06
Preoperative severity of patient condition, % Satisfactory Medium Severe	 56 (41.1) 67 (49.2) 13 (9.5)	 36 (43.3) 37 (44.5) 10 (12)	 20 (37.7) 30 (56.6) 3 (5.6)	0.24
AH, %	116 (85.9)	69 (84.1)	47 (88.6)	0.61
DM, %	25 (18.3)	17 (20.4)	8 (15)	0.50
CKD, %	13 (9.6)	8 (9.6)	5 (9.4)	0.60
CHD, %	73 (53.6)	37 (44.5)	36 (67.9)	0.009
c/a AMI, %	18 (3.2)	8 (9.6)	10 (18.8)	0.13
CCVA, %	40 (29.4)	26 (31.3)	14 (26.4)	0.54
c/a ACVA, %	12 (8.8)	8 (9.6)	4 (7.5)	0.76
CHF, %	71 (52.2)	43 (51.8)	28 (52.8)	0.90
HRD, %	41 (30.1)	27 (32.5)	14 (26.4)	0.44
GC, %	41 (30.1)	26 (31.3)	15 (28.3)	0.70
Anemia, % Minor Moderate	 89 (65.4) 22 (16.1)	 51 (61.4) 13 (15.6)	 38 (71.7) 9 (16.9)	0.23
History of AO, %	57 (42.2)	31 (37.8)	26 (49)	0.21

AH – arterial hypertension. AO – abdominal operations. GD – gastrointestinal diseases. CHF – congestive heart failure. BMI – body mass index. CHD – coronary heart disease. IO – intestinal obstruction. KPS – Karnofsky performance scale. HRD – heart rhythm disturbances. CUD – complications of the underlying disease. PFI – perifocal inflammation. CAS – cancer associated stenosis. DM – diabetes mellitus. c/a AMI – condition after acute myocardial infarction. c/a ACVA – condition after acute cerebrovascular accident. TLS – tumor lysis syndrome. TAS – toxic anemic syndrome. CKD – chronic kidney disease. CCVA – chronic cerebrovascular accidents.

Table 1. *Comparative analysis of baseline demographic and clinical characteristics of patients with colorectal cancer (CRC)*

Таблица 1. *Сравнительный анализ исходных демографических и клинических характеристик групп пациентов с раком ободочной кишки (РОК)*

(2017) classification (p=0.58). However, most patients had stage II disease. Histopathological analysis revealed adenocarcinoma in 118 (90.7%) patients, as well as rare cases of mucinous adenocarcinoma and carcinoma. The results are shown in **Tables 2** and **3**.

According to the ASA anesthetic and surgical risks, class II was found in 112 (82.3%) cases, followed by class III (21 (15.4%)).

The results of operative data and their analysis is shown in **Table 4**.

Despite similar operative time values for both groups (p=0.19), intraoperative blood loss was significantly higher in the LT group than in the LS group (p≤0.001) (**Fig. 1**). The overall postoperative status was comparable between the groups, the majority of patients being in satisfactory condition (p=0.15). Both the total hospitalization time and the postoperative hospitalization time were significantly

Parameter	Incidence (percentage)
ASA Class, % I II III IV	 1 (0.74) 112 (82.35) 21 (15.44) 2 (1.47)
Non-surgical postoperative complications, % Acute urinary retention Hemorrhagic anemia Pneumonia Pulmonary thromboembolism Encephalopathy Mesenteric thrombosis Hypoglycemia Pancreatitis Fever	 5 (3.85) 4 (3.08) 4 (3.08) 2 (1.54) 2 (1.54) 1 (0.77) 1 (0.77) 1 (0.77) 1 (0.77)
Histopathological landscape Adenocarcinoma (AC) Mucinous AC AC with mucinous component Carcinoma	 118 (90.7) 5 (3.8) 4 (3.0) 3 (2.3)

Table 2. *Descriptive results of perioperative data*

Таблица 2. *Описательные результаты периоперационных данных*

Parameter	Total (n=136)	LS (n=83)	LT (n=53)	p-value
TNM stage after surgery I II III	 29 (21.3) 63 (46.3) 44 (32.3)	 20 (24.1) 36 (43.3) 27 (32.5)	 9 (16.9) 27 (50.9) 17 (32)	0.58
Hb level before surgery, mg/dl	107.2±18.3	107.7±18.2	106.3±18.5	0.68
Hb level after surgery, mg/dl	102.5±13.3	102.9±13.1	101.9±13.7	0.66
CRP on day 3 after surgery, mg/dl	106 (73–147)	93 (68–136)	127 (98–183)	≤0.001
CRP on day 5 after surgery, mg/dl	64 (35–89)	51 (25–75)	81 (50–103	≤0.001
TOT, min.	145 (122–182)	150 (125–180)	135 (115–190)	0.19
IBL, ml	60 (50–150)	50 (30–50)	150 (100–250)	≤0.001
Severity of condition after surgery, % Satisfactory Moderate Severe	 67 (49.2) 50 (36.7) 19 (13.9)	 46 (55.4) 28 (33.7) 9 (10.8)	 21 (39.6) 22 (41.5) 10 (18.8)	0.15
Postsurgical pain syndrome, % Mild Moderate Severe	 94 (69.1) 41 (30.1) 1 (0.7)	 80 (96.3) 2 (2.4) 1 (1.2)	 14 (26.4) 39 (73.5) 0	≤0.001
PNSC, %	24 (17.6)	6 (7.2)	18 (33.9)	≤0.001
Wound infections, %	13 (9.5)	5 (6)	8 (15)	0.13
Anastomotic bleeding, %	2 (1.4)	0	2 (3.7)	0.15
Anastomotic leakage	4 (2.9)	1 (1.2)	3 (5.6)	0.16
Post-operative peritonitis	6 (4.4)	3 (3.6)	3 (5.6)	0.1
Abdominal abscess	6 (4.4)	2 (2.4)	4 (7.5)	0.25
Adhesive intestinal obstruction	1 (0.73)	0	1 (1.8)	0.16
THT, days	11 (9–13)	10 (9–12)	13 (10–17)	≤0.001
PHT, days	7 (7–10)	7 (6–8)	9 (7–13)	≤0.001
Postoperative mortality	4 (2.94)	3 (3.6)	1 (1.8)	1.0

Hg – уровень гемоглобина, TOT – total operating time, IBL – intraoperative blood loss, THT – total hospitalization time, PNSC – postoperative non-surgical complications, PSC – postoperative surgical complications, PHT – postoperative hospitalization time, CRP – C-reactive protein.

Table 3. *Comparative analysis of surgical, laboratory, and early postoperative outcomes*

Таблица 3. *Сравнительный анализ хирургических, лабораторных и ранних послеоперационных результатов*

longer in the LT group (p≤0.001) (Fig. 2). Median values and interquartile ranges for the duration of hospital stay are shown in **Table 3**.

Pre- and post-operative hemoglobin values did not differ between groups (p=0.68 and p=0.66, respectively). At the same time, the CRP levels both on the third and fifth day after the surgery differed significantly between the groups and were higher in the LT group (p≤0.001 for both measurements). Mild postsurgical pain was found in 94 (69.1%) patients, moderate pain in 41 (30.1%) patients; the patients of LT group suffered more from moderate pain as compared to the patients of the LS group (39 (73.5%) vs. 2 (2.4%), p≤0.001). Overall, 67 (49.2%) patients were in satisfactory, 50 (36.7%), in moderate, and 19 (13.9%), in severe condition. Comparative analysis of the groups by general condition showed similar results without statistically significant differences (p=0.15). The comparative results are presented in **Table 3**.

A total of 24 (17.6%) non-surgical complications and 8 (5.8%) surgical complications were reported (**Table 2**). The majority of non-surgical complications were urinary retention, posthemorrhagic anemia and pneumonia, as well as isolated cases of pulmonary embolism, pancreatitis and hypoglycemia (**Table 2**). No severe complications, such as sepsis and multiple organ failure were reported. Non-surgical complications were found mainly in patients in the RT group (p≤0.001). Major surgical complications such as anastomotic leakage, postoperative peritonitis, and complications related to wound infection and abdominal abscesses were recorded without statistically significant differences between groups (p>0.05).

After surgery, slightly more patients were recorded with severe condition, but no significant differences were observed (p=0.25). In contrast, laboratory parameters changed significantly depending on the period: the level of Hb in the blood decreased significantly after surgery (107.2±18.3 vs. 102.5±13.3 mg/dL, respectively, p≤0.001), while the level of

Parameter	Before the surgery (n=136)	After the surgery (n=136)	p-value
Severe patients	13 (9.5)	19 (13.9)	0.25
Intestinal obstruction	32 (27.1)	1 (0.7)	≤0.001
Hemoglobin	107.2±18.3	102.5±13.3	≤0.001
C-reactive protein	106 (73–147)*	64 (35–89)**	≤0.001

**day 3, **day 5*

Table 4. *Comparative analysis of clinical, laboratory, and surgical characteristics before and after surgery*

Таблица 4. *Сравнительный анализ клинических, лабораторных и хирургических характеристик до и после операции*

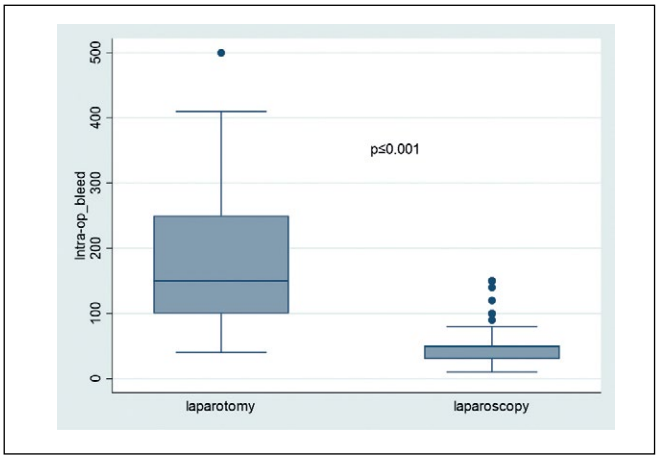

Figure 1. *The total intraoperative blood loss was higher in the LT group.*

Рисунок 1. *Общая интраоперационная кровопотеря была выше в группе ЛТ.*

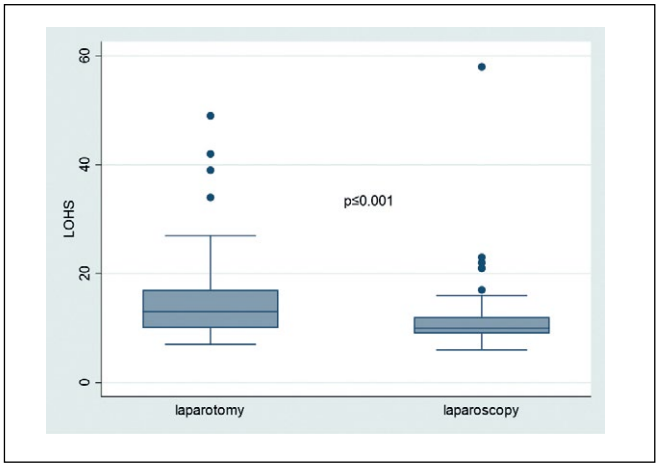

Figure 2. *The duration of postoperative hospital stay (DPHS) was shorter in the LS group than in the LT group.*

Рисунок 2. *Длительность послеоперационного пребывания в стационаре (ДППС) была короче в группе ЛС, чем в группе ЛТ*

Factor	Variable type	Coding
Age	Quantitative	-
Sex	Qualitative	Male Female
CKD	Qualitative	No Yes
Surgical approach	Qualitative	LS LT
TOT	Quantitative	-
CRP-3	Quantitative	-
PSC	Qualitative	No complications Pneumonia MT Hypoglycemia Pancreatitis Fever HA

HA – hemorrhagic anemia, LS – laparoscopy, LT – laparotomy, MT – mesenteric thrombosis, TOT – total operating time, PSC – postsurgical complications, CKD – chronic kidney disease, CRP-3 – C-reactive protein on the third day

Table 5. *Characteristics and coding of independent variables in the selected multiple logistic regression model*

Таблица 5. *Характеристика и кодировка независимых переменных выбранной модели МЛР*

CRP decreased significantly from the third to the fifth day (p≤0.001).

Postoperative mortality in the main group was 3.61% (3/83), while in the control group it was 1.89% (1/53). The statistical analysis of the frequency of deaths between the groups did not reveal any significant differences (p=1.0). This indicates the absence of a statistically significant effect of the studied factor on postoperative mortality.

Results of multivariate linear regression analysis (MLR)

Multivariate linear regression analysis was performed to identify factors that influence the overall length of hospital stay, other than surgical approaches. In addition to surgical approach, variables that showed statistical significance in univariate analysis were selected as independent variables: sex, age, presence of chronic kidney disease (CKD), total operative time, CRP, and presence of non-surgical postoperative complications (**Table 5)**.

The regression model demonstrated acceptable accuracy: the hat value was p=0.96, and the hatsq value was p=0.007 in the linearity test (linktest). The level of explainability of the model, estimated through the Nagelkerke R^2 coefficient, was 0.42. Among the independent variables, the following were statistically significant factors: method of laparoscopy (β = -2.62; p = 0.03; 95% CI: -4.999 – -0.250), CRP level on the third day (β = 0.03; p = 0.002; 95% CI: 0.016 – 0.063), total operating time (β = 0.03; p = 0.002; 95% CI: 0.011 – 0.050), and postoperative complications, including pneumonia (β = 0.01; p = 0.001; 95% CI: 1.205 – 11.328), mesenteric thrombosis (β = 22.49; p ≤ 0.001; 95% CI: 13.843 – 31.146), and hemorrhagic anemia (β = 6.69; p = 0.01; 95% CI: 1.439 – 11.952). Postoperative hypoglycemia and pancreatitis showed borderline statistical significance (p=0.05). At the same time, such variables as sex, age and presence of CKD did not demonstrate significant interaction with the total duration of hospitalization within this model (p>0.05). The data are presented in Table 6.

DISCUSSION

The results of our study showed that the groups of patients operated by laparoscopic and laparotomic methods were comparable in key parameters, which allowed us to conduct a comparative assessment of the impact of surgical access on early postoperative outcomes. The absence of significant differences in such parameters as age, sex, BMI, functional status and comorbidities confirms the balance of the initial data between the groups.

The histopathological analysis confirmed the predominance of adenocarcinoma in both groups, which is consistent with the literature data on CRC [1, 11, 12]. At the same time, despite similar demographic characteristics, the LS and LT groups differed significantly in a number of operative and early postoperative factors. One of the most significant differences was the difference in the volume of blood loss, which was significantly higher in the LT group.

This fact confirms the advantages of the laparoscopic method known for its lower trauma and better visualization due to optical magnification. This allows for less intraoperative blood loss, which also contributes to faster recovery of patients [3, 13, 14].

Besides, the patients of the LT group showed longer hospital stay periods and higher CRP levels on the third and fifth days after the operation, which shows a demonstrated inflammatory response and prolonged recovery [15–17]. The patients in the LT group reported moderate postoperative pain more frequently, which might be related to a more traumatic character of surgical access. These differences highlight not only the advantages of laparoscopic surgery in terms of minimizing trauma, but also a more comfortable recovery in a complex category of patients with multiple comorbidities [14, 18].

Regarding complications, non-surgical complications such as urinary retention, anemia and pneumonia were more prevalent in the LT group, which is associated with the more traumatic nature of this approach and an increased inflammatory response [13, 18]. At the same time, no serious complications such as sepsis or multiple organ failure were registered, indicating the high safety of both techniques. In addition, isolated complications were noted without significant differences between the groups, indicating the safety of both types of surgical approaches.

Parameter	ncβ	cβ	SE	Z/T	p	95% CI
Age		0.14	0.14	0.99	0.32	-0.142 – 0.426
Male sex		-0.07	1.16	-0.07	0.94	-2.396 – 2.240
CKD		3.23	1.87	1.73	0.08	-0.475 – 6.953
LC	-4.18	-2.62	1.19	-2.19	**0.03**	-4.999 – -0.250
TOT		0.03	0.01	3.40	**0.001**	0.016 – 0.063
Pneumonia	5.98	6.26	2.55	2.45	**0.01**	1.205 – 11.328
MT	24.5	22.49	4.36	5.15	**≤0.001**	13.843 – 31.146
Hypoglycemia	15.5	11.64	6.06	1.92	0.05	-0.379 – 23.670
Pancreatitis	10.5	8.28	4.32	1.92	0.05	-0.286 – 16.847
HA	11.2	6.69	2.65	2.53	**0.01**	1.439 – 11.952
Fever		5.95	6.01	0.99	0.32	-5.96 – 17.864
CRP-3	0.04	0.03	0.009	3.19	**0.002**	0.011 – 0.050

HA – hemorrhagic anemia, LS – laparoscopy, MT – mesenteric thrombosis, TOT – total operating time, CRP-3 – C-reactive protein on the third day, CKD – chronic kidney disease; ncβ – non-corrected beta, cβ – corrected beta, SE – standard error, CI – confidence interval, Z/T – Z/T test.

Table 6. *Multiple logistic regression (MLR) results showed significant outcomes*

Таблица 6. *Результаты МЛР показали значимые результаты*

The obtained results of postoperative mortality show that mortality in both groups remains low and does not demonstrate significant differences.

Laboratory data, such as a decrease in Hb levels and CRP dynamics, demonstrate typical physiological responses of the body to surgical intervention [15]. Despite the increase in the number of patients with decompensation in the postoperative period, this indicator did not reach statistical significance, which highlights the importance of further research to understand the impact of the surgical method on the overall status of the patient in a better way.

The results of our study support the hypothesis that laparoscopic surgery has significant advantages over laparotomy in elderly patients. We also successfully achieved the primary endpoint of overall hospital stay, which differed significantly between groups, as well as secondary endpoints such as intraoperative blood loss, postoperative complications, inflammatory response, and postoperative pain severity. Multivariate linear regression confirmed the importance of factors such as surgical method, CRP on day 3, intraoperative blood loss and postoperative complications in determining the total length of hospital stay, which further strengthens the conclusion about the advantages of the laparoscopic method in the context of rapid recovery and minimization of complications in a complex category of patients.

Shortcomings

The limitations of our study include the limited sample size and lack of randomization, which reduces the validity of generalizations and the ability to control of all influencing variables. The study is also limited by early postoperative outcomes and the lack of long-term outcome databases.

CONCLUSION

The conclusions of this study confirm that laparoscopic access shows considerable advantages as compared to conventional laparotomy in the surgical treatment of colon cancer, especially in patients above 75 years of age. Laparoscopic surgery is associated with less intraoperative blood loss, which confirms its lower trauma. The patients who underwent a laparoscopic surgery showed better outcomes in postoperative recovery with lower levels of C-reactive protein and lower indicators of inflammatory process. Post-surgery complications were seen mainly in the laparotomy group. These data emphasize the importance of choosing a laparoscopic approach to improve postoperative recovery and reduce the risk of complications in elderly patients with colonic malignancies.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical Approval Statement. The study was approved by the Local Ethics Committee of Sechenov University, protocol No. 21-23, dated 16.11.2023	***Этическая экспертиза.*** Исследование одобрено локальным этическим комитетом ФГАОУ ВО «Первый Московский государственный медицинский университет имени И.М. Сеченова (Сеченовский Университет)», протокол № 21–23 от 16.11.2023.
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Galkin V.N.: project management, editing of the manuscript. Erygin D.V.: concept and design of the study. Orozbekov A.O., Baktybek uulu A.: data collection, writing of the original text. Sklyar I.A.: literature review. Abibillaev D.A., Konurbaev B.T.: statistical analysis, interpretation of results. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Галкин В. Н. – руководство проектом, редактирование рукописи. Ерыгин Д.В. – концепция и дизайн исследования. Орозбеков А.О., Бактыбек уулу А. – сбор данных, написание оригинального текста. Скляр И.А. – обзор литературы. Абибиллаев Д.А., Конурбаев Б.Т. – статистический анализ, интерпретация результатов. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Retrospective analysis of surgical outcomes of delayed pharyngeal defect reconstruction in patients with advanced laryngeal and laryngopharyngeal cancer after laryngectomy

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Abstract

Aim – to retrospectively analyze the results of surgical treatment of delayed reconstruction of pharyngeal defects in patients with advanced laryngeal and laryngopharyngeal cancer after laryngectomy.

Material and methods. We performed a retrospective analysis of 437 case histories of patients treated in Samara Regional Clinical Oncology Center in the period from 2015 to 2019 with malignant neoplasms of the larynx and laryngeal pharynx, who had previously undergone combined and extended-combined laryngectomies. In the retrospective analysis, we studied the structure of complications after delayed reconstructive surgeries of type 0-II pharyngeal and pharyngo-esophageal defects. Local tissue, pectoral flap, and deltopectoral flap were used as plastic material. Complications in the postoperative period were observed in all types of plasty.

Results. The most frequent complications included inflammation of the postoperative wound, anastomosis failure with subsequent formation of fistulas or secondary faryngostomas. In type 0 pharyngeal defects, plastic surgery with the use of local tissues showed a good result, postoperative complications occurred in 11% of cases. In I type pharyngeal defects, fistulas and secondary stomas in the postoperative period were formed in 83% of cases when local tissues were used, in 45.8% when pectoral flap was used and in 66.5% when deltopectoral flap was used. In type II of the defect, the percentage of postoperative complications when using a pectoral flap was 75% and deltopectoral flap – 100%.

Conclusion. Complications in the postoperative period were observed in all types of plasty. The study of risk factors and creation of the algorithm for selection of patients for delayed plasty will allow to determine the terms and indications for delayed reconstructive-reconstructive surgery, as well as to reasonably reduce the risk of postoperative complications.

Keywords: laryngeal cancer, laryngopharyngeal cancer, pectoral flap, deltopectoral flap, plastic material.

Conflict of interest: nothing to disclose.

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Ретроспективный анализ результатов хирургического лечения отсроченных реконструкций дефектов глотки у пациентов с распространенным раком гортани и гортаноглотки после ларингэктомии

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Аннотация

Цель – провести ретроспективный анализ результатов хирургического лечения отсроченных реконструкций дефектов глотки у пациентов с распространенным раком гортани и гортаноглотки после ларингэктомии.

Материал и методы. Проведен ретроспективный анализ 437 историй болезни пациентов, прошедших лечение в СОКОД в период 2015–2019 гг. со злокачественными новообразованиями гортани и гортанного отдела глотки, которым ранее были выполнены комбинированные и расширенно-комбинированные ларингэктомии. При ретроспективном анализе нами была изучена структура осложнений после отсроченных реконструктивных операций фарингеальных и фарингоэзофагеальных дефектов 0-II

типов. В качестве пластического материала применялись местные ткани, пекторальный лоскут, дельтопекторальный лоскут. При всех видах пластики наблюдались осложнения в послеоперационном периоде.

Результаты. Наиболее частыми осложнениями являлись воспаление послеоперационной раны, несостоятельность анастомоза с последующим формированием свищей или рефарингостом. При 0 типе дефекта глотки хороший результат показала пластика с использований местных тканей, послеоперационные осложнения возникли в 11% случаев. При I типе дефекта глотки свищи и рестомы в послеоперационном периоде сформировались в 83% случаев при использовании местных тканей, в 45,8% – при использовании пекторального лоскута и в 66,5% – при использовании дельтопекторального лоскута. При II типе дефекта процент послеоперационных осложнений при применении пекторального лоскута составил 75% и дельтопекторального лоскута – 100%.

Заключение. При всех видах пластики наблюдались осложнения в послеоперационном периоде. Изучение факторов риска и создание алгоритма отбора пациентов позволит определить сроки и показания к отсроченной реконструктивно-восстановительной операции, а также обоснованно снизить риск послеоперационных осложнений.

Ключевые слова: рак гортани, рак гортаноглотки, пекторальный лоскут, дельтопекторальный лоскут, пластический материал.

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ПЛ – пекторальный лоскут, ДЛП – дельтопекторальный лоскут, ПМ – пластический материал.

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INTRODUCTION

Laryngeal cancer and cancer of the hypopharynx are the most common diseases among malignant neoplasms of the head and neck. The incidence of malignant neoplasms of the larynx and the laryngeal part of the pharynx in Russia has been increasing over the years; in 2021, it reached 29.1 and 12.8 per 100 thousand people, respectively [1]. As many as 83% patients have stage III or IV of cancer of the larynx and the laryngeal part of the pharynx at the moment of diagnostics, and the overall 5-year survival is from 15% to 45% [1, 2]. Malignant neoplasms of the larynx and laryngopharynx are most often observed in men aged 50 to 65 years [2]. Patients with a locally advanced stage and complications in the form of stenosis and dysphagia receive surgical treatment at the first stage, which often leads to disability, namely, to disruption of the integrity of the alimentary tract, and requires subsequent surgical rehabilitation, viz. delayed reconstruction [3]. The stages of surgical rehabilitation and time of the delayed reconstruction depend on the time of completion of specialized treatment, usually, the radiotherapy. According to the literature, the average period of delayed reconstruction of pharyngeal defects is 3-4 months after completion of specialized treatment [4]. To restore the alimentary canal and reduce complications, it is necessary to determine the type of pharyngeal defects and the option of delayed reconstruction [5].

One of the papers suggests the following classification of defects: type 0 – small defects closed primarily without the introduction of tissue; type 1 – non-circumferential defects that preserve a viable strip of mucosa from the hypopharynx to the cervical esophagus; type 2 – circumferential defects extending from the vallecula, i.e. the depression between the root of the tongue and the lingual surface of the epiglottis, to the thoracic inlet; type 3 – circumferential defects that extend from the level of the vallecula cranially to the oropharynx; type 4 – extensive defects that extend below the clavicles to the thoracic esophagus. Depending on the type, different grafts are used. The following frequent complications are seen on the stage of delayed reconstruction: inflammation of the surgical wound, anastomotic leakage, marginal necrosis of the tissue flap, and restomas [7]. At the same time, there is no analysis of the treatment results for delayed reconstruction of pharyngeal defects depending on the timing, somatic status and a number of other factors affecting healing in the scientific literature, although it can help determine the indications, as well as the choice of material and method for plastic surgery for each patient based on the principle of a personalized approach [5, 8].

AIM

To retrospectively analyze the results of surgical treatment of delayed reconstruction of pharyngeal defects in patients with advanced laryngeal and laryngopharyngeal cancer after laryngectomy.

MATERIAL AND METHODS

A retrospective analysis of 437 case histories of patients treated at the head and neck tumor department of the Samara Region Clinical Oncology Dispensary in 2015–2019 with malignant tumors of the larynx and the laryngeal section of the pharynx, who had undergone combined and extended combined laryngectomies.

The group of patients (n=40) underwent delayed reconstruction of pharyngeal and pharyngo-esophageal defects after specialized treatment in various terms, from 3 to 6 months. Of the 40 patients, there were 38 men (95%) and 2 women (5%). The age of patients was from 42 to 74 years. The study included patients with advanced laryngeal (n=21) and laryngopharyngeal (n=19) cancer, T3-4N0-2M0. In their first stage, they had a radical surgical treatment and post-surgery radiotherapy (**Table 1**).

All patients underwent laryngopharyngectomy with selective cervical dissection and formation of the

Localization		Larynx		Laryngopharynx	
		n=21 (52,5%)		n=19 (47,5%)	
		Abs.	%	Abs.	%
T Symbol	T3	15	37.5%	8	20%
	T4	6	15%	11	27.5%
N Symbol	N0	17	42.5%	3	7.5%
	N1	3	7.5%	9	22.5%
	N2	1	2.5%	7	17.5%

Table 1. *Number of patients depending on localization and T and N criteria*

Таблица 1. *Количество пациентов в зависимости от локализации и критериев T, N*

pharyngostoma or pharyngo-esophagostoma. In 20 patients, metastases were confirmed to the regional lymph nodes. The patients in the incipient phases, remote metastases, severe concomitant pathologies were not included in the study. In 9 patients, minor defects of the pharynx were found that were of the Type 0. In 25 patients, the defects of the pharynx were non-circumferential, preserved a viable strip of mucosa and were of Type I. In 6 patients, there were minor circumferential defects of Type II. Patients with defects of Types III and IV were not included in this study due to the large size of defects that required several stages of reconstruction and use of free microvascular flaps. The types of pharyngeal defects depending on the tumor localization are shown in **Table 2**.

The patients underwent delayed reconstructions of pharyngeal defects with the use of local tissue, delta-pectoral and pectoral musculocutaneous flap on axial blood supply, depending on the defect type (**Fig. 1**).

The repair of pharyngeal defects with local tissue was used mainly in Type 0 and Type I defects as follows: at a distance of 1.0–1.5 cm from the edge of the defect, a bounding incision was made along the entire circumference of the defect with preparation of cutaneous edges to the center of the defect. The latter were drawn together and sewn with noose sutures with formation of the internal lining of the pharynx. The defect on the neck was then covered with the prepared cutaneous flaps from the cervical area. In pharyngeal defects of Types I and II, the reconstruction was performed with the use of deltopectoral and pectoral flaps with axial blood supply. The use of the deltopectoral flap involved a bounding incision along the entire circumference of the defect with preparation of cutaneous edges to the center of the defect. The latter were drawn together and sewn with noose sutures with formation of the internal lining of the pharynx. Afterwards, the defect on the neck was covered with the deltopectoral flap on axial blood supply from the perforating branches of the internal thoracic artery by rotating the flap. The cutaneous edges of the defect on the neck and the edges of the flap skin were sewn to the skin with noose sutures. In the case of the pectoral flap, the internal lining was also formed after a bounding incision along the entire circumference of the defect with

Localization	Defect type		
	Type I	Type II	II тип
Larynx (n=21)	8 (20%)	13 (32,5%)	0 (0%)
Laryngopharynx (n=19)	1 (2,5%)	12 (30%)	6 (15%)

Table 2. *Types of pharyngeal defects depending on tumor location*

Таблица 2. *Типы дефектов глотки в зависимости от локализации опухоли*

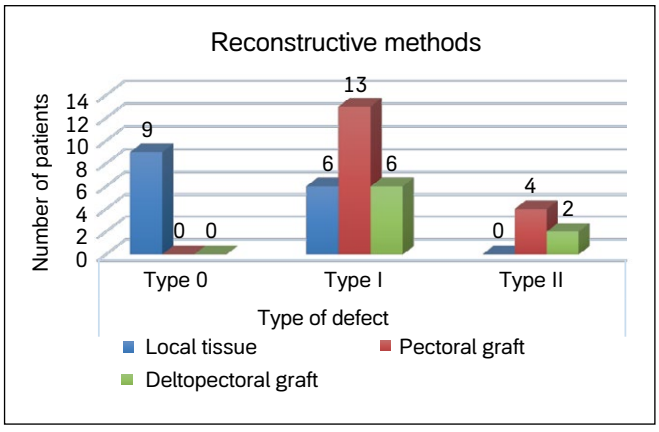

Figure 1. *Reconstruction methods depending on the type of pharyngeal defect.*

Рисунок 1. *Методы реконструкции в зависимости от типа дефекта глотки.*

preparation of cutaneous edges to the center of the defect, which were also drawn together and sewn with noose sutures. In the next step, the defect on the neck was covered with the pectoral musculocutaneous autogenous graft on axial blood supply from the descending branches of acromiothoracic vessels by rotating the flap. The cutaneous edges of the defect on the neck and the edges of the flap skin were sewn to the skin with noose sutures.

RESULTS

Plastic surgery of Type 0 pharyngeal defects was performed in 9 patients using only local tissues. Among these patients, only in one case there was seen an inflammation of the surgical wound, suture failure and, consequently, development of the fistula (**Fig. 2**).

Plastic surgery of Type I pharyngeal defects was performed in 25 patients. In 6 patients, the surgery involved local tissue, where 4 out of 6 (66.7%) patients had inflammation of the surgical wound, failure of the anastomotic suture in the early postoperative period; this resulted in one case out of six (16.7%) in the development of a fistula, and in three cases out of six (50%), development of a repharyngostoma (**Fig. 3**).

In one case out of six, the inflammation of the surgical wound, failure of the anastomotic suture and development of

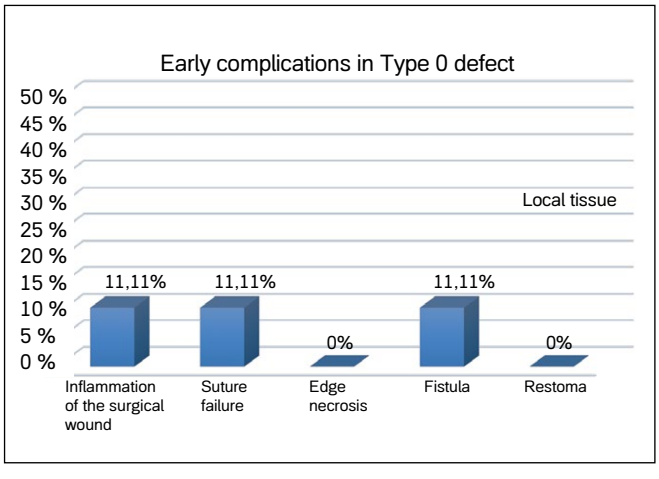

Figure 2. *Early complications in type 0 pharyngeal defect.*

Рисунок 2. *Ранние осложнения при 0 типе дефекта глотки.*

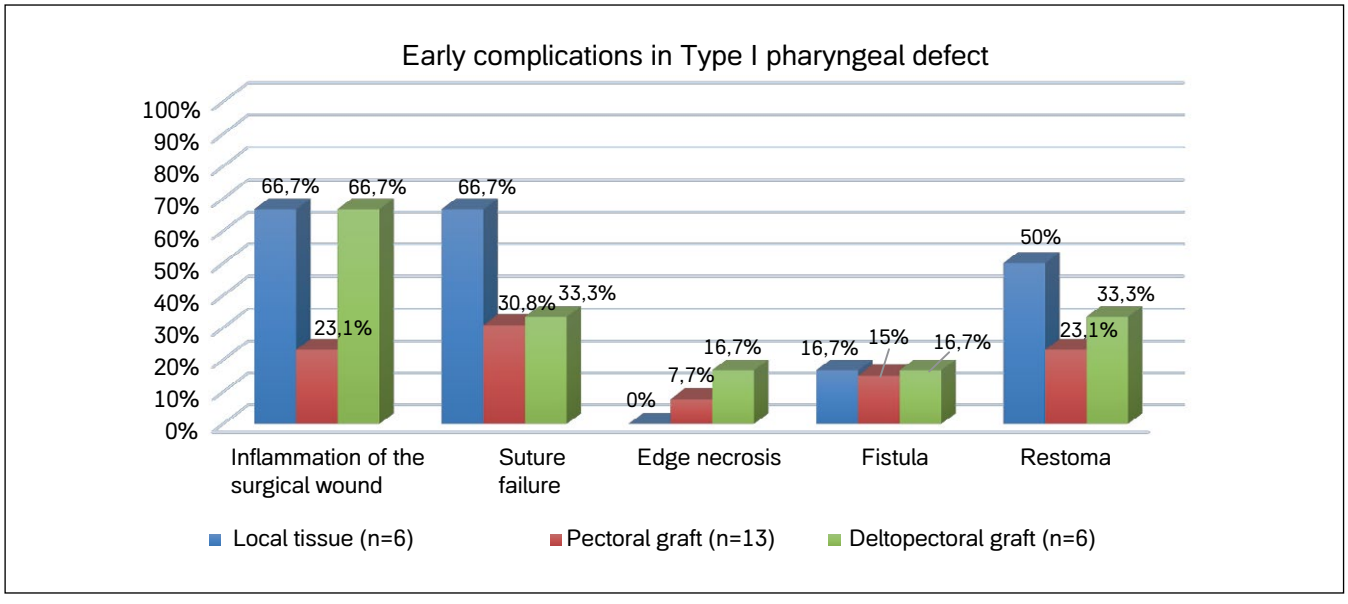

Figure 3. *Early complications in type I pharyngeal defect.*
Рисунок 3. *Ранние осложнения при I типе дефекта глотки.*

repharyngostoma were seen on the sixth day, i.e. in the late postoperative period (**Fig. 4**).

In 13 out of 25 patients, the pectoral flap was used as the grafting material. In the early postoperative period, in 3 cases out of 13 (23.1%), inflammation of the surgical wound was seen, in 4/13 cases (30.8%), failure of anastomotic suture, in 1/13 patients (7.7%), edge necrosis of the graft was observed, in 2/13 cases (15%), fistulae developed, and in 3/13 cases (23.1%), the repharyngostoma (Fig. 3). In the late postoperative period, in 1 patient out of 13 (7.7%) failure of anastomotic suture with formation of the fistula was observed (**Fig. 4**). In 6 out of 25 patients, the deltopectoral flap was used as the grafting material. In the early postoperative period, in 4 out of 6 (66.7%) patients, inflammation of the surgical wound was seen, in 2/6 cases (33.3%), failure of anastomotic suture, which resulted in one case in the formation of a fistula and in another, of a repharyngostoma; in 1 case out of 6 (16.7%), edge necrosis of the graft with formation of a repharyngostoma was observed (**Fig. 3**). In the late postoperative period, on the seventh day, in 1 case out of 6 (16.6%) the inflammation, edge necrosis of the flap, and formation of the repharyngostoma were observed (**Fig. 4**). Plastic surgery of Type II pharyngeal defects was performed in 6 patients. In 4 cases out of 6, the pectoral flap was used as the grafting material. In the early postoperative period, in 2 cases out of 4 (50%), failure of the surgical wound was seen, in 1 case out of 4 (25%), the inflammation of the surgical wound. In 1 patient out of 4 (25%), a fistula developed, and in 1 case out of 4 (25%), a repharyngostoma (**Fig. 5**).

In the late postoperative period, on the seventh day, in 1 patient out of 4 (25%), the inflammation of the surgical

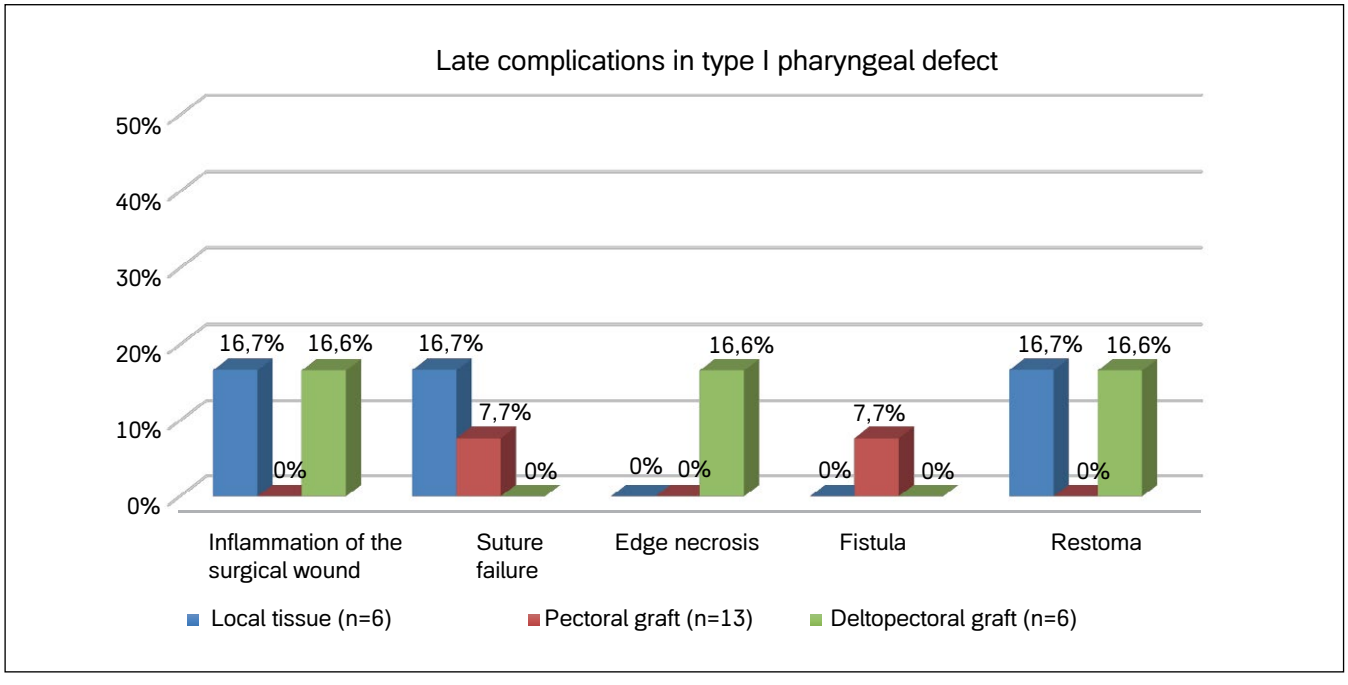

Figure 4. *Late complications in type I pharyngeal defect.*
Рисунок 4. *Поздние осложнения при I типе дефекта глотки.*

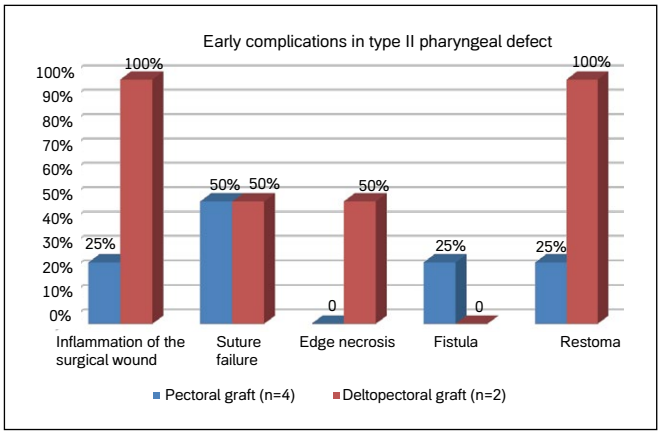

Figure 5. *Early complications in type II pharyngeal defect.*
Рисунок 5. *Ранние осложнения при II типе дефекта глотки.*

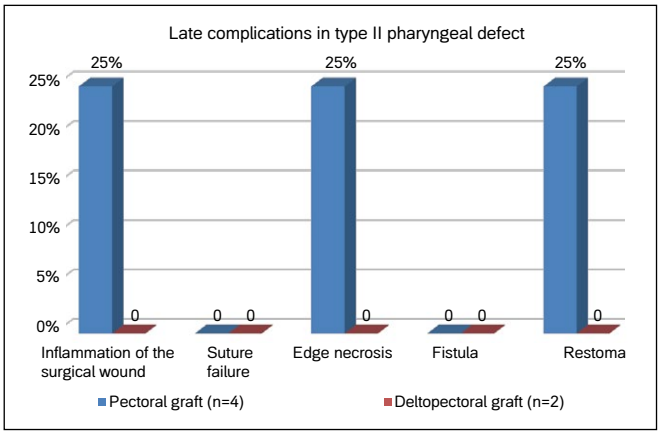

Figure 6. *Late complications in type II pharyngeal defect.*
Рисунок 6. *Поздние осложнения при II типе дефекта глотки.*

wound, edge necrosis of the graft and formation of the repharyngostoma were observed (**Fig. 6**).

In two patients out of six, the plastic surgery of the defect used the deltopectoral flap. In all cases, inflammation of the postoperative wound was observed in the early postoperative period, in one patient of two (50%), failure of anastomotic suture was observed, and in one patient of two (50%), the edge necrosis of the flap was seen. In both these patients, repharyngostomas formed (**Fig. 5**).

DISCUSSION

Reconstruction of pharyngeal and pharyngo-esophageal defects after laryngopharyngectomies is a complex task. The types of reconstructive techniques and types of grafts or flaps used can be divided into many categories depending on the size, shape, extent and whether the underlying defect being reconstructed is circumferential or not. Each type of plastic surgery has its own advantages and disadvantages [9].

In case of Type 0 pharyngeal defect, plastic surgery using local tissues showed a good functional result. The study of N. Süslü et al. (2016) used the data of 602 patients and showed that early that early enteral nutrition can be initiated even when using local tissue as the graft. In these patients, early enteral nutrition was initiated within 3 days of surgery, with a fistula incidence of approximately 11% [10]. In our study, during reconstruction of Type 0 pharyngeal defect with local tissues, only 1 patient out of 9 showed failure and fistula formation.

In type I pharyngeal defects, the best reconstructive method in terms of low probability of fistula and repharyngostoma formation is the use of the pectoral flap. Similar results were observed by other authors. Among 24 cases of pectoral flap use for non-circular pharyngeal defects described in the literature, swallowing was achieved in most patients within 7 to 14 days, and the incidence of fistula and repharyngostoma formation was 13% [3]. The use of the deltopectoral flap in the reconstruction of Type I pharyngeal defects has lower functional results. Some of the adverse postoperative complications reported in the literature are flap necrosis, fistula formation, and stenosis, with incidences of 67% among 12 patients who underwent pharyngeal reconstruction using the deltopectoral flap [11]. In our study, in 66% of cases, anastomotic suture failure and edge necrosis of the flap were observed; as a consequence, in all these cases, fistulas and refaryngostomas were formed.

In type II pharyngeal defects, the use of grafts on the axial blood supply led to a high rate of postoperative complications, resulting in the formation of fistulas and refaryngostomas. The incidence rate of postoperative complications was 75% with the use of the pectoral flap and 100% with the use of the deltopectoral flap. According to modern literature, the best options for reconstructing circular defects of the pharynx are free flaps (radial forearm flap, anterolateral thigh flap), and visceral flaps from fragments of intestinal tract. Complications in these types of grafting material may develop, according to different sources, in 7–26% cases [12, 13].

CONCLUSION

In this retrospective analysis, we studied the structure of complications after delayed reconstructive surgeries of pharyngeal and pharyngoesophageal defects of Types 0-II. Local tissue, pectoral and deltopectoral flaps were used as grafting material. Complications in the postoperative period were observed with all types of plastic surgery. The most common complications included: anastomotic failure with subsequent fistula formation and repharyngostoma. The reasons for the occurrence of these complications, given the viability of the grafting material, include post-radiation changes, the presence of an inflammatory process in the tissues in the area of the defect, the weakened nutritional status of the patient and a number of other reasons [14]. Thus, when planning delayed reconstruction of pharyngeal defects, in choosing the timing and type of grafting material, a personalized approach is needed in each clinical case, namely, determining the exact indications for delayed plastic surgery.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. A.O. Sidorenko: writing of the text. O.I. Kaganov, A.G. Gabrielyan: research design, editing of manuscript. A.A. Makhonin, A.E. Orlov: material processing. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** А.О. Сидоренко – написание текста. О.И. Каганов, А.Г. Габриелян – дизайн исследования, редактирование рукописи. А.А. Махонин, А.Е. Орлов – обработка материала. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Original research | Оригинальное исследование
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Comparative safety of intracorporeal versus extracorporeal anastomoses in laparoscopic right colectomy

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Abstract

Aim – to assess the safety of a hand-sewn intracorporeal ileo-transverse anastomosis.

Material and methods. The retrospective study included patients from the Omsk Regional Cancer Registry from 2015 to 2023. It included patients with colon cancer (ICD-10 C18), who underwent a laparoscopic right colectomy. In the study group patients had hand-sewn intracorporeal anastomoses dene under an original method, terminus-terminal invagination ileo-transverse anastomosis; in the control group patients had hand-sewn 'side-to-side' extracorporeal anastomoses.

Results. 89 patients were enrolled: 42 in the study group and 47 in the control group. No cases of anastomotic leakage were found in the study group versus 2 (4.3%) in the control group (p=0.496). Grade 3 and higher surgical morbidity was equal in both groups: 2 (4.8%) versus 5 (10.7%), p=0.550.

Conclusion. The hand-sewn original intracorporeal anastomosis is safe and can be considered by experienced laparoscopic surgeons. Further study is needed for a detailed comparative analysis with established techniques.

Keywords: colon cancer, right colectomy, intracorporeal anastomosis, laporoscopic surgery.

Conflict of interest: nothing to disclose.

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Сравнение безопасности интракорпоральных и экстракорпоральных анастомозов при лапароскопической правосторонней гемиколэктомии

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Аннотация

Цель – оценка безопасности формирования ручного интракорпорального илеотрансверзоанастомоза.

Материал и методы. Данная работа является ретроспективным исследованием, материалом для которого послужил онкологический регистр Омской области за период с 2015 по 2023 гг. В исследование включали всех пациентов с диагнозом «рак ободочной кишки», кодом по МКБ-Х С18, которым была выполнена лапароскопическая правосторонняя гемиколэктомия. В исследуемой группе формировали интракорпоральные анастомозы с использованием авторской методики – термино-терминальный инвагинационный илеотрансверзоанастомоз, в контрольной группе формировали ручной экстракорпоральный анастомоз «бок в бок».

Результаты. В исследование вошли данные 89 пациентов: 42 – в исследуемой и 47 – в контрольной группе. Случаев развития несостоятельности анастомоза в исследуемой группе не отмечено, в контрольной группе – у 2 (4,3%) пациентов (p=0,496). Общая частота послеоперационных осложнений 3 степени и выше также не различалась: у 2 (4,8%) и 5 (10,7%) пациентов соответственно (p=0,550).

Выводы. Предложенный нами метод формирования илеотрансверзоанастомоза безопасен и может быть рассмотрен для применения хирургами, прошедшими кривую обучения малоинвазивной колоректальной хирургии. Требуются дальнейшие исследования для оценки воспроизводимости полученных результатов и сравнения с другими техниками на более крупных исследуемых группах.

Ключевые слова: рак ободочной кишки, правосторонняя гемиколэктомия, интракорпоральный анастомоз, лапароскопическая хирургия.

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НА – несостоятельность анастомоза; ПГ – правосторонняя гемиколэктомия.

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INTRODUCTION

Anastomotic leak (AL) is the most hazardous complication of the right colectomy (RC). The incidence of the complication may vary significantly from clinic to clinic and from one surgical technique to another [1]. According to the data from the Australian and New Zealand registers, the AL incidence rate was 2% among 13,512 patients who had undergone right colectomy [2]. The multicenter study EAGLE, which engaged numerous clinics from developing countries, found that the incidence of leaks of ileo-transverse anastomosis reached 12.2% at the initial evaluation of complications incidence prior to training of surgeons [3].

Laparoscopic surgery provided a new approach towards performance of the resection stage of surgery; it provided a better cosmetic effect and improved patient rehabilitation. It became, therefore, a preferred method of treatment in clinical recommendations [4]. At the same time, the first studies did not modify the method of anastomosis formation vs. methods of open surgery [5]. Formation of an intracorporal anastomosis provides a potential of a fuller implementation of minimally invasive surgery based on a free choice of the zone of minilaparotomy incision or removal of the preparation through natural orifices. The meta-analysis of 7 randomized clinical trials found no differences in the incidence rate of AL development in the formation of intra- or extracorporal anastomoses [6]. At the same time, the method of anastomosis formation in these studies was not standardized. The classic intracorporal anastomosis is formed mechanically. The analysis of data of the Denmark national register shows that the use of staplers doubles the risk of AL in right colectomies, from 2.4 to 5.4% (p=0.004).

AIM

To evaluate safety of a hand-sewn intracorporeal ileo-transverse anastomosis.

MATERIAL AND METHODS

This retrospective study used the material from the Omsk regional cancer register for the period from 2015 to 2023 including all patients diagnosed with 'colon cancer' (C18 in the ICD-10) who had undergone laparoscopic right colectomy. The following patients were excluded: patients who had laparoscopic right colectomy with mechanical anastomosis, patients who had right colectomy not related to cancer of the right section of the colon, and patients who had palliative surgeries (bypass anastomosis), surgeries in the volume of colectomy, resection of the transverse colon, and surgeries without formation of the ileo-transverse anastomosis.

The patients were divided into two groups. In the study group, the anastomosis was formed using the author's original method (official filing receipt for the invention No.2018111234 dated 29.03.2018 "Method of formation of the intracorporal laparoscopic terminus-terminal invagination ileo-transverse

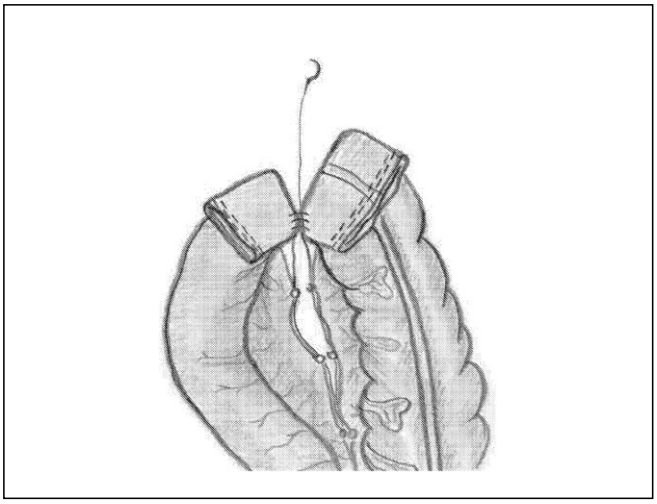

Figure 1. *Formation of the external posterior row of ileo-transverse anastomosis (side view).*

Рисунок 1. *Формирование наружного заднего ряда илеотрансверзоанастомоза (вид сбоку).*

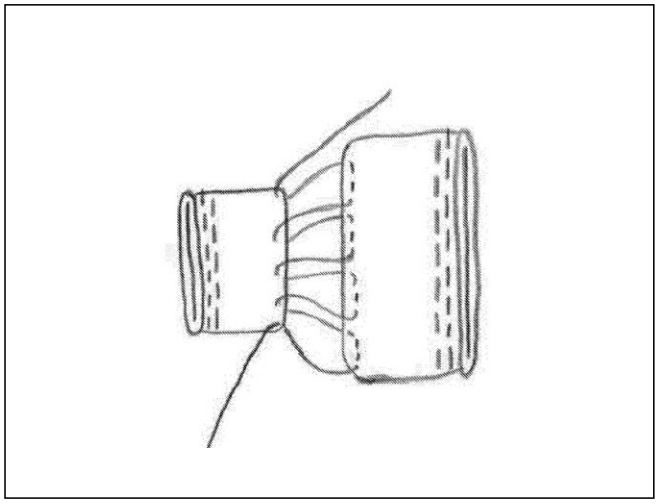

Figure 2. *Formation of the external posterior row of ileo-transverse anastomosis (top view).*

Рисунок 2. *Формирование наружного заднего ряда илеотрансверзоанастомоза (вид сверху).*

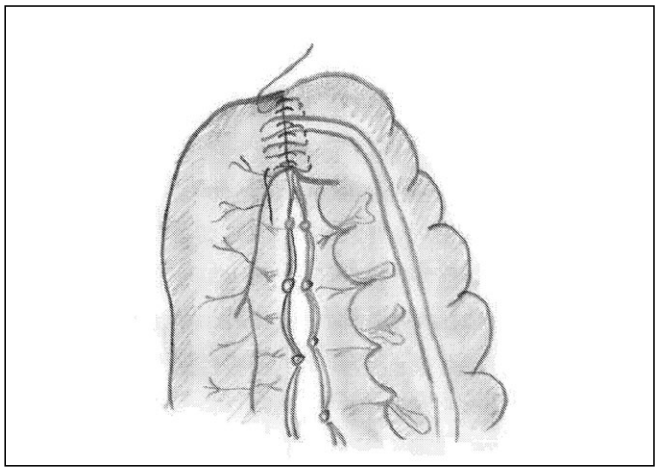

Figure 3. *Final appearance of the anastomosis formed with the use of the author's technique.*

Рисунок 3. *Окончательный вид анастомоза, сформированного по авторской методике.*

anastomosis"). Complete mobilization of the right colon was performed laparoscopically. At the operating surgeon's discretion, the middle colic vessels were transsected at the base or only the fight branch of the meddle colic artery was transsected. D3 or D3 lymphadenectomy was also performed at the operating surgeon's discretion. After transsecting the mesentery, the ileum and the colon were transsected at the line of adequate vascular supply using the linear stapler. Following that, the exterior posterior wall of the anastomosis was formed with barbed absorbable sutures; at the same time, to ensure adaptation of diameters, the interval between the punctures was made larger than on the ileum (**Fig. 1, 2**).

After that, the lines of staples of the transverse colon and the ileum were sheared opening the lumens to form the interior wall of the anastomosis. The continuous intracorporal seam was formed with a polyfilament thread: the anterior curve with the Multanovsky suture, the posterior, with the Schmieden suture. The anterior curve of the exterior wall of the anastomosis was formed with barbed absorbable sutures, similar to the posterior wall. In this way, the invagination ileo-transverse 'end-to-end' anastomosis was formed (**Fig. 3, 4**). The choice of the area for the minilaparotomic access was at the operating surgeon's discretion.

In the control group, the resection phase of the surgery was performed in the same way as that in the study group; however, the transverse colon and the ileum were not transsected. After mobilization, a minilapatoromic incision was made, through which the resected section of the colon was removed from the abdominal cavity. The preparation was removed, and a hand-sewn extracorporal ileo-transverse 'side-to-side' anastomosis was formed.

The main assessed parameter was the incidence rate of the anastomotic leak. Additionally, the general incidence of post-surgery complications using the Clavien – Dindo was assessed [7], time of the operation, intraoperative blood loss, time of hospitalization.

Statistical processing of material was performed in the IBM SPSS v.23 software suite. To compare categorical variables, 2×2 tables and the Chi-square test were used. To compare continuous variables, the medians were compared and the Mann-Whitney test was used.

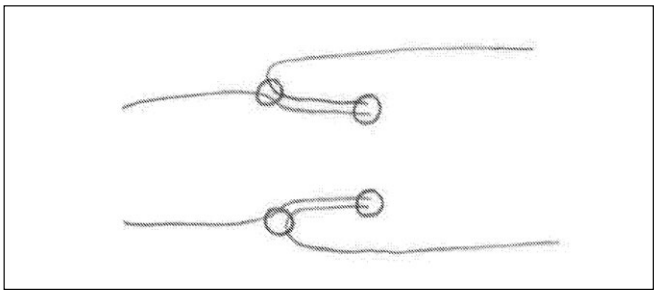

Figure 4. *Final appearance of the anastomosis formed with the use of the author's technique (schematic image).*

Рисунок 4. *Окончательный вид анастомоза, сформированного по авторской методике (схематичное изображение).*

RESULTS

The search query in the archive for the specified period returned 2114 entries. After removal of duplicating records (cases of readmission of the same patient), 1991 records remained. After removal of information on palliative surgeries and data of patients not diagnosed with colon cancer, 1729 records remained. 1050 patients were excluded due to localization of the tumor in the left sections of the colon. 493 patients were excluded due to open surgery performed on them. 14 patients were excluded, for a mechanical intracorporal anastomosis was formed for them. 9 patients were excluded because they had undergone colectomies, 74 patients were excluded due to resections of the colon. Thus, our study included the data of 89 patients: 42 in the study group, and 47 in the control group.

The general characteristics of the observed groups are shown **in Table 1**.

It follows from Table 1, there were less patients with the tumor localized in the hepatic flexure of the colon in the study group, 6 (14.3%) vs. 19 (40.4%) in the control group and there

Parameter	Study group N=42 (100%)	Control group N=47 (100%)	P
Sex			
Male	16 (34.0%)	13 (31.0%)	0.823
Female	31 (66.0%)	29 (69.0%)	
Age			
Under 65	15 (35.7%)	14 (29.8%)	0.652
65 and older	27 (64.3%)	33 (70.2%)	
Tumor localization			
Cecum	15 (35.7%)	11 (23.4%)	0.023
Ascending colon	21 (50%)	17 (36.2%)	
Hepatic flexure of the colon	6 (14.3%)	19 (40.4%)	
Stage (UICC TNM. 7th revision)			
I	7 (16.7%)	6 (13.0%)	0.191
II	15 (35.7%)	26 (56.5%)	
III	18 (42.9%)	11 (23.9%)	
IV	2 (4.8%)	3 (6.5%)	
Residence			
Rural area	15 (31.9%)	11 (26.2%)	0.643
City	32 (68.1%)	31 (73.8%)	
Body mass index (BMI)			
Below 30 kg/m^2	24 (57.1%)	36 (76.6%)	0.070
30 kg/m^2 and higher	18 (42.9%)	11 (23.4%)	

Table 1. *Characteristics of the study groups*
Таблица 1. *Характеристика исследуемых групп*

Parameter	Study group N=42 (100%)	Control group N=47 (100%)	P
Surgery time, min.			
Median	120	105	0.580
Min. and max.	75–205	40–270	
Q1-Q3	90–140	80–152	
Blood loss			
Median	50	50	0.132
Min. and max.	10–150	50–200	
Q1-Q3	50–100	50–100	
Bed days			
Median	9	10	0.013
Min. and max.	4–20	6–21	
Q1-Q3	7–11	9–11	

Table 2. *Characteristics of the operations performed*
Таблица 2. *Характеристика выполненных операций*

were more patients with BMI 30 kg/m2 and higher, 18 (42.9%) vs. 11 (23.4%). In other criteria, the studied groups did not show significant differences. The intraoperative characteristics are shown **in Table 2**.

No postoperative lethality was found in the studied groups. The general rate of complications and incidence rate of development of anastomotic leak did not differ between the groups. In the study group, no cases of anastomotic leak were registered. One patient in the study group had an iatrogenic damage of the small intestine that resulted in the development of peritonitis and a recurrent operation. In another patient, the seroma of the abdominal cavity developed that required drainage under X-ray control. In the control group, there were four recurrent operations: two related to anastomotic leak, one, to postoperative hemorrhage, and one, to eventration of the minilaparotomic wound.

DISCUSSION

Within this retrospective study, we demonstrated the safety of hand-sewn intracorporal ileo-transverse anastomosis using the original method suggested by us. It is to be noted also, that 42.9% patients in the study group were obese, which shows the feasibility of the operation in a difficult category of patients.

In the study group, no cases of development of anastomotic leak were registered, which was the most significant parameters we assessed. We did not find significant differences in the main postoperative parameters in comparison to the extracorporal anastomosis group, except reduction of the number of post-operative bed-days by one day. Earlier, M. Widmar et al. (2020) in their single-center retrospective study also reported reduction of the number of post-operative bed-days by one day after formation of intracorporal anastomoses, also with no effect on the risk of postoperative complications [8]. Similar data was obtained by R. Cleary et al. (2018) in a larger study with pseudo-randomization, where the majority of surgeries were performed using robotic surgery [9]. In both these studies, the intracorporal anastomosis was formed 'side-to-side' using linear staplers, and in them, like in our study, no cases of development of anastomotic leak were registered. E.M. Romanova et al. (2024) performed a randomized study that compared safety of intracorporal mechanical and extracorporal hand-sewn anastomosis in right colectomy in 79 patients. One case (2.6%) of anastomotic leak was registered, the general

Parameter	Study group N=42 (100%)	Control group N=47 (100%)	P
Clavien – Dindo 3a	1 (2.4%)	1 (2.1%)	0.550
Clavien – Dindo 3b	0	2 (4.3%)	
Clavien – Dindo 4a	1 (2.4%)	2 (4.3%)	
Anastomotic leak	0	2 (4.3%)	0.496

Table 3. *Postoperative complications*
Таблица 3. *Послеоперационные осложнения*

rate of incidence of complications between groups not being different [10].

The most convincing evidence was obtained in the meta-analysis of 21 retrospective studies performed by A. Squillaro et al. (2023). The formation of the intracorporal anastomosis did not influence the risk of postoperative complications. Differences were identified between the groups of robot-assisted intracorporal anastomosis and laparoscopic extracorporal anastomosis: they were in the duration of postoperative period and amounted to one day [11].

Manual sowing of the intracorporal anastomosis is only rarely implemented in clinical practice. All studies included in the meta-analysis of A. Squillaro et al. used the mechanical method of 'side-to-side' anastomosis formation. An alternative method was suggested by H. Su et al. (2019): in their retrospective study of 36 patients they described the technique of delta-shaped formation of ileo-transverse anastomosis using three linear staplers, no cases of anastomotic leak were registered [12]. No randomized studies compared various techniques of formation of intracorporal anastomosis. Manual formation of the anastomosis is technically simpler and is more frequently performed in using robot-assisted techniques. However, the meta-analysis of 30 studies that focused on the results of robot-assisted right colectomies, no differences were shown in the rate of development of complications following the manual and mechanical sowing of the anastomosis [13]. Regardless of the surgical method used, the mechanical formation of the ileo-transverse anastomosis was related in the Cochrane systematic review (2011) with a reliably lower risk of development of the leak, OR 0.48 [95%CI 0.24; 0.95] p=0.03 [14].

The advantage of our study is the analysis of a new and novel method of formation of ileo-transverse anastomosis in a representative population of patients. Its limitations are its retrospective character, lack of standardization of techniques of anastomosis formation in the control group, some differences in the clinical characteristics of patients. It is to be remembered that intracorporal anastomosis was formed, in all cases, by one surgeon completing the training curve in minimally invasive surgery. In the control group, this parameter was not taken into account.

CONCLUSION

Thus, the method of formation of ileo-transverse anastomosis proposed by us is safe and may be regarded for use by surgeons completing the training curve in minimally invasive colorectal surgery. To assess the reproducibility of obtained results and comparison with other techniques in larger studied groups, further research is needed.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. M.P. Salamakhin: development of the research concept, direct conduct of the research, statistical calculations, preparation, creation and design of the manuscript. O.V. Leonov, Z.Z. Mamedli: editing of the manuscript. A.Z.Milovanova: collection and processing of data. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** М.П. Саламахин – разработка концепции исследования, непосредственное проведение исследования, статистические расчеты, подготовка, создание и оформление рукописи. О.В. Леонов, З.З. Мамедли – редактирование рукописи. А.З. Милованова – сбор и обработка данных. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Development and risk factors of chronic pain due to trauma to the anterior cruciate ligament and/or meniscus of the knee joint

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Abstract

Aim – to evaluate the incidence and risk factors of chronic post-traumatic pain in patients who suffered an anterior cruciate ligament (ACL) and/or knee joint meniscus (CC) injury.

Material and methods. The study group consisted of 148 patients (48.0% women, 37.9 ± 13.1 years old) who had suffered an injury to the PC and/or meniscus of the CS, confirmed by magnetic resonance imaging (MRI). The inclusion criterion was moderate/severe pain (≥4 on the numerical rating scale, NRS 0-10) 1 month after the injury. Patients were examined after 3, 6, and 12 months with an assessment of pain (NRS) and the KOOS index, signs of neuropathic pain (painDETECT), anxiety and depression (HADS a and HADS d), central sensitization index (CSI), pain catastrophization (PCS), fibromyalgia symptoms (FiRST), fatigue (FACIT). An MRI scan was performed after 6 and 12 months. The plasma concentrations of a number of biomarkers (HCRP, NTX, ADAMTS-5, COMP, MMP3, MMP9, MMP13, substance P) were studied.

Results. After 3 months, pain with movement ≥4 NRS was observed in 58 (39.2%) patients. These patients formed the group with chronic post-traumatic pain (CPTP+), patients with lower pain intensity or absence (≤4 NRS) formed the control group (CPTP-). In patients with CPTP+, compared with the CPTP- group, pain at rest and at night was significantly higher (p <0.001). A significant difference in pain during movement, at rest, and at night, as well as all KOOS scales, remained between the CPTP+ and CPTP- groups after 6 and 12 months. In the CPTP+ group, there was a tendency to a higher frequency of signs of neuropathic pain, anxiety and depression, central sensitization index, pain catastrophization scale and fatigue, however, the difference with the CPTP- group was unreliable. The concentration of biomarkers in the CPTP+ and CPTP- groups did not differ. There was a significant association between CPTP and the female sex (odds ratio = 3.18; 95% confidence interval 1.606-6.297, p<0.001), meniscus injury (OR = 2.132; 95% CI 1.07-4.252, p=0.03), osteitis (OR = 5.734; 95% CI 2.106-15.609, p<0.001) and synovitis (OR = 2.35; 95% CI 1.186-4.656, p=0.013) according to MRI, surgery (reduced the risk of CPTP, OR = 0.385; 95% CI 0.195-0.759, p<0.005), initially severe pain (≥7 NRS, OR = 5.553; 95% CI 1.696-18.179, p=0.002), signs of highly probable CS (CSI ≥40, OR = 3.915; 95% CI 1.147-13.368, p=0.021) and severe depression (HADS ≥ 11, OR = 4.12; 95% CI 1.672-21.983, p=0.05).

Conclusion. CPTP occurs in almost 40% of patients after knee joint meniscus injury. Risk factors for CPTP are female gender, meniscus injury, osteitis and synovitis (MRI data), initially severe pain, central sensitization, and depression.

Keywords: anterior cruciate ligament/meniscus injury, chronic post-traumatic pain.

Conflict of interest: nothing to disclose.

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Развитие и факторы риска хронической боли после травмы передней крестообразной связки и/или мениска коленного сустава

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Аннотация

Цель – оценить частоту развития и факторы риска ХПТБ у пациентов, перенесших травму передней крестообразной связки (ПКС) и/или мениска коленного сустава (КС).

Материал и методы. Исследуемую группу составили 148 пациентов (женщины 48,0%, 37,9 ± 13,1 года), перенесших травму ПКС и/или мениска КС, подтвержденную магнитно-резонансной томографией (МРТ). Критерием включения была умеренная/выраженная боль (≥4 по числовой рейтинговой шкале, ЧРШ 0–10) через 1 месяц после травмы. Пациенты обследовались через 3, 6 и 12 месяцев с оценкой боли (ЧРШ) и индекса KOOS, признаков невропатической боли (PainDETECT), тревоги и депрессии (HADS a и HADS d), центральной сенситизации, ЦС (CSI), катастрофизации боли, КБ (PCS), симптомов фибромиалгии, ФМ (FiRST), утомляемости (FACIT). Через 6 и 12 месяцев проводилась МРТ. Была исследована плазменная концентрация ряда биомаркеров (вчСРБ, NTX, ADAMTS-5, COMP, ММП3, ММП9, ММП13, субстанция Р).

Результаты. Через 3 месяца боль при движении ≥4 ЧРШ отмечена у 58 (39,2%) пациентов. Эти пациенты составили группу с ХПТБ (ХПТБ+), пациенты с меньшей интенсивностью или отсутствием боли (≤4 ЧРШ) – контроль (ХПТБ-). У пациентов ХПТБ+ в сравнении с группой ХПТБ- была достоверно выше боль в покое и ночью (p <0,001). Достоверное различие боли при движении, в покое и ночью, а также всеми шкалами KOOS сохранялось между группами ХПТБ+ и ХРТБ- через 6 и 12 месяцев. В группе ХПТБ+ была тенденция к большей частоте признаков невропатической боли, тревоги и депрессии, ЦС, КБ и усталости, однако различие с группой ХПТБ- было недостоверным. Концентрация биомаркеров в группах ХПТБ+ и ХПТБ- не различалась. Отмечена достоверная связь между ХПТБ и женским полом (отношение шансов, ОШ = 3,18; 95% доверительный интервал, ДИ 1,606-6,297, p<0,001), травмой мениска (ОШ = 2,132; 95% ДИ 1,07-4,252, p=0,03), остеитом (ОШ = 5,734; 95% ДИ 2,106-15,609, p<0,001) и синовитом (ОШ = 2,35; 95% ДИ 1,186-4,656, p=0,013) по МРТ, проведенной операцией (снижала риск ХПТБ, ОШ = 0,385; 95% ДИ 0,195-0,759, p<0,005), исходно сильной болью (≥7 ЧРШ, ОШ = 5,553; 95% ДИ 1,696-18,179, p=0,002), признаками высоко вероятной ЦС (CSI ≥40, ОШ = 3,915; 95% ДИ 1,147-13,368, p=0,021) и выраженной депрессией (HADS ≥ 11, ОШ = 4,12; 95% ДИ 1,672-21,983, p=0,05).

Заключение. ХПТБ возникает у почти 40% пациентов после травмы КС. Факторы риска ХПТБ – женский пол, травма мениска, остеит и синовит (данные МРТ), исходно сильная боль, ЦС и депрессия.

Ключевые слова: травма передней крестообразной связки/мениска, хроническая посттравматическая боль

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КС – коленный сустав; ПКС – передняя крестообразная связка; ПТОА –посттравматический остеоартрит; ХПТБ – хроническая посттравматическая боль; ЧРШ – числовая рейтинговая шкала; ОА – остеоартрит; ОШ – отношение шансов; ЦС – центральная сенситизация; ФМ – фибромиалгия.

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INTRODUCTION

Injuries are a serious medical and social problem, one of the main reasons of death, disablement, and considerable decrease of quality of life in the modern world [1]. According to official statistics, the ‘external causes’ (including injuries) in the Russian Federation in 2020 ranked fourth among causes of death (139,600), after cardiovascular diseases (938,500), neoplastic diseases (295,900), and COVID-19 (144,700). The absolute number of injuries was 8.92 million cases, of which 6.17 were injuries of upper and lower extremities [2].

In the structure of injuries of the lower extremities, the injuries to the knee joint (KJ) and ankle joint prevail, whose cumulative incidence rate is over 50% from the total number of injuries to the skeletomuscular system [3]. The most frequent traumatic injuries of the knee joint are the meniscal tear and the anterior cruciate ligament tear (ACL) [4, 5].

Notwithstanding the wide range of conservative and surgical methods of treatment of injuries, their sequelae are often adverse. Injury complications may present themselves as a permanent loss of capacity, neurological and infectious complications, post-traumatic osteoarthritis (PTOA), and chronic post-traumatic pain (CPTP) [6–10].

Chronic post-traumatic pain is a syndrome characterized by moderate or significant pain in the area of the sustained injury that persist for three or more months after the injury [11]. This is a frequent complication: after injuries of the knee

joint, depending on their severity, CPTP sets on in 10–50% patients. CPTP significantly affects the general well-being, affects physical and social activity, affects quality of life, and incurs significant expenses on treatment and rehabilitation [6–10].

Besides, the CPTP may be regarded as the first manifestation of the emerging PTOA. The international experts' council Optimizing Knee Health after Injury (OPTIKNEE) identified the PTOA of the knee joint thus: "structural or symptomatic osteoarthritis developing after a traumatic injury of the knee joint". PTOA of the knee joint is considered symptomatic in the presence of a clinic picture matching the criteria of at least one professional associations working on osteoarthritis, e.g., ACR (American College of Rheumatology), but excludes age limitations regardless of the presence of structural changes identified by instrumental methods [12].

This shows that the CPTP and PTOA are serious challenges of modern medicine that require adequate approaches to prevention and treatment. At the same time, proper management of PTOA is not possible without a clear understanding of the mechanism of its development and without identification of risk factors of the pathology. Therefore, the fundamental task in studying CPTP is the creation of a prognostic model that will analyze a complex of symptoms and assess the probability of development of the pathology, its pathway and phenotypic features.

AIM

To evaluate the incidence rate and risk factors of chronic post-traumatic pain in patients who suffered an anterior cruciate ligament and/or knee joint meniscus injury.

MATERIAL AND METHODS

This study is a part of a prospective scientific study "PHOBOS" ("Factors Defining Chronization of Pain: Evaluation and Systematization") performed from 2022 to 2024 at the V.A. Nasonova Research Institute of Rheumatology. The study group included 148 patients compliant with the *inclusion criteria*: age from 18 to 50; traumatic injury of the anterior cruciate ligament and/or knee joint meniscus confirmed by the magnetic resonance tomography findings (MRI); moderate or significant pain in the knee joint area (>4 on the 0-10 numeric rating scale (NRS), where 0 stands for no pain and 10 for unbearable pain) for ≥1 month after the injury; availability of the patient's informed consent. *The exclusion criteria* were as follows: fracture of the bony structures in the knee joint area (diagnosed as per X-ray data), availability of reliable signs of a rheumatic disease (including earlier diagnosed OA and fibromyalgia), functional disorders of the skeletomuscular system and comorbid conditions precluding regular check-ups required by the study protocol.

All patients included in the study were recommended to wear orthoses, exercise regularly and use non-steroid anti-inflammatory drugs either systemically or locally (ointments and gels) to stop the pain as needed.

The patients were divided into the main group (moderate/severe pain in the knee joint) and the control group (mild pain or no pain in the knee joint) during their second visit, three months after the start of observation.

The criterion for inclusion in the CPTP group (main group) was persistence of moderate or severe pain in the knee joint on activity or at rest (>4 NRS) that persisted for the majority of days within the past 3 months. The studied group consisted mainly of young people with comparable number of males and females who sustained an injury of the ACL, the meniscus, or a combination thereof. Among patients engaged in the study, 48.6% had undergone surgery (ACL restoration, meniscal suture), 51.4% of patients received only conservative treatment. The consolidated initial parameters of patients included in the study follow in **Table 1**.

According to the plan of the work, all patients, at the time of inclusion in the study, underwent a comprehensive examination to identify a group of promising clinical parameters that can be considered subsequently as risk factors for the development of CPTP.

Studies of clinical manifestations of each patients were performed during the first admission, and 3, 6 and 12 months after the injury. To that end, the following indicators were used: pain severity on the NRS in motion, at rest and at

Parameter	Value
Sex (F/M, %)	48.0 / 52.0
Age, years; M±σ	37.9 ± 13.1
Body mass index, kg/m²; M±σ	25.8 ± 5.1
Damage of knee joint structures as per MRI data, %	ACL: 40.0, meniscus: 58.7, combined ACL + meniscus injury: 16.7, ACL + other condition (tendinitis, cysts, ligament strain, etc.): 26.0
Surgery (ACL restoration, meniscal suture, meniscus resection, combined surgeries), %	48.6
Conservative methods of treatment, %	51.4
Pains on activity; Me [25th; 75th percentiles]	5.0 [4.0; 7.0]
Pains at rest; Me [25th; 75th percentiles]	2.0 [0.75; 3.0]
Pain during the night; Me [25th; 75th percentiles]	2.0 [0.0; 3.0]
Functional disorder; Me [25th; 75th percentiles]	4.0 [3.0; 6.0]
KOOS total; M±σ	48.9 ± 17.5
KOOS symptoms; M±σ	59.1 ± 19.6
KOOS pain; M±σ	58.5 ± 16.8
KOOS activity; M±σ	65.0 ± 20.1
KOOS sports; M±σ	33.1 ± 18.7
KOOS quality of life; M±σ	39.8 ± 19.8
PainDETECT; Me [25th; 75th percentiles]	6.0 [3.0; 9.0]
PainDETECT >12, %	10.0
HADS depression; Me [25th; 75th percentiles]	4.0 [1.0; 6.0]
HADS depression >11, %	4.7
HADS anxiety; Me [25th; 75th percentiles]	5.0 [2.0; 7.0]
HADS anxiety >11, %	4.0
CSI; Me [25th; 75th percentiles]	22.5 [14.75; 32.25]
CSI ≥ 40, %	8.6
PCS; Me [25th; 75th percentiles]	12.5 [7.0; 21.0]
PCS >30, %	14.0
FiRST; Me [25th; 75th percentiles]	1.0 [0.5; 2.0]
FiRST >5, %	1.3
FACIT; Me [25th; 75th percentiles]	11.0 [5.0; 19.25]
FACIT 0–13, %	57.3
HAQ; Me [25th; 75th percentiles]	0.375 [0.0; 0.75]

Table 1. *Characteristics of the initial data of patients included in the PHOBOS study (n=148)*

Таблица 1. *Характеристика исходных данных пациентов, включенных в исследование ФОБОС (n=148)*

nighttime; symptom intensity and functional disorders on the Knee Injury and Osteoarthritis Outcome Score – KOOS ('symptoms', 'pain', 'daily activities', 'sports', 'quality of life', 'total' scores); symptoms of neuropathic pain as per the PainDETECT questionnaire; psycho-emotional disorders as per Hospital scale of Anxiety and Depression (HAD); central sensitization (CS) as per the Central Sensitization Inventory (CSI); pain catastrophizing as per the Pain Catastrophizing Scale (PCS); fibromyalgia symptoms as per the Fibromyalgia Rapid Screening Tool (FiRST); fatigue and tiredness as per the Functional Assessment of Chronic Illness Therapy (FACIT).

During the study process, the following laboratory indicators were evaluated in dynamics (as of the moment of inclusion and 3 months later): hemoglobin level (Hb, g/l), ESR (mm/h), CRP (mg/l), hsCRP (ME/l), NTX, ADAMTS-5, COMP, MMP3 (ng/ml), MMP9 (ng/ml), MMP13 (ng/ml), substance P (pg/ml).

Besides, in 6 and 12 months, MRI of the knee joint was performed to visualize the damage to the meniscus and the ACL, the cartilage, the subchondral bone, presence of effluent to the joint cavity and their objective assessment (degree of synovitis, severity of damage to the ACL and the meniscus, presence of osteitis, etc.). In the course of the study, the MRI scans of the knee joint were compared at the outset, in 6 and 12 months.

Statistical analysis of results of this study was performed in the IBM SPSS Statistics 23 software suite. Quantitative values are presented as averages with the respective standard deviation (M±σ), and in the vase of the lack of the normal distribution within the group, as medians with inter-quartile range Me [25th; 75th percentiles]. Qualitative variables were described with absolute values and respective percentages. In order to analyze the data, statistical tests were used: Pearson's $\chi 2$-test (contingency table analysis), unpaired Student's t-test, for the comparison of quantitative values, Wilcoxon test ($\chi 2$) for related samples, Mann–Whitney test for independent samples, Spearman's rank correlation coefficient. To assess the impact of various factors on the outcome of therapy, odds ratio (OR) calculation with the corresponding 95% confidence interval (CI) was used. Differences were considered statistically significant at $p < 0.05$.

The study was carried out in compliance with the provisions of the Helsinki Declaration of Human Rights. All patients signed informed consent to participate in this work. The study was approved by the local ethics committee of the V.A. Nasonova Research Institute of Rheumatology (Protocol No. 23 dated 23.11.2022).

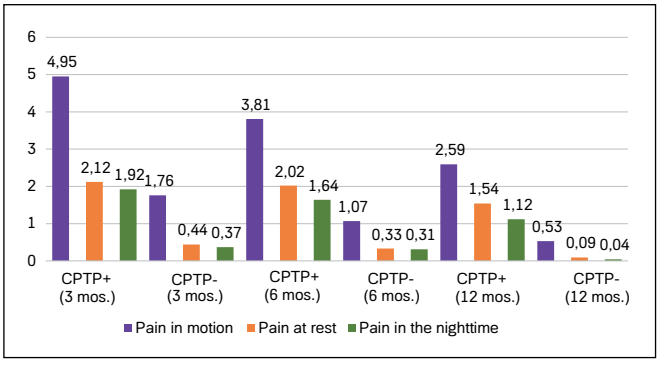

Figure 1. *Pain dynamics in patients with and without CPTP from 3 to 12 months of follow-up.*

Рисунок 1. *Динамика боли у пациентов с ХПТБ и без ХПТБ с 3 по 12 месяц наблюдения.*

RESULTS

Three months after the inclusion, moderate and severe pain in motion (≥4 NRS) was registered in 58 (39.2%) patients. Pursuant to the aim of the study, these patients formed the CPTP group (CPTP+), and patients experiencing less or no pain (≤4 NRS) formed the control group (CPTP-). Besides more intense pain in motion, the CPTP+ patients had reliably more intense pain at rest and in the nighttime as compared to the CPTP- group ($p<0.001$). The reliable difference in the pain intensity in motion, at rest and in the nighttime remained between the CPTP+ and CPTP- groups in the follow-ups after 6 and 12 months (**Fig. 1**).

Manifestations of neuropathic pain, central sensitization and fibromyalgia were found in a minor share of patients at the outset of the study: PainDETECT >12 in 9.8%, CSI ≥40 in 8.7%, FiRST >5 in 1.4%; manifested psycho-emotional disorders, in individual patients: HADS depression >11 in 4.6%, HADS anxiety >11 in 3.9%.

Statistically reliable difference between the CPTP+ and CPTP- groups was found 3, 6 and 9 months in all scores of the KOOS scale. Other quantitative parameters measured with PainDETECT, HADS, CSI, PSC, FIRST and FACIT

Parameters M+δ. Me [25th; 75th percentiles]	CPTP+ (3 mos.)	CPTP- (3 mos.)	CPTP+ (6 mos.)	CPTP- (6 mos.)	CPTP+ (12 mos.)	CPTP- (12 mos.)
KOOS total*	57.8 ± 18.2	77.3 ± 20.2	60.9 ± 16.7	85.3 ± 21.4	79.0 ± 18.4	88.5 ± 18.8
KOOS symptoms*	57.5 ± 19.4	79.4 ± 16.7	62.8 ± 15.2	85.3 ± 17.4	72.9 ± 19.0	90.4 ± 22.1
KOOS pain*	54.0 ± 13.3	78.5 ± 17.4	63.6 ± 17.2	82.3 ± 20.1	71.9 ± 18.6	90.6 ± 18.5
KOOS activity*	58.9 ± 15.6	82.3 ± 16.7	63.8 ± 20.1	85.1 ± 19.4	71.9 ± 18.2	90.6 ± 21.6
KOOS sports*	39.2 ± 12.4	62.2 ± 18.7	45.1 ± 19.3	69.3 ± 20.3	52.8 ± 17.3	78.6 ± 19.1
KOOS quality of life*	45.7 ± 11.0	68.1 ± 18.1	52.3 ± 14.8	70.0 ± 19.7	67.5 ± 18.4	85.1 ± 22.2
PD	8.0 [6.0: 10.0]	4.5 [3.0; 5.5]	7.0 [5.0; 8.0]	2.0 [3.0; 4.5]	6.0 [4.0; 7.0]	1.0 [0.0; 2.5]
HADS d	4.5 [3.0; 5.5]	2.0 [1.0; 3.0]	5.0 [3.0; 6.5]	2.5 [2.0; 4.0]	4.0 [5.0; 6.0]	2.0 [1.0; 3.0]
HADS a	6.0 [4.0; 8.0]	3.0 [2.0; 4.0]	7.0 [6.0; 8.0]	3.5 [3.0; 4.5]	6.0 [4.0; 7.0]	2.5 [1.0; 3.0]
CSI	26.0 [14.0; 35.0]	16.0 [12.0; 18.0]	21.0 [13.0; 25.5]	9.0 [6.0; 12.0]	15.0 [10.0; 19.0]	4.0 [3.0; 5.0]
PCS	17.0 [14.0; 19.0]	8.0 [6.0; 9.5]	13.0 [11.0; 15.0]	5.0 [3.0; 6.5]	10.0 [7.0; 12.0]	1.5 [0.0; 2.5]
FiRST	1.0 [0.0; 2.0]	0.5 [0.0; 1.0]	1.0 [0.0; 2.0]	0.5 [0.0; 1.0]	1.0 [0.0; 1.5]	0.5 [0.0; 1.0]
FACIT	13.0 [11.0; 17.0]	9.0 [7.0; 11.0]	11.0 [9.0; 13.5]	6.0 [4.0; 8.0]	10.0 [8.0; 12.0]	3.5 [2.0; 5.5]

*Note. * The difference between the CPTP+ and CPTP- groups after 3, 6 and 12 months is statistically reliable in all KOOS parameters ($p < 0.05$).*

Table 2. *Dynamics of clinical parameters in the CPTP+ and CPTP- groups after 3.6 and 12 months*

Таблица 2. *Динамика клинических показателей в группах ХПТБ+ и ХПТБ- через 3, 6 и 12 месяцев*

questionnaires, also differed between the compared groups in the follow-ups after 3, 6 and 12 months, but this difference was not statistically reliable (**Table 2**).

A correlation between the MRI-indicated signs of synovitis and osteoitis showing the persistent joint inflammation and the presence of CPTP was found. The data and the outcomes of recurrent MRI scans after 6 and 12 months showed statistically significant differences in the frequency of synovitis and osteoitis finding in the CPT+ group versus the CPTP- group (**Fig. 2**).

The incidence rate pf MRI signs of synovitis in CPTP patients decreased significantly within the follow-up period: initially, the parameter was found in 67.8% patients, and in 12 months, in 40.7% (p=0.0308). According to the MRI data, the incidence rate of osteisis did not statistically decrease within the tear of follow-up: 28.6% at the outset and 20.3% (p=0.107) by the end of the study.

A credible correlation was found between the development of CPTP and the female gender (OR = 3.18 (95% CI 1.606-6.297), p<0.001),injury of the meniscus (OR = 2.132 (95% CI 1.07-4.252), p=0.03), presence of osteitis (OR = 5.734 (95% CI 2.106-15.609), p<0.001) and synovitis (OR = 2.35 (95% CI 1.186-4.656), p=0.013) as per the MRI data, past surgery (decreasing the risk of CPTP development, OR = 0.385 (95% CI 0.195-0.759), p<0.005), initial severe pain in motion (≥7 NRS, OR = 5.553 (95% CI 1.696-18.179), p=0.002), signs of highly likely central sensitization (CSI ≥40, OR = 3.915 (95% CI 1.147-13.368), p=0.021) and manifested depression (HADS ≥11, OR = 4.12 (95% CI 1.672-21.983), p=0.05).

No credible differences between the groups of patients with and without CPTP were found when comparisons were made in the values of BMI, ALC injury, signs of tendinitis, concentration of CRP (standard analysis), initial pain at rest (≥7 NRS) and in the nighttime (≥5 NRS), severity of functional disorder (≥7 NRS), signs of neuropathic pain (PainDETECT questionnaire), anxiety (HADS questionnaire), catastrophization (PCS questionnaire), signs of fibromyalgia (FIRST questionnaire), and fatigue (FACIT questionnaire).

We saw no statistically significant differences in the plasma concentrations of the biomarkers (hsCRP, NTX, ADAMTS-5, COMP, MMP-3, MMP-9, MMP-13 and substance P) in patients with and without CPTP after 3 and 12 months of follow-up. There was no statistically credible correlation between the severity of CPTP and the level of the studies substances.

DISCUSSION

CPTP was identified in 39.3% patients who suffered ACL and/or meniscus rupture. In CPTP patients, throughout the entire follow-up period, greater manifestation of clinical symptoms was seen that were related to the consequences of the injury of the knee joint: pain in motion, at rest and in the nighttime, functional disorders. In each follow-up, credible differences were seen in all sections of the KOOS scale (total score, symptoms, pain, activity, sport, quality of life). Even though after 6 and 12 months the severity of symptoms decreased in many CPTP patients, their numerical value (both in the NRS and KOOS) remained statistically credibly high that those of the patients in the control group.

Despite the fact that the signs of the 'central constituent' of chronic pain were seen only in a minor quantity of patients,

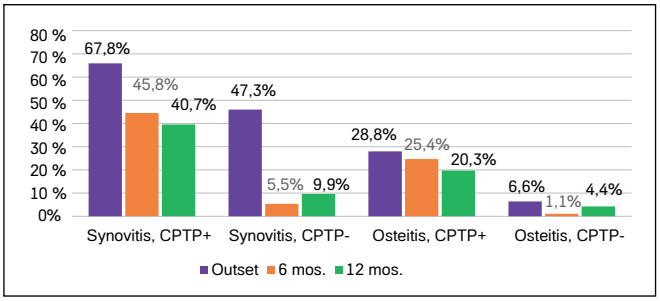

Figure 2. *Dynamics of synovitis and osteitis according to MRI data depending on the presence or absence of CPTP.*

Рисунок 2. *Динамика синовита и остеита по данным МРТ в зависимости от наличия или отсутствия ХПТБ.*

the numerical values of anxiety and depression (HADS), neuropathic pain (PainDETECT), central sensitization (CSI), catastrophization (PCS), fatigue (FACIT) and fibromyalgia (FIRST) were higher on all stages of follow-up in patients with CPTP.

The results obtained by us show that CPTP is a pathophysiological phenomenon related to the specifics of the 'response' of the macro-organism to the injury and associated damage, inflammation and reparative process. At the same time, the formation and the persistence of CPTP may indicate development of PTOA.

The high incidence rate of CPTP in this study may be related to criteria of patient selection for the study. It included only those patients in whom one month after the injury of the knee joint at lease moderately severe pain persisted, which was the reason for seeking medical attention. Our data is close to the results of foreign research of similar topics. Thus, L. Lohmander et al. performed a cohort study of 121 young athletes (average age of 26 years) suffering a rupture of ACL and showed dissatisfaction of 1/3 of respondents with their condition (PASS "-") [13]. S. Van der Graaff et al. followed up 82 patients with ACL rupture and delayed operation; in 29 (35.4%) of which the pain level 3-6 months after the injury was >3 NRS points [14]. C. Anthony et al. assessed the need in opioid analgesics in 4946 patients suffering a knee joint injury and requiring surgical reconstruction of the ACL [15]. Three months before the surgery, 35% of patients had to take opioid analgesics on a regular basis, because they were in intense pain.

We identified a correlation between CPTP and female sex. Higher risk of development of chronic pain in women is confirmed by a meta-analysis of 71 studies performed by H.Andreoletti et al. [16]. This work focused on risk factors of post-surgery pain. One of the main factors was the female sex, OR = 1.34. In the review of S. Mills et al. on the problem of chronic pain it is reported that CPTP is seen more often in women because they describe the sensation of pain in a more pronounced, emotional manner [17].

We also found a correlation between the development of CPTP and structural changes, such as damage to the meniscus, osteitis and synovitis. The contribution of meniscal damage to the development of chronic pain was mentioned earlier in other studies. E.g., C. Maia et al. compared the progress of the primary OA (n=641) and PTOA (n=104) and showed that the presence of meniscal injury is associated with severe pain and disrupts its function [18]. The contribution of meniscal damage to the development of symptomatic PTOA is confirmed in

the study of Y. Lu et al. [19]. The authors followed up 974 patients with injuries of the ACL and meniscus and subsequent reconstruction of the ligament and treatment of the meniscus averagely 7.5 years after the first surgery. They found development of PTOA in 22.1% of the cases. The conclusions of this study confirm that the meniscal damage was a risk factor of development of post-traumatic osteoarthritis.

Effusion to the knee joint and synovitis (proliferative and/or exudative) are widely spread visual symptoms identified in patients both immediately after the joint injury and long after it. The relation of synovitis and clinical symptoms remains a controversial question. Thus, T. Perry et al. studied 174 patients with OA for three years and saw no correlation between the pain as per WOMAC index and thickening of the synovium [20]. At the same time, synovitis of specific areas, viz. Infrapatellar, was associated with severe pain: OR 5.96 (95% CI 1.22-10.7). On the contrary, in the study of G.Wallace et al. found a strong correlation between the synovitis identified by MRI findings and pain in 104 patients with OA [21]. According to the data of a meta-analysis of 18 studies (n=5907 patients), E. Alaia et al. established a relation between clinical and MRI symptoms of OA [22]. Among the latter, synovitis and bone marrow edema were identified as manifestations of osteitis.

In the study of J. Driban et al., who evaluated the MRI data of 121 young patients with injuries of the ALC, found bone marrow edema in 96% patients, but there was no correlation of this MRI-identified symptom with severity of pain: $\beta = -0.09$, $P = 0.25$ [23]. Persistence of the bone marrow edema or its augmentation (increase of area or strengthening of signal from the existing edema without the increase of the osteitis area) according to the MRI data for a long period of time may point at progression of osteodestructive and inflammatory changes, which shows in the persistence or increase of paint in such patients. The study of K. Moradi et al. is demonstrative in this respect: for a period of 4 years, 2430 patients with OA who underwent MRI were followed up. In 1106 patients, the bone marrow edema was found to increase, which was associated with elevated risks of progression of OA as compared to patients in which the intensity of the edema remained the same or decreased: OR 1.3; $P<0.001$ [24].

Development of CPTP is related to initially intense pain (≥7 NRS). In such patients, the level of pain in 6 months credibly correlated with the level of pain at the outset and with functional disorder. Based on this is can be suggested that severe pain and functional disorders point at development of structural disorders, persistence of inflammation and dysfunction of nociceptive system. The significance of initial pain as a risk factor of CPTP development was confirmed in the meta-analysis of 18 studies (n=5372 patients) presented in the article by O. Alkassabi et al. [25].

Another factor influencing progression of CPTP was the presence of depression (HADS ≥11) and highly probable CS (CSI≥40). The severity of CPTP correlated with the numerical value of the central sensitization index (CSI), number of patients with CSI≥40 and number of patients with HADS ≥11.

Despite the absence of the statistically reliable correlation between the progression of CPTP and BMI, severity of neuropathic pain (PainDETECT), anxiety (HADS) and catastrophization (PCS), numeric values of these factors were higher in patients with CPTP in comparison with patients without CPTP. Lack of reliable differences is likely accounted for by the low prevalence of these manifestations in the group generally.

The importance of psycho-emotional disorders, CS and catastrophization in the progression of CPTP was shown in several articles [26–28]. Specifically, the work of S. Heijbel et al. evaluated outcomes of total replacement of the knee joint (TKR) in 8745 patients and found that dissatisfaction with the surgery depended on the presence of depression and anxiety: before the surgery, OR 1.23 (95% CI 1.09-1.40), after the surgery, OR 2.65 (95% CI 2.33-3.00) [26]. The meta-analysis of 32 studies (n=18792) by J. Li et al. concentrated on risk factors of postoperative pain in patients after TKR, and showed the significant contribution of CS, anxiety, and moderate depression [27]. The data of a meta-analysis of 29 studies (n=10360) by U. Olsen et al. demonstrated a correlation between pain progression one year after the surgery and catastrophization: $r=0.36$ (95% CI 0.24-0.47; $p<0.0001$) [28].

The influence of psycho-emotional disorders, catastrophization and CS on the development of CPTP is caused by a decrease in the pain threshold, hyperalgesia, increased pain afferentation, the development of neuroplastic changes and dysfunction of the nociceptive system, which determine an excessive and emotionally charged reaction to pain [29, 30].

We were not able to find a reliable correlation between the level of biochemical markers, namely hsCRP, NTX, ADAMTS-5, COMP, MMP-3, MMP-9, MMP-13 and substance P and progression of CPTP. In some papers, these biomarkers had some correlations with structural changes in the joints in OA (C-terminal telopeptide of type II collagen (CTx-II), COMP, MMP-3) [31, 32]. Some inflammatory cytokines may elevate immediately following the injury and remain in the synovial fluid of the injured joint and plasma of the blood for many months and years (IL-1β, IL-17, IL-6, TNF-α, macrophage inflammatory protein (MIP)-1, MMP, tissue inhibitor of metalloproteinase, TIMP), which may point at chronization of the inflammatory process and progression of PTOA [33]. The meta-analysis of L.Batty et al. showed the predictive value of IL-6, MMP-3, CTx-II in the evaluation of progression of adverse changes after the injury to and reconstruction of the ALC [34]. The article of H. Higuchi et al. reports that elevated concentrations of IL-6, MMP-3 and TIMP-1 in the synovial fluid persisted in persons with ALC injury for six months [35]. The study of K. Elsaid et al. found that in 30 cases of injury of ALC, one year after the injury the synovial fluid still had elevated levels of IL-1β, IL-6, TNF-α, neutrophilic elastase and sulfated glycosaminoglycan. At the same time, the synovial fluid of the opposite non-injured joint did not shoe biomarker levels different from the norm [36].

Biomarker concentration may correlate with signs of joint inflammation identified on MRI scans. In the article of Z. Zhu et al., biomarkers of 193 patients with active OA were studied. It was found that the increase of concentration of IL-6, IL-17 and IL-23 correlated with bone marrow edema [37].

However, some studies do not confirm data on the correlation between the level of biomarkers and progression of CPTP. For example, C. Lisee et al. studied the correlation between development of symptoms after the injury to and restoration of ACL and levels of MCP-1, COMP, MMP-3 and

CTx-II in 30 patients. After six months of the study, there was no correlation between the symptoms and concentration of biomarkers [38]. The systematic review of O. O'Sullivan et al. presented the data of 8 studies (n=879 patients), in which the correlation between concentration of IL-1, IL-6, TNF-α, COMP and some other biomarkers with clinical and structural changes in PTOA was not confirmed. The authors concluded that the differences in methods do not allow comparison of the results of different studies, and the overall weak connection between laboratory and clinical data [39].

The absence of correlations between biomarkers and clinical manifestations in our study may indicate both methodological problems with the analysis of biomarkers (a small number of observations, a heterogeneous group), and a true absence of differences in their concentrations associated with the peculiarities of the choice of the study cohort (all patients initially had severe pain and a similar spectrum of structural changes in the knee joint).

CONCLUSION

Thus, some of the main risk factors for the development of CPTP are intense pain, as well as the presence of structural changes: meniscus damage, synovitis and osteitis according to MRI data. There is no doubt that in the early stages of the post-traumatic process, it is such objective factors, indicating the presence of damage and inflammation, that play a leading role in the development of chronic post-traumatic pain. Later, they are joined by elements of dysfunction of the nociceptive system and psycho-emotional disorders. Although we were unable to detect statistical significance of the influence of catastrophization, fibromyalgia symptoms, depression and anxiety, there is an obvious tendency for these parameters to be more frequent in patients with CPTP. Therefore, it makes sense to take into account the signs of dysfunction of the nociceptive system and psycho-emotional disorders, which can be considered an important element in predicting the negative trajectory of the course of PTP and the development of PTOA.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical review. This work was carried out in compliance with human rights defined by the Helsinki Accords. All patients gave informed consent to participate in the study. The study was approved by the Ethics Committee of the V.A. Nasonova Research Institute of Rheumatology (Protocol No. 8 dated 10/25/2022).	***Этическая экспертиза.*** Настоящая работа проводилась с соблюдением прав человека, определенных Хельсинкским соглашением. Все пациенты дали информированное согласие на участие в исследовании. Исследование было одобрено этическим комитетом ФГБНУ «НИИ ревматологии им. В.А. Насоновой» (протокол № 8 от 25.10.2022).
Study funding. The work was carried out using budgetary funding for the implementation of the state assignment on topic FURS-2022-0009 (state assignment number 1021062512064-0).	***Источник финансирования.*** Работа выполнена за счет средств бюджетного финансирования на выполнение государственного задания по теме FURS-2022-0009 (номер государственного задания 1021062512064-0).
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. A.A. Byalik: collection of database, writing of the text of article. S.A. Makarov: patient selection. A.E. Karateev, E.I. Byalik, V.A. Nesterenko, D.M. Kudinsky: idea of study, editing of article. V.E. Byalik: statistical processing of results. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** А.А. Бялик – сбор базы данных, написание текста статьи. С.А. Макаров – отбор пациентов. А.Е. Каратеев, Е.И. Бялик, В.А. Нестеренко, Д.М. Кудинский – идея исследования, редактирование статьи. В.Е. Бялик – статистическая обработка результатов. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Kinematic analysis of gait in children with rigid flatfoot before and after surgical treatment

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Abstract

Aim – to study the kinematics and kinetics of walking in children with rigid flatfoot by comparing data before and after surgical operations.

Material and methods. The study included 51 patients (42 boys, 9 girls) with rigid flatfoot, with a mean age of 10.5 ± 1.4 years. They were stratified by disease stage and underwent surgical treatment using the author's technique: 'transposition of the m. peroneus longus tendon medially, shortening of the m. tibialis posterior tendon, and arthrodesis of the cuneo-navicular joint'.

Results. It was found that higher disease stages correlated with increased step time and support time, and decreased swing time, average walking speed, and step frequency (<0.01 to <0.001). Disease progression also exacerbated pathomorphological changes in the foot, driven by biomechanical dysfunction of the lower leg's pronator and supinator muscles, alongside reduced gait energy efficiency.

Conclusion. Gait kinematic assessment, when combined with standard diagnostic tools for rigid flatfoot (e.g., radiography and podometry), enhances the identification of effective and precise treatment strategies. The proposed disease stage-adjusted corrective approach addresses all components of rigid flatfoot: it eliminates pathological pronation, restores supination and plantar flexion function, and achieves adequate foot arch reconstruction.

Keywords: flatfoot, muscle rigidity, kinematics, children.

Conflict of interest: nothing to disclose.

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Исследование кинематики ходьбы детей с ригидным плоскостопием до и после хирургического лечения

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Аннотация

Цель – изучить кинематику и кинетику ходьбы у детей с ригидным плоскостопием путем сравнения данных до и после проведенных хирургических операций.

Материал и методы. В исследование включен 51 пациент (42 мальчика и 9 девочек) с ригидным плоскостопием. Средний возраст пациентов составил 10,5 ± 1,4 года. Пациенты разделены на группы с учетом стадии заболевания. Всем пациентам проведено хирургическое лечение с применением авторской методики – «транспозиция сухожилия m. peroneus longus в медиальную сторону стопы, укорочение сухожилия m. tibialis posterior и артродезирование клиноладьевидного сустава».

Результаты. Определено, что чем выше стадия заболевания, тем более увеличены показатели «время шага», «время опоры» и уменьшены показатели «время переноса», «средняя скорость ходьбы» и «частота шагов» (<0,01–0,001). Также от стадии заболевания зависят степень патоморфологических изменений в области стопы на фоне нарушения биомеханической особенности мышц-пронаторов и мышц-супинаторов области голени и потеря высокой энергии при ходьбе.
Заключение. Оценка кинематики ходьбы в дополнение к таким методам диагностики ригидного плоскостопия, как рентгенография и подометрия, полезна для определения эффективных и точных методов лечения заболевания. Предложенный метод коррекции с учетом стадии заболевания позволяет устранить все компоненты ригидной формы плоскостопия, ликвидировать патологическую пронацию, улучшить функцию супинации и подошвенного сгибания с адекватным восстановлением свода стопы.
Ключевые слова: плоскостопие, мышечная ригидность, кинематика, дети.
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INTRODUCTION

Rigid flatfoot represents the most prevalent form of foot dysfunction [1]. It is characterized by a lowered longitudinal foot arch, but in fact represents a three-dimensional deformity comprising hind-foot valgus, forefoot abduction, and pronation due to the severity of foot pathology [2, 3]. Rigid flatfoot disrupts the normal gait pattern and establishes a new pathological walking type. Analysis of these abnormal movement patterns enables diagnosis of disease etiology and pathogenesis, while identifying individual and clinical variants [4, 5].

The treatment of rigid flatfoot differs significantly from the mobile form of this pathology and often requires invasive surgical interventions [6]. Surgical correction of rigid flatfoot varies in technique and scope, from soft tissue procedures involving talar bone reshaping with tendon/muscle transfers to osseous methods utilizing various metal fixation devices [7]. However, long-term postoperative outcomes remain unpredictable and often prove unsatisfactory for patients, their parents and orthopedic surgeons, particularly due to the need for permanent orthotic use to manage clinical symptoms [8]. This stems from insufficient data on pathogenetic features of rigid flatfoot, biomechanical impairment of lower leg/foot neuromuscular structures across disease stages and severity levels, and the disregard of these factors when selecting corrective procedures for rigid flatfoot patients [9].

A current priority is investigation of rigid flatfoot kinetics and kinematics using advanced methods such as gait videography and 3D motion capture in gait laboratories.

AIM

To study the kinematics and kinetics of walking in children with rigid flatfoot by comparing data before and after surgical operations.

MATERIAL AND METHODS

The study group included 51 patients (42 boys and 9 girls) with rigid flatfoot, who were observed and treated in the Andizhan Children's Multi-disciplinary Clinic in 2019–2024. The mean age of patients was 10.5 years (from 7 to 16).

Based on the classification of M.S. Myerson (1997), we developed a new algorithm for classification of children with rigid flatfoot[1]. Unlike the Myerson classification, we included the spastic contracture of the tendon of m. peroneus longus, which has a special role in the pathomorphological changes of the lower leg and foot in rigid flatfoot (**Table 1**).

It is seen from Table 1 that among clinical forms the acquired form was most prevalent, in 41 (80.5%) vs. 10 (19.5%) cases of congenital form of the disease. Most frequently, patients were registered with stage III, in 22 (43.1%) cases, and there were also cases with spastic contracture of the tendon of m. peroneus longus, in 13 (25.5%) cases (subgroup III B) among patients with stage III, and in 8 (15.7%) cases (subgroup IV B) among patients with stage IV of the disease.

The functional condition of the m. peroneus longus is principal in the transformation of the mobile flatfoot into rigid flatfoot. Tendon reposition to the supinator side is also critical for surgical correction.

All patients (n=51) underwent surgical treatment using following technique: 'transposition of the m. peroneus longus tendon medially, shortening of the m. tibialis posterior tendon, and arthrodesis of the cuneo-navicular joint'[2].

The technique involves the following steps: wedge resection of the navicular and cuneiform articular surfaces (wedge angle oriented plantarly), creating a cuneiform bone tunnel; reinserting the m. tibialis posterior tendon attachment, shortening its tendon via tensioning and embedding into the formed tunnel of the cuneiform bone; transferring the m. peroneus longus tendon medially to attach to the m. tibialis posterior tendon; and triangular pin fixation of the cuneo-navicular joint to reconstruct the foot arch.

It is to be remembered that in rigid flatfoot, even after its restoration, the patients' gait will vary. To distinguish between these variations of gait, we analyzed it in the gait laboratory. Our study considered the severity of the disease, age of patients and their anthropometric data. The study involved 13 patients with stage II of disease, 22 patients with stage III, and 16 patients with stage IV. The mean height of patients was 126.5 cm (126-162 cm) for boys and 138.6 cm (133-146 cm) for

[1] The Algorithm is registered in the Agency for Intellectual Property of the Republic of Uzbekistan (No. DGU42326, 2024).
[2] Invention patent No.FAP 2416 (2024), registered in the Agency for Intellectual Property of the Republic of Uzbekistan.

Clinical forms \ Disease stage	I	II (n=13)	III (n=22)		IV (n=16)	
				III B (n=13)	IV A (n=8)	IV B (n=8)
Congenital, n=10 (19.5%)	0	2 (3.9%)	2 (3.9%)	2 (3.9%)	3 (5.9%)	1 (1.9%)
Acquired, n=41 (80.5%)	0	11 (21.6%)	7 (13.7%)	11 (21.6%)	5 (9.9%)	7 (13.7%)

Table 1. *Distribution of patients by clinical form and stage of rigid flatfoot*
Таблица 1. *Распределение больных по клинической форме и стадии ригидного плоскостопия*

girls. The mean weight of patients was 32.5 ± 2.4 kg (21-62 kg) among boys, and 28.2 ± 3.1 kg (26-41 kg) among girls, respectively.

Gait analysis was performed using video recording and 3D motion capture at the Gait Laboratory of the Republican Specialized Scientific-Practical Medical Center of Traumatology and Orthopedics.

Range of motion for each joint was measured using a goniometer, including ankle plantarflexion and dorsiflexion. During dorsiflexion measurement, the foot was slightly everted to stabilize the subtalar joint and prevent compensatory motion.

For 3D motion capture, passive reflective markers were placed according to the Helen Hayes protocol. Marker trajectories were recorded using the BTS Bioengineering system (Italy, 2023) with eight digital infrared cameras.

The participants' gait was recorded during multiple trials on a 12-meter walkway at self-selected speed, with motion capture at 120 frames per second (120 Hz).

Ground reaction force (GRF) was measured using four force plates embedded in the midpoint of the walkway. GRF between the limb and surface during stance phase was quantified by the force platforms.

The coordinate system of Euler angles for measuring GRF was placed as shown in **Fig. 1**.

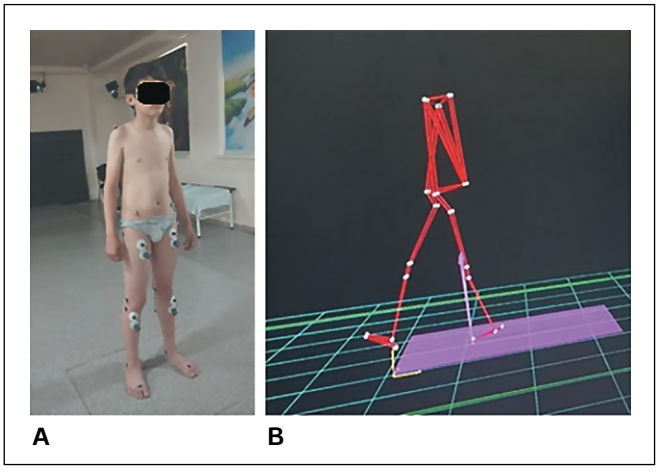

Figure 1. *A – appearance of the patient under study;*
B – coordinate system of Euler angles for measuring GRF.
Рисунок 1. *А – внешний вид исследуемого пациента;*
Б – система координат углов Эйлера для измерения GRF.

RESULTS

In the gait laboratory, we tested such parameters as step time (sec), stance time (sec), swing time (sec), stance phase (%), swing phase (%), single-limb support phase (%), double-limb support phase (%), average velocity (m/s), and cadence (steps/min). The obtained results were compared with normative values. Step time, the key gait parameter, was calculated as the sum of 'stance time' and 'swing time'.

The analysis of data of 13 patients with stage II of the disease showed that the step time of both lower limbs were 43% above normative values (p=0.001). The values of such parameters as stance time and swing time were 52% and 31% higher than the normative values, respectively. Statistical significance was found between the results (p=0.001).

Analysis of pre-operative gait data (videography and 3D motion capture) in stage II rigid flatfoot revealed minimal

Parameter	Right lower limb	Left lower limb	Normative values	p-value
Step time (s)	1.33 ± 0.07	1.33 ± 0.04	0.93 ± 0.04	<0.001
	0.98 ± 0.05	0.97 ± 0.04		
Stance time (s)	0.82 ± 0.04	0.80 ± 0.03	0.54 ± 0.05	<0.001
	0.60 ± 0.02	0.56 ± 0.05		
Swing time (s)	0.51 ± 0.03	0.53 ± 0.01	0.39 ± 0.03	0.01
	0.38 ± 0.02	0.41 ± 0.02		
Stance phase (%)	61.2 ± 2.88	61.2 ± 3.4	57.97 ± 1.93	<0.05
	60.2 ± 2.1	60.1 ± 1.4		
Swing phase (%)	38.6 ± 2.4	38.8 ± 2.1	42.03 ± 1.93	<0.001
	40.5 ± 2.6	41.8 ± 2.5		
Single-limb support phase (%)	37.3 ± 2.9	40.5 ± 1.4	39.28 ± 0.25	<0.05
	38.3 ± 2.9	40.1 ± 1.1		
Double-limb support phase (%)	10.75 ± 2.4	8.5 ± 2.3	12.4 ± 2.21	>0.05
	11.5 ± 2.2	11.9 ± 2.1		
Average velocity (m/s)	0.86 ± 0.1		1,2 ± 0,2	1.2 ± 0.2
	1.16 ± 0.3			
Cadence (steps/min)	86.3 ± 5.6		129,6 ± 8,4	129.6 ± 8.4
	125.5 ± 4.5			

Table 2. *Comparative analysis of results of 13 patients with stage II of the disease before and after surgery*
Таблица 2. *Сравнительный анализ результатов 13 больных со II стадией заболевания до и после операции*

Parameter	Right lower limb	Left lower limb	Normative values	p-value
Step time (s)	1.39 ± 0.07	1.40 ± 0.04	0.93 ± 0.04	<0.001
	1.15 ± 0.05	1.16 ± 0.03		
Stance time (s)	0.83 ± 0.04	0.87 ± 0.02	0.54 ± 0.05	0.01
	0.61 ± 0.03	0.60 ± 0.02		
Swing time (s)	0.56 ± 0.03	0.53 ± 0.02	0.39 ± 0.03	0.01
	0.54 ± 0.02	0.56 ± 0.01		
Stance phase (%)	61.6 ± 3.6	61.8 ± 2.8	57.97 ± 1.93	0.01
	59.6 ± 4.4	59.8 ± 1.8		
Swing phase (%)	38.4 ± 1.9	38.2 ± 2.2	42.03 ± 1.93	<0.001
	39.1 ± 2.9	40.3 ± 3.1		
Single-limb support phase (%)	37.4 ± 2.7	40.9 ± 1.7	39.28 ± 0.25	0.01
	38.6 ± 3.5	39.9 ± 1.1		
Double-limb support phase (%)	10.75 ± 2.4	9.7 ± 2.6	12.4 ± 2.21	<0.05
	11.6 ± 1.6	11.8 ± 1.04		
Average velocity (m/s)	0.79 ± 0.1		1,2 ± 0,2	1.2 ± 0.2
	1.12 ± 0.2			
Cadence (steps/min)	82.7 ± 5.2		129,6 ± 8,4	129.6 ± 8.4
	124.9 ± 3.1			

Table 3. *Comparative analysis of results of 22 patients with stage of the disease before and after the surgery*
Таблица 3. *Сравнительный анализ результатов 22 больных с III стадией заболевания до и после операции*

energy loss during walking, attributable to the following: absence of rigid contracture or spasm of the m. peroneus longus tendon, and preserved foot arch mobility with minimal degenerative changes in tarsometatarsal joints. Fibrous coalition between metatarsals was also diagnosed in patients with stage II of the disease.

The preoperative values of such parameters as step time, stance time, and swing time significantly influenced the average velocity and cadence, which were below the norm. The average velocity was 0.86 ± 0.1 m/s (norm: 1.2 ± 0.2 m/s), cadence, 86.3 ± 5.6 steps per minute (norm: 129.6 ± 8.4). The obtained results demonstrated statistical significance (p=0.001) (**Table 2**).

The surgical interventions created optimal conditions for improving foot spring function with minimal energy loss during gait, eliminating the need for metatarsal coalition resection. Postoperative correction in stage II patients demonstrated statistically significant improvements: step time bilaterally reached 0.93 ± 0.05 sec (p<0.01–0.001), stance time 0.60 ± 0.02 sec (all p=0.001), and swing time 0.38 ± 0.02 sec (p=0.001). The enhancements of parameters of step increased average walking velocity from 0.86 ± 0.1 m/s to 1.16 ± 0.3 m/s (normal range: 1.2 ± 0.2; p=0.001) and cadence from 86.3 ± 5.6 to 125.5 ± 4.5 steps/min (norm: 129.6 ± 8.4; p=0.001).

In 22 patients in stage III of the disease, the step time, stance time and swing time parameters were significantly above the norm, by 49%, 54% and 43% respectively (p=0.001). The parameters of the step significantly influenced the average velocity and cadence. The average velocity in the preoperative period was 0.79 ± 0.1 m/s, which is significantly lower than the normative value of 1.2 ± 0.2 m/s. The cadence was 82.7 ± 5.2 steps per minute, also significantly below the norm of 129.6 ± 8.4. The results demonstrated statistical significance (p=0.001) (**Table 3**).

In stage III rigid flatfoot, prolonged arch collapse and the rigid spasm of the m. peroneus longus tendon induce severe

Parameter	Right lower limb	Left lower limb	Normative values	p-value
Step time (s)	1.43 ± 0.04	1.44 ± 0.05	0.93 ± 0.04	<0.001
	1.18 ± 0.06	1.19 ± 0.06		
Stance time (s)	0.86 ± 0.02	0.86 ± 0.03	0.54 ± 0.05	<0.001
	0.63 ± 0.02	0.62 ± 0.03		
Swing time (s)	0.57 ± 0.02	0.58 ± 0.02	0.39 ± 0.03	<0.001
	0.55 ± 0.04	0.57 ± 0.03		
Stance phase (%)	63.1 ± 4.6	63.5 ± 4.6	57.97 ± 1.93	<0.05
	60.8 ± 4.5	60.9 ± 4.6		
Swing phase (%)	35.9 ± 5.3	35.2 ± 5.1	42.03 ± 1.93	<0.001
	38.2 ± 2.3	38.8 ± 6.1		
Single-limb support phase (%)	35.6 ± 4.7	38.6 ± 4.9	39.28 ± 0.25	<0.05
	38.4 ± 2.2	38.9 ± 0.35		
Double-limb support phase (%)	8.72 ± 2.9	8.6 ± 2.7	12.4 ± 2.21	<0.05
	10.79 ± 3.9	10.89 ± 1.85		
Average velocity (m/s)	0.73 ± 0.30		1,2 ± 0,2	1.2 ± 0.2
	1.05 ± 0.05			
Cadence (steps/min)	76.2 ± 9.1		129,6 ± 8,4	129.6 ± 8.4
	115.2 ± 7.4			

Table 4. *Comparative analysis of results of 16 patients with stage IV of disease before and after the surgery*
Таблица 4. *Сравнительный анализ результатов 16 больных с IV стадией заболевания до и после операции*

degenerative changes, producing fibrous or cartilaginous tarsometatarsal coalitions. Concomitant dysfunction of the m. tibialis posterior tendon further compromises the spring function of the foot, resulting in excessive energy expenditure during gait.

In stage III of the disease, priority is given to coalition resection that yields limited intermetatarsal joint mobility. This step is followed by the transfer of the m. peroneus longus tendon to the supinator side and shortening of the m. tibialis posterior tendon. This converts rigid flatfoot to a mobile form, significantly improving muscle function supporting lower leg and foot spring mechanics while minimizing gait energy loss. Postoperative outcomes demonstrated near-normal improvement of parameters (p=0.001).

In 16 patients with stage IV of the disease, the values of step time, stance time and swing time were significantly increased versus the norm by 54%, 59% and 46% respectively (p<0.001). The values of average velocity and cadence were also significantly lower: in the preoperative period, the average velocity was 0.73 ± 0.03 m/s, statistically significantly lower than the norm of 1.2 ± 0.2 m/s, and the cadence was decreased to 76.2 ± 9.1 steps per minute versus the normative value of 129.6±8.4 steps per minute (p=0.001) (**Table 4**).

Stage IV patients exhibit bony or cartilaginous tarsometatarsal coalitions with severe rigid spasm of the m. peroneus longus tendon, indicating profound arch spring dysfunction and talocalcaneal osteoarthritis. The energy-absorbing capacity of the foot is markedly impaired, resulting in excessive energy loss even during short-distance walking.

We first resected the bony or cartilaginous coalition, then performed medial transfer of the m. peroneus longus tendon with shortening of the m. tibialis posterior tendon, thus achieving essential mobilization of the foot arch.

Postoperative supinator muscle function and foot spring mechanics were adequately restored, though ankle pain persisted due to tarsometatarsal osteoarthritis. Postoperative values of the step time, stance time and swing time parameters significantly decreased to 1.18 ± 0.06 from 1.43 ± 0.04 sec, to 0.63 ± 0.02 from 0.86 ± 0.02 sec, and to 0.55 ± 0.04 from 0.57 ± 0.02 sec, respectively (p<0.001). The average velocity increased in the postoperative period to 1.05 ± 0.05 m/s (norm: 1.2±0.2 m/s). The cadence value also increased to 115.2 ± 7.4 steps per minute, which is significantly closer to the norm (129.6 ± 8.4 steps per minute). The obtained results demonstrated statistical significance (p<0.001).

DISCUSSION

Rigid flatfoot is characterized with lever arm shortening due to forefoot abduction and heel valgus, reducing lever strength and mid-foot flexibility, respectively [10]. This impairs kinetic lever function, causing loss of kinetic energy. From the standpoint of clinical symptoms, this manifests as muscle fatigue after prolonged walking, discomfort or pain the in foot, leg, or knee [11,12].

Studies revealed comparable reductions in both plantarflexion and dorsiflexion range of motion at the ankle joint in these patients. Flatfoot was associated with an increased angle between the talar and navicular bones. Consequently, greater energy expenditure was required for supination and inversion to achieve foot stabilization during gait [13,14].

Podiatric practice recognizes over 100 surgical techniques for the correction of the planovalgus deformity, yet no optimal treatment protocol exists. Pediatric surgical interventions are categorized as follows: soft-tissue procedures, extra-articular bony operations, and intra-articular surgeries [15,16]. Combined approaches yield superior outcomes in most cases [17,18].

At the same time, the incidence rate of various complications and relapses is rather high reaching 23.7%. Given the multicomponent nature of the morphological changes of the foot joint and the multifactorial etiology of the flatfoot, each case requires individual indications and corrective method selection [19–22].

CONCLUSIONS

1. Gait kinematic analysis complements standard rigid flatfoot diagnostics (radiography, podometry) to optimize treatment precision.

2. The analysis included measurements of the degree of kinetic energy loss in the gait of flatfoot patients and identified a biomechanical correlation between the degree of energy loss and the stage of rigid flatfoot.

3. The suggested method of correction, taking into account the disease stage, allows immediate elimination of all components of the rigid form of flat foot, eliminate pathological pronation, improve supination and plantar flexion of the foot, and adequate restoration of the foot arch.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical review. All patients (their legal representatives) gave informed consent to participate in the study.	***Этическая экспертиза.*** Все пациенты (их законные представители) дали информированное согласие на участие в исследовании.
Study funding. The study was carried out with the financial support of the State Institution "Republican Specialized Scientific and Practical Medical Center for Traumatology and Orthopedics" (Tashkent, Republic of Uzbekistan).	***Источник финансирования.*** Исследование выполнено при финансовой поддержке ГУ «Республиканский специализированный научно-практический медицинский центр травматологии и ортопедии» (Ташкент, Республика Узбекистан).
Conflict of Interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. I.Yu. Khodjanov: idea of the research, editing of the article. X.I. Umarov: writing of the text. Sh.K. Khakimov: statistical data processing, literature review. A.G. Mirzaev: performing gait in lab analysis and data processing. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work	***Участие авторов.*** И.Ю. Ходжанов – идея исследования, редактирование статьи. Х.И. Умаров – написание текста. Ш.К. Хакимов – статистическая обработка данных, обзор литературы. Мирзаев А.Г. – проведение анализа в лаборатории походки и обработка данных. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Comparative analysis of accuracy and time of calculation of wound surface area using mobile applications

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Abstract

Aim – to carry out a comparative assessment of the accuracy and time of calculating the area of the wound surface using mobile applications.

Material and methods. Wound areas were measured using mobile applications +WoundDesk, ImitoWound and V2F in four blocks of the study: schematic 2D image of soft tissue wounds (block I), volumetric (3D) models of wounds in fractures of the shoulder and leg (block II), experimental wounds in laboratory animals (block III) and assessment of combined wound defects upper and lower jaws in patients (IV block). In the first block, four groups were identified: the 1st group was measured by the area of schematic wounds on a flat surface; in the 2nd, 3rd and 4th groups, by the area of schematic wounds painted on cylindrical surfaces with a diameter of 7, 10 and 20 cm, imitating the surfaces of the forearm, shoulder and head, respectively.

Results. In block I, there is a direct relationship between the curvature of the examined wound surface and the accuracy of determining its area. In the second block, the measurements obtained using the ImitoWound mobile application turned out to be the most accurate, 96.22±3.41% and 97.80±2.37%. In the III block of the study conducted on laboratory rats of the Wistar line, the average deviation when using +WoundDesk was 90.84±7.51%, V2F – 88.96±9.52%, ImitoWound – 92.51±2.54%. In the IV block of the study, when analyzing the accuracy of determining the area of defects of superficial soft tissues in patients with facial defects, the ImitoWound mobile application and the Autoplan complex showed similar results.

Conclusion. Most wounds encountered in medical practice have a complex configuration that changes during treatment, changing from one form to another, which calls into question the expediency of using the presented mobile applications as the main method of conducting planimetric studies in medicine.

Keywords: wounds, wound area, planimetry, mobile applications, Autoplan, reconstruction of facial defects.

Conflict of interest: nothing to disclose.

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Сравнительный анализ точности и времени расчета площади раневой поверхности с использованием мобильных приложений

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Аннотация

Цель – провести сравнительную оценку точности и времени расчета площади раневой поверхности с использованием мобильных приложений.

Материал и методы. Выполнено измерение площадей ран с использованием мобильных приложений +WoundDesk, ImitoWound и V2F в четырех сериях исследования. Серия I – схематическое 2D изображение ран мягких тканей. Серия II – объемные (3D) муляжи ран при переломе плеча и ноги. Серия III – экспериментальные раны у лабораторных животных. Серия IV – оценка комбинированных раневых дефектов верхней

и нижней челюстей у пациентов с помощью программного комплекса «Автоплан». В серии I выделили четыре группы: в первой группе проводили измерение площади схематических ран на плоской поверхности; во второй, третьей, четвертой группах измерялись схематические раны, нарисованные на цилиндрических поверхностях диаметром 7, 10 и 20 см, имитирующих поверхности предплечья, плеча и головы соответственно. **Результаты.** В серии I прослеживается прямая связь между кривизной исследуемой раневой поверхности и точностью определения ее площади. В серии II наиболее точными оказались измерения, полученные с помощью мобильного приложения ImitoWound – 96,22±3,41% и 97,80±2,37%. В серии III исследования, проведенного на лабораторных крысах линии Wistar, среднее отклонение при использовании +WoundDesk составило 90,84±7,51%, V2F – 88,96±9,52%, ImitoWound – 92,51±2,54%. В серии IV исследования при анализе точности определения площади дефектов поверхностных мягких тканей у пациентов с дефектами лица мобильное приложение ImitoWound и комплекс «Автоплан» показали схожие результаты.

Выводы. Большинство ран, встречающихся во врачебной практике, имеют сложную, изменяемую в процессе лечения конфигурацию, переходящую из одной формы в другую, что ставит под сомнение целесообразность использования представленных мобильных приложений как основного метода проведения планиметрических исследований в медицине.

Ключевые слова: раны, площадь ран, планиметрия, мобильные приложения, «Автоплан», реконструкция дефектов лица.

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СР – схематическая рана.

INTRODUCTION

Treatment of soft tissue wounds is one of the costliest items of surgical care worldwide that increases greatly in case of complications [1–3]. The cost of care of patients with this kind of pathology comprises expenses on medications, patient's stay in the hospital, treatment itself, medical manipulations, rehabilitation, etc. [4]. These facts, as well as high rate of incidence of onset of surgical site infections indicate a necessity of development of new methods of treatment of this condition.

Studies of effectiveness of various methods of treating soft tissue wounds increases the need for an objective assessment of the wound surface area and monitoring the dynamics of defect closure [5–6]. This data is necessary for clinical work, experimental and scientific practice. The calculation of the area of soft tissue defect makes it possible to calculate the amount of dressing material or medications needed to treat the wound surface, which may assist standardization of various surgical procedures or monitor economic efficiency of different methods of treatment [7–9]. Considering the difficulty of planning the reconstructive stage for patients with combined facial defects, this data can be used to calculate the required area of the flap skin paddle to repair defects of skin cover [10, 11]. Given the rapid development of modern technology, there are many IT approaches to the task that are gaining momentum: applications for mobile devices and computer programs including laser grids and three-dimensional scanning [12–16]. The mobile applications generate much interest: patients and doctors have mobile phones, which facilitates remote monitoring of regenerative processes of the wounds [17]. According to the website of the developer of the mobile application ImitoWound, their product is used in more than 30 clinics worldwide[1].

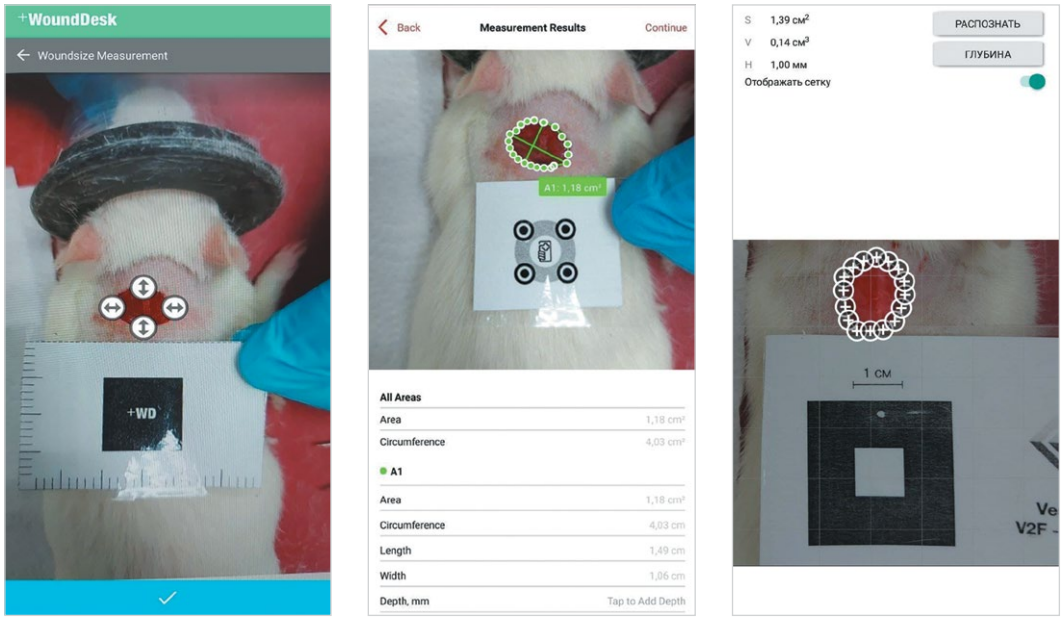
AIM

To carry out a comparative assessment of accuracy and time of calculating the area of the wound surface using mobile applications.

MATERIAL AND METHODS

We measured wound surface areas using mobile applications +WoundDesk, ImitoWound and V2F most frequently mentioned in scientific literature [18–22]. To calculate the area, a special target is required that is placed next to the wound, after which a photo is taken with the aid of the application (**Fig. 1**). In the +WoundDesk application, the target is a 2×2 cm black square on a white background with a centimeter scale on the sides; ImitoWound uses a target sized 1.5×1.5 cm; V2F uses a 1×1 cm white square within a 3×3 cm black square. After capturing the image, the user confirms the contours of the wound defect recognized automatically or makes manual adjustments. After this, the area is calculated, and the data is saved in the patient's profile or in the history of measurements depending on the functionality of the app.

[1] Available online: https://imito.io/en/references-and-partners#clinicalresearch



+WoundDesk *ImitoWound* *V2F*

Figure 1. *Measurement of wound surface area using the mobile applications under inquiry.*
Рисунок 1. *Измерение площади раневой поверхности с использованием исследуемых мобильных приложений.*

The study did not include measurements of the depth and the volume of wounds due to the lack of such functions in the apps under inquiry.

When taking photos for subsequent processing with mobile apps, the same distance of 25 cm from the lens to the wound surface was observed, the same positioning of targets to determine scale relative to the wound surface, the defect contours were manually adjusted in all cases, and any foreign objects were removed from the frame. The photos were taken using the Google Pixel 7 mobile phone with Android 14 operating system. The main camera was 50+12 megapixels.

The study was performed in four blocks: schematic 2D image of soft tissue wounds (Block I), three-dimensional (3D) wound models of arm and leg fracture (Block II), experimental wounds in laboratory animals (Block III), and evaluation of combined wound defects of the maxilla and mandible of patients (Block IV).

Block I of the study was performed in four groups. In the first group, areas of wound schemes (WS) on flat surface were measured; in groups two, three and four, the WS were measured drawn on cylindrical surfaces with diameters of 7, 10 and 20 cm simulating the surfaces of the forearm, shoulder and head, respectively.

In each group, subgroups were made which studied the round, oval, square, rectangular, triangular and trapezoidal WS of soft tissues with known area drawn on paper.

The WS area was calculated using L.N. Popova's method, using the mobile apps +WoundDesk, ImitoWound, V2F. The obtained data were compared with the base area calculated using standard geometric equations: round, 12.5±0.003 cm^2, oval, 39.2±0.007 cm^2, square, 4.8±0.002 cm^2, rectangular, 12.3±0.004 cm^2, triangular, 13.7±0.006 cm^2, and trapezoidal, 14.9±0.004 cm^2.

Among the obtained areas of WS, the average area values were taken as 100% to be used as reference values;

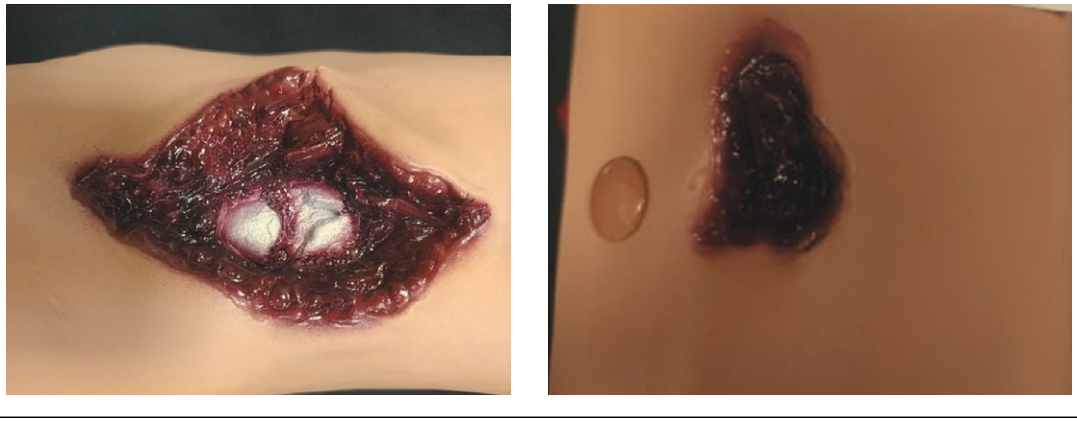


Figure 2. *Models of arm fracture wounds and leg wounds used in the second series of the study.*
Рисунок 2. *Муляжи ран перелома плеча и раны на ноге, используемых во II серии исследования.*

after which measurements were performed using mobile apps.

Block II of the study was performed at the multidisciplinary accreditation and simulation center of the N.N. Burdenko Voronezh State Medical University. This block included models of wounds of shoulder fracture (Simulaids compound fracture humerus) and leg amputation wound for accident simulation kit, fragment (**Fig. 2**).

Block III of the study (experimental wounds in laboratory animals) was performed in the Experimental Biology and Medicine Research Institute of the N.N. Burdenko Voronezh State Medical University. For the purposes of the experiment, Wistar line rats were used. The experiment is an addition to the scientific research in various fields whose objectives did not include measurement of wound area; e.g. studies of wounds after laparotomy or thoracotomy access to allow main stages of surgeries. The length of laparotomy wounds was 9.7±1.4 cm, and the length of thoracotomy wound was 4.7±0.5 cm. After the linear incision was made, the edges of the wound were spread out, forming the wound contour of a complex arbitrary shape, and the obtained defect was measured using L.N. Popova's method, and then using the mobile apps.

Block IV of the study was performed in the Clinics of the Samara State medical University. It involved an analysis of precision of the apps under consideration in the measurement of defects of cover tissues of the head. The range of defects analyzed with the above mentioned apps and the "Autoplan" software suite included defects of the cover tissues of the head of post-traumatic and post-cancer treatment type, and defects of the skin due to post-surgery cicatrical deformations. Some defects had an end-to-end component that was not regarded due to the lack of the respective functionality of the programs. Intra-oral defects of the mucosa were not accounted. Clinical data of 100 patients with combined wound defects of the head were used, including post-cancer treatment (70) and post-traumatic (30) defects of the maxilla and the mandible.

The study is implemented in accordance with the plan of research work of the N.N. Burdenko Voronezh State Medical University within the complex topic "Vital Problems of Prevention and Treatment of Surgical Diseases" (State registration No. 121060700037-3) in compliance with the effective regulations of work with laboratory animals.

The method of L.N. Popova was chosen as the gold standard to evaluate the efficiency of using mobile apps in Blocks II, III and IV of the study due to the high precision of the former not depending on the curvature of the surface [23]. At first, measurements were taken using L.N. Popova's method, the results of which were taken as 100%, afterwards, the results obtained with mobile apps were compared. The measurement of the wound surface area by L.N. Popova's method included covering the wound with a transparent sterile millimeter-squared plastic sheet, making an outline of the defect, and manual calculation of its area [24–26].

Block IV of the study used the "Autoplan" software suite, since it is the base of a three-stage algorithm of performance if reconstructive plastic surgeries for patients with combined facial defects.

Statistic processing of obtained data. Methods of descriptive statistics with preliminary assessment of normality of distribution were used both for the accuracy of measurement of wound surfaces using the proposed methods, and for the time required to perform the study: graphical, numerical and quantitative tests (Kolmogorov-Smirnov, Shapiro-Wilk). Calculations were performed of the average value of the obtained results, mean root square deviation, standard error of mean within the studied groups. The first stage included one-way ANOVA. After the differences were identified, the Student's t-test was applied to identify significance of differences in the samples. The level of validity of obtained result difference was taken to be 5% ($p<0.05$).

The data processing was performed in the Statictica 10.0 and Microsoft Office Excel 2010 software suites.

The total number of measurements using all suggested methods was 4480 in the four blocks of the study: Block I, 960; Block II, 80; Block III, 1440; Block IV, 2000, respectively. Each wound defect was measured with the mobile apps under inquiry and with the L.N. Popova's method (Blocks II, III and IV). The obtained results are presented as percent ratios for the following reasons: in the course of the study, we were interested in the accuracy of measurement of the wound surface area with the suggested methods with respect to the original area and to the L.N. Popova's method, which is the most important factor from the standpoint of looking into the posiibility of using these apps in clinical practice. In Blocks III and IV, 3440 measurements were performed (190 unique wounds). The use of other methods would result is a significant increase of amount of results; the numerical expression of area measurements prevents their graphic interpretation.

RESULTS AND DISCUSSION

Group 1 of Block I of the study included measurements of WS of soft tissues on a flat surface using the methods under consideration (**Table 1**).

In the measurement of area of round and oval WS, the +WoundDesk app showed the highest accuracy as compared to other apps, 98.92±6.55% and 98.57±8.32% from the base area, respectively. In the calculation of area of square and rectangular WS, V2F and ImitoWound demonstrated accuracy above 95%. The use of +WoundDesk in the calculation of the area of triangular WS results in a significant overestimation of area, 158.78±4.71% from the base value. The V2F app shows the lowest accuracy, 70%, in the measurement of area of triangular and trapezoidal WS.

In the second group of the study, WS were placed on a cylinder with a diameter of 10 cm to simulate wounds of the shoulder (**Table 2**).

We see a decrease in accuracy in all of the apps used. At the same time, ImitoWound yielded the average accuracy value above 85% in all subgroups, the use of

WS Type	Mobile apps used to measure WS area		
	+WoundDesk	V2F	ImitoWound
Round	98.92±6.55 (p1=0.068) (p3=0.038) (p4=0.048)	72.05±15.34 (p1=0.024) (p2=0.038) (p4=0.045)	92.43±8.82 (p1=0.041) (p2=0.048) (p3=0.045)
Oval	98.57±8.32 (p1=0.071) (p3=0.032) (p4=0.041)	71.97±13.92 (p1=0.019) (p2=0.032) (p4=0.024)	92.5±9.41 (p1=0.034) (p2=0.041) (p3=0.024)
Square	79.25±5.17 (p1=0.045) (p3=0.028) (p4=0.031)	97.81±9.12 (p1=0.053) (p2=0.028) (p4=0.074)	96.25±6.47 (p1=0.026) (p2=0.031) (p3=0.074)
Rectangular	74.63±9.24 (p1=0.027) (p3=0.039) (p4=0.042)	96.49±5.94 (p1=0.038) (p2=0.039) (p4=0.055)	99.47±3.52 (p1=0.078) (p2=0.042) (p3=0.055)
Triangular	158.78±4.71 (p1=0.031) (p3=0.015) (p4=0.024)	66.9±15.64 (p1=0.022) (p2=0.015) (p4=0.026)	93.52±8.10 (p1=0.042) (p2=0.024) (p3=0.026)
Trapezoidal	101±4.61 (p1=0.043) (p3=0.019) (p4=0.045)	69.53±7.73 (p1=0.029) (p2=0.019) (p4=0.023)	92.48±13.75 (p1=0.019) (p2=0.045) (p2=0.023)

Notes: p^1 – significance of differences vs. L.N. Popova's method; p^2 – significance of differences vs. WoundDesk app; p^3 – significance of differences vs. V2F app; p^4 – significance of differences vs. ImitoWound app.

Table 1. *Accuracy of WS measurement on a flat surface in the 1st group of the 1st block of the study in relation to the initial area, %*

Таблица 1. *Точность измерения СР на плоской поверхности в 1-й группе I серии исследования по отношению к исходной площади, %*

WS Type	Mobile apps used to measure WS area		
	+WoundDesk	V2F	ImitoWound
Round	97.21±8.44 (p1=0.059) (p3=0.039) (p4=0.047)	70.15±16.26 (p1=0.020) (p2=0.039) (p4=0.031)	90.17±13.55 (p1=0.018) (p2=0.047) (p3=0.031)
Oval	96.83±5.31 (p1=0.055) (p3=0.026) (p4=0.045)	69.34±26.81 (p1=0.024) (p2=0.026) (p4=0.036)	89.58±14.73 (p1=0.015) (p2=0.045) (p3=0.036)
Square	76.32±8.81 (p1=0.034) (p3=0.041) (p4=0.028)	93.34±9.48 (p1= 0.017) (p2=0.041) (p4=0.056)	97.32±5.63 (p1=0.027) (p2=0.028) (p3=0.056)
Rectangular	74.27±4.63 (p1=0.029) (p3=0.048) (p4=0.023)	89.77±7.29 (p1=0.023) (p2=0.048) (p4=0.054)	96.31±7.85 (p1=0.033) (p2=0.023) (p3=0.054)
Triangular	161.78±11.52 (p1=0.021) (p3=0.008) (p4=0.015)	64.53±28.25 (p1=0.028) (p2=0.008) (p4=0.039)	89.44±14.48 (p1=0.035) (p2=0.015) (p3=0.039)
Trapezoidal	103.00±4.17 (p1=0.045) (p3=0.012) (p4=0.019)	68.71±31.73 (p1=0.025) (p2=0.012) (p4=0.017)	87.58±5.83 (p1=0.038) (p2=0.019) (p3=0.017)

Notes: p^1 – significance of differences vs. L.N. Popova's method; p^2 – significance of differences vs. WoundDesk app; p^3 – significance of differences vs. V2F app; p^4 – significance of differences vs. ImitoWound app.

Table 2. *Accuracy of WS measurement on cylindrical surfaces with a diameter of 10 cm, simulating the surface of the shoulder, %*

Таблица 2. *Точность измерения СР на цилиндрических поверхностях диаметром 10 см, имитирующих поверхность плеча, %*

+WoundDesk in the measurement of square and rectangular WS produces accuracy of 67.51% to 85.13%, and still gives overestimation of the area of triangular defects. V2F demonstrated the greatest mean square root deviation in all groups of the study, and accuracy above 85% was only obtained to square and rectangular WS.

In the third group, WS were placed on a cylinder with the diameter of 7 cm to simulate wounds of the forearm (**Table 3**).

With a further decrease in the diameter of the cylindrical surface and an increase in the curvature of the object, the measurement accuracy of the proposed methods continues to decrease. The greatest accuracy in the measurement of WS area is still shown by +WoundDesk for round, oval and trapezoidal WS, V2F for square and rectangular WS, ImitoWound for all types, the average accuracy was 91.73±8.58%.

In the fourth group, WS were placed on a cylinder with the diameter of 20 cm, simulating the surface of the head (**Table 4**).

We observe an increase in the accuracy of measurement results in this group in comparison with the first and third groups of Block I of the study; this relates to a lower curvature of the object. In comparison with the third group, we see a minor increase in accuracy of the value in question. Therefore, there is a direct correlation between the curvature of the examined wound and the accuracy of measurement of its area. It follows from the obtained results that the ImitoWound app is the all-purpose tool to perform planimetry measurements of wound schemes thanks to its high accuracy, which is 92.81±6.52%, on average.

Block II of the study is performed on wound models of shoulder and leg fractures. Using L.N. Popova's method to measure the area of the soft tissue defects, we obtained the following measurement results 34.7±1.2 cm^2 and

WS Type	Mobile apps used to measure WS area		
	+WoundDesk	V2F	ImitoWound
Round	96.21±4.14 (p1=0.036) (p3=0.015) (p4=0.047)	70.15±19.48 (p1=0.024) (p2=0.015) (p4=0.033)	90.17±11.38 (p1=0.031) (p2=0.047) (p3=0.033)
Oval	97.14±5.48 (p1=0.047) (p3=0.011) (p4=0.042)	69.34±21.22 (p1=0.037) (p2=0.011) (p4=0.026)	89.58±8.29 (p1=0.022) (p2=0.042) (p3=0.026)
Square	76.32±4.51 (p1=0.029) (p3=0.022) (p4=0.044)	93.34±9.27 (p1=0.023) (p2=0.022) (p4=0.064)	97.32±7.15 (p1=0.026) (p2=0.044) (p3=0.064)
Rectangular	76.83±7.11 (p1=0.031) (p3=0.040) (p4=0.037)	89.77±8.35 (p1=0.042) (p2=0.040) (p4=0.039)	96.31±4.63 (p1=0.045) (p2=0.037) (p3=0.039)
Triangular	158.78±9.52 (p1=0.018) (p3=0.016) (p4=0.034)	64.53±24.51 (p1=0.041) (p2=0.016) (p4=0.025)	89.44±11.73 (p1=0.037) (p2=0.034) (p3=0.025)
Trapezoidal	103±6.18 (p1=0.045) (p3=0.019) (p4=0.045)	68.71±31.16 (p1=0.033) (p2=0.019) (p4=0.018)	87.58±8.30 (p1=0.043) (p2=0.045) (p3=0.018)

Notes: p^1 – significance of differences vs. L.N. Popova's method; p^2 – significance of differences vs. WoundDesk app; p^3 – significance of differences vs. V2F app; p^4 – significance of differences vs. ImitoWound app.

Table 3. *Accuracy of WS measurement on cylindrical surfaces with a diameter of 7 cm, simulating the surface of the forearm, %*

Таблица 3. *Точность измерения СР на цилиндрических поверхностях диаметром 7 см, имитирующих поверхность*

WS Type	Mobile apps used to measure WS area		
	+WoundDesk	V2F	ImitoWound
Round	96.47±4.59 (p1=0.065) (p3=0.023) (p4=0.047)	71.05±17.34 (p1=0.029) (p2=0.023) (p4=0.034)	91.55±9.19 (p1=0.038) (p2=0.047) (p3=0.034)
Oval	95.14±8.74 (p1=0.063) (p3=0.025) (p4=0.051)	70.72±21.44 (p1=0.027) (p2=0.025) (p4=0.031)	90.34±6.11 (p1=0.031) (p2=0.051) (p3=0.031)
Square	76.32±6.04 (p1=0.028) (p3=0.021) (p4=0.039)	95.78±7.15 (p1=0.081) (p2=0.021) (p4=0.054)	98.03±4.32 (p1=0.062) (p2=0.039) (p3=0.054)
Rectangular	74.83±7.41 (p1=0.021) (p3=0.028) (p4=0.033)	90.74±5.29 (p1=0.026) (p2=0.028) (p4=0.041)	98.61±3.24 (p1=0.059) (p2=0.033) (p3=0.041)
Triangular	158.78±5.12 (p1=0.016) (p3=0.014) (p4=0.042)	65.56±28.42 (p1=0.035) (p2=0.014) (p4=0.025)	90.76±9.01 (p1=0.027) (p2=0.042) (p3=0.025)
Trapezoidal	102.00±4.15 (p1=0.072) (p3=0.020) (p4=0.047)	69.97±31.13 (p1=0.038) (p2=0.020) (p4=0.039)	90.82±7.92 (p1=0.025) (p2=0.047) (p3=0.039)

Notes: p^1 – significance of differences vs. L.N. Popova's method; p^2 – significance of differences vs. WoundDesk app; p^3 – significance of differences vs. V2F app; p^4 – significance of differences vs. ImitoWound app.

Table 4. *Accuracy of WS measurement on a spherical surface with a diameter of 20 cm, simulating the surface of the head, %*

Таблица 4. *Точность измерения СР на сферической поверхности диаметром 20 см, имитирующих поверхность головы, %*

9.5±0.8 cm^2, respectively. After this, measurements were taken using other methods (**Table 5**).

In both models, the measurements taken with the ImitoWound app had the highest accuracy: 96.22±8.05% and 97.80±7.46%. +WoundDesk and V2F yielded the accuracy of 86.83±12.74% and 70.86±18.11% for the model of the shoulder fracture wound and 85.26±9.13% and 82.21±15.62% for the model of the leg wound, respectively.

In Block III of the study performed on Wistar line laboratory rats, the average deviation when using +WoundDesk was 90.84±9.48%, V2F, 88.96±13.41%, and ImitoWound, 92.51±6.94% (**Table 6**). Another important parameter was the time required to perform the measurements: the +WoundDesk app required the least time, because manual adjustment of outlines requires matching of a lower number of defect boundary to identify it.

In Block IV of the study, the following average deviations were registered in the analysis of accuracy of the measurement of the area of superficial defects of facial soft tissue using the mobile apps and the "Autoplan" software suite: +WoundDesk, 89.86±10.31%, V2F, 86.56±18.94%, ImitoWound 91.34±9/52%, Autoplan, 91.48±10.14% (**Table 7**).

Model type	L.N. Popova's method	Mobile apps used to measure WS area		
		+WoundDesk	V2F	Imito Wound
Wound in shoulder fracture	100%	86.83±12.74 (p1=0.039) (p3=0.045) (p4=0.041)	70.86±18.11 (p1=0.022) (p2=0.045) (p4=0.027)	96.22±8.05 (p1=0.061) (p2=0.041) (p1=0.027)
Leg wound	100%	85.26±9.13 (p1=0.042) (p3=0.057) (p4=0.044)	82.21±15.62 (p1=0.031) (p2=0.057) (p4=0.043)	97.80±7.46 (p1=0.065) (p2=0.044) (p3=0.043)

Notes: p^1 – significance of differences vs. L.N. Popova's method; p^2 – significance of differences vs. WoundDesk app; p^3 – significance of differences vs. V2F app; p^4 – significance of differences vs. ImitoWound app.

Table 5. *Accuracy of determining the area of wound models for shoulder and leg fractures, %*

Таблица 5. *Точность определения площадей муляжей ран при переломе плеча и на ноге, %*

CONCLUSIONS

The results of measuring the area of wounds using the studied mobile applications in conditions close to ideal in terms of illumination, distance from the object and camera fixation, which is not always feasible in clinical conditions, often differ significantly from the actual sizes of defects and depend on their shape and degree of curvature of the surfaces.

In Block I of the study, the +WoundDesk app showed the lowest accuracy in the measurement of area of square, rectangular and triangular wound schemes; the V2F app showed low accuracy in round, oval, triangular and trapezoidal wound schemes. The most accurate average results in measurements of different wounds were produced in the ImitoWound app.

The analysis of accuracy of measurement of wound areas on models showed that the +WoundDesk app yielded better results than V2F, however, they reliably differ from the values obtained by the L.N. Popova's method, by 14.27±7.51% and 21.85±13.85% on average, respectively.

The most accurate app to measure wound area in laboratory animals was ImitoWound showing 92.51±5.93% from the values obtained by the L.N. Popova's method. The +WoundDesk and V2F apps measure the wound area with the accuracy of 90.84±12.77% and 88.96±15.36%, respectively.

	L.N. Popova's method	+WoundDesk	V2F	ImitoWound
Accuracy of mound area measurement, %	100%	90.84±9.48 (p1=0.041) (p3=0.066) (p4=0.053)	88.96±13.41 (p1=0.023) (p2=0.066) (p4=0.081)	92.51±6.94 (p1=0.021) (p2=0.053) (p3=0.081)
Time required for measurement, min	3.05 ±0.22	0.67 ±0.07	0.98 ±0.15	1.11 ±0.12

Notes: p^1 – significance of differences vs. L.N. Popova's method; p^2 – significance of differences vs. WoundDesk app; p^3 – significance of differences vs. V2F app; p^4 – significance of differences vs. ImitoWound app.

Table 6. *Accuracy and time of measuring wound areas using L.N. Popova's method and mobile applications in Wistar laboratory rats in the III block of the study, %*

Таблица 6. *Точность и время измерения площадей ран методом Л.Н. Поповой и с использованием мобильных приложений у лабораторных крыс линии Wistar в III серии исследования, %*

	L.N. Popova's method	+WoundDesk	V2F	ImitoWound	Autoplan
Defects of the maxilla and mandible	100%	89.86±10.31 (p1 = 0.025) (p3 = 0.062) (p4=0.054) (p5=0.081)	86.56±18.94 (p1 = 0.031) (p2 = 0.062) (p4 = 0.055) (p5 = 0.073)	91.34±9.52 (p1 = 0.029) (p2 = 0.054) (p3 = 0.055) (p5 = 0.063)	91.48±10.14 (p1 = 0.025) (p2 = 0.081) (p3 = 0.073) (p4 = 0.063)

Notes: p^1 – significance of differences vs. L.N. Popova's method;
p^2 – significance of differences vs. WoundDesk app;
p^3 – significance of differences vs. V2F app;
p^4 – significance of differences vs. ImitoWound app;
p^5 – significance of differences vs. Autoplan software suite..

Table 7. *Accuracy of determining the area of defects in superficial soft tissues in patients with facial defects using mobile applications and the Autoplan software, %*

Таблица 7. *Точность определения площади дефектов поверхностных мягких тканей у пациентов с дефектами лица с использованием мобильных приложений и программного комплекса «Автоплан», %*

It has been proven that most of the results we obtained differ significantly from the known initial area (Block I) and the area measured by the L.N. Popova's method (Blocks II, III and IV), which calls into question the appropriateness of using the presented mobile apps as the main method of conducting planimetric studies in medicine, since most wounds encountered in medical practice have a complex configuration that changes during treatment, changing from one shape to another.

In calculating the area of wound surfaces in patients with defects of the upper and lower jaws, the ImitoWound mobile app shows a similar result to the Autoplan software suite, however, the latter has significantly greater potential in planning and performing reconstructive plastic surgeries in patients with head defects, and therefore it can be recommended for use in assessing these defects.

Based on the conducted research, it is obvious that both the development of new methods or applications for calculating the area of the wound defect and the refinement of existing algorithms are required. A possible alternative to the studied mobile apps could be the laser grid and 3D scanning; however, these methods are complicated for use in practical healthcare, which leaves the L.N. Popova's method the main tool for planimetric studies.

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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Compliance with Ethical Standards. The authors confirm that the rights of the people who participated in the study were respected, including obtaining informed consent.	***Соответствие нормам этики.*** Авторы подтверждают, что соблюдены права людей, принимавших участие в исследовании, включая получение информированного согласия.
Contribution of individual authors. Mikhailov N.O., Laptieva A.Yu., Denisenko A.S.: conducting of the research, writing of the text, preparation and analysis of literature. Glukhov A.A., Andreev A.A., Ivashkov V.Yu.: creation of research design, scientific editing. Sudakov O.V.: statistical data processing. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Михайлов Н.О., Лаптиёва А.Ю., Денисенко А.С. – проведение исследования, написание текста, подготовка и анализ литературы. Глухов А.А., Андреев А.А., Ивашков В.Ю. – создание дизайна исследования, научное редактирование. Судаков О.В. – статистическая обработка данных. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Analysis of clinical effectiveness of complex treatment of limited border burns

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Abstract

Aim – to evaluate the effectiveness of the developed method for local treatment of limited border burns.

Material and methods. The results of treatment of 39 patients with limited first- and second-degree burns were studied. In patients of the main group (19 people), during the changing of the gel with silver ions, the wound was irradiated with ultraviolet light, followed by exposure to a low-frequency pulsating magnetic field. Patients in the comparison group (20 patients) received conservative treatment using the gel with silver ions only, without physiotherapy. Monitoring of the healing of burn wounds was carried out using the "Complex automated system for assessing the area of burn wounds" (certificate of state registration of the computer program No. 2015660700 dated 10/06/2015). The effectiveness of the proposed method was assessed by clinical results, as well as by the time patients spent in the hospital. The obtained data were analyzed using clinical statistics methods.

Results. The developed method for treating local I-II degree burn wounds, which consists of covering the wound with gel with silver plus ultraviolet irradiation of the wound and magnetic therapy, turned out to be more effective compared to the method of wound coating with gel with silver, which was previously introduced into the clinic, without physiotherapeutic treatment.

Conclusions. The use of the proposed method in the treatment of burn wounds statistically significantly reduces the likelihood of the development of suppuration and accelerates the cleansing of wounds, and leads to a faster recovery.

Keywords: conservative treatment of burn wounds; wound coverings; documentation of wounds.

Conflict of interest: nothing to disclose.

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Анализ клинической эффективности комплексного лечения ограниченных пограничных ожогов

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Аннотация

Цель – оценка эффективности разработанного способа местного лечения ограниченных пограничных ожогов.

Материал и методы. Изучены результаты лечения 39 больных с ограниченными ожогами I и II степеней. Пациентам основной группы (19 человек) при смене геля с ионами серебра рана облучалась ультрафиолетовым светом с последующим воздействием низкочастотным пульсирующим магнитным полем. Пациенты группы сравнения (20 пациентов) получали консервативное лечение с использованием геля с ионами серебра без физиотерапевтического воздействия. Контроль заживления ожоговой раны выполнялся с использованием «Комплексной автоматизированной системы оценки площади ожоговых ран» (свидетельство о государственной регистрации программы для ЭВМ № 2015660700 от 06.10.2015 г.). Эффективность предложенного способа оценивали по клиническим результатам, а также по времени нахождения пациентов в стационаре. Полученные данные анализировались с помощью методов клинической статистики.

Результаты. Разработанный способ лечения локальных ожоговых ран I и II степеней, заключающийся в покрытии гелем с серебром в комбинации с ультрафиолетовым облучением раны и магнитотерапией, оказался более эффективным по сравнению с ранее внедренным в клинику покрытием с гелем и серебром, но без физиотерапевтического воздействия. Предложенный способ при лечении ожоговых ран статистически достоверно уменьшает вероятность развития нагноений и ускоряет очищение ран, а также приводит к более быстрому выздоровлению.

Ключевые слова: консервативное лечение ожоговых ран; раневые покрытия; документация ран.

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INTRODUCTION

In Russia, more than 315 thousand cases of burn injury are registered annually, or 220.6±6.5 burns per 100 thousand people of the country's population [1, 2]. Burn injury usually leads to long-term or permanent disability. Since about 75% of burn victims are of working age (16-59 years old), the development of modern methods of burn treatment is especially urgent [3]. Given that a skin burn area of less than 10% of the body surface area is reported in 52.2% of adult trauma patients and 65.2% of children, respectively, it is important to personalize the treatment method for the most common limited borderline burns [3–5]. With the right choice of treatment method and its timely implementation, healing of the burn wound occurs without the development of complications and without the need for surgical treatment [6–8].

The basis of first aid and subsequent treatment, especially in patients with limited burns of I and II degrees are modern wound coatings of “Activtex” and “APPOLO” series, as well as aerosol preparations, such as “Hitopran”, “Amprovisol”, “Olazol”, “Panthenol” [8–10].

Despite the effectiveness of wound coatings that activate the regeneration of superficial skin layers, preparations are required that have the ability to resist the development of infectious complications in the wound and simultaneously improve tissue repair.

According to many authors and scientists who have studied the processes of regeneration of wounds of various etiologies in experimental conditions, the advantages of using drugs with antimicrobial action have been proved. In particular, the inclusion of silver nanoparticles in the composition leads to a less pronounced inflammatory process in the site, which promotes faster development of granulation and subsequent epithelialization of the damaged area of the skin surface. Silver has a wide range of antimicrobial activity against aerobic and anaerobic microflora, including antibiotic-resistant, exhibits virucidal and fungicidal activity, and has anti-inflammatory effect [11–14]. We developed a complex of therapy measures to treat burn injuries using gels with silver nanoparticles and physiotherapeutic effect on the damaged area[1].

AIM

To evaluate the effectiveness of the developed method for local treatment of limited border burns.

MATERIAL AND METHODS

Evaluation of the effectiveness of the developed method of local treatment of limited border burns with the use of gel with silver ions and physiotherapeutic effect was performed on the results of treatment of 39 patients with limited burns of I and II degrees. The patients were divided into two groups. The primary (main) group included patients aged 19 to 67 years (mean age 44), with 17 men and 2 women. The comparison group comprised 20 patients aged 21 to 69 years (mean age 45), including 16 men and 4 women. The study participants were comparable in age, body mass index, and comorbidities. All patients had thermal burns. The primary etiological factors of burns were hot water, steam, and contact burns. The groups were matched in terms of burn severity, location, and affected surface area.

In the main group, during silver-ion gel dressing changes, the wound was irradiated with ultraviolet (UV) light at a dose of 50 μW·min/cm^2 for 30 seconds. The exposure duration was increased daily by 30 seconds. This was followed by low-frequency pulsed magnetic field therapy (50 Hz, 30 mT) for 5 minutes, with daily 1-minute increments in duration. A total of 7-10 sessions were performed.

The comparison group received conventional treatment using silver-ion gel without physiotherapy.

The monitoring of the burn wound healing was performed using the “Complex automated system for assessing the area of burn wounds” (certificate of state registration of the computer program No. 2015660700 dated 10/06/2015). The technology involves computer-assisted processing of wound area photographs. A wound surface image is uploaded to a computer system, where specialized software determines the wound boundaries and calculates its area. Additionally,

[1] Tolstov A.V., Novikov I.V. Method of treatment of localized burn wounds of II-III A degree. Patent: RU 2648869 C1. Available online: https://patentimages.storage.googleapis.com/70/63/f3/77f5ff89052568/RU2648869C1.pdf

Figure 1. *Photograph of the wound of patient I. (main group), loaded into the computer program.*
Рисунок 1. *Фотография раны больного И. (основная группа), введенная в программу ЭВМ.*

the software analyzes healing progression through dynamic assessment of color gradient changes across the wound surface.

The efficacy of the proposed method was evaluated based on the following: wound epithelization time, suppurate development and wound cleansing time, length of hospital stay. Data were analyzed using descriptive statistics and Student's t-test. Statistical processing was performed with Microsoft Office Excel 2010, with additional clinical statistical methods applied to the dataset.

RESULTS

The treatment method for localized borderline burns, involving silver gel dressing combined with ultraviolet wound irradiation and magnetotherapy, was evaluated based on wound epithelialization time, wound cleansing duration, and length of hospital stay.

The assessment of topical treatment efficacy proved highly informative and evidence-based when performed using our custom-developed computer program (**Figure 1**).

After uploading the patient's wound photograph to the computer program, the boundaries of relevant wound process parameters were marked with color-coded markers, and the program displayed the initial results (**Figure 2**).

The monitoring of the progress of the wound process was performed in the computer program on days three, five, and six (**Figures 3, 4**).

The obtained parameters were assessed using descriptive statistics and Student's t-test (**Table 1**). Analysis of the main group's parameters over the 5-day observation period, acquired through the developed computer program, revealed the following findings: the burn wound area decreased by 2.3-fold; the granulation area decreased by 2.6-fold; and the wound epithelialization area increased by 1.8-fold.

Similarly, wound surfaces were examined in the control group receiving silver-ion gel alone without physiotherapy. Evaluation of computer-program-analyzed data in the control group over the 13-day observation period demonstrated: the burn wound area decreased by 1.4-fold; the granulation area decreased by 1.6-fold; and the wound epithelialization area increased by 1.5-fold.

The mean wound cleansing time was 5.65 ± 0.86 days in the main group versus 8.87 ± 1.23 days in the control group. The average hospital stay duration was 13.24 ± 0.83 days for the main group compared to 16.87 ± 1.25 days for the control group ($p=0.02$).

To confirm the clinical significance of the obtained results from the proposed topical treatment method for localized borderline burns using silver nanoparticle gel combined with physiotherapy, we performed a treatment outcomes assessment through calculation of clinical statistical measures.

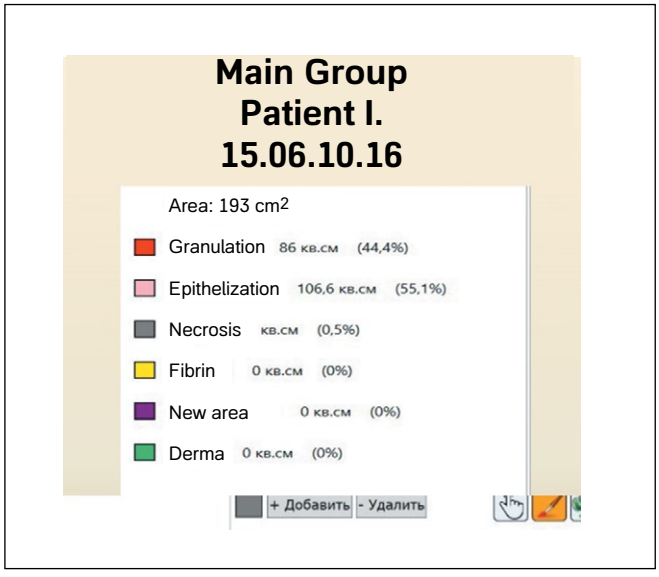

Figure 2. *Parameters of the wound of patient I. on the 1st day.*
Рисунок 2. *Параметры раны больного И. на первые сутки.*

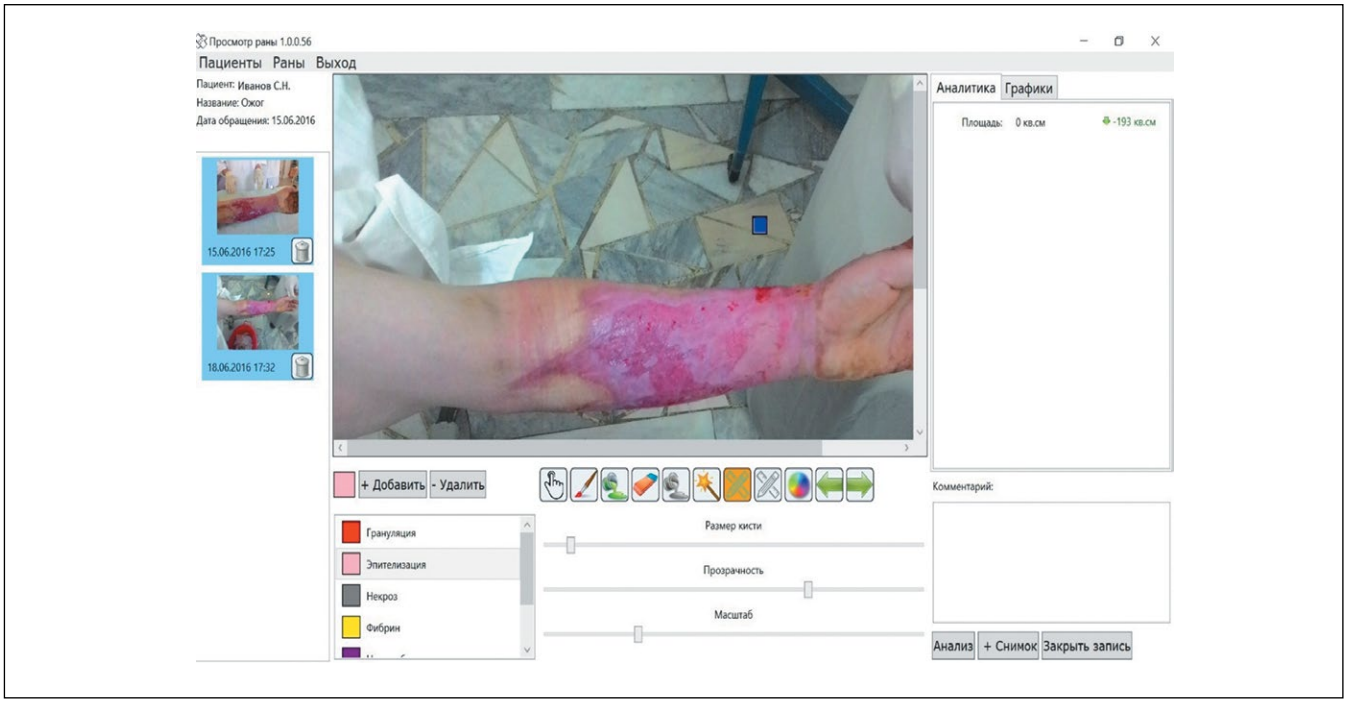

Figure 3. *Indicators of the wound of patient I. (main group) on the 3rd day.*
Рисунок 3. *Показатели раны больного И. (основная группа) на третьи сутки.*

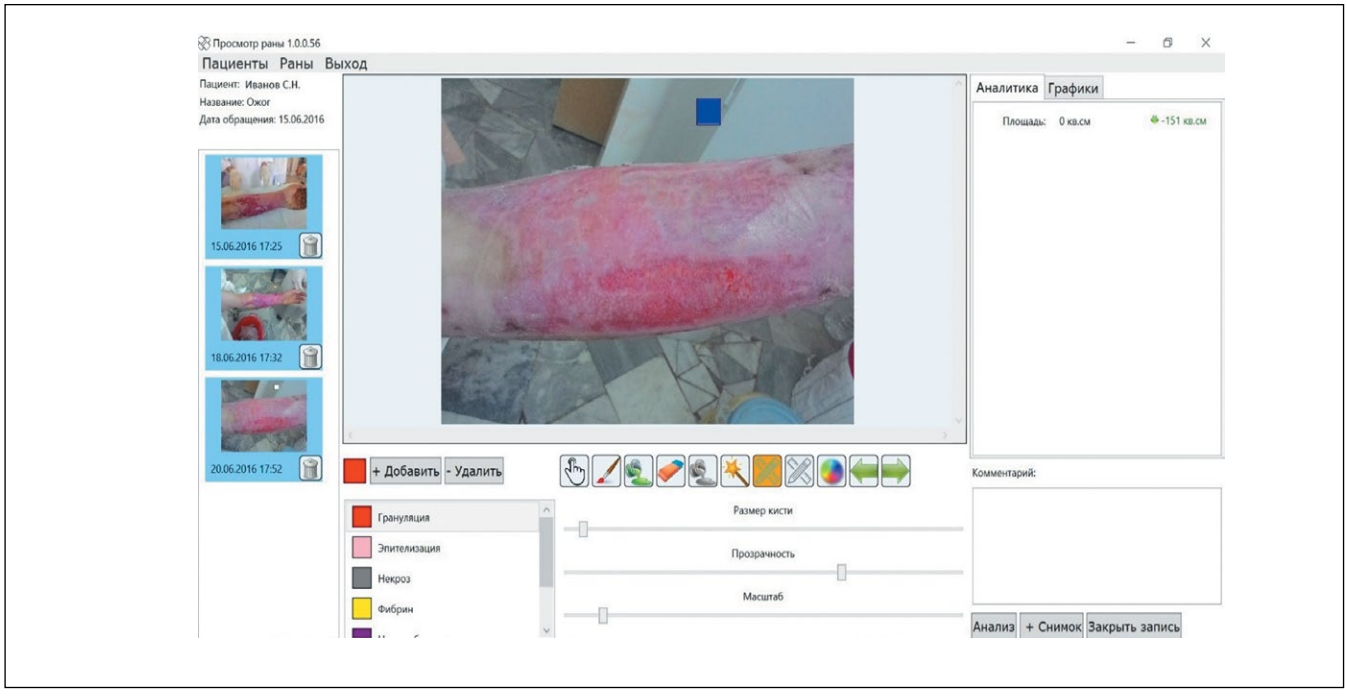

Figure 4. *Wound parameters of patient I. (main group) on the 5th day.*
Рисунок 4. *Параметры раны больного И. (основная группа) на пятые сутки.*

	Main group (n=19) M±m	Comparison group (n=20) M±m	t-test	<p
Wound cleansing time (days)	5.65 ± 0.86	8.87 ± 1.23	0.447 t<1.990	p<0.05
Hospital stay time (days)	13.24 ± 0.83	16.87 ± 1.25	0.447 t<1.990	p<0.05

Table 1. *Efficiency of using of wound dressings combined with physiotherapeutic interventions*
Таблица 1. *Эффективность применения раневого покрытия в комбинации с физиотерапевтическим воздействием*

The treatment success rate in the main group is represented as TSM = A / (A + B), where A is the onset of an adverse outcome (incidence rate of wound suppuration) in the study group, B is the absence of adverse outcomes. TSM = 3 / 19 = 0.158.

The treatment success rate in the control group is represented as TSC = C / (C + D), where C is the onset of an adverse outcome (incidence rate of wound suppuration), D is the absence thereof. TSC = 5 / 20 = 0.25.

RRD (relative risk decrease) = (TSM – TSC) / TSC. RRD = -0.38 = 38%, which meets a clinically significant effect.

ARD (absolute risk decrease) = (TSM – TSC). ARD = -0.094.

NPT, or the number of patients to be treated with this method over a specified period to prevent adverse outcomes per one patient is calculated as -1 / ARD. NPT = 10.76.

The odds ratio (OR) is calculated as (A / B) / (C / D). OR = 0.437.

DISCUSSION

The search for effective burn wound infection treatments has been ongoing for decades. Certain milestones in addressing this challenge were marked by remarkable achievements, when many issues of purulent surgery appeared resolved as surgeons gained access to promising antibacterial agents (antibiotics) and physical treatment modalities, e.g. laser therapy, ultrasound, and hyperbaric oxygenation [3,4,7]. However, subsequent experience revealed that all these methods, despite demonstrating positive outcomes, exhibited biological, technical, and economic limitations. None provided universal efficacy across all wound healing stages, thus the clinical challenges of burn wound management and wound infection treatment remain unresolved, necessitating further therapeutic development.

The application of various pharmaceutical agents and conservative burn treatment methods ultimately aims to establish conditions that suppress local wound infection and promote accelerated healing of burn injuries. Collectively, these interventions constitute a system of topical pharmacological burn therapy. Grounded in evidence-based evaluation of different conservative treatment modalities, this system is now becoming the standard of care [7].

Numerous modern methods exist for treating thermal burns of varying degrees, primarily involving dressings with different wound coverings. A key limitation of these approaches is that the applied coverings target only one phase of the wound healing process, resulting in persistent microbial contamination, prolonged debridement of necrotic tissue, delayed regeneration, insufficient stimulation of reparative processes in affected tissues, requirement for daily dressing changes (2-3 times per day), and high consumption of medical supplies and wound care materials.

Most publications on the use of wound dressings report the efficacy of only specific types of bandages, many of which are essentially similar. Furthermore, reviews discussing the applications of these dressings are largely promotional in nature.

It should be noted that contemporary wound treatment must be strictly tailored to the specific phase and characteristics of the wound healing process. The cornerstone of local burn wound therapy lies in comprehensive, appropriate treatment combining pharmacological intervention, antimicrobial-impregnated wound dressings, and physiotherapy [8]. However, the scope and methods of therapeutic intervention must create optimal conditions for the wound healing process, while accounting for individual wound biology considering existing comorbidities, treatment setting (inpatient, outpatient, treatment by general practitioner), and cost effectiveness. These principles guided the development of our burn wound treatment method.

Analysis of outcomes from the developed topical treatment protocol for localized borderline burns (using silver-ion gel combined with physiotherapy) revealed insufficient efficacy in preventing infectious complications in 3 patients (15.78%) of 19 in the main group, and 5 patients (25.0%) of 20 in the comparison group. However, the topical treatment protocol for localized borderline burns combining silver-ion gel with physiotherapy demonstrated significantly greater efficacy compared to silver-ion gel treatment without physiotherapy. Statistical analysis confirmed that this combined approach reduces complication rates and enhances rehabilitation effectiveness in patients with this condition.

The antimicrobial effect of ultraviolet irradiation during early stages of skin defect regeneration prevents suppurative complications. Gradual increase in both UV exposure dosage and duration of magnetic field application promotes proper differentiation of newly formed cellular structures and facilitates development of specialized connective tissue in the wound area. The combined use of physiotherapy and silver-ion gel significantly accelerates wound epithelialization compared to dressings without ultraviolet irradiation and magnetotherapy. The efficacy of our proposed dressings combined with physiotherapy enables complete wound epithelialization within 13–14 days, whereas conventional dressings (Chitopran, Amprovizol, Olazol, Panthenol) require 18–20 days for epithelialization of borderline dermal burns, with additional dressing changes needed for further burn wound management [8–10].

CONCLUSION

Thus, the clinical trial of this topical treatment protocol for localized borderline burns, combining silver-ion gel with physiotherapy, demonstrates statistically significant reductions in suppuration risk and accelerated wound cleansing and epithelialization.

The addition of physiotherapy to burn wound management ensures proper progression through all phases of wound healing, with timely transition between regenerative stages and prevention of suppurative complications in patients admitted to hospital within 24 hours after the injury. Therefore, the combined use of ultraviolet irradiation and magnetotherapy can be recommended for widespread clinical implementation in burn treatment protocols.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Compliance with Ethical Standards. The authors confirm that the rights of the people who participated in the study were respected, including obtaining informed consent.	***Соответствие нормам этики.*** Авторы подтверждают, что соблюдены права людей, принимавших участие в исследовании, включая получение информированного согласия.
Contribution of individual authors. Tolstov A.V.: development of the concept and design of the study, analysis of the obtained data, editing of the text. Kolsanov A.V.: analysis of the obtained data, statistical processing of the data. Novikov I.V.: collection of material, statistical processing of the data, analysis of the obtained data. Milyudin E.S.: study design, analysis of the obtained data, preparation of the text. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Толстов А.В. – разработка концепции и дизайна исследования, анализ полученных данных, редактирование текста. Колсанов А.В. – анализ полученных данных, статистическая обработка данных. Новиков И.В. – сбор материала, статистическая обработка данных, анализ полученных данных. Милюдин Е.С. – дизайн исследования, анализ полученных данных, подготовка текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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