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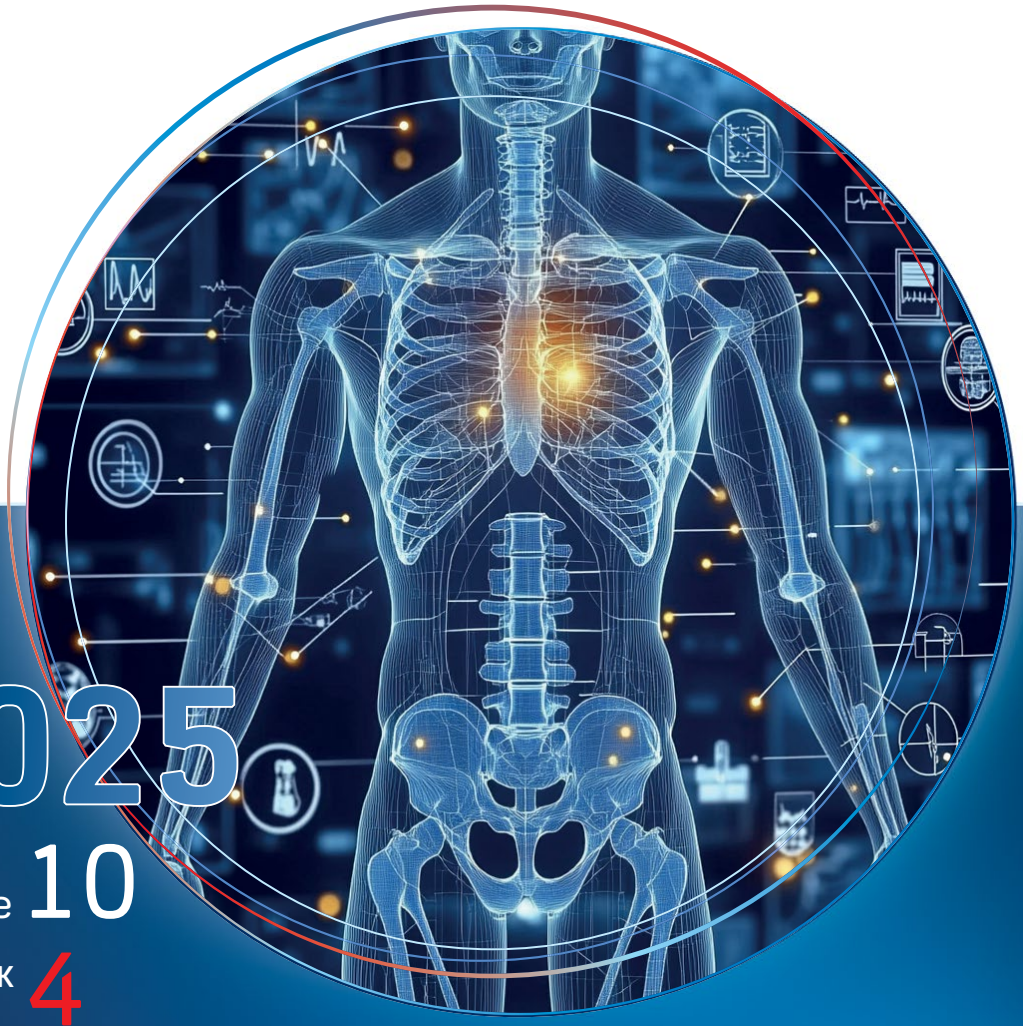

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Научный обзор | Review
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Myocardial bridges and proximal atherosclerosis of the coronary arteries: pathogenetic interrelation and clinical significance

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Abstract

Myocardial bridges (MB) are a congenital anomaly in which the coronary artery is partially immersed in the myocardium. The prevalence of MB varies from 0.5% to 87%, depending on the diagnostic method: selective angiography detects 0.5-18% of cases, whereas CT angiography, up to 73%.

An analysis of 22 peer-reviewed papers (1986-2023) showed that in 98% of the cases MB is associated with proximal atherosclerosis due to hemodynamic disorders (turbulent blood flow, high pressure gradient). However, some studies deny a direct link or point to the potential protective effect of MB. Systolic compression of the artery causes myocardial ischemia, especially in cases of left ventricular hypertrophy or microvascular dysfunction. Clinical manifestations range from asymptomatic to angina pectoris, ACS, and sudden death. Treatment includes beta-blockers, stenting, and myotomy, but the lack of randomized trials limits universal recommendations. The contradictions in the data emphasize the need to integrate morphological and functional imaging, as well as to personalize therapy. Long-term cohort studies, risk stratification algorithms using AI, study of the angular anatomy of coronary arteries may be prospective lines of further research.

Keywords: myocardial bridge, atherosclerosis, coronary arteries, hemodynamics, myocardial ischemia.

Conflict of interest: nothing to disclose.

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Миокардиальные мостики и проксимальный атеросклероз коронарных артерий: патогенетическая взаимосвязь и клиническая значимость

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Аннотация

Миокардиальные мостики (ММ) – врожденный вариант анатомии, при которой коронарная артерия частично погружена в миокард. Распространенность ММ варьирует от 0,5% до 87% в зависимости от метода диагностики: селективная ангиография выявляет 0,5–18% случаев, КТ-ангиография – до 73%.

Анализ 22 рецензируемых работ (1986–2023 гг.) показал, что ММ ассоциированы с проксимальным атеросклерозом в 98% случаев из-за гемодинамических нарушений (турбулентный кровоток, высокий градиент давления). Однако часть исследований отрицает прямую связь или указывает на потенциальный защитный эффект ММ. Систолическая компрессия артерии вызывает ишемию миокарда, особенно при гипертрофии левого желудочка или микрососудистой дисфункции. Клинические проявления варьируют от бессимптомного течения до стенокардии, ОКС и внезапной смерти. Лечение включает β-блокаторы, стентирование и миотомию, но отсутствие рандомизированных исследований ограничивает универсальные рекомендации. Противоречия в данных подчеркивают необходимость интеграции морфологической и функциональной визуализации, а также персонализации терапии. Перспективными представляются долгосрочные когортные исследования, разработка алгоритмов стратификации риска с использованием ИИ, а также изучение ангулярной анатомии коронарных артерий.

Ключевые слова: миокардиальный мостик, атеросклероз, коронарные артерии, гемодинамика, ишемия миокарда.

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Список сокращений
ММ – миокардиальный мостик; КТ – компьютерная томография; ПАБ – проксимальная атеросклеротическая бляшка; ИБС – ишемическая болезнь сердца; ИМ – ишемия миокарда; ОКС – острый коронарным синдром; КАГ – селективная коронарная ангиография; КА – коронарная артерия; КТ-КАГ – компьютерная томографическая коронарная ангиография; ПМЖВ – передняя межжелудочковая ветвь.

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INTRODUCTION

A myocardial bridge (MB) is an anatomical phenomenon in which the coronary artery is partially immersed in the myocardium and exposed to systolic compression. According to autopsy and modern visualization data, the prevalence of MB is 40-86%, however, their clinical significance remains a subject of discussion. Historically, the MB were considered benign, but the newest research data relate them with the ischemia of the myocardium, proximal atherosclerosis and acute coronary events.

In this review, we systematized the data on the correlation of the MB with the development of proximal atherosclerotic plaques (PAP), their role in the pathogenic mechanism of the coronary heart disease (CHD) and the efficiency of therapeutic approaches. We focused on the need of risk stratification and integration of functional methods of assessment of hemodynamics (fractional flow reserve) to optimize case management of patients with MB.

We analyzed over one hundred publications from PubMed and eLibrary databases and selected over twenty peer-reviewed articles published in 1986-2023 for a detailed analysis. The articles selected for analysis meet at least two of the following criteria: focus on the presence or absence of the correlation between MB and PAP; MB incidence rate; presence or absence of the correlation between MB and myocardial ischemia (MI); use of visualization methods (CT-angiography, invasive coronography), as well as autopsy data; clinical, experimental or histological data; additional parameters such as age group; patients with acute coronary syndrome (ACS); number of investigated patients **(Table 1)**. The articles used in this review were additionally structured and analyzed for descriptions of localization and parameters of MB, pathophysiological mechanisms in the tunneled artery, clinical significance and therapeutic methods.

ANALYSIS OF METHODS OF IDENTIFICATION OF MYOCARDIAL BRIDGES

Many researchers conclude that MB is found in every third case. The least sensitive (0.5% [1] to 18% [2]) method of MB diagnostics is selective coronary angiography (CAG) **(Fig. 1)**.

A diagnostic symptom of the MB is the ‘milking effect’ and/or the ‘step up-step down’ phenomenon caused by the muscle contraction during systole. It is to be noted that the CAG of the coronary arteries (CA) is the gold standard in diagnosing hemodynamically significant stenosis of the coronary arteries or bypass angiography. It has some technical limitations as compared to other new methods of visualization, e.g. intravascular ultrasound imaging and multi-slice spiral computed coronary angiography (CT-CAG). CT-CAG allows for a better visualization of the MB, from 26.6% [3] to 73% [4] of cases. CT identifies the MB as a fragment of an artery partially or completely immersed in the myocardium. The latest developments in functional assessment further improve the diagnostic value of CT-CAG in the identification of hemodynamically significant MBs **(Fig. 2)**.

It follows from the autopsy data that MBs present greater variability than identified by the above mentioned examination methods. The lowest result (8% [5]) was described in the sample of 975 autopsies (without regard to ACS status). In another study, also without ACS sample, the authors were able to identify presence of MBs in 40% of the cases [6]. The study involving surgical treatment of pediatric patients with MBs aged 11-20 with ACS symptoms reported high incidence of MBs, up to 86% [7]. It is worthwhile mentioning the results of a study of 1986 reporting a similar result of 84% [8]. Review articles and meta-analyses show the average incidence rate of в 19% [9], 24.8% [10], and intervals of 0.5–86% [11] and 5–86% [12]. Such a significant variance of the interval of identified MBs within the same study method may be related to specifics of interpretation and classification. Thus, the relatively superficial MBs (0.5 mm) may have been disregarded by some researchers. Another important factor is that out review considers publications both with a single clinical observation [13] and a largest study involving CAG in 11267 patients [14].

PATHOPHYSIOLOGY OF THE MYICARDIAL BRIDGE

Almost all of researchers concluded that the great majority of the MBs are localized in the anterior interventricular branch of the left descending artery (LAD). The most prevalent localization is the middle third of the branch (68.7%), proximal third (4.5%), distal third (26.8%), and the entire basin of the LAD (92.6%). In such locations as the circumflex of the left coronary artery, the obtuse marginal branch, diagonal branches and the basin of the right coronary artery, the bridges are represented in equally minimal quantities [15]. The depth of the MB location varies within 1.0-2.7 mm, the length within 8.9-15.8 mm; the muscle index of the MB (product of the length and depth of the bridge) was 10.1–42.4. Another study produced the following results: depth of 1-10 mm, length of 10-30 mm [15, 16]. No credible correlation with

Author, year	Methods	N	Age	MBs identified	ACS patients	MB-MI correlation	MB-PAP correlation
Bagmanova ZA. 2007 [1]	Review	-	Adults	0.5–86%	-	Y	Y/N
Jiang L, et al. 2018 [2]	CAG	6774	Adults	18%	Y	N	N
Nakaura T, et al. 2014 [3]	CT-CAG	188	Middle age	26.60%	Y	-	Y
Aparci M, et al. 2016 [4]	CT-CAG	34	Adults	73%	Y	-	Y
Micic-Labudovic J, et al. 2015 [5]	Autopsy	975	Adults	8%	-	Y	-
Lucena JD, et al. 2023 [6]	Autopsy	50	Adults	40%	-	Y	-
Alsoufi B, et al. 2018 [7]	Surgery	14	Children	86%	Y	Y	Y
Ishii T, et al. 1986 [8]	Autopsy	642	-	84%	Y	Y	Y
Hostiuc S, et al. 2018 [9]	Meta-analysis	-	Adults	19%	-	-	Y/N
Hong L, et al. 2014 [10]	Meta-analysis	5486	-	24.80%	Y	N	-
Yuan SM, et al. 2016 [11]	Review	-	-	0.5–86%	-	Y	Y
Starodubov OD, et al. 2023 [12]	Review	-	-	5–86%	-	Y	Y/N
Zhalilov AK, et al. 2023 [13]	Clinical case	1	50 y.o.	Y	Y	Y	-
Jiang X, et al. 2021 [14]	CAG	11267	Adults	9.41%	Y	Y	-
Kabak SL, et al. 2020 [15]	CT-CAG	61	-	36%	Y	-	Y/N
Lee MS, et al. 2015 [16]	Review	-	Adults	5–86%	Y	Y	-
Tian SP, et al. 2014 [17]	CT-CAG	9862	Adults	32.30%	Y	-	Y
Hong H, et al. 2014 [18]	CT-CAG	644	Adults	100%	Y	-	Y
Corban MT, et al. 2014 [19]	Review	-	Adults	40–80%	-	-	Y
Bruce C, et al. 2023 [20]	Meta-analysis	3008	Children and adults	-	Y	Y	-
Mirzoev NT, et al. 2023 [21]	Review	883	Adults	14.40%	Y	Y	Y
Sizov AV, et al. 2023 [22]	Clinical case	1	43	5–87%	Y	Y	Y

Table 1. *Selection and analysis of literature. MB – myocardial bridge; ACS – acute coronary syndrome; MI – myocardial ischemia; PAB – proximal atherosclerotic plaque; CT-CAG – computed tomographic coronary angiography; CAG – selective coronary angiography*

Таблица 1. *Отбор и анализ литературы. ММ – миокардиальный мостик; ОКС – острый коронарный синдром; ИМ – ишемия миокарда; ПАБ – проксимальная атеросклеротическая бляшка; КТ-КАГ – компьютерная томографическая коронарная ангиография; КАГ – селективная коронарная ангиография*

the sex was found: one publication states that women demonstrate higher incidence of MBs than men (10.75% vs. 7.31%) [2], while another states a reverse proportion (4.03% vs. 9.35%) [5].

A direct average correlation was established between the morphometric parameters of the MB: the deeper the position of the fragment of the coronary artery, the greater the length of that section (direct average credible non-linear relation) [16]. Almost in all studies, along with multiple morphometric data on MB parameters (length, depth and their relation, distance to bifurcation, etc.), their localization and incidence rate, the authors were consistent in ignoring the angular structure of the coronary arteries and the nearest branches with respect to the tunneled segment. We believe that this could be quite significant with respect to the major driver of the proximal atherogenesis of the coronary artery, namely, the hemodynamic mechanisms in the vessel.

Compression of the tunneled fragment of the coronary artery during systole is above doubt, whereas the hemodynamic significance of the vessel stenosis is disputable and requires functional diagnostic methods. The degree of stenosis depends on the depth and the length of the MB and lies within 20% to 99%. The effective perfusion of the myocardium depends on the heart rate [13, 15]. The greater portion of the coronary circulation occurs during the diastole, and the average ratio of the systolic and diastolic circulation is 0.22 and 0.85 in the left and right coronary arteries, respectively. It would seem that the systolic compression of the MB is to cause but a mild effect on the total effective perfusion of the

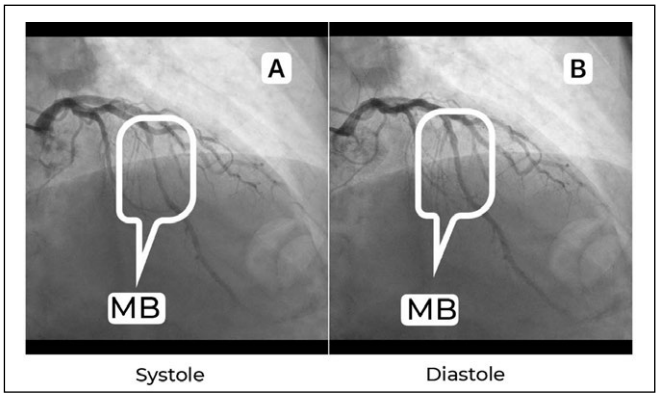

Figure 1. *Typical characteristics of the myocardial bridge under angiography. Image (A) shows a MB fragment undergoing systole compression. In the same artery, the MB segment is not compressed during diastole (B).*

Рисунок 1. *Типичные характеристики ММ при КАГ. На изображении (А) визуализируется фрагмент ММ, подвергающийся компрессии в систолу. В той же артерии во время диастолы (В) сегмент ММ не подвергается компрессии.*

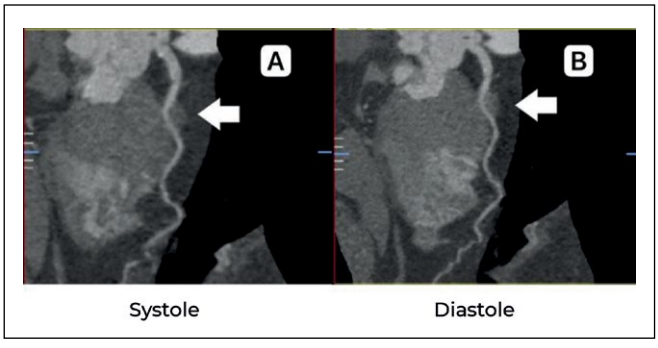

Figure 2. *A tunneled fragment and a pronounced myocardial bridge (arrows) in the systole (A) and diastole (B) in the proximal segment of the LAD (CT angiography of the coronary arteries).*

Рисунок 2. *Туннелированный фрагмент и выраженный миокардиальный мостик (стрелки) в систолу (А) и диастолу (В) в проксимальном сегменте ПМЖВ (КТ-КАГ).*

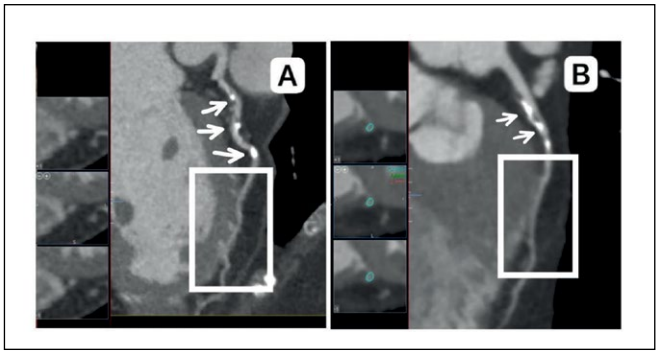

Figure 3. *A. The myocardial bridge in the distal third of the LAD (rectangle) with proximal atherosclerotic plaques (arrows). B. Myocardial bridge in the middle third of the LAD (rectangle) with proximal atherosclerotic plaques (arrows).*

Рисунок 3. *А. ММ в дистальной трети ПМЖВ (прямоугольник) с проксимальными атеросклеротическими бляшками (стрелки). В. ММ в средней трети ПМЖВ (прямоугольник) с проксимальными атеросклеротическими бляшками (стрелки).*

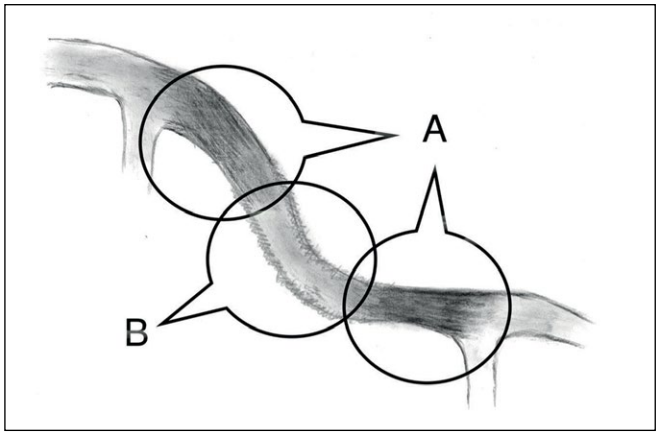

Figure 4. *Schematic representation of the relative profile of wall shear stress (WSS) during LAD angiography systole in a patient with MB. A: Segments located proximal and distal to MM demonstrate a relatively low WSS compared to the bridge segment (B).*

Рисунок 4. *Схематическое изображение относительного профиля напряжения сдвига стенки при ангиографии ПМЖВ во время систолы у пациента с ММ. А – сегменты, расположенные проксимальнее и дистальнее ММ, демонстрируют относительно низкое напряжение сдвига стенки по сравнению с мостовидным сегментом (В).*

myocardium. It was proven, however, that the systolic compression of the tunneled fragment of the coronary artery continues during the diastole as well, affecting the main phase of the coronary perfusion. Thus, the hemodynamic disorders are characterized with a persistent shrinkage of the diastolic diameter of the artery, increased blood flow velocity and the onset of the retrograde blood flow, which results in the decrease of the flow reserve. The diameter of the tunneled fragment of the coronary artery is not only less than that of the proximal segment of the vessel on the whole; moreover, during the diastole there is a persistent decrease of the intramural section by 34 to 51%. Furthermore, the greater the systolic stenosis, the lesser the diastolic diameter of the artery, which leads to the respective decrease of the blood flow and flow reserve [15]. Similar data was obtained in a different study: at the moment of diastolic contraction, the diameter of the coronary artery decreases by 80.6±9.2%, and the constant diastolic decrease is 35.3±11% in the tunneled fragment. The diastolic blood flow velocity in the bridge segment was much higher than that in the proximal and distal thereof [11]. The assessment of the fraction reserve proved to be an important tool for the physiological assessment of the MB. The researchers measured the fraction reserve both in the baseline condition and in the dobutamine stress test. Hemodynamic changes caused by the myocardial bridge were most manifested in the decrease of the diastolic fraction reserve (from 0.88 to 0.77), while the average value of the fraction reserve decreased to a lesser degree (from 0.90 to 0.84). It is considered that the average value of the fraction reserve is artificially skewed upwards due to peak systolic pressure; therefore, the preferred method of assessment is the diastolic fraction reserve [16].

Some studies involved multifactor analyses with consideration of the patients' age, diabetes and cardiomyopathy status credibly established a correlation of PAP and LAD, specifically, the presence of MB considerably increased the risk of coronary atherosclerosis [3, 4, 8, 11, 16–18]. In the proximal segment of the coronary artery, the atherosclerotic changes in the vessel wall are identified in 98% cases, and the segment of the MB itself never undergoes atherosclerotic changes, because the walls of the vessel lack the smooth muscle cells of the synthetic type, the ones that have the main role in the formation of the atherosclerotic plaque [19]. The higher pressure gradients in the arterial segments, located more proximally than the MB, may be the most powerful driver for the cholesterol to move to the endothelial layers when the patients demonstrate high cholesterol levels. The ingress of cholesterol, particles of lipoproteins of phagocytic cells may be identified as the 'inoculation effect' under high pressure gradient only in the proximal segment of the tunneled artery **(Fig. 3)**.

Lack of atherosclerosis in patients without hyperlipidemia may be the grounds for lowering the cholesterol levels in the blood serums using statins or by altering food habits and lifestyle to prevent further development of the atherosclerosis [4].

Some authors also think that MB could supposedly act as a protective factor against severe obstructive atherosclerosis in the entire coronary artery system with respect to the sex, age, diabetes status, hypertension and other risk factors [2, 16]. Some papers demonstrate mixed results precluding concrete results for this question [9, 12].

The microscopic inspection of the tunneled fragment of the coronary arteries found initial signs of the vascular wall lesion in 49% of cases in the form of fibrous-muscular dysplasia and lipidosis. The study using the results of CT-CAG failed to establish the cause and effect relation between the presence of MBs and atherosclerosis of the coronary arteries located subepicardially [15].

The rather contradictive data on the relation between the MB and PAP and on the possible protective effect of the tunneled fragment leave sufficient room for further research. The protective mechanism of the coronary artery mentioned by scientists is of special value: a more detailed study of this aspect may provide grounds for the development of methods of protection of the entire cardiovascular system from the adverse effects of atherogenesis.

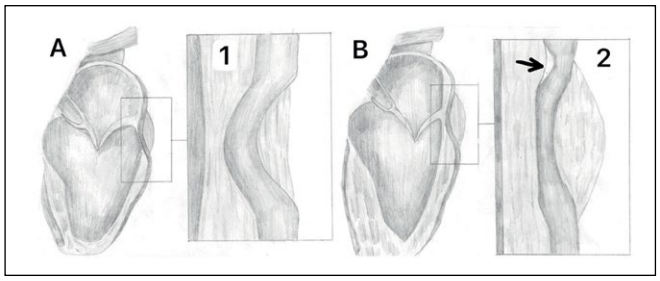

Figure 5. *A: Heart with MB, young age, early stage. 1: Longitudinal incision MB. B: Heart with MB, advanced age, advanced stage, with ventricular hypertrophy and diastolic dysfunction. 2: Longitudinal incision of MB with hypertrophied muscle and progressive proximal atherosclerotic plaque (arrow), negative remodeling of the vessel with a decrease in the diameter of the lumen.*

Рисунок 5. *А: Сердце с ММ, молодой возраст, ранняя стадия. 1 – продольный разрез ММ. В: Сердце с ММ, пожилой возраст, поздняя стадия, с гипертрофией желудочков и диастолической дисфункцией. 2 – продольный разрез ММ с гипертрофированной мышцей и прогрессирующей проксимальной атеросклеротической бляшкой (стрелка), негативное ремоделирование сосуда с уменьшением диаметра просвета.*

Hemodynamic mechanisms of the artery with a myocardia bridge are the main driver of proximal atherogenesis of the coronary artery. Models of computational fluid dynamics during the end of systole of the left coronary artery were used to demonstrate a rather low flow velocity in the proximal segment from the MB with a high flow velocity within the bridge **(Fig. 4)**.

The compression at the entry to the bridge results in a sharp cutoff of the antegrade systolic wave disturbing the flow structure, aggravating the low velocity of the flow, aggravating the endothelial lesion and stimulating the formation of atherosclerotic plaques [19]. Researchers also mention the importanc of effect of mechanical forces occurring due to the motion and deformation of the coronary bed. Systolic compression of the artery causes a turbulent blood flow and an increased vascular wall shear stress in the proximal segments thus stimulating the atherogenesis. Specifically, the compression within the bridge and the strong flexion of the vessel at the connection of the bridge with the intact proximal vascular wall result in a heterogeneous stressed condition in the proximal segment. It is suggested that this stressed condition contributes to the formation of plaques and the possible formation of cracks in the proximal segments [16].

Many studies point out that cardiac angina and heart rhythm disorders are registered more frequently in MB patients, as well as higher ACS and myocardial infarction risks [5–8, 11–14, 16, 19]; moreover, MBs may be the only known reason of the sudden cardiac death. At the same time, there are studies that do not identify any direct relation of MBs with the major adverse cardiovascular events [2, 10].

The findings of a large meta-analysis found no relation between the MB in the hypertrophic cardiomyopathy and the onset of non-fatal adverse cardiovascular events, but revealed a confirmed potential importance of their relation with the MI [20]. Development of clinically manifested cardiovascular diseases in patients with atherosclerotic lesion of the coronary artery might take several decades. The development of hypercholesterolemia and MB occur in the fourth and fifth decades of the patients' lives more frequently than in patients without MB [4].

In addition to the above mentioned mechanisms, life-long pathophysiological changes in the myocardium may cause MI symptoms in patients who had not earlier had any symptoms. Firstly, the increase of the diastolic function of the left ventricle related to age, hypertension and coronary atherosclerosis may aggravate the imbalance between the demand and supply of the blood perfusion caused by the presence of the bridge. Secondly, the development of hypertrophy of the left ventricle may increase the compression and decrease the coronary microvascular reserve **(Fig. 5)**.

Thirdly, the coronary angiospasm, microvascular or endothelial dysfunction related to cardiovascular risk factors, combined with the presence of the bridge, may result in the myocardial infarction. Fourthly, the formation of the plaques proximally to the bridge section may aggravate the coronary obstruction based by the bridge section. Finally, negative remodulation within the zone of the bridge section might reduce the blood flow in the myocardium. Each of these factors alone may foster development of symptoms in patients with tunneled segments in the myocardium to a lesser or greater extent [19]. The relation of MB with the symptoms of myocardial ischemia, lipidosis and different types of arrhythmia necessitates the search for new approaches towards early visualization of MB, especially in symptom-free patients, with the end of timely diagnostics of this pathology and prevention of cardiovascular complications that stem from it [21].

THERAPEUTIC METHODS

Despite the fact that the presence of a myocardial bridge may be related to such various complications as cardiac angina, acute myocardial infarction, arrhythmia and even sudden death, the myocardial bridge may be considered a positive outcome of the progress of coronary arteries. The necessity of treatment of MBs still causes doubt due to lack of solid evidence of their direct correlation with the manifestations of ACS. In clinical practice, β-blockers are usually drugs of first line of treatment of patients with symptoms likely related to MBs. Conservative approach (statins, β-blockers) is quite effective; however, refractory cases call for intervention and surgery treatment methods. Other therapeutic methods (coronary stents, myotomy, bypass surgery) are considered methods of the second and third order [2, 22].

Symptomatic patients are to be treated by conservative, intervention or surgical methods depending on their condition. The surgical procedure of choice to alleviate symptoms, improvement of coronary blood flow and decrease of compression of the coronary artery caused by the myocardial bridge is the myotomy [11, 13, 16, 19]. The choice of the surgery as the treatment method is complicated due the risk of development of restenosis, obstruction of the stent, and trauma of the myocardium. All CHD patients need cardiac rehabilitation procedures in accordance with the official recommendations and with respect to individual features, with strict supervision of hemodynamic parameters and ECG [22]. Patients with MB

and PAP require special attention due to the risk of ACS. The lack of clinical recommendations further complicates the choice of treatment.

Limitation of research: the majority of conducted studies are retrospective in nature and have no regard to genetic factors. Moreover, there are no long-term follow-up observations of PAP dynamics in the cases of MB.

Prospects of research. Firstly, long-term cohort studies focusing on PAP dynamics in cases of MB. Secondly, development of algorithms of risk stratification using AI and genetic markers. Thirdly, studies of the role of angular anatomy of coronary arteries and mechanisms of 'protection' of intramural segments from atherosclerosis.

CONCLUSION

Myocardial bridges are now recognized as a factor related to hemodynamic disorders, proximal atherosclerosis of the coronary artery, and myocardial infarction. Despite the protection of the intramural segment from atherosclerosis, the proximal segments are affected in 98% cases, and researchers relate this to the turbulent blood flow, endothelial dysfunction and high-pressure gradient, which contributes to the accumulation of lipids.

The sensitivity of MB diagnostic methods is varied: CT-CAG identifies up to 73% cases, while the selective endovascular coronary angiography identifies only 0.5 to 18%. Integration of functional methods (fractional flow reserve, induced stress tests) are required for the assessment of the hemodynamic significance of MB and stratification of risk. The data on the correlation of MB with cardiac angina, ACS and sudden cardiac death remain disputable: while some studies deny direct correlation, others emphasize the role of MB as the trigger of ischemia, especially on the background of myocardial hypertrophy, age-related diastolic dysfunction or microvascular disorders.

Conservative therapy (β-blockers, statins) demonstrates some efficiency; however, refractory forms require invasive therapy (stenting, myotomy). The lack of randomized studies restricts the formation of universal recommendations. Myocardial bridges necessitate revision of diagnostic and therapeutic approaches. The key areas of optimization of management of patients with this anomaly are the integration of morphological and functional visualization as well as personalization of treatment based on the individual risk of ischemia and atherosclerosis.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethics approval: Not applicable.	***Этическая экспертиза.*** Неприменимо.
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. Kolyan B.Yu.: idea, literature search, writing of the text. Margaryan A.V., Chemidrov S.N.: scientific supervision, editing of the manuscript. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Колян Б.Ю. – идея, поиск литературы, написание текста. Маргарян А.В., Чемидров С.Н. – научное руководство, редактирование рукописи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	***Доступ к данным.*** Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	***Генеративный искусственный интеллект.*** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	***Рассмотрение и рецензирование.*** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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Dynamics of morphotopometric characteristics and X-ray density of T_{VI} vertebra in men from the first period of mature age to old age

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Abstract

Aim – to evaluate the dynamics of anteroposterior dimensions and X-ray density of the T_{VI} vertebra in men from the first period of adulthood to old age according to computed tomography (CT) of the chest.

Material and methods. The work is based on the results of CT scans of patients undergoing chest examinations. The height, width, anterioposterior dimension, and X-ray density of the T_{VI} vertebra body were measured. The study sample consisted of individuals with normal body weight, mesomorphic body type, without history of injuries and skeletal abnormalities. 60 patients were randomly selected from 78 subjects, so that each group had the same number of patients: 20 people. The first group consisted of men of the first period of adulthood (22-35 years of age), the second group included men of the second period of adulthood (36-60 years of age), the third group consisted of elderly men (61-75 years of age).

Results. The study revealed a tendency for the T_{VI} vertebral body height parameters to decrease by 7.8% in old age (t=2.01; p>0.05). A tendency for the T_{VI} vertebral body width parameters to increase by 2.18% in old age (t=0.54; p>0.05) was revealed. At the same time, a tendency for the anteroposterior size parameters of the T_{VI} vertebral body to increase by 2.25% was determined (t=0.60; p>0.05). The X-ray density indices of the T_{VI} vertebral body are characterized by a significant decrease in parameters with increasing age (p<0.001).

Conclusion. As a result of the conducted intravital study, new data on the age-related anatomy of the T_{VI} vertebra in men were obtained. Since the anatomical parameters of the vertebra are not static values and change with age, this information will useful in clinical practice of such specialists as gerontologists, traumatologists, vertebrologists, radiation diagnosticians, in sports medicine and in the work of exercise therapy doctors.

Keywords: vertebra T_{VI}, age-related changes, morphometry, CT, X-ray density.

Conflict of interest: nothing to disclose.

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Динамика морфотопометрических характеристик и рентгеновской плотности T_{VI} позвонка у мужчин от первого периода зрелого до пожилого возраста

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Аннотация

Цель – оценить динамику высоты, ширины, передне-заднего размера и рентгеновской плотности тела T_{VI} позвонка у мужчин от первого периода зрелого до пожилого возраста по данным компьютерной томографии (КТ) грудной клетки.

Материал и методы. В основу работы положены результаты КТ пациентов, проходивших обследование органов грудной клетки. Определяли высоту, ширину, передне-задний размер и рентгеновскую плотность тела T_{VI} позвонка. Выборку исследования составили лица с нормальной массой тела, мезоморфным типом телосложения, без травм и аномалий развития скелета в анамнезе. Из 78 обследуемых случайным образом были отобраны 60 пациентов так, чтобы в каждой группе было их одинаковое количество – 20 человек. Первая группа состояла из мужчин первого периода зрелого возраста (22–35 лет), вторая группа включала мужчин второго периода зрелого возраста (36–60 лет), третью группу составили мужчины пожилого возраста (61–75 лет).

Результаты. В ходе исследования установлена тенденция к снижению параметров высоты тела T_{VI} позвонка к пожилому возрасту на 7,8% (t=2,01; p>0,05). Выявлена тенденция к увеличению параметров ширины тела T_{VI} позвонка к пожилому возрасту на 2,18% (t=0,54; p>0,05). Наряду

с этим определена тенденция к увеличению параметров передне-заднего размера тела T_{VI} позвонка на 2,25% (t=0,60; p>0,05). Показатели рентгеновской плотности тела T_{VI} позвонка характеризуются достоверным снижением параметров к пожилому возрасту (p<0,001).

Заключение. В результате проведенного прижизненного исследования получены новые данные о возрастной анатомии T_{VI} позвонка у мужчин. Поскольку анатомические параметры позвонка не являются статичными величинами и изменяются с возрастом, полученные сведения будут востребованы в клинической практике у таких специалистов, как геронтологи, травматологи, вертебрологи, лучевые диагносты, врачи спортивной медицины и лечебной физкультуры.

Ключевые слова: позвонок T_{VI}, возрастные изменения, морфометрия, КТ, рентгеновская плотность.

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INTRODUCTION

The thoracic section of the sine is a peculiar, interesting region of the body for researchers of various disciplines. It is the bases of the rib cage and the most rigid part of the spine; at the same time, it retains some degree of mobility required for normal vital activities. Usually, biomechanical stability and mobility are opposite characteristics: as stability increases, the mobility decreases. However, the thoracic section of the spine is unique in combining the two properties [1].

The object of our study is the sixth thoracic vertebra (TVI). It is the 'center' of the thoracic section of the spine and plays a number of clinically important roles. It borders on the main primary bronchus forming the thoracic kyphosis and undertaking a complex load: the posterior of the base of this spinous process is usually exposed to tensile forces, and the anterior side, conversely, to forces of compression [2–4].

We studied the changes of the TVI vertebra in the aspect of age in men. Such data is practically absent in the scientific literature despite its importance for a number of reasons. Firstly, according to the medical statistics, men of advanced and old age are a category of population fairly vulnerable to trauma. Several factors are at work: coordination disorders due to age-associated changes in the cerebral structures, vestibular sickness, sedentary lifestyle, and excess body mass [5–7]. According to the findings of a study of Irish researchers in 2022, duration of hospital stay of patients aged over 65 with spinal traumas was 1.5 times longer than that of younger patients (21 vs. 14 days), and the mortality in the older group was more than 4 times higher (4.6% vs. 0.97% in the younger group) [8]. Secondly, men, even in the advanced age, are an important element in the economy of developing countries. Quite a significant number of them are actively working and are in demand in the labor market. The above factors pose global tasks for the development of personalized medicine [9].

AIM

To evaluate the dynamics of anteroposterior dimensions and X-ray density of the TVI vertebra in men from the first period of adulthood to old age according to computed tomography (CT) of the chest.

MATERIAL AND METHODS

The work is based on the results of CT scans of patients undergoing chest examinations in the admissions department of Perm Region City Clinical Hospital No. 3 in 2023-2024. All patients provided a consent for the study that was performed to exclude possible pulmonary pathologies according to indications.

The height, width, anterioposterior dimension, and X-ray density of the TVI vertebra body were measured on the Optima 660 computed tomography scanner (**Fig. 1–3**).

The analysis of CT scans was performed with the RadiAnt specialized software suite. The subjects of the study were individuals with normal body weight, mesomorphic build, no history of skeletal trauma or development abnormalities.

Of the 78 examined subjects, 60 patients were randomly selected in such a way that each group had an equal number of patients (20). The first group consisted of males of the first adult period (22–35 years of age), the second, men of

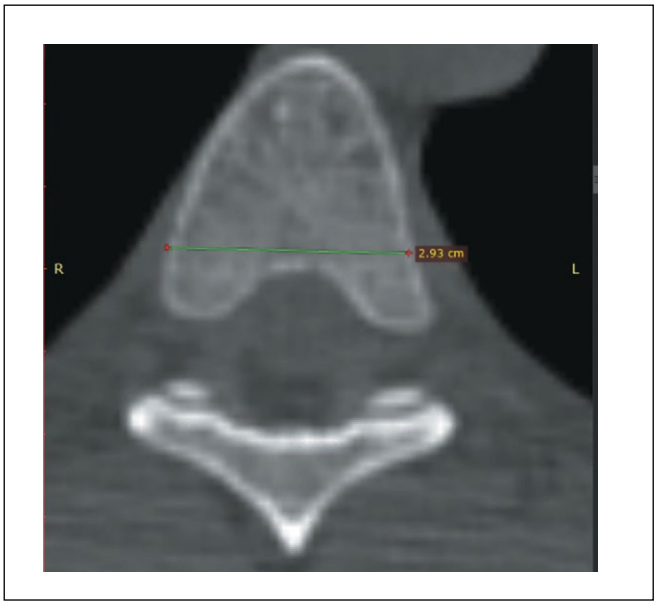

Figure 1. *Example of width measurement of the vertebral body in a 23-year-old man.*

Рисунок 1. *Пример измерения ширины тела позвонка у мужчины 23 лет.*

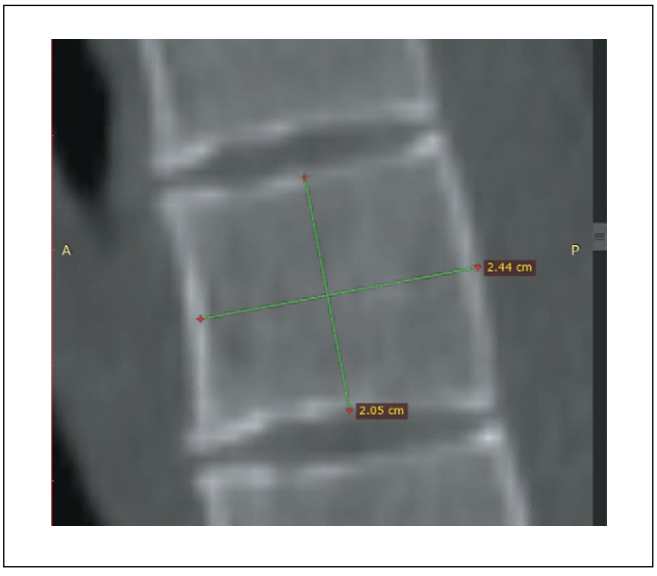

Figure 2. *Example of height and anteroposterior size measuring of the vertebral body in a 23-year-old man.*

Рисунок 2. *Пример измерения высоты и передне-заднего размера тела позвонка у мужчины 23 лет.*

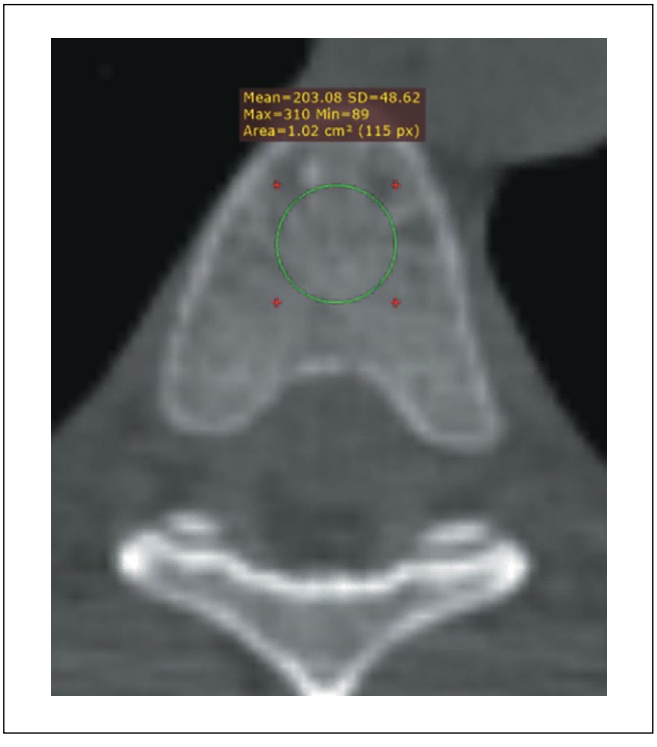

Figure 3. *Example of X-ray density measurement of the vertebral body in a 23-year-old man.*

Рисунок 3. *Пример измерения рентгеновской плотности тела позвонка у мужчины 23 лет.*

the second adult period (36–60 years), third group, elderly men (61–75 years).

The statistical analysis was performed in Microsoft Excel 2019. The results were presented as the arithmetic mean (M) and standard error (m), median and variation coefficient. To check the normality of distribution of variation rows, the Kolmogorov-Smirnov test was used. Student's parametric t-test was used to test the equality of average values in the two samples. Differences were considered statistically significant at $p<0.05$.

Age period	M±m	Max	Min	σ	Cv	Me
First adult period (n=20)	19,09±0,27	20	17,5	0,76	0,04	19,3
Second adult period (n=20)	18,78±0,59	21,4	16	1,88	0,10	18
Elderly age (n=20)	17,60±0,69	20,4	14,9	1,83	0,10	17,3

Table 1. *Body height indicators T_{VI} spine in men in the studied age periods according to CT-scans, mm (n=60)*

Таблица 1. *Показатели высоты тела T_{VI} позвонка у мужчин в исследуемых возрастных периодах по данным КТ, мм (n=60)*

Age period	M±m	Max	Min	σ	Cv	Me
First adult period (n=20)	27,92±0,94	32,7	25,3	2,65	0,09	28,1
Second adult period (n=20)	27,55±0,65	31,4	25,3	2,05	0,07	27,6
Elderly age (n=20)	27,31±0,64	29,9	25,2	1,68	0,06	27,2

Table 2. *Indicators of the body width of the T_{VI} vertebra in men in the studied age periods according to CT- scans, mm (n=60)*

Таблица 2. *Показатели ширины тела T_{VI} позвонка у мужчин в исследуемых возрастных периодах по данным КТ, мм (n=60)*

Age period	M±m	Max	Min	σ	Cv	Me
First adult period (n=20)	26,27±0,64	28,3	23,6	1,80	0,07	27,3
Second adult period (n=20)	26,41±0,65	29,3	23,5	2,04	0,08	26,3
Elderly age (n=20)	26,86±0,75	29,6	23,5	1,99	0,07	26,4

Table 3. *Indicators of anterior-posterior body size of the T_{VI} vertebra in men in the studied age periods according to CT- scans, mm (n=60)*

Таблица 3. *Показатели передне-заднего размера тела T_{VI} позвонка у мужчин в исследуемых возрастных периодах по данным КТ, мм (n=60)*

Age period	M±m	Max	Min	σ	Cv	Me
First adult period (n=20)	217,27±2,00	373	165	63,31	0,29	215
Second adult period (n=20)	206,00±1,07	296	143	30,48	0,15	205
Elderly age (n=20)	194,13±2,48	253	104	65,77	0,34	186

Table 4. *Indicators of X-ray body density of the T_{VI} vertebra in men in the studied age periods according to CT- scans, HU (n=60)*

Таблица 4. *Показатели рентгеновской плотности тела T_{VI} позвонка у мужчин в исследуемых возрастных периодах по данным КТ, HU (n=60)*

RESULTS

The data on the dimensions and X-ray density of the TVI vertebral body in the tested age groups follow in **Tables 1–4**.

In the course of the study, a tendency was identified for the parameter of height of the TVI vertebra body to decrease over elderly age by 7.8% ($t=2.01$; $p>0.05$). There was a tendency for the width of the TVI vertebra body to increase over the elderly age by 2.18% ($t=0.54$; $p>0.05$). At the same time, a tendency was identified for the anterio-posterior dimension of the TVI TVI vertebra body to increase by 2.25% ($t=0.60$; $p>0.05$). The value of the X-ray density of the TVI TVI vertebra body demonstrates a reliable decrease over the elderly age ($p<0.001$).

In other words, when discussing age-related dynamics, it can be stated that the vertebral body flattens with age, meaning its height decreases, while its width and anteroposterior

dimension, conversely, increase. Radiographic density decreases by advanced age.

DISCUSSION

Aging is a systemic process with its proper laws and changes taking place on the molecular and cellular level. The aging of an organism can be defined as the state of progressive functional deterioration of its tissues. Accumulated cellular damage by mitochondrial oxidation, disorders in the DNA molecular structure by 'incorrect' proteins affects the operation of their organelles. The changes that follow lead to accumulation of dysfunctional cells in the tissues, which complicates maintenance of homeostatic mechanisms thereby limiting the regenerative potential [10–12].

There are several interesting publications in the literature that focus on biomechanical features of the aging spine. In their paper, M. Papadakis et al. (2011) presented a brief review of pathophysiological processes taking place in the aging spine and described the outcomes of these changes for the spine biomechanics. According to this review, the body of the vertebra is subjected to a greater part of the load that the spine is exposed to. The vertebra body consists of a spongy bone that becomes more dense and strong at the periphery forming the external layer; however, the main factor that defines the mechanical strength of the vertebra body is not that external layer but the microarchitecture. The osseous trabeculae adjoining the end plate and located in the posterior area of the body are much larger and their network denser. Conversely, the central and the anterior parts of the vertebra body have lower regional density, thinner and less ordered trabeculae. At the same time, the mechanical properties of the vertebra body are directly related to its mineral density. The correlation between the bone density and strength under compression is exponential; therefore, a minor decrease in the former parameter leads to a major decrease in the latter [13].

The review of S.J. Ferguson and T. Steffen was published much earlier (2003). According to this study, starting from the fourth decade of life men can easily lose up to 30%, and women up to 50% of bone mass. The researchers also noted heterogeneity in the microstructure of the vertebra bodies. They explain these differences in the mechanical properties with adaptation to environment; in the specific case of the spine this is explained by higher axial loads transferred by the central area adjacent to the nucleus pulposus, unlike the peripheral area adjacent to the annulus fibrosus [14].

One should also mention the study of Swiss scientists published in 2018. D. Ignasiak et al. studied the effect of age-related changes of the spine on its kinematic features in the course of daily activities with respect to segmental loads. The researchers found that the maximum compression loads predicted in elderly people were lower than those in young people at the following levels: L2/L3 and L3/L4 of the lumbar spine during flexure; upper thoracic levels during transition from standing to sitting position (T1/T2–T8/T9), and from the sitting to the standing position (T3/T4–T6/T7) [15].

CONCLUSION

As a result of the conducted intravital study, new data on the age-related anatomy of the TVI vertebra in men were obtained. Since the anatomical parameters of the vertebra are not static values and change over age, this information will be useful in clinical practice of such specialists as gerontologists, traumatologists, vertebrologists, radiation diagnosticians, in sports medicine and in the work of exercise therapy doctors.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethics approval: Approval of the LEC is obtained (No. 9 dated 23.10.2024).	***Этическая экспертиза.*** Получено положительное решение ЛЭК (№ 9 от 23.10.2024 г.).
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. Balandin A.A., Chudinov O.A.: collection of material, data analysis, writing of the text of the article. Balandina I.A., Balandin A.A.: study design, interpretation of results, editing of the article. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Баландин А.А., Чудинов О.А. – сбор материала, анализ данных, написание текста статьи. Баландина И.А., Баландин А.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.
Statement of originality. No previously published material (text, images, or data) was used in this work.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	***Доступ к данным.*** Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	***Генеративный искусственный интеллект.*** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	***Рассмотрение и рецензирование.*** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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Original study article | Оригинальное исследование
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The relationship between the level of Nt-proBNP and indicators of clinical and metabolic status in comorbid elderly patients with type 2 diabetes mellitus

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Aim – to determine the specific features of the use of the semi-quantitative Nt-proBNP immunochromatographic assessment technique for the diagnosis of chronic heart failure (CHF) in comorbid elderly patients with type 2 diabetes mellitus (DM2) in relation to indicators of clinical and metabolic status.
Material and methods. The study was performed using a cross-sectional design; 97 clinical and laboratory-instrumental indicators were studied, including the determination of Nt-proBNP by a semi-quantitative method, in a sample of 50 comorbid elderly patients with T2DM; groups were identified according to the threshold value of Nt-proBNP 450 pg/ml; the interrelationships and significance of differences in variables in the groups were analyzed, including the number of average values of biomarkers for achieving the goals of DM2 treatment and the structure of drug therapy.
Results. A high prevalence of comorbid pathology (arterial hypertension: 90%, obesity: 74%, dyslipidemia: 72%) and a high proportion of participants' failure to achieve therapeutic goals, comparable in the Nt-proBNP groups, were revealed; a significant association between the Nt-proBNP group and the previously established stage of CHF (χ^2 = 6.4; p = 0.041), a positive correlation with the ratio of transmittal blood flow rates in early and late diastole E/A (r = 0.309; p = 0.003); Indirect evidence has been obtained for the high sensitivity of the semi-quantitative assessment of Nt-proBNP for the diagnosis of early-stage CHF.
Conclusion. The majority of comorbid elderly patients with DM2 (72%) have Nt-proBNP levels above the general population threshold of 125 pg/ml and need to verify the diagnosis of CHF. The assessment of the Nt-proBNP test result in T2DM has its own specifics due to polymorbid pathology (obesity and CKD) and the presence of multidirectional "disturbing" factors. When planning a follow-up program for elderly patients with DM2 and hypertension, the indications for Nt-proBNP screening should be taken into account, and if the result is positive, for an in-depth Echocardiography examination.
Keywords: old age, type 2 diabetes mellitus, N-terminal brain-promoting natriuretic peptide, chronic heart failure, comorbid pathology.
Conflict of interest: nothing to disclose.

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Взаимосвязь уровня Nt-proBNP и показателей клинико-метаболического статуса у коморбидных пожилых пациентов с сахарным диабетом 2 типа

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Аннотация

Цель – определить специфические особенности применения иммунохроматографической полуколичественной методики оценки Nt-proBNP для диагностики хронической сердечной недостаточности (ХСН) у коморбидных пожилых пациентов с СД 2 типа (СД2) во взаимосвязи с показателями клинико-метаболического статуса.

Материал и методы. Исследование выполнено по кроссекционному дизайну. Изучено 97 клинических и лабораторно-инструментальных показателей, включая определение Nt-proBNP полуколичественным методом, в выборке 50 коморбидных пожилых пациентов с СД2. Выделены группы по пороговому значению Nt-proBNP 450 пг/мл. Проанализированы взаимосвязи и значимость различий переменных в группах, в том числе средних значений биомаркеров достижения целей лечения СД2 и структуры медикаментозной терапии.

Результаты. Выявлены высокая распространенность коморбидной патологии (артериальной гипертензии (АГ) – 90%, ожирения – 74%, дислипидемии – 72%) и высокая доля недостижения терапевтических целей участников, сопоставимые в группах Nt-proBNP. Определена значимая ассоциация между группой Nt-proBNP и ранее установленной стадией ХСН (χ^2=6,4; p=0,041), а также положительная корреляция с показателем соотношения скоростей трансмитрального кровотока в раннюю и позднюю диастолу E/A (r=0,309; p=0,003). Получены косвенные доказательства высокой чувствительности полуколичественной оценки Nt-proBNP для диагностики ХСН ранних стадий.

Выводы. Большинство (72%) коморбидных пожилых пациентов с СД2 имеют уровень Nt-proBNP выше общепопуляционного порогового значения 125 пг/мл и нуждаются в верификации диагноза ХСН. Оценка результата теста Nt-proBNP при СД2 имеет специфику, обусловленную полиморбидной патологией (ожирение и ХБП) и наличием разнонаправленных «возмущающих» факторов. При планировании программы диспансерного наблюдения пожилых пациентов, имеющих СД2 и АГ, следует учитывать показания к скринингу Nt-proBNP, а при положительном результате – к углубленному эхоКГ-обследованию.

Ключевые слова: пожилой возраст, сахарный диабет 2 типа, N-терминальный промозговой натрийуретический пептид, хроническая сердечная недостаточность, коморбидная патология.

Конфликт интересов: не заявлен.

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Список сокращений
АГ – артериальная гипертензия; АД – артериальное давление; АРМЭ – автоматизированное рабочее место врача-эндокринолога; ДАД – диастолическое АД; иДПП-4 – ингибитор дипептидилпептидазы 4 типа; ИБС – ишемическая болезнь сердца; ИММ – индекс массы миокарда; ИМТ – индекс массы тела; иНГЛТ-2 – ингибитор натрий-глюкозного котранспортера 2-го типа; ИС_СКФ – индекс снижения скорости клубочковой фильтрации; КДР – конечный диастолический размер; КСР – конечный систолический размер; ЛП – левое предсердие; ЛЖ – левый желудочек; ОИМ – острый инфаркт миокарда; ОНМК – острое нарушение мозгового кровообращения; САД – систолическое АД; СКФ – скорость клубочковой фильтрации; СППВР – система поддержки принятия врачебных решений; СД2 – сахарный диабет 2 типа; ТЗС – толщина задней стенки; ТМЖП – толщина межжелудочковой перегородки; ХБП – хроническая болезнь почек; HbA1c – гликированный гемоглобин; Nt-proBNP – N-терминальный промозговой натрийуретический пептид.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) significantly increases risks of cardiovascular complications win an inevitable outcome of chronic heart failure (CHF) [1]. In many T2DM patients, CHF may manifest as the first cardiovascular event [2]. Even the clinical manifestations of pre-diabetes vs. normoglycemia increase the risk of CHF development [3], cardiovascular death and all-cause mortality [4] by 9–58%.

CHF of clinically manifested stages is confirmed in 10–30% patients with T2DM, and it is especially often registered in the age over 70 [5]. At the same time, the prevalence of non-diagnosed CHF (specifically, pre-heart failure) in T2DM patients [6], as well as non-diagnosed disorders of carbohydrate metabolism (impaired glucose tolerance, pre-diabetes, T2DM) in the general population is significant [6]. For example, the results of a meta-analysis of a screening study in the Netherlands showed that up to 4.2% of adults has objective EchoCG signs of CHF, which was considerably higher than the official registry data of 1-2% [7]. According to epidemiology data, the overall survival of patients 10 years after diagnosis of CHF is 24.5% [8].

Many scientists now consider T2DM the major risk factor of CHF onset, and patients with T2DM are regarded as patients likely having Stage A CHF (ACC/AHA Guidelines) [9].

One of priority components of T2DM management strategy in the senior age is prevention of cardiovascular risks and mortality, which necessitates search for and studies of methods of early diagnostic confirmation or exclusion of CHF. Studies of clinical significance of evaluation of natriuretic peptide concentration, including Nt-proBNP, for the screening of CHF have confirmed that this method allows for a reliable exclusion of CHF diagnosis in patients [10] and is economically feasible for the public health care [11]. It was established that values over the threshold level of Nt-proBNP are an indication for further in-depth diagnosis, confirmation of CGF status, identification of its form and severity [12].

The main goal of any screening method is to provide an answer of what threshold level of a biomarker allows for a highly reliable establishment or exclusion of some diagnosis or other. To that end, available simple qualitative and semi-quantitative tests are used [13]. We performed a focused search for studies with evidence-based findings of a relation between the level of natriuretic peptides and the parameter of clinical and metabolic status of comorbid patients with T2DM; however, it yielded no results.

The key factors complicating the determination of threshold values of Nt-proBNP in diabetes mellitus are the specific phenotype of CHF with preserved ejection fraction and prevalence of restrictive lesions of the myocardium, and status of comorbid factors and conditions significantly affecting the concentration of Nt-proBNP (obesity, diabetic nephropathy, age).

AIM

To determine the specific features of the use of the semi-quantitative Nt-proBNP immunochromatographic assessment technique for the diagnosis of chronic heart failure (CHF) in comorbid elderly patients with type 2 diabetes mellitus (T2DM) in relation to indicators of clinical and metabolic status.

MATERIAL AND METHODS

Study design. One-time cross-sectional clinical study in the population sample of comorbid elderly patients with T2DM.

Clinical base. The study is performed by the Department of Endocrinology and Geriatrics of the Samara State Medical University at the Department of endocrinology of the Samara Regional Clinical Hospital named after V.D. Seredavin.

Characteristics of participating group. The sample of participants (n=50) was formed on a random basis. It consisted of comorbid patients with a confirmed T2DM diagnosis hospitalized to the Department of endocrinology for a planned correction of therapy.

Inclusion criteria: patients with T2DM aged 60 to 74.9 years with confirmed concomitant diseases (arterial hypertension, coronary heart disease, obesity), GFR within 30 to 120 ml/min/1.73 m^2. Exclusion criteria: acute complications of diabetes mellitus, exacerbation of comorbid diseases at the moment of hospitalization, acute vascular diseases within 3 preceding months, availability of objective signs of a severe cardiac stasis (Stage II on the classification of the Russian Society of Cardiology of 2023 [14]), CKD Stage 4 and later, concomitant system pathology with a significant impact on the heart and kidney function (anemia with hemoglobin concentration below 90 g/l, gouty arthritis, malignant growth), dementia, limited functional self-care capacity, lack of informed consent.

Forming of the study sample and identification whether or not the participants meet the selection criteria were performed on the basis of medical data of preceding stages of outpatient observation, i.e. in the period before the official approval of the new CHF classification. Considering these circumstances, the old Strazhesko-Vasilenko classification was used.

The clinical characteristics of the general sample of participants follows in **Table 1**.

Since the value of the mean square deviation of creatinine level was comparable with the absolute value, the data is presented in two variants, the arithmetic mean and the standard deviation (M±SD), and the median and quartiles (Me [Q1; Q3]).

The laboratory tests included the classic indicators of clinical monitoring of DM patients as well as methods of in-depth analysis of objective parameters of CHF. Firstly, the concentration of N-terminal brain natriuretic peptide (Nt-proBNP) was determined using a domestic semi-quantitative immunochromatographic assay test (Scientific Production Company "BioTest" LLC, Novosibirsk). The test earlier demonstrated high diagnostic value as compared to the quantitative assessment of Nt-proBNP with an immunochemical assay test in the DREAM study [15], allowing identification of five ranges of values: 0-124 pg/mL; 125-449 pg/mL; 450-899 pg/mL; 900-1799 pg/mL; ≥1800 pg/mL. Secondly, an assessment of diastolic dysfunction (DD) and structural and functional disorders was performed by non-contrastive transthoracic echocardiography using the Vivid E9 ultrasonic scanner.

Collection of primary clinical material. The software suite "Endocrinologist's Automated WorkplaceARME 2.0" was used to collect the primary material. The software complex systematizes the data and stores them on digital media during outpatient visits. The matrix of formalized consultation protocol of the ARME 2.0 includes 97 history, clinical and laboratory indicators of DM patients that belong to the standard of dispensary monitoring;

Participants, n	50	
Sex (M/F), n (%)	13/37 (26,0/74,0)	
Mean age, years	65,64±4,01	
Diabetes age, years	14,52±8,12	
BMI, kg/m2	34,07±5,99	
HbA1c, %	8,93±2,58	
Creatinine, μmol/L	94,21±39,97	84,25 [73,85; 107,66]
GFR CKD-EPI (ml/min/1.73 m^2)	65,42±19,15	

Table 1. *Clinical characteristics of the general sample*
Таблица 1. *Клиническая характеристика генеральной выборки*

Clinical parameter	N	% in the group
CKD 3a-b (GFR < 60 mL/min/1.73 m²)	20	40,0
Retinopathy	15	30,0
Foot polyneuropathy	42	84,0
Stable angina	20	40,0
History of acute MI	4	8,0
History of ACVA	9	18,0
Chronic obliterative arterial disease of the lower limbs	4	8,0
Confirmed CHF	12	24,0
Arterial hypertension	45	90,0
Obesity	37	74,0
Dyslipidemia	36	72,0

Table 2. *Prevalence of complications of DM and comorbid pathology in the general sample*

Таблица 2. *Распространенность осложнений СД и коморбидной патологии в генеральной выборке*

Clinical parameter	M±SD
HbA1c, %	9,47±2,92
delta HbA1c = HbA1c-ЦУ, %	1,48±2,59
Glycaemia on admission, mmol/L	8,49±3,53
Glycaemia on self-control, min, mmol/L	7,31±2,51
Glycaemia on self-control, max, mmol/L	15,54±3,80
Glycaemia variability, mmol/L	8,23±4,06
Cholesterol_ mmol/L	5,00±1,27
LDL_ mmol/L	2,82±1,01
delta LDL = LCL-TL, %	1,41±0,96
SBP_office	131,60±6,50
DBP_office	78,48±12,99

Table 3. *Indicators of therapeutic control of diabetes in the general sample*

Таблица 3. *Показатели терапевтического контроля СД в генеральной выборке*

integrated and external modules of the medical decision-making support system (MDMSS) ensure identification of the variables (BMI, GFR under the CKD-EPI formula, stages of obesity and CKD, dyslipidemia status, arterial hypertension risk groups, target values of HbA1c, blood pressure, LDLs, SCORE2 risk, and others).

Statistical analysis. The primary material from the ARME DM database to a Microsoft Excel file was done with automation tools and a pre-set query script. Specialized software was used for the purposes of statistical analysis and mathematical modeling: SPSS 26.0 (IBM Corporation, Armonk, New York, USA). Nominal features were coded with numbers with respective labels assigned. The values of text fields of pharmacological therapy were validated using the nominal scale with segregation of drug classes.

Normality of distribution for quantitative variables was assessed graphically using visual analysis of histograms and the Shapiro-Wilk test. In cases of significant deviations from normality, non-parametric analytical methods were applied. Descriptive statistics for quantitative variables are presented as mean standard deviation (M±SD) or, in cases of substantial non-normality, as median and quartiles [Me (Q1; Q3)]. Categorical variables are described using counts and percentages of the group size.

Mann-Whitney and Student's tests were used to compare the quantitative parameters in groups. The frequencies of nominal features were compared by calculating the Pearson's χ^2 test and Fisher's two-tail exact test. The strength of associations between variables was assessed using Spearman's rank correlation for quantitative variables and Kendall's tau-b correlation for pairs of ordinal and quantitative variables. Results were considered statistically significant at $p < 0.05$ for all types of statistical analysis.

RESULTS AND DISCUSSION

The structure of the concomitant pathology and vascular complications in elderly T2DM patients is shown in **Table 2**.

Among the microvascular complications of the DM, worthy of note are the high prevalence of CKD with filtration function value below 60 mL/min/1.73 m² (40%) and polyneuropathy of the lower limbs (84%). The incidence rate of chronic forms of CHF was between 8% and 40%. The diagnosis of CHF in the study participants was established and verified by outpatient cardiologists in the preceding stages of outpatient monitoring. Considering the dedicated profile of the department and decompensated progression of diabetes in the majority of patients, the evaluation of functional disorders of the myocardium was performed using standard EchoCG parameters without functional stress tests. The CHF prevalence, according to history data, was 24%.

The concomitant comorbid diseases were present in all participants of the sample: the incidence of arterial hypertension was close to 100%, BMI was higher than the threshold value of obesity diagnosis in 74% cases, and dyslipidemia found in 72%.

Quantitative indicators of therapeutic control of elderly comorbid T2DM patients are shown in **Table 3**.

The average values of HbA1c (9.47±2.92%), its difference with the target and actual value (delta HbA1c 1.48±2.59%), glycaemia on admission (8.49±3.53 mmol/L), as well as its high variance in self-control (8.23±4.06 mmol/L) shows unsatisfactory control of glycemic status of T2DM patients. One of the most important parameters of the lipid profile, the LDL, are also outside the target range with the average value being 2.82±1.01 mmol/L, which is 1.41±0.96 mmol/L different from the target value. According to current recommendations, the target level of systolic BP is 120–130 mmHg, and the evaluation of its average value (131.60±6.50 mmHg) leads to believe that it is close to the target value. However, the analysis of the qualitative parameter of SBP meeting the target range shows a less positive situation (**Table 4**).

Clinical parameter	N	% in the group
Glycemic control (HbA1c < 7.5%)	17	34,0
Lipid control (LDL < 1.4 mmol/L)	3	6,0
SBP < 130 mmHg	7	14,0
DBP < 80 mmHg	41	82,0
All parameters (HbA1c, LDL, BP)	0	0,0

Table 4. *Frequency of achieving target levels of therapeutic control in elderly patients with DM*

Таблица 4. *Частота достижения целевых уровней терапевтического контроля у пожилых пациентов с СД*

Drug	n (%)	% in the group
Insulin	40	80,0
Sulphonylurea	18	36,0
Biguanides	29	58,0
DPP4i	6	12,0
Gliflozins	27	54,0
Monotherapy	7	14,0
Two drugs in tablets	21	42,0
Three drugs in tablets and more	10	20,0

Table 5. *Structure of hypoglycemic therapy in elderly patients with DM2*

Таблица 5. *Структура гипогликемической терапии пожилых пациентов с СД2*

Nt-proBNP	Range	N	% in the sample
0-124 pg/mL	1	12	24,0
125-449 pg/mL	2	7	14,0
450-899 pg/mL	3	16	32,0
900-1799 pg/mL	4	10	20,0
≥1800 pg/mL	5	5	10,0

Table 6. *Distribution structure of elderly patients with DM2 by Nt-proBNP ranges*

Таблица 6. *Структура распределения пожилых пациентов с СД2 по диапазонам Nt-proBNP*

The data shows that the goals of glycemic control were formally met in 34% of examined elderly T2DM patients, lipid control, in 6%, SBP, in 14%, the DBP meeting the target level in the majority of participants (82%). Thus, two most serious problems of efficient compensation of DM in the elderly age were localized, viz. meeting the SBP and LDL target levels.

The analysis of drugs used to control carbohydrate metabolism in the group of elderly T2DM patients is shown in **Table 5**.

The vast majority of hospitalized elderly patients with T2DM received insulin therapy (80%). Among oral antidiabetic drugs, biguanides were the most prescribed (58%), followed by SGLT-2 inhibitors (54%). The most common regimen involved two concomitant medications (42% of cases). Analysis of the table indicates that glucose-independent insulin secretagogues and irrational pharmacotherapy regimens were used with considerable frequency.

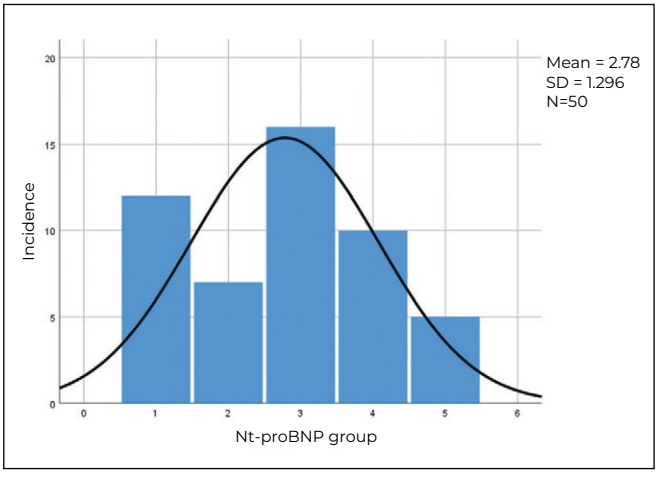

Figure 1. *Histogram of the sample distribution over the Nt-proBNP ranges.*

Рисунок 1. *Гистограмма распределения выборки по диапазонам Nt-proBNP.*

	Nt-proBNP < 450 pg/mL, n=19		Nt-proBNP ≥ 450 pg/mL,		p
	n=31	%	N	%	
No Ds CHF	14	73,7%	24	77,4%	1,000
CHF Stage 1	5	26,3%	2	6,5%	0,089
CHF Stage 2a	0	0,0%	5	16,1%	0,142

Note: p – significance of difference between groups as per Fischer's exact test
Примечания: p – значимость различий между группами: по точному критерию Фишера.

Table 7. *Frequency of previously established stages of CHF in the Nt-proBNP groups*

Таблица 7. *Частота ранее установленных стадий ХСН в группах Nt-proBNP*

The frequency of distribution of the sample participants by ranges of Nt-proBNP determined by semi-quantitative method is shown in Table 6.

The majority of comorbid elderly T2DM patients belong to range 3 with Nt-proBNP values of 450 to 899 pg/mL, which, according to the current clinical recommendations [12], is to be regarded as the necessity for further in-depth examination for CHF. The histogram of distribution of participants of the sample over the Nt-proBNP ranges is shown in **Figure 1**.

Considering the limitations of the semi-quantitative method of Nt-proBNP determination, it order to evaluate the correlations with clinical and metabolic indicators the sample was divided into groups with the threshold value of 450 pg/mL: groups A (Nt-proBNP < 450 pg/mL, n=19) and group B (Nt-proBNP ≥ 450 pg/mL, n=31). The histogram of participant distribution in the groups is shown in **Fig. 2**.

Based on a preliminary analysis of this histogram, it is admissible to suggest the following: semi-quantitative immuno-chromatographic assay of Nt-proBNP shows high sensitivity, especially in the subclinical stage of CHF development. In 22 participants (44%) with no history of CHF diagnosis, Nt-proBNP ≥ 450 pg/mL was found. This may indicate low detection of initial manifestations of CHF in elderly T2DM patients.

The diagram of incidence rates based on the threshold value of 125 pg/mL, standard cutoff point in CHF screening for general population (**Fig. 3**) clearly demonstrates that over a half of study participants (72%) without a confirmed

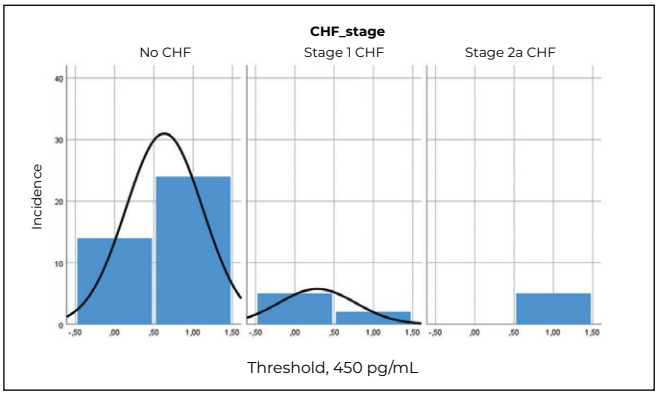

Figure 2. *Histogram of the distribution of NT-proBNP groups with a threshold value of 450 pg/ml according to previously established stages of CHF.*

Рисунок 2. *Гистограмма распределения групп NT-proBNP с пороговым значением 450 пг/мл по ранее установленным стадиям ХСН.*

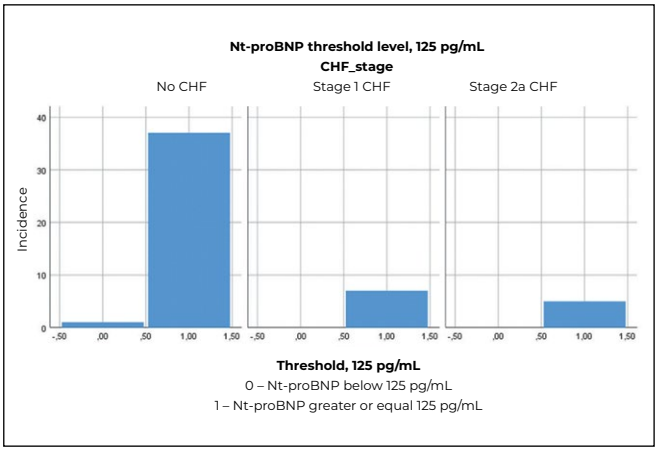

Figure 3. *Histogram of the distribution of NT-proBNP groups with a threshold value of 125 pg/ml according to previously established stages of CHF.*

Рисунок 3. *Гистограмма распределения групп NT-proBNP с пороговым значением 125 пг/мл по ранее установленным стадиям ХСН.*

diagnosis of CHF as per previous stages of dispensary follow-up, require a deeper diagnostic [12].

A closer assessment of the strong relation of the Nt-proBNP groups with the earlier established CHF stages allows for an analysis of contingency tables (**Table 7**).

The general Pearson's χ^2 for the contingency table was χ^2=6.4; p=0.041, which allows for a conclusion of a significant association between the Nt-proBNP group and the clinical CHF stage. The number of patients with 2a CHF stage was only 5 patients, but they all were within the elevated Nt-proBNP group. In the assessment of paired contingency tables, in accordance with the strict rules of medical statistics, Fisher's exact test was used. However, if Pearson's χ^2 test is to be used as maximum likelihood (p=0.024), a trend for higher incidence of CHF stage 2a is identified in patients with Nt-proBNP ≥ 450 pg/mL.

To clarify the correlation between groups identified as per Nt-proBNP category, with DM complications and comorbid pathologies, paired contingency tables were analyzed by nominal features (**Table 8**).

Following from literature data, a concomitant pathology may have various effects on the Nt-proBNP concentration. Excessive body mass and obesity may reduce the Nt-proBNP level thus masking the CHF [16]; patients with reduced kidney filtration function may accumulate the Nt-proBNP, which reversely affects the level of this parameter [17]. In our study, we checked the incidence rate of concomitant diseases in the Nt-proBNP groups but found no significant differences, which might have been related to non-inclusion of patients with extreme manifestations of these pathologies in the sample. The interaction of these competing factors (high BMI and reduced GFR), characteristic for most elderly T2DM patients, and their joint effect on the Nt-proBNP concentration necessitates a separate in-depth analysis on large samples.

To clarify the effect of conventional indicators of DM therapeutic control on the Nt-proBNP value in the groups, their average values were compared (**Table 9**).

No significant differences were found in the average values of the glycemic, lipid and hemodynamic control as well as rated parameters of reaching their target values mediated by the level of. One may suggest that despite the common links in the pathogenetic mechanism of DM and CHF, concentration of Nt-proBNP reflects only the increased extension of the cardiac chambers and has no direct connection with the compensation of DM. Noteworthy is the trend of the indicator of glycaemia variance towards significance (p=0.065) that had not reached the threshold value: this is a new indicator of glycemic control that demonstrated a significant relation with the development of vascular complications in DM patients [18, 19]. The data on the lack of relation between HbA1c and Nt-proBNP were tested by correlation analysis, and a single relation was found: that between the relative proportion of patients who reached the target level of glycemic control, and adherence to the segregated Nt-proBNP groups, Spearman's correlation having a negative sign and nearing the significance threshold (r=-0.276; p=0.052).

The following stage included a comparison of the average values of standard indicators of blood biochemical test in the Nt-proBNP groups (**Table 10**).

Clinical parameters	Group A, n (%)	Group B, n (%)	p
3a-b CKD (GFR < 60 mL/min/1.73 m²)	6 (31,6)	14 (45,2)	0,387
Retinopathy	4 (21,1)	11 (35,5)	0,351
CAD	12 (63,2)	18 (58,1)	0,774
Stable angina, FC2	10 (52,6)	10 (32,3)	0,235
History of acute MI	2 (10,5)	2 (6,5)	0,629
History of ACVA	2 (10,5)	7 (22,6)	0,452
Chronic obliterative arterial disease of the lower limbs	1 (5,3)	3 (9,7)	1,000
Arterial hypertension	19 (100,0)	30 (96,8)	1,000
Obesity	14 (73,7)	23 (76,7)	1,000
Dyslipidemia	14 (52,6)	26 (32,3)	0,474

Note: p – significance of difference between groups as per Fischer's exact test
Примечания: p – значимость различий между группами по точному критерию Фишера.

Table 8. *Structure of DM complications and concomitant pathology in the Nt-proBNP groups*

Таблица 8. *Структура осложнений СД и сопутствующей патологии в группах Nt-proBNP*

Clinical parameters	Group A M±SD	Group B M±SD	p
HbA1c, %	8,58±1,66	9,14±3,01	0,395
delta HbA1c = HbA1c-ЦУ, %	1,10±1,65	1,71±3,02	0,365
Glycaemia on admission, mmol/L	8,51±3,79	8,48±3,43	0,977
Glycaemia on self-control, min, mmol/L	7,66±2,46	7,08±2,55	0,436
Glycaemia on self-control, max, mmol/L	14,63±2,93	16,14±4,22	0,151
Glycaemia variability, mmol/L	6,97±3,29	9,06±4,35	0,065
Cholesterol_ mmol/L	2,62±0,95	2,93±0,96	0,284
LDL_ mmol/L	1,22±0,95	1,53±0,96	0,283
SBP_office	132,11±6,31	131,29±6,70	0,667
DBP_office	79,47±5,24	80,97±5,98	0,374

Note: p – significance of differences
Примечания: p – значимость различий

Table 9. *Indicators of therapeutic control of diabetes in the Nt-proBNP groups*

Таблица 9. *Показатели терапевтического контроля СД в группах Nt-proBNP*

Clinical parameters	Group A M±SD	Group B M±SD	P
Cholesterol, mmol/L	4,82±1,27	5,16±1,20	0,342
HDL, mmol/L	1,22±0,23	1,26±0,41	0,699
TG, mmol/L	2,18±0,92	1,99±0,85	0,445
Creatinine, μmol/L	87,32±27,99	98,44±45,72	0,345
GFR CKD-EPI (ml/min/1.73 m²)	69,35±20,82	63,02±17,98	0,261
IS_GFR, ml/min/1.73 m² per year	1,20±1,14	2,92±3,71	0,023*

*Note: p – significance of differences, * – p<0.05*
*Примечания: p – значимость различий; * – p<0,05.*

***Table 10.** Biochemical parameters in Nt-proBNP groups*

***Таблица 10.** Биохимические показатели в группах Nt-proBNP*

Clinical parameters	Group A M±SD	Group B M±SD	P
LV end diastolic size, mm	48,28±4,60	48,61±3,71	0,790
LV end systolic size, mm	32,11±4,56	31,46±3,60	0,595
LV posterior wall thickness, mm	11,14±1,19	11,52±1,15	0,287
IV septum thickness in diastole, mm	11,88±1,39	12,52±1,41	0,138
MMI_LV, g/m²	117,24±40,21	119,98±30,16	0,807
LA, mL	34,84±4,29	37,56±11,75	0,366
Ejection fraction, mL	61,89±6,88	62,68±6,04	0,684
E/A	0,83±0,24	0,89±0,25	0,528
TAPSE, mm	21,62±1,19	22,76±4,04	0,328
LA, mm	22,13±1,89	22,77±1,99	0,305

Note: p – significance of differences
Примечания: p – значимость различий.

***Table 11.** Indicators of instrumental examinations in Nt-proBNP groups with a threshold value of 450 pg/ml*

***Таблица 11.** Показатели инструментальных обследований в группах Nt-proBNP с пороговым значением 450 пг/мл*

The concentration of all studies biomarkers demonstrated no significant differences in the Nt-proBNP groups. These data confirm, yet again, the high diagnostic value of the Nt-proBNP level providing to the researcher some unique highly selective information about the pathological process of CHF development that finds no specific reflection in no other biochemical parameters of the blood. The exception was the calculated parameter IS_GFR (p=0.023), the original diagnostic parameter developed in the Department of Endocrinology and Geriatrics of SamSMU, that allows for a quantitative characteristics of the rate of progression of CKD in diabetes. Our earlier research provided a detailed clinical justification of the predictive value of IS_GFR exceeding the threshold value of 3.83 mL/min/1.73 m² per year as a new biomarker of adverse outcome in elderly patients with T2DM[1]. The control analysis of the paired contingency table confirmed the established correlation of the IS_GFR groups with the threshold value of 3.83 mL/min/1.73 m² and Nt-proBNP groups with the threshold value of 450 pg/mL with a high level of significance (Fisher's exact test value was 0.018).

Most interesting is the analysis of average values of EchoCG in the Nt-proBNP groups (**Table 11**).

The key EchoCG indicators of CHF demonstrated a monotonous line of values with no significant differences in the Nt-proBNP groups. At the same time, the correlation analysis identified a highly significant correlation of the diastolic function of the myocardium, i.e. ratio of velocities of transmitral flow in the early and late diastole E/A (r=0.309; p=0.003) with a complete absence of correlation with ejection fraction (r=-0.031; p=0.784). One may suggest that the data stem from a specific CHF phenotype with preserved ejection fraction and predominantly restrictive damage of the myocardium, characteristic of T2DM [20] and obese patients [21]. In a recent study [22], an attempt was made to identify independent EchoCG indicators to establish a prognosis for CHF patients with preserved ejection fraction. The authors make it a point that such indicators are only the global longitudinal strain of the left ventricle and the ratio of the systolic excursion of the ring of the triscupid valve and the systolic pressure in the pulmonary artery. In any case, the obtained data emphasize the necessity of studying and clarifying the changes in the EchoCG parameters specific for elderly T2DM patients, and of a wider use of up-to-date methods of instrumental confirmation of CHF (tissue Doppler velocimetry with E/e' ratio measurement, assessment of systolic pressure in the pulmonary artery, LV global longitudinal strain, LA index), the indications for which may be provided by the Nt-proBNP semi-quantitative test.

Brugs	Group A M±SD	Group B M±SD	P
Insulin	15 (78,9)	25 (80,6)	0,884
Sulphonylurea	6 (31,6)	12 (38,7)	0,610
Biguanides	13 (68,4)	16 (51,6)	0,242
DPP4i	2 (10,5)	4 (12,9)	0,802
Gliflozins	12 (63,2)	15 (48,4)	0,309
Monotherapy	5 (26,3)	2 (6,5)	0,049*
Two drugs in tablets	8 (42,1)	13 (41,9)	0,991
Three drugs in tablets and more	4 (21,1)	6 (19,3)	0,884

*Note: p – significance of differences, * – p<0.05*
*Примечания: p – значимость различий; * – p<0,05.*

***Table 12.** Structure of hypoglycemic therapy in Nt-proBNP groups with a threshold value of 450 pg/ml*

***Таблица 12.** Структура гипогликемической терапии в группах Nt-proBNP с пороговым значением 450 пг/мл*

One of the most important factors determining the dynamics of CHF progression is the timely prescription of a complex multi-component pharmacological therapy. In this study, we evaluated the structure of hypoglycemic drugs in groups of various levels of NT-proBNP, determined frequency of their prescription by pharmacological classes, and significance of differences in the segregated groups (**Table 12**).

Significant differences between the Nt-proBNP groups were observed only for the frequency of monotherapy prescription, which is primarily used in the early stages of DM. It is reasonable to assume that such patients are less prone to developing macrovascular complications and, even more so, clinically manifest CHF. This likely explains why the relative proportion of patients receiving

[1] Первышин Н.А. Способ прогнозирования риска высокого темпа прогрессирования хронической болезни почек у пациентов пожилого возраста при сопутствующем сахарном диабете 2 типа. Патент на изобретение № 2825048. Доступно по: https://www.fips.ru/cdfi/fips.dll/ru?ty=29&docid=2825048

a single glucose-lowering drug is higher in Group A compared to patients exceeding the 450 pg/mL threshold.

Limitations of study. The present study was designed as a phase analysis, and its clinical interpretability was limited by the insufficient sample size. The application of more advanced medical statistics methods, particularly logistic regression, requires a more extensive primary dataset and additional participant enrollment, which is currently underway.

CONCLUSIONS

1. In three out of four elderly comorbid patients with T2DM, the level of Nt-proBNP was found to be higher than the general population threshold value, which necessitates further verification and clarification of the CHF stage in such patients.

2. All elderly comorbid patients with T2DM, previously diagnosed with CHF in earlier stages of outpatient monitoring, demonstrated an elevation of the Nt-proBNP level above 125 pg/mL, which allows to conclude that the sensitivity of the semi-quantitative Nt-proBNP test is 100%.

3. The application of the semi-quantitative Nt-proBNP test in elderly T2DM patients has its proper specifics stemming from the polymorbid pathology and presence of competing contributing factors, i.e. BMI, GFR, age.

4. Insufficient specificity of the semi-quantitative Nt-proBNP test in elderly T2DM patients may be accounted for by low detection of early-stage CHF in T2DM, and availability of concomitant diseases (obesity and CKD).

5. When planning outpatient management of elderly comorbid patients with T2DM and concomitant arterial hypertension, it is to be taken into account that Nt-proBNP screening is indicated for this group. Its positive result is an indication for a detailed echocardiographic examination.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethics approval: Protocol LEC of the SamSMU No. 269 of September 13, 2023.	***Этическая экспертиза.*** Протокол ЛЭК СамГМУ №269 от 13 сентября 2023 г.
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. N.A. Pervyshin: study design, criteria for matching participants, statistical processing of clinical material, writing of the text. S.V. Bulgakova: organization of research, editing. O.A. Shtegman: clinical interpretation of the results, editing of the text. V.N. Vasilkova, L.A. Sharonova: clinical interpretation of results. 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.*** Н.А. Первышин – дизайн исследования, критерии соответствия участников, статистическая обработка клинического материала, написание текста. С.В. Булгакова – организация исследования, редактирование рукописи. О.А. Штегман – клиническая интерпретация результатов, редактирование текста. О.Н. Василькова, Л.А. Шаронова – клиническая 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.
Statement of originality. No previously published material (text, images, or data) was used in this work.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	***Доступ к данным.*** Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	***Генеративный искусственный интеллект.*** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	***Рассмотрение и рецензирование.*** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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Role of the plasma level of plasminogen activator inhibitor type-1 (PAI-1) and genetic polymorphism of *PAI-1* gene in patients with ischemic heart disease in Uzbek population

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Abstract

Aim – to study the distribution of allele frequencies of the polymorphic marker 4G(-675)5G of the *PAI-1* gene among patients with coronary heart disease and individuals with risk factors for the development of coronary heart disease.

Material and methods. The study included 63 patients with diagnosed coronary heart disease, especially with stable angina (48 men and 15 women) hospitalized in the 1st Cardiology Department of the Multidisciplinary Clinic of the Tashkent Medical Academy. The average age of patients was 56.8±6.40 years (42-66 years old). The state of hypercoagulability was assessed by measures of polymorphism gene of *PAI-1* and plasma level of PAI-1.

Results. The assessment of the frequency of various variants of the 4G(-675)5G polymorphic marker of the *PAI-1* gene showed that differences in the distribution of the 5G/5G, 4G/5G, 4G/4G genotypes depending on the functional class of coronary artery disease are not statistically significant, since the chi-square test value was χ^2=1.85 (p>0.05). Based on the obtained results, it can be assumed that the presence of hetero- and homozygous variants of the 4G allele of the *PAI-1* gene does not affect the severity of the disease, in particular, the functional class of stable angina.

Conclusion. The 4G/5G polymorphism of the *PAI-1* gene was significantly associated with the risk of coronary heart disease in the Uzbek population. When stratified by angina functional class, the results showed that the 4G/5G polymorphism is associated with an increased risk of coronary heart disease and higher plasma PAI-1 levels.

Keywords: ischemic heart disease, plasminogen activator inhibitor, genetic polymorphism, hypercoagulation, risk factors.

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Роль уровня ингибитора активатора плазминогена-1 (PAI-1) в плазме и генетического полиморфизма гена *PAI-1* у пациентов с ишемической болезнью сердца узбекской популяции

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Аннотация

Цель – изучение распределения частот аллелей полиморфного маркера 4G(-675)5G гена *PAI-1* среди пациентов с ишемической болезнью сердца (ИБС) и лиц с факторами риска развития ИБС.

Материал и методы. В исследование было включено 63 пациента с диагнозом «ишемическая болезнь сердца» (ИБС), а именно со стабильной стенокардией (48 мужчин и 15 женщин), госпитализированных в первое

кардиологическое отделение многопрофильной клиники Ташкентской медицинской академии. Средний возраст пациентов составил 56,8±6,40 года (от 42 до 66 лет). Состояние гиперкоагуляции устанавливалось по анализу полиморфизма гена *PAI-1* и уровню PAI-1 в плазме крови.
Результаты. Оценка встречаемости различных вариантов полиморфного маркера 4G(-675)5G гена *PAI-1* показала, что различия в распределении генотипов 5G/5G, 4G/5G, 4G/4G в зависимости от функционального класса ИБС не являются статистически значимыми, поскольку значение критерия хи-квадрат составило χ^2=1,85 (p>0,05). На основании полученных результатов можно предположить, что наличие гетеро- и гомозиготных вариантов аллеля 4G гена *PAI-1* не влияет на тяжесть заболевания, в частности на функциональный класс стабильной стенокардии.
Выводы. Полиморфизм 4G/5G гена *PAI-1* был достоверно ассоциирован с риском ишемической болезни сердца в узбекской популяции. При стратификации по функциональному классу стенокардии результаты показали, что полиморфизм 4G/5G связан с повышенным риском ИБС и более высокими уровнями PAI-1 в плазме.
Ключевые слова: ишемическая болезнь сердца, ингибитор активатора плазминогена, генетический полиморфизм, гиперкоагуляция, факторы риска.
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ССЗ – сердечно-сосудистое заболевание; ИБС – ишемическая болезнь сердца; ФК – функциональный класс; СС – стабильная стенокардия; ИМ – инфаркт миокарда; ТДР – тревожно-депрессивное расстройство; ГХС – гиперхолестеринемия.

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INTRODUCTION

According to a 2022 report from the State Statistics Committee of the Republic of Uzbekistan, the total number of deaths between January and December was 172,100. Among these, diseases of the circulatory system accounted for 55.5% of all registered mortality (source: State Statistics Committee of the Republic of Uzbekistan, 2022). Young survivors of arterial thrombotic events face higher mortality and morbidity rates compared to the general population, primarily due to an elevated risk of cardiovascular recurrences [1,2]. These findings emphasize the urgent need for novel diagnostic and therapeutic strategies for cardiovascular disease. This is particularly critical for younger patients, as the impact on their quality of life and the resulting socioeconomic burden are magnified by their longer life expectancy.

It is commonly known that hypercoagulability is a significant risk factor for myocardial ischemia. While hypercoagulability increases the risk of arterial thrombosis, the magnitude of this effect may vary across different clinical manifestations of arterial disease [3]. Platelets play a pivotal role in thrombus formation and propagation, making them the primary target of antithrombotic therapy in arterial disease [4]. Nevertheless, arterial thrombus formation is also driven by the activation of the plasma coagulation cascade [5].

Fibrinolysis is a process governed by the complex interplay of various plasminogen activators and inhibitors, forming an enzymatic cascade that ultimately leads to fibrin degradation. The plasminogen activator system is pivotal in numerous physiological and pathological contexts. Plasminogen activator inhibitor-1 (PAI-1), a member of the serine protease inhibitor (serpin) superfamily, is the primary physiological inhibitor of both tissue-type (tPA) and urokinase-type (uPA) plasminogen activators, the enzymes responsible for converting plasminogen into its active form, plasmin [6]. Plasminogen is mainly found in the plasma and is synthesized predominantly in the liver. Its conversion into plasmin is facilitated by two main activators: the urokinase-type plasminogen activator (uPA) and the tissue-type plasminogen activator (tPA). The actions of these activators are tightly controlled by specific plasminogen activator inhibitors (PAIs), the most important one being plasminogen activator inhibitor type 1 (PAI-1), initially characterized as the endothelial cell-derived inhibitor [7]. Elevated PAI-1 expression in vivo inhibits fibrinolysis, leading to abnormal fibrin deposition and subsequent tissue injury [8]. PAI-1 levels are influenced by several factors, including age, renal insufficiency, systolic blood pressure, insulin resistance, obesity, and triglyceride levels, but show no association with cholesterol levels or smoking [8]. Both PAI-1 and TPA antigen levels are predictive of cardiovascular disease (CVD) events, even after adjustment for established risk factors. Furthermore, a serial increase in PAI-1 is associated with a progressively higher risk. These findings underscore the importance of the fibrinolytic system in the pathogenesis of CVD.

Additionally, there is evidence that PAI-1 plasma concentration is influenced by genetic variation. Several genetic polymorphisms have been identified at the *PAI-1* gene locus on chromosome 7 [10, 11]. Among these, a guanine insertion/deletion polymorphism known as −675 4G/5G, located in the promoter region, has been reported in numerous studies to be associated with PAI-1 plasma levels [12]. Of the known polymorphic sites in the *PAI-1* gene region, only the −675 4G/5G insertion/deletion polymorphism is suspected of having functional significance [13,14]. This polymorphism is considered an independent risk factor for ischemic heart disease and/or acute myocardial infarction (MI). A large cohort study (n=1179) demonstrated that the 4G/4G genotype is more common in first-degree relatives of patients with

Drug name	Patients, n=63
Acetylsalicylic acid 75 mg 100 mg	 8 (12,6%) 17 (26,9%)
Clopidogrel, 75 mg	38 (60,3%)
ACE inhibitors	19 (45,2%)
Angiotensin-II receptor blockers	12 (28,5%)
Beta-blockers	35 (55,5%)
Calcium channel blockers	38 (60,3%)
Statins	28 (44,4%)
Diuretics	17 (26,9%)
Nitrates	14 (22,2%)

Table 1. *Drug therapy of patients included in the study*
Таблица 1. *Фармакологическая терапия включенных в исследование пациентов*

coronary heart disease than in individuals without a family history of the condition [15].

The strength of this association may vary significantly across populations, and some ethnic groups may show a weak or absent link. This variability is likely due to the complex interaction of population-specific genetic and environmental factors.

The relationship between the PAI-1 4G/5G polymorphism and traditional ischemic heart disease risk factors in patients with stable coronary artery disease remains a subject of ongoing research. Al-Wakeel et al. found no significant association between the PAI-1 4G/5G polymorphism and coronary artery disease risk in an Egyptian population [16].

AIM

To study the distribution of allele frequencies of the polymorphic marker 4G(-675)5G of the PAI-1 gene among patients with coronary heart disease and individuals with risk factors for the development of coronary heart disease.

MATERIAL AND METHODS

Our study included 63 patients diagnosed with ischemic heart disease, specifically stable angina, who were hospitalized in the I Cardiology Department of the Multidisciplinary Clinic of Tashkent Medical Academy. The patient group consisted of 48 men and 15 women, with a mean age of 56.8 ± 6.40 years (range 42-66 years). The mean age was 56.4 ± 6.60 years for men and 58.0 ± 5.52 years for women. The control group comprised 65 apparently healthy individuals.

The diagnosis of stable angina was established according to the ischemic heart disease classification adopted at the IV Congress of Cardiologists (2000). The functional class (FC) of stable angina was determined using the Canadian Cardiovascular Society classification and exercise stress testing (bicycle ergometry).

Exclusion criteria: unstable angina, acute or chronic heart, kidney or liver failure, arrhythmia, acute cerebrovascular accident, diabetes mellitus associated myocardial infarction, malignant neoplasia.

To address the study objectives, all patients were divided into two groups based on the functional class of stable angina. The first group included 24 patients (38.1%) with FC II stable angina, while the second group consisted of 39 patients (61.9%) with FC III stable angina.

Hypercoagulability was assessed by measuring the *PAI-1* gene polymorphism and plasma PAI-1 levels. Venous blood samples (3 mL) were collected from the cubital vein for genetic analysis. DNA analysis of the *PAI-1* gene (4G/5G) was performed using multiplex PCR on CG-1-96 ("Corbett Research", Australia) and 2720 ("Applied Biosystems", USA) thermal cyclers with reagent kits from "Geno Technology" according to the manufacturer's protocol. Plasma PAI-1 levels were measured using ELISA with commercially available kits.

Additionally, our study evaluated major IHD risk factors including obesity, smoking, and anxiety-depressive disorder (ADD). Obesity was assessed using Quetelet's index. Smoking status was evaluated with the Fagerström test, while anxiety-depressive disorder was measured using the Hospital Anxiety and Depression Scale (HADS). The patients included in the study received pharmacological therapy (**Table 1**).

RESULTS

This study is the first to examine the frequency distribution of PAI-1 gene genotypes and their association with major IHD risk factors in Uzbek patients with stable angina. Patients of Uzbek nationality with stable angina were selected to identify additional prognostic criteria. To clarify the pathogenetic significance of *PAI-1* gene polymorphism across different functional classes of stable angina, PCR analysis of the PAI-1 gene was performed in the study population.

During genotyping of 63 IHD patients with stable angina, 2 patients (3.3%) were excluded from the study due to blood storage errors. The resulting data on allele and genotype frequencies of the PAI-1 4G/5G polymorphism in the specified stable angina groups are presented in **Tables 2-3**.

The population distribution of *PAI-1* gene alleles was investigated in 61 IHD patients (122 chromosomes). The frequency of the 4G allele in this group was 45.1% (n=55). We identified 13 homozygous and 29 heterozygous carriers of this allele. The frequency of the 5G allele in the main patient group was 54.9% (n=67). This allele in homozygous state was found in 19 individuals. The distribution patterns of *PAI-1* gene allele genotypes in IHD patients are visualized on the PCR product electrophoregram and presented in **Figure 1**.

Group	N	Allele frequency				Genotype distribution frequency					
		5G		4G		5G/5G		G5/G4		4G/4G	
		N	%	N	%	N	%	N	%	N	%
Main group (n=61)	61	67	54,9	55	45,1	19	31,1	29	47,5	13	21,3

Table 2. *Frequency of distribution of alleles and genotypes of G5/G4 polymorphism of PAI gene in group of patients with IHD and healthy individuals*
Таблица 2. *Частота распределения аллелей и генотипов полиморфизма G5/G4 гена PAI в группе пациентов с ИБС и здоровых пациентов*

Group	Genotype frequency distribution			Total	χ^2	P
	5G/5G	G5/G4	4G/4G			
Main group (n=61)	19	29	13	n=61	7,00	0,03
Expected frequency (n=61)	25,66	26,14	9,2			
Control group (n=65)	34	25	6	n=65		
Expected frequency (n=65)	27,34	27,86	9,8			
Total	53	54	19	n=126		

Notes: χ^2 = AMOUNT (observed - expected)2/ expected = ((19-25,66)2/25,66)+((29-26,14)2/26,14)+((13-9,2)2/9,2)+((34-27,34)2/27,34)+ ((25-27,86)2/27,86)+((6-9,8)2/9,8)=7,00.
Degree of freedom (df)=(number of columns-1)(Number of lines-1)=(3-1)*(2-1)=2*
Our indicator is in the area p<0.05, calculated with the help of Microsoft Excel p=0.03.

***Table 3.** Distribution of frequencies of genotypes under Hardy-Weinberg's law. Expected and observed frequencies of distribution of genotypes in the main and control groups*

Примечания: χ^2 = AMOUNT (набл. – ожид.)2 / ожид. = ((19-25,66)2/25,66)+((29-26,14)2/26,14)+((13-9,2)2/9,2)+((34-27,34)2/27,34)+((25-27,86)2/27,86)+ ((6-9,8)2/9,8)=7,00.
*Степень свободы (df) = (кол-во столбцов - 1) * (Кол-во строк - 1) = (3-1)*(2-1)=2*
Показатель находится в зоне p<0,05, рассчитан с помощью Microsoft Excel, p=0.03.

***Таблица 3.** Распределение частот генотипов в соответствии с законом Харди – Вайнберга. Наблюдаемые и ожидаемые частоты генотипов в основной и контрольной группах*

For this polymorphism in patients with stable angina and conditionally healthy donors, the observed genotype distribution corresponded to theoretical expectations and showed relatively high observed (Hobs) and expected (Hexp) heterozygosity under Hardy-Weinberg equilibrium (p<0.05). Based on the Chi-square statistic (χ^2=7.00), statistically significant differences in the distribution of genotypes 5G/5G, 5G/4G, and 4G/4G were established between patients in the main group and probands in the control group (p<0.05).

Genetic analysis of Uzbek individuals revealed that the 4G allele of the *PAI-1* gene occurs more frequently in IHD patients than in healthy controls. The homozygous and heterozygous states of this allele were observed in 21.3% and 47.5% of patients respectively, compared to 9.2% and 38.5% in the control group. These findings indicate the potential influence of the PAI-1 4G allele, particularly in heterozygous state, on IHD development.

The 5G/5G genotype, considered favorable, was reliably more frequent in the group of healthy controls: in 34 individuals (52.3%) vs. 19 patients (31.1%) in the IHD group. Thus, the identified differences are statistically significant and are not random (p<0.05).

The distribution of the frequencies of the polymorph marker 4G(-675)5G of the *PAI-1* gene in the IHD patient groups depending on the stable angina functional class is presented in **Table 4**.

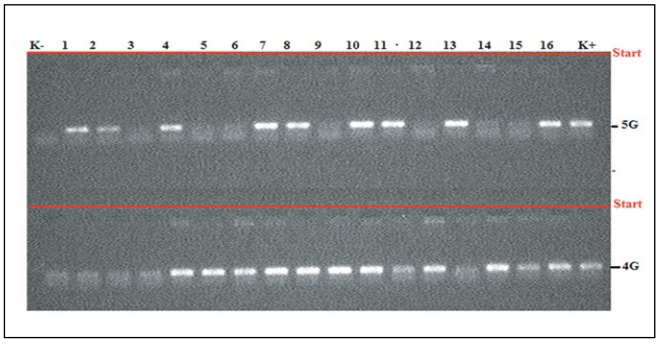

***Figure 1.** Electrophoregram of PCR products of G5/G4 polymorphism of PAI gene.*

***Рисунок 1.** Электрофореграмма продуктов ПЦР полиморфизма G5/G4 гена PAI.*

Analysis of IHD patient subgroups stratified by functional class revealed differences in allele and genotype frequency distribution of the 4G(-675)5G polymorphism of the *PAI-1* gene (rs1799768). Among 24 patients with FC II stable angina, genotype distribution was as follows: 4G/4G – 4 patients (16.7%), 4G/5G – 14 patients (58.3%), and 5G/5G – 6 patients (25.0%). In contrast, among 37 patients with FC III stable angina, the distribution was as follows: 4G/4G – 9 patients (24.3%), 4G/5G – 15 patients (40.5%), and 5G/5G – 13 patients (35.1%).

Assessment of genotype distribution for the 4G(-675)5G polymorphism in the PAI-1 gene established that differences in 5G/5G, 4G/5G, and 4G/4G genotype distribution across cardiovascular disease functional classes were not statistically significant (χ^2=1.85, p>0.05). These results suggest that the presence of heterozygous and homozygous 4G alleles of the PAI-1 gene does not influence disease severity as measured by stable angina functional class.

When genotyping the studied groups for the frequency of the favorable homozygous 5G/5G genotype of the *PAI-1* gene, a low frequency of this genotype was recorded in the group of patients with CVD at 31.1% of cases, compared to a statistically significant higher occurrence of the 5G/5G genotype at 52.3% of cases among healthy individuals. The occurrence of the heterozygous polymorphic genotype 4G/5G of the PAI-1 gene in patients with CVD was statistically significantly higher at 47.5% of cases compared to 38.5% in the control group (p<0.05), indicating the probability of high prevalence of this genotype among persons of Uzbek nationality.

Correlation of IHD risk factors and PAI-1 gene polymorphism

This study is the first to examine the frequency of mutagen genotypes of the *PAI-1* gene and to clarify their association with major IHD risk factors in cardiovascular disease development.

No clear indications of synergistic interaction effects were observed between the PAI-1 4G/5G polymorphism and the environmental exposures considered (smoking, physical inactivity, overweight, diabetes mellitus,

Group	PAI-1 gene, identified genotypes, n (%)			Total
	5G/5G	4G/5G	4G/4G	
Stable angina, II FC	6 (25%)	14 (58,3%)	4 (16,7%)	24 (39,4%)
Stable angina, III FC	13 (35,1%)	15 (40,5%)	9 (24,3%)	37 (60,6%)

Table 4. *Distribution of frequencies of genotypes of a polymorphic marker 4G(-675)5G of PAI-1 gene in the main group*

Таблица 4. *Распределение частот генотипов полиморфного маркера 4G(-675)5G гена PAI-1 в основной группе*

Group	PAI-1, gene, identified genotypes, N			Total	χ^2	P
	5G/5G	4G/5G	4G/4G			
Stable angina, II FC	6	14	4	n=24	1,85	0,39
Expected frequency	7,48	11,41	5,11			
Stable angina, III FC	13	15	9	n=37		
Expected frequency	11,52	17,59	7,89			
Total	19	29	13	n=61		

Notes: χ^2 =AMOUNT (observed - expected)2/observed = 1,85. Degree of freedom (df)=(Number of columns-1)(Number of lines-1)=(3-1)*(2-1)=2. On the p<0.05 significance level, with 2nd degree of freedom, the number in the table must be equal to 5,99. But we have 1,85. Our indicatorpis in the areap>0.05, calculated in calculations with the help of Microsoft Excel p=0.39.*

Table 5. *Distribution of frequencies of genotypes of a polymorphic marker 4G(-675)5G of PAI-1 gene in subgroups of IHD patients*

Примечания: χ^2 =AMOUNT (набл. – ожид.)2/ожид. = 1,85. Степень свободы (df)=(кол-во столбцов-1)(кол-во строк - 1)=(3-1)*(2-1)=2. При уровне значимости p<0,05 со II степенью свободы табличное значение должно быть равным 5,99. В нашем случае данная величина равна 1,85. Показатель находится в зоне p>0,05, рассчитан с помощью Microsoft Excel, p=0,39.*

Таблица 5. *Частота распределения генотипов полиморфного маркера 4G(-675)5G гена PAI-1 в подгруппах пациентов с ИБС*

hypercholesterolemia, hypertension, elevated C-reactive protein, and hypertriglyceridemia) [17].

Given the multifactorial nature of IHD pathogenesis, i.e., the presence of multiple risk factors leading to disease development and progression, we analyzed the association of the 4G(-675)5G polymorphism of the *PAI-1* gene with clinical and anamnestic data such as smoking, concomitant arterial hypertension, obesity, hypercholesterolemia, and hypodynamia in the studied groups. The analysis of genotyping for favorable (5G/5G), polymorphic (4G/5G), and mutagen (4G/4G) genotypes of the *PAI-1* gene depending on the presence of various IHD risk factors is presented in **Table 6**.

The analysis of the relationship between non-modified and modified risk factors with 5G/5G, 4G/5G and 4G/4G genotypes of the *PAI-1* gene established that genotyping between groups did not differ significantly by age, while hereditary burden for IHD was more frequently observed in heterozygous polymorphic genotype (61.5%) and also in homozygous 4G/4G genotype (65.5%) of IHD patients. Among patients of the main group with 4G/4G genotype, obesity of varying degrees was recorded in 46.2% of cases, with 4G/5G genotype in 37.9%, and with 5G/5G in 26.3%, therefore more frequently in patients with SA with obesity including third degree, the 4G/4G genotype was identified.

The association of the 4G/4G genotype with smoking was among the most significant findings: among patients with

Parameter	IHD patients (n=61)		
	4G/4G genotype n=13 (21,3)	4G/5G genotype n=29 (47,5)	5G/5G genotype n=19 (31,1)
Age, years	59,4	56,7	57,6
Hereditary burden	8 (61,5)	19 (65,5)	9 (47,4)
Obesity degree (kg/m2): Normal BMI Excess weight 1 degree 2 degree 3 degree	 1 (7,6) 6 (46,2) 4 (31) 1 (7,6) 1 (7,6)	 3 (10,3) 15 (51,7) 5 (17,2) 6 (20,7) 0	 5 (26,3) 9 (47,4) 3 (15,8) 2 (10,5) 0
Smoking, n (%)	8 (61,5)*	9 (31,0)	5 (26,3)
Arterial hypertension, n (%) Subclinical manifestations Arterial hypertension, n (%), Clinical manifestations	 3 (23,1) 9 (69,3)	 7 (24,1) 21 (72,4)	 2 (10,5) 12 (63,1)
Hypercholesterolemia	11 (84,6)*	18 (62,1)	9 (47,4)

Notes: P<0.001.

Table 6. *The characteristic of RF at patients with different genotypes of a polymorphic marker 4G(-675)5G of gene PAI-1*

Примечания: P<0.001.

Таблица 6. *Характеристика факторов риска у пациентов с различными генотипами полиморфного маркера 4G(-675)5G гена PAI-1*

the heterozygous genotype, smokers accounted for 61.5% of cases, compared to 31% and 26.3% of smokers among patients with the 4G/4G genotype and homozygous wild-type 5G/5G genotype, respectively. The presence and severity of concomitant arterial hypertension in the main patient group were highest in individuals with the 4G/4G genotype (92.4%) and 4G/5G genotype (96.5%), while among patients with the 5G/5G genotype, arterial hypertension was detected less frequently in 73.6% of cases. Additionally, we measured plasma PAI-1 levels and obtained the following results (**Table 7**).

The mean PAI-1 level in patients with the 5G/5G genotype was 33.3 ± 2.07 ng/mL, while in those with the 4G/4G genotype it was 72.0 ± 7.6 ng/mL, a statistically significant difference (P < 0.001). Plasma PAI-1 levels were significantly higher in patients with FC III stable angina compared to those with FC II. All patient groups were comparable in age, lipid profile, and coagulogram parameters. Furthermore, patients carrying the 4G/4G genotype with FC III stable angina demonstrate an increased risk of elevated PAI-1 levels.

DISCUSSION

Cardiovascular disease involving disturbances in the haemostatic system may lead to thrombotic complications with clinical manifestations such as acute myocardial infarction (AMI) and stroke [18]. Some individuals demonstrate an

Group	PAI-1 gene, identified genotypes		
	5G/5G	4G/5G	4G/4G
PAI-1 level in stable angina patients (ng/mL)	33,3±2,07*	54,8±3,47	72,0±7,6*

*Примечания: *P<0,001.*

Table 7. *Plasma level of PAI-1 depending of genotypes of PAI-1 gene in patients with ischemic heart disease*

Таблица 7. *Уровень PAI-1 в плазме в зависимости от полиморфизма гена PAI-1 у пациентов с ИБС*

*Notes: *P<0.001.*

abnormal propensity to develop venous or arterial thrombosis, experiencing thromboembolic events relatively early in life or suffering recurrent events [19]. Based on these findings, we aimed to investigate hemostasis system alterations at the genetic level in patients with stable coronary artery disease. While well-defined associations have been established between hypercoagulable states and thrombosis in the venous system, determining causative or contributing roles of these same thrombophilic conditions in arterial thrombosis has proven considerably more challenging [20].

Our findings suggest that increased coagulation tendency, associated with high plasma PAI-1 levels and polymorphic genotypes of the *PAI-1* gene (particularly 4G/4G), elevates the risk of cardiovascular events in patients with stable ischemic heart disease. The coagulation assessment included fibrinolytic markers of hypercoagulability, weighted by acute myocardial ischemia risk, as these markers proved primary in stable coronary heart disease where hypercoagulability plays a major role. Several studies have identified PAI-1 as an informative marker for assessing hypercoagulability in acute coronary syndrome patients. The first study demonstrating association between the PAI-1 4G allele and higher myocardial infarction risk in 100 young Swedish men (35-45 years) was published in 1995 [21]. Individuals homozygous for the 4G allele exhibit higher plasma PAI-1 levels than those homozygous for the 5G allele. The molecular mechanism underlying these allelic differences in PAI-1 synthesis was determined by examining allele binding capacity: both alleles bind to gene transcription activators, but the 5G allele additionally contains a binding site for a transcriptional repressor [21]. Various studies report approximately 25% higher PAI-1 levels in 4G/4G genotype carriers compared to 5G/5G carriers. Compared to the 5G allele, 4G allele carriers demonstrate higher PAI-1 concentrations and thrombosis risk. Both heterozygous and homozygous 4G allele carriers show elevated plasma PAI-1 levels [22] and increased risk of acute coronary syndromes [23].

Several studies have demonstrated the relationship between plasminogen activator inhibitor-1 levels and both stable and unstable coronary artery disease [23, 24]. In patients with myocardial infarction, a clear association exists between PAI-1 levels and response to fibrinolytic therapy, as confirmed by multiple studies [25]. However, data remain limited regarding the association between stable ischemic heart disease and both PAI-1 levels and its polymorphisms. In our study, no differences were observed between groups in terms of age or gender. Plasma PAI-1 levels and 4G/4G genotype frequency were significantly elevated, particularly in patients with FC III stable angina compared to FC II. Furthermore, patients with the 4G/4G genotype showed significantly higher plasma PAI-1 levels than those with the 5G/5G genotype [26]. A 2022 meta-analysis indicated that the PAI-1 4G>5G SNP was associated with decreased IHD risk in the overall population and in Asian, Caucasian, and Arab subgroups. In contrast, the PAI-1 gene -844 G>A polymorphism demonstrated no significant association with IHD susceptibility [27].

Our genetic analysis revealed that individuals with the 4G/4G genotype exhibit elevated plasma concentrations of PAI-1. This finding aligns with in vitro studies demonstrating that the 4G allele is associated with enhanced transcriptional activity of the PAI-1 promoter compared to the 5G allele, which creates an additional repressor-binding site in 5G carriers [28].

This finding holds clinical significance, as fibrinolysis plays a crucial role in the pathogenesis of both acute myocardial infarction and stable coronary artery disease.

CONCLUSION

The 4G/5G polymorphism of the *PAI-1* gene was significantly associated with the risk of coronary heart disease in the Uzbek population. When stratified by stable angina functional class, the results showed that the 4G/5G polymorphism is associated with an increased risk of ischemic heart disease and higher plasma PAI-1 levels.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethics approval: The study was approved by the LEC of TMA (protocol No.85 dated 27.05.2020).	***Этическая экспертиза.*** Проведение исследования одобрено ЛЭК Ташкентской медицинской академии (протокол №85 от 27 мая 2020 г.).
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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Kadirova N.A.: study design and concept, data collection; statistical analysis; wring of the manuscript; Nurillaeva N.M.: study concept, design and supervision. Petrova V.B., Lapteva E.S., Shumkov V.A.: review and editing. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Кадирова Н.А. – разработка концепции и дизайна исследования, сбор данных; проведение статистического анализа; написание текста. Нуриллаева Н.М. – руководство, разработка концепции и дизайна исследования. Петрова В.Б., Лаптева Е.С., Шумков В.А. – рецензирование и редактирование. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
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Original study article | Оригинальное исследование
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Gender and age effects on coronary calcium index in patients with suspected CHD

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Abstract

Aim – to assess the influence of sex and age on the coronary artery calcium (CAC) score in patients with suspected coronary heart disease (CHD).

Material and methods. A prospective, observational, single-center study was conducted. The study included 733 patients (mean age 67 [58; 73] years, 43.37% male) with suspected CHD who underwent multi-slice computed tomography (MSCT) of the coronary arteries with CAC scoring (using the Agatston method), as well as a biochemical blood test assessing lipid profile, glucose level, creatinine level, and estimated glomerular filtration rate (eGFR). An analysis of baseline clinical and laboratory parameters and the distribution of CAC scores according to patient age and sex was performed. Statistical analysis was performed using SPSS Statistics 21.0, employing the Shapiro-Wilk test, Student's t-test, and ANOVA.

Results. It was found that CAC scores increased with advancing age, and men had significantly higher CAC scores than women of the same age category. In the group of patients with higher CAC scores, older men were more prevalent, and there were higher creatinine levels and a higher incidence of atrial fibrillation. The correlation analysis revealed moderate and strong associations between CAC scores and parameters of lipid metabolism, as well as eGFR.

Conclusion. The assessment of CAC scores, taking into account sex and age, improves the accuracy of cardiovascular risk stratification in patients with suspected CHD. The implementation of this approach into clinical practice helps optimize preventive and therapeutic strategies for reducing cardiovascular morbidity and mortality.

Keywords: coronary calcium, sex, dyslipidemia, risk factors, coronary artery disease, MSCT, calcium score.

Conflict of interest: nothing to disclose.

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Влияние пола и возраста на индекс коронарного кальция у пациентов с подозрением на ИБС

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Аннотация

Цель – оценить влияние пола и возраста на индекс коронарного кальция (ИКК) у пациентов с подозрением на ишемическую болезнь сердца (ИБС).

Материал и методы. Проведено проспективное наблюдательное одноцентровое исследование. В исследование включено 733 пациента (средний возраст 67 (58; 73) лет, из которых мужчин 43,37%, с подозрением на ИБС, проходивших мультиспиральную компьютерную томографию (МСКТ) коронарных артерий с определением ИКК (по методу Agatston), а также биохимическое исследование крови с оценкой липидного профиля, уровня глюкозы, креатинина и расчетом скорости клубочковой фильтрации. Был проведен анализ исходных клинико-лабораторных параметров и распределения ИКК в зависимости от возраста и пола пациентов. Статистическую обработку данных выполняли с использованием SPSS Statistics 21.0, применяли критерии Шапиро – Уилка, Стьюдента, ANOVA.

Результаты. Установлено, что с увеличением возраста пациентов возрастает значение ИКК, причем у мужчин ИКК значительно выше, чем у женщин той же возрастной категории. В группе пациентов с более

высокими значениями ИКК чаще встречались мужчины старших возрастных групп, наблюдались повышение уровня креатинина и фибрилляция предсердий. Проведенный корреляционный анализ выявил умеренную и высокую связи между ИКК и параметрами липидного обмена, а также скоростью клубочковой фильтрации.

Заключение. Оценка ИКК с учетом пола и возраста повышает точность стратификации риска сердечно-сосудистых осложнений у пациентов с подозрением на ИБС. Внедрение данного подхода в клиническую практику способствует оптимизации профилактических и лечебных стратегий снижения сердечно-сосудистой заболеваемости и смертности.

Ключевые слова: коронарный кальций, пол, дислипидемия, факторы риска, ишемическая болезнь сердца, МСКТ, кальциевый индекс.

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ССЗ – сердечно-сосудистое заболевание; ИБС – ишемическая болезнь сердца; ИКК – индекс коронарного кальция; МСКТ – мультиспиральная компьютерная томография; КА – коронарная артерия; АГ – артериальная гипертензия; ХБП – хроническая болезнь почек; СД – сахарный диабет; ФП – фибрилляция предсердий; ФК – функциональный класс; ОХ – общий холестерин; ТГ – триглицериды; ЛНП – липопротеины низкой плотности; ЛВП – липопротеины высокой плотности.

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INTRODUCTION

Cardiovascular diseases (CVD), including coronary heart disease (CHD), represent a major medical and socioeconomic challenge and remain the leading cause of mortality worldwide [1]. Despite significant progress achieved in recent years, the risk of adverse cardiovascular events remains high.

Recommendations of the European Society of Cardiology on treatment of the chronic coronary syndrome (2024) suggest the use of the multi-slice computed tomography (MSCT) of the coronary arteries with coronary artery calcium (CAC) scoring to re-stratify the risk of CHD [2, 3]. According to the national clinical recommendations (2024), in cases of suspected CHD it is also recommended to perform MSCT with CAC calculation as a method of assessment of CHD probability [4]. The final choice of diagnostic strategy is to be based on sensitivity, specificity and accuracy of methods of visualization in each clinical case [5, 6]. At the same time, the recommendations do not specify the age of patients for whom such strategy is to be used.

AIM

To assess the influence of sex and age on the coronary artery calcium (CAC) score in patients with suspected coronary heart disease (CHD).

MATERIAL AND METHODS

The prospective, observational, single-center study was conducted from January to December 2023. Inclusion criteria: age over 18; suspected CHD based on clinical data and/or results of stress test (bicycle ergometry); availability of consent for analysis. Exclusion criteria: permanent atrial fibrillation; an episode of atrial fibrillation at the time of the study; exacerbation of chronic hematologic, hepatic, renal, or autoimmune diseases; decompensated diabetes mellitus; pregnancy at any stage; body weight over 140 kg; allergic reactions to iodine and iodine-containing drugs.

MSCT of the coronary arteries was performed with pro- and retrospective ECG-synchronization and intravenous administration of non-ionic iodine-containing radiopaque agent on the RevolutionEVOGE scanner with 128 rows of detecting elements and detector width of 160 mm. In order to assess the degree of the coronary bed lesion, modified criteria of the American Heart Association were used; the CAC was assessed using the Agatston method by adding the scores of all identified areas of calcification [7].

All patients underwent biochemical blood assays with analysis of the following parameters: total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, and creatinine with subsequent calculation of glomerular filtration rate (GFR) using the CKD-EPI formula for individuals of Caucasian ethnicity.

Parameter	N=733
Male sex, %	43,37%
Mean age, years M [25; 75]	67 (58; 73)
AH, %	93,7
CKD, n/%	212/28,9
Stage 1	*109/14,9*
Stage 2	*76/10,4*
Stage 3a	*22/3,0*
Stage 3b	*5/0,7*
AF, %	12,4
DM, %	28,6
CHF, n/%	
FC I	*112/15,2*
FC II	*574/78,2*
FC III	*46/6,2*
FC IV	*1/0,1*
Smoking, %	11,8
TC, mmol/L	5,37±1,73
LDL, mmol/L	3,23±1,13
HDL, mmol/L	1,39±0,44
TG, mmol/L	1,68±1,14
Creatinine, μmol/L	133,45±29,85
Glucose, mmol/L	5,8±1,19
Hemoglobin, g/L	139,32±13,59

Table 1. *Initial clinical and laboratory characteristics of the patients*
Таблица 1. *Исходные клинико-лабораторные характеристики пациентов*

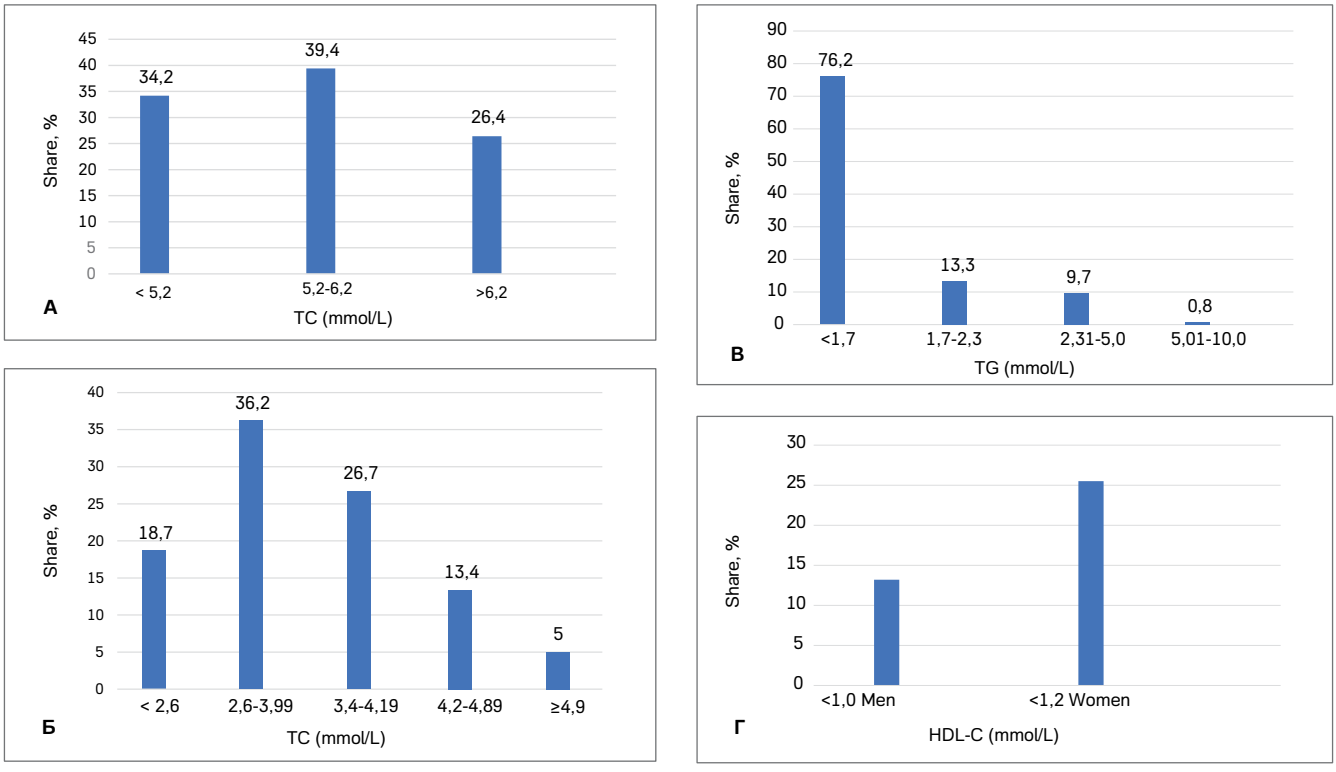

Figure 1. *Distribution of patients according to lipid profile parameters. A: total cholesterol (TC) Level; B: low-density lipoprotein cholesterol (LDL-C) level; C: triglyceride (TG) Level; D: proportion of patients with low high-density lipoprotein cholesterol (HDL-C) level.*

Рисунок 1. *Распределение пациентов по уровню показателей липидного спектра. А – по уровню ОХС; Б – по уровню ХС ЛНП; В – по уровню ТГ; Г – доля пациентов с низким уровнем ХС ЛВП.*

The obtained data was processed in SPSS Statistics 21.0. To test the normality of data distribution, Shapiro-Wilk test was used, and to test the significance of differences between groups, Student's t-test was used. To compare statistically significant differences in mean values between data groups, ANOVA was used. Differences were considered significant at $p < 0.05$.

RESULTS

The study consecutively included 733 patients (mean age: 67 (58; 73) years, 43.37% men) with suspected CHD based clinical data and/or results of stress test (bicycle ergometry). The initial data of all patients is shown in Table 1. Smoking status was determined as smoking at the time or long-term (5+ years) history of smoking. The average score on the Fagerström test was 6. Atrial fibrillation (AF) was determined as per history data and medical documents; at the moment of MSCT no paroxysms of AF were registered.

The presented patient cohort is characterized by a very high overall cardiovascular risk. It is attributed to advanced age, a high prevalence of key modifiable risk factors (arterial hypertension, dyslipidemia, and diabetes mellitus), and the

Parameter	Group 1	Группа 2 (n=217)	Группа 3 (n=169)	Группа 4 (n=129)	ANOVA
CAC, mean value	Group 2	34,45 [22,7; 59,3]	222,99 [164,1; 307,5]	966,19 [505,6; 1233,8]	<0,001
Age, years	Group 3	56,6±6,7	61,4±8,8	72,3±13,2	<0,001
Men, n/%	Group 4	84/38,7	71/42,3	77/60,4	<0,001
TC, mmol/L	ANOVA	5,46±1,57	5,31±2,19	4,93±1,56	0,852
LDL, mmol/L	3,36±1,07	3,31±1,14	3,13±1,13	2,98±1,13	0,088
HDL, mmol/L	1,42±0,44	1,38±0,36	1,37±0,5	1,37±0,49	0,534
TG, mmol/L	1,68±1,12	1,76±1,27	1,7±1,08	1,58±0,98	0,612
Creatinine, μmol/L	89±18,52	92,29±21,34	95,82±22,82	100,72±57,12	0,021
Glucose, mmol/L	6,06±2,12	6,38±2,12	6,29±1,89	7,25±3,59	0,534
Hemoglobin, g/L	140,81±14,81	139,04±17,99	139,16±17,56	138,07±18,08	0,789
Smoking, %	11,9±2,33	9,2±2,08	10,6±1,65	10,0±1,45	0,693
DM, %	24,7±1,47	26,0±2,09	25,8±1,89	27,3±2,54	0,554
Hypertension, %	95,9±2,08	92,2±3,78	93,5±3,06	93,0±2,45	0,602
AF, %	8,9±1,56	9,3±2,16	15,49±2,5	15,03±1,53	0,031

Note. Quantitative features are presented as mean values and standard deviation M±SD, p – significance of difference of parameters between patients in the studied groups in their comparison, statistically significant differences at p < 0.05.

Примечания. Количественные признаки представлены в виде среднего значения и стандартного отклонения M±SD, p – значимость отличия признаков между пациентами в исследуемых группах в сравнении, статистически достоверные различия при p < 0,05.

Table 2. *Patient baseline characteristics stratified by coronary artery calcium (CAC) score*

Таблица 2. *Исходные характеристики пациентов в зависимости от ИКК*

Total, n=733	CAC=0, n=218	CAC=1–100, n=217	CAC=101–399, n=169	CAC=400+n=129	p-value(paired comparison) ANOVA	p-значение (парное сравнение) ANOVA
below 40	23	22	1	0	0	
M	15	14	1	0	0	0,899
F	8	8	0	0	0	
40–49	63	37	17	8	1	***, #, ##
M	40	25	12	2	1	0,285
F	23	12	5	6	0	
50–59	135	55	36	25	19	*,**, #, ##
M	88	23	28	19	18	<0,001
F	47	29	8	6	4	
60–69	232	56	79	56	41	*,**,***
M	103	15	29	26	33	<0,001
F	129	41	51	30	7	
70+	280	51	83	83	63	*,**,***
M	71	8	14	24	25	<0,001
F	209	43	66	59	41	
p-value (multiple group comparison)	<0,001					

*Notes. 1. Statistically significant differences at p < 0.05, * p<0.05 as compared to the group of patients below 40 years of age, ** p<0.05 as compared to the group of patients of 40–49 years of age, *** p<0.05 as compared to the group of patients of 50–59 years of age, # p<0.05 as compared to the group of patients of 60–69 years of age, ## p<0.05 as compared to the group of patients of 70+ years of age; ANOVA - testing the hypothesis of similarity of mean values in \ groups. M – male, F – female patients.*

*Примечания. 1. Статистически достоверные различия при p < 0,05, * p<0,05 по сравнению с группой пациентов до 40 лет, ** p<0,05 по сравнению с группой пациентов 40–49 лет, *** p<0,05 по сравнению с группой пациентов 50–59 лет, # p<0,05 по сравнению с группой пациентов 60–69 лет, ## p<0,05 по сравнению с группой пациентов возраста 70+; ANOVA – для проверки гипотезы о равенстве средних значений в группах. 2. М – мужской, Ж – женский.*

Table 3. *Age and sex characteristics stratified by coronary artery calcium (CAC) score*

Таблица 3. *Половозрастные характеристики в зависимости от ИКК*

presence of target organ damage (chronic kidney disease, chronic heart failure).

The specific features of lipid metabolism disorders are shown in Fig. 1. Every third patient's TC level was below 5.2 mmol/L, LDL-C level > 3.4 mmol/L was observed in 45% (n=330) patients, triglyceride level > 1.7 mmol/L in 24% (n= 176) patients, low level of HDL-C was seen almost twice as often in women. Lipid-lowering therapy started in 41.4% of patients prior to inclusion in the study. However, none of the patients reached target levels of TC and LDL-C, thus, the efficiency of that therapy may be evaluated as insufficient and requiring adjustment.

The patients were then divided into groups depending on the CAC: 0 – no calcification (low risk of cardiovascular complications); 1–10 – low level of calcification (moderate risk); 11–100 – moderate level of calcification (increased risk); 101–400 – high level of calcification (high risk); over 400 – very high level of calcification (very high risk). The group characteristics are sown in Table 2.

CAC increased over the age of patients; at the same time, with the increasing age in the subgroups the number of male patients increased as well. Besides, with the increasing age the increase of creatinine level in the blood increased as well as the number of patients with AF. In other parameters, the groups did not differ.

For a more detailed assessment of sex and age differences on the CAC level, we studies the value in five age groups: below 40 years, 40–49 years, 50–59 years, 60–69 years, and over 70 years of age (Table 3).

In the groups below 40 years and 40–49 years of age, the CAC score did not reliably differ. In the remaining age periods, there is a statistically significant difference in the CAC score between men and women (comparison using

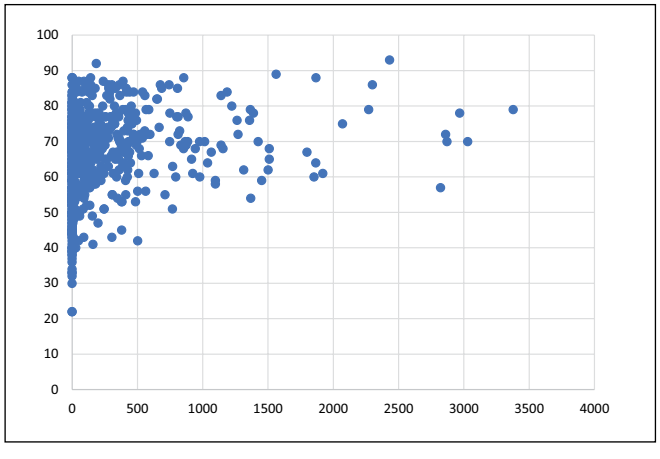

Figure 2. *Correlation between age and coronary artery calcium (CAC) score.*

Рисунок 2. *Взаимосвязь возраста с ИКК.*

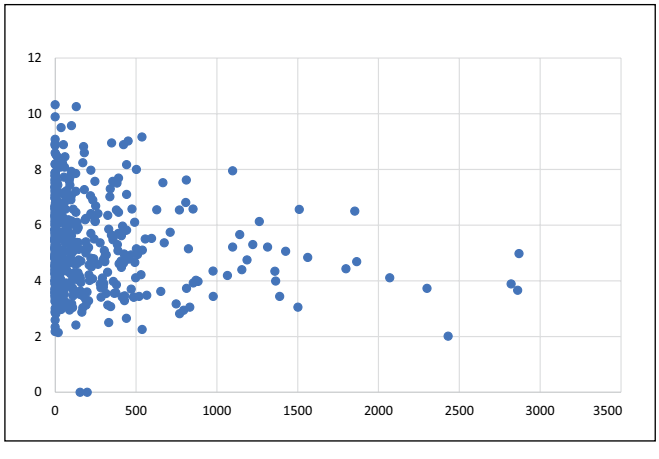

Figure 3. *Correlation between total cholesterol (TC) and coronary artery calcium (CAC) score.*

Рисунок 3. *Взаимосвязь ОХС и ИКК (r=0,64; p=0,047).*

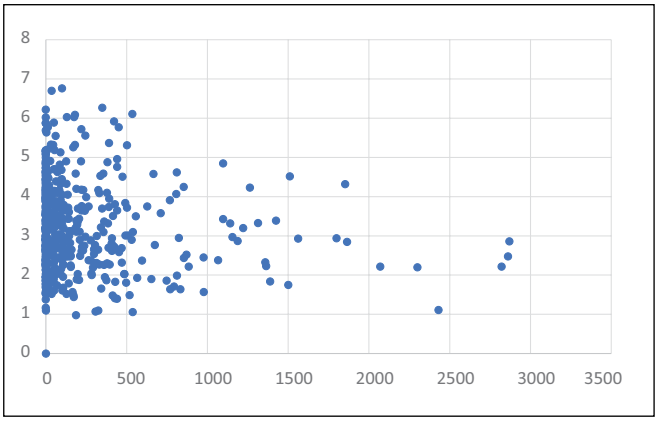

Figure 4. *Correlation between LDL-C and coronary artery calcium (CAC) score.*
Рисунок 4. *Взаимосвязь ХС ЛНП и ИКК (r=0,58; p=0,057).*

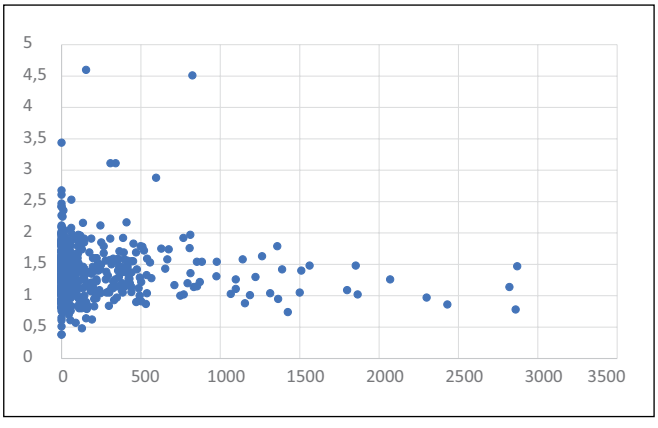

Figure 5. *Correlation between HDL-C and coronary artery calcium (CAC) score.*
Рисунок 5. *Взаимосвязь ХС ЛВП и ИКК (r=0,47; p=0,049).*

Pearson's test). On the whole, there was a high level of correlation between the age and the CAC score (Fig. 2).

The high correlation (r=0.71) indicates that age largely predetermines the "calcium burden" in the coronary arteries. However, despite the strong correlation, age is not the sole factor. CAC is also significantly influenced by sex, genetic predisposition, smoking, dyslipidemia, hypertension, and diabetes mellitus. We demonstrated that the CAC score showed a moderate to high correlation with lipid profile parameters (Fig. 3–6).

The graph shown in Fig. 3 illustrates a positive correlation between the TC level and the CAC score. The graph shows a cloud of dots demonstrating the ascending trend meaning that the growth of total cholesterol in the blood comes with the CAC score tending to increase as well. This visualizes an important pathophysiological process: the high level of cholesterol promotes development and progression of atherosclerosis, the key manifestation of which is the calcification of coronary arteries.

The graph in Fig. 4 demonstrates a moderate trend of CAC score with increasing levels of LDL-C, a trend that had not yet achieved statistical significance. This means that in the specific group of patients the strength of relation was not sufficient to reach statistical significance; however the result does not disprove the generally recognized role of LDLs in the development of atherosclerosis and calcinosis.

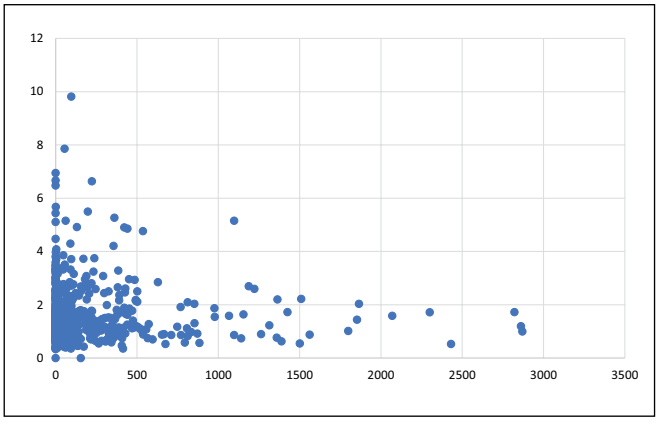

Figure 6. *Correlation between triglyceride levels (mmol/L) and coronary artery calcium (CAC) score. r=0.62 (p=0.043).*
Рисунок 6. *Взаимосвязь уровня ТГ (ммоль/л) с ИКК. r=0,62 (p=0,043).*

Graph 5 shows a statistically unstable relation between the level of HDL-C and CAC score. This is most likely explained by the influence of confounding factors (in the first place, age), not by the presence of a direct cause-and-effect relation. This finding does not deny the significant role of the HDLs but emphasizes its relation to other factors.

The result presented in Fig. 6 is clinically expected and justified. Triglycerides are not only an independent risk factor of atherosclerosis but a key component of metabolic syndrome and diabetes mellitus. The high level of TGs promotes formation of small dense particles of LDLs that are most atherogenic. The moderately high correlation (r=0.62) confirms that the TG level is an important marker associated with the burden of atherosclerosis. At the same time, this correlation does not indicate a cause-and-effect correlation; the high level of TG is most likely a part of the total negative metabolic profile that leads to artery calcification. The chart shows a moderately positive relation between the TG level and CAC score.

DISCUSSION

The CAC score may be seen as a marker of re-stratification of cardiovascular risk which, taken together with other (conventional) risk factors may increase or decrease the patient's global cardiovascular risk. We noted a clear correlation between the parameters of the lipid profile (TC, LDL-C, HDL-C, TG) and the increase of CAC score. It is important that despite the earlier initiated lipid-lowering treatment in 41.4% of patients included in the study, none has reached target values. It is well known that the used of visualization methods in the early stage (CA MSCT, ultrasonic examination of vessels) results in the patients' stronger compliance with the optimal pharmacological therapy.

In the near future, the cornerstone of CVD prevention will be a personalized approach based on assessing both traditional and individual risk factors of a particular patient. This approach will require the integration of new risk factors into traditional risk scores, as well as the use of various biological and instrumental markers that enable highly accurate and reliable stratification of the risk for developing CHD [8, 9].

In the last two decades, the prognostic value of the CAC score has been studied causing its inclusion in the national

and international recommendations for CVD prevention [10, 11]. Measurement of CAC score, according to clinical recommendations, is a promising approach to identify people with high risks and to expand the range of preventive measures [12, 13]. Among the most notable projects there are the MESA study that included 6814 patients aged 45–84 and showed that the CAC score was instrumental in predicting cardiovascular diseases independently from conventional risk factors [14].

To perform a more detailed analysis of sex and age influences on the CAC score, we performed it in five age groups. The CAC score increased with the increase of the patients' age, especially in men, and in patients with a high level of GFR and, respectively, positive status of CKD. This, the important factors influencing the development of CVDs included not only the age, but the gender as well. Besides, it follows from literature that the CAC score may have prognostic value in patients with arterial hypertension, oncological diseases, high level of sudden death, and be a predictor of development of dementia [15–17]. L.M. Severance et al. (2021) showed a correlation between the polygenic risk assessment and identification of CAC score ИКК [11].

Thus, CAC scoring is an accessible, well-reproducible, and low-cost method for the stratification and re-stratification of cardiovascular complication risk, particularly in asymptomatic patients, for the purpose of planning primary prevention measures [18]. Integrating artificial intelligence systems into the analysis and prediction process, which enables evaluative judgments based on the mathematical processing of large datasets, improves the final outcome [19, 20]. Currently, such systems are rapidly evolving, incorporating and analyzing an increasing number of prognostic factors.

Evaluation of calcination of coronary arteries may become clinically important in various stages of life. At the same time, the predictive value of CAC score in advanced age group is not yet clear: despite the high CAC scores, the patients may have no significant lesions of the coronary arteries [21–22].

CONCLUSION

CAC scoring, taken with traditional risk factors, may significantly improve early diagnostics and prevention of CHD. Our study confirms the importance of inclusion of measurement of coronary artery calcification in the standards of patient examination, including those with mild cardiovascular risk. This will enable optimization of treatment strategies and improvement of prevention measures aimed at lowering morbidity and mortality of cardiovascular diseases.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethics approval. The study was approved by the LEC of SamSMU (protocol No.11 dated 16.12.2024).	***Этическая экспертиза.*** Проведение исследования одобрено ЛЭК СамГМУ (протокол №11 от 16 декабря 2024 г.).
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. Zolotovskaya I.A., Duplyakov D.V., Rubanenko O.A.: study concept and design; critical analysis and interpretation of clinical trial data; editing of the article. Shatskaya P.R., Adonina E.V.: analysis and summary of current literature data on the topic; writing of the text. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Золотовская И.А., Дупляков Д.В., Рубаненко О.А. – концепция и дизайн исследования; критический анализ и интерпретация данных клинических исследований; редактирование статьи. Шацкая П.Р., Адонина Е.В. – анализ и обобщение современных литературных данных по теме; написание текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	***Доступ к данным.*** Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	***Генеративный искусственный интеллект.*** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	***Рассмотрение и рецензирование.*** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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Diagnostic potential for detecting upper limb arthropathy in ischemic stroke patients with RRS score of 4–6 points

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Abstract

Aim – to identify the features of the formation of upper limb arthropathy in patients with ischemic stroke with 4-6 points on the rehabilitation routing scale (RRS) depending on the type of treatment and rehabilitation procedures.
Material and methods. Ninety-eight patients with ischemic stroke were examined in two periods: Period 1, 13.2±0.8 days and Period 2, 189.2±2.1 days. Ultrasound and X-ray examinations were performed to determine the nature of damage to the joint complex of the upper limb. The severity of the neurosomatic status was assessed using the NIHSS, MRS, MMSE, VAS, and RRS scales.
Results. Post-stroke hemiparesis in the acute period of ischemic stroke was registered in 86 patients (88%), and upper limb arthropathy in 36 (37%) of the examined patients. In 12 (32%) patients with ischemic stroke the arthropathy of the shoulder joint combined with damage to other joints. In the majority of patients with ischemic stroke with arthropathy, according to the ultrasound data of the joints, synovitis was detected in 27 (76%), and tendon tendinitis in 17 (47%) that form the structure of the shoulder joint. In dynamics, contracture of the upper limb was revealed in 12 (26%) of the examined and was combined with a more pronounced cognitive defect, which required development of preventive and corrective methods.
Conclusion. It is proposed to introduce into the diagnostic standard of patients with ischemic stroke with paresis of 0-3 points ultrasound of the affected joint to identify early markers of arthropathy in order to promptly prevent contracture of the upper limb.
Keywords: ischemic stroke, arthropathy, contracture, ultrasound examination of the joint.
Conflict of interest: nothing to disclose.

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Диагностические возможности выявления артропатии верхней конечности у больных ишемическим инсультом с ШРМ 4–6 баллов

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Аннотация

Цель – выявить особенности формирования артропатии верхней конечности у больных ишемическим инсультом с 4–6 баллами по шкале реабилитационной маршрутизации (ШРМ) в зависимости от характера лечебно-реабилитационных мероприятий.
Материал и методы. Обследовано 98 больных ишемическим инсультом в два временных периода: первый период – 13,2±0,8 дня и второй период – 189,2±2,1 дня. Характер поражения суставного аппарата верхней конечности оценивали при помощи ультразвукового и рентгенологического исследования. Выраженность нейросоматического статуса оценивали по шкалам NIHSS, MRS, MMSE, ВАШ, ШРМ.
Результаты. Постинсультные гемипарезы в остром периоде ишемического инсульта зарегистрированы у 86 пациентов (88%), при этом артропатия верхней конечности выявлена у трети – 36 (37%) обследованных. У 12 (32%) больных ишемическим инсультом артропатия плечевого сустава сочеталась с поражением других суставов. У большинства больных ишемическим инсультом с артропатией – 27 (76%), согласно данным УЗИ суставов, выявлено наличие синовита, у 17 (47 %) – тендиниты сухожилий, формирующих каркас плечевого сустава, что в динамике проявилось формированием контрактуры верхней конечности у четверти – 12 (26%) обследованных и сочеталось с более выраженным когнитивным дефектом, что требует разработки превентивных методик их коррекции.
Выводы. Предложено внедрение в диагностический стандарт больных ишемическим интсультом с парезом 0–3 балла УЗИ заинтересованного сустава как убедительного метода исследования для выявления ранних маркеров артропатии с целью своевременной профилактики контрактуры верхней конечности.
Ключевые слова: ишемический инсульт, артропатия, контрактура, ультразвуковое исследование сустава.
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Список сокращений
ИИ – ишемический инсульт; ШРМ – шкала реабилитационной маршрутизации; MRS – Medical Research Council Weakness Scale; ВАШ – визуально-аналоговая шкала; УЗИ – ультразвуковое исследование; ЭНМГ – электронейромиография; NIHSS – National Institutes of Health Stroke Scale.

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INTRODUCTION

According to modern concepts, the clinical notion of arthropathy includes the presence of the pain syndrome and restricted articular movement of varied amplitude. Development of post-stroke arthropathy is regarded as highly important in the course of formation of contractures of the upper limb, resulting not only in deteriorating quality of life, but in disablement regardless of age [1–3]. Therefore, the effort of the medical community is focused on searching for early diagnostic criteria of the risk of formation of post-stroke contracture and medical and rehabilitation technologies of its correction.

Post-stroke pain syndrome may be related to several underlying factors including local damage of paraarticular tissue, myogenic pain from the scalene muscles, neuropathic pain, including complex regional pain syndrome, central post-stroke pain, or may be stem from spasticity. In order to measure the intensity of pain, the visual analog scale (VAS) is used. Instrumental assessment of condition of peripheral nerves in the course of formation of neuropathis pain syndrome involved ultrasonic investigation (US) and electroneuromyography (ENMG). Assessment of tone and turgor of spasmed muscles is performed using the Ashworth scale. The measurement of articular movement is performed by goniometry on the Tardieu scale [4–6].

Combined methods of diagnostics, treatment and rehabilitation allow not only decrease of the pain syndrome but also restoration of the motor function of the extremity, as well as positive prevention of contractures in patients with ischemic stroke (IS) with early spasticity. To improve the motor control and restore the sensorimotor function of extremities, both pharmacological and non-pharmacological methods are used (injections of botulinum A-toxin in the subscapular and/or greater pectoral muscle, injections of glucocorticoids in the shoulder and/or subacromial joint, block anesthesia of the suprascapular nerve). From the first day of the patient's stay in the intensive care unit, positioning should be performed. Besides, in patients with spastic paresis, sparing mobilization techniques for shoulder muscles are recommended, as well as exercising of the upper extremities including target-oriented movements with lots of repetitions, massage and acupuncture therapy, use of postural positioning, kinesio tape, thermal procedures, tapes, braces, and frames [7–10].

The current organizational mechanisms of routing and consideration of severity of comorbid pathologies in patients with IS and 4 to 6 points on the rehabilitation routing scale (RRS) are far from being perfect. Therefore, at the end of inpatient care within the department of vascular surgery (DVS) only half of examined patients are timely diagnosed in the most acute period of causes of deep motor disorders, and successive medical rehabilitation of stages 1 to 3 is performed. The remaining IS patients face severe disablement in the early period of recovery [11, 12].

AIM

To identify the features of the formation of upper limb arthropathy in patients with ischemic stroke with 4-6 points on the rehabilitation routing scale depending on the type of treatment and rehabilitation procedures.

MATERIAL AND METHODS

A clinical study of the neurosomatic status of 90 IS patients was performed in two periods. First period: 13.2±0.8 days (Group 1). Second period: 189.2±2.1 days including dynamic follow-up of IS patients depending on the presence (Group 1A) or absence (Group 1B) of stage 2 medical rehabilitation within 1-2 months of the disease. The subjects were IS patients over 18 of age with RRS score of 4–6 points. The exclusion criteria were IS patients with RRS score of 1–3 points, with hemorrhagic stroke, oncological and mental diseases, as well as inflammatory or demyelinating diseases of the central nervous system (CNS).

Part from the standard neurological examination method, the following was assessed: neurological deficiency using the NIHSS scale, muscular strength using the five-point quantitative muscular strength assessment scale MRC. The intensity of the pain syndrome was assessed using the VAS, the degree of loss of self-care capability, using the RRS scale. The nature of damage to the articular apparatus of the upper extremity was assessed using ultrasonic and radiological diagnostics of the joint in question. The level of cognitive deficiency was assessed using the MMSE scale.

Treatment and rehabilitation procedures included basic pharmacological treatment (antiplatelet or anticoagulant drugs, anti-hypertension, lipid lowering and anti-arrhythmic drugs. etc.) and a complex of device-assisted rehabilitation and kinesiotherapy within stage two of medical rehabilitation.

The obtained quantitative and qualitative findings of the examinations were collected in Excel spreadsheets. The data was then processed using StatSoft STATISTICA 10.0.1011.0 Russian Portable and included identification of average and sampled shares, assessment of statistical significance of variance between groups, methods of variation statistics and correlation analysis. In the description of investigated groups, the absolute and the relative number of carriers of the qualitative findings was indicated, n (%), the mean value and

the standard deviation (M ± SD) in normal distribution of the quantitative variable, or the median value and the interquartile interval (Me [Q1; Q3]) in deviation of the distribution from the normal. The results of statistical analysis were considered significant in the probability of alpha error below 5% ($p < 0.05$).

RESULTS

The assessment of deterioration of self-care capability showed that among the studied IS patients, the prevailing RRS score was 4 points: 56 patients (57%, p = 0.004); less frequent RRS values were 5 points, in 40 patients (41%), and RRS of 6 points in 2 patients (2%). The severity of neurological deficit on the NIHSS scale in the acute period was moderate at 10.9 [10.0; 11.8] points, white the share of moderate stroke (5–15 points) was seen in 77 patients (79%), and severe (≥16 points) in 21 patients (21%, p =0.03). A direct correlation was identified (r=0.77) between the NIHSS and RRS levels.

The evaluation of the motor function revealed post-stroke hemipareses of various severity in 86 examined IS patients (88%).

The study of muscle strength of the upper limb on the MRC scale showed that the share of patients with plegia was 21 cases (25%); number of cases of 1 point was 14 cases (16%), cases of 2 points, 13 (15%), cases of 3 points, 20 (23%), and cases of 4 points, 18 (21%). The data is shown in **Fig. 1**.

Thus, the share of severe disorders (0-2 points) in 55 cases (56%) prevailed over the mild motor disorders (3-4 points) in 43 cases (44%).

The analysis of condition of the musculoskeletal apparatus showed that during the acute period of IS arthoropathy of the upper limb was identified in 36 (37%) of investigated patients. Among them, the visual inspection by the neurologist identified not only restriction of movement in all patients, but the pain syndrome of various severity in the joint under consideration in the prevailing number of patients (31 (86%)), as well as muscular hypotrophy of the upper limb and the edema of the joint capsule in 16 (45%) patients. Isolated damage of the shoulder joint was found in all 36 (100%) patients, and its combination with arthropathies of other joints (knee, elbow, wrist), in 12 (32%) patients. Left-sided arthropathy of the shoulder join was registered more frequently, in 21 (22%) cases, than the right-sided in15 (15%) cases. Its features were more frequently identified in women, in 22 (61%, p = 0.005) cases, than in men, in 14 (39%) cases.

In order to specify the nature of the bone defect, X-ray examination of the joints was performed. In the presence of clinical manifestations of the shoulder joint arthropathy, the signs of shoulder periarthritis were found in16 (46%) IS patients with the RRS score of 4-6 points. At the same time, according to the data of additional examination, US of the joint of practically all patients with arthropathy (27 patients (76%)) revealed synovitis of various severity, and the tendonitis of the tendons forming the shoulder joint complex was found in 17 patients (47%). We believe that ultrasonic examination of the joint in question to be necessary for patients in the acute phase of IS with paresis of 0-3 points in order to identify early markers of arthropathy and provide timely prevention of contracture of the upper limb; since this method provides finer data as compared to the routine X-ray examination of the joint.

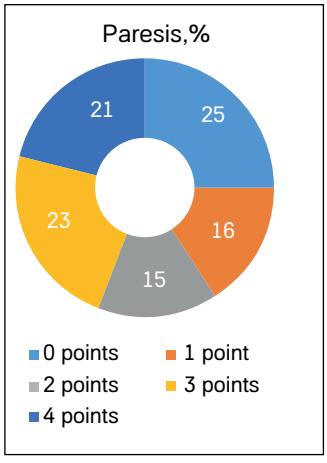

Figure 1. *The structure of paresis on the MRS scale.*
Рисунок 1. *Структура выраженности пареза по шкале MRS верхней конечности.*

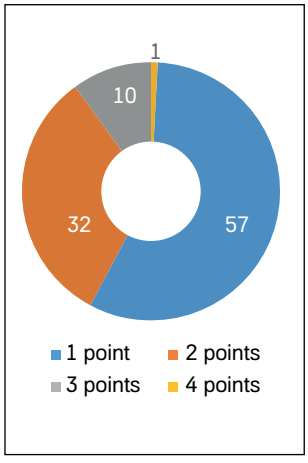

Figure 2. *Structure of paresis severity on the MRS scale in stroke patients with arthropathy.*
Рисунок 2. *Структура тяжести пареза по шкале MRS у больных ИИ с артропатией верхней конечности, %.*

In all 36 IS patients (100%) with arthropathy of the upper limb, signs of paresis of various severity were identified, which had a negative relation to the severity of the pain syndrome of the joint in question on the VAS scale (r = -0.72) (**Fig. 2**). The comparison of pain severity on the VAS scale demonstrated its prevalence in patients with arthropathy: 4.8 ± 0.3 and 2.8 ± 0.1, respectively.

Besides, the presence of shoulder joint arthropathy was related to formation of severe paresis of the upper limbs in 32 cases (89%, p=0.002), predominantly with 0-1 points on the MRC scale. Such disorders form a determining criterion of disablement of IS patients.

The analysis of neurological deficiency on the NIHSS scale registered a credible difference in patients with and without signs of arthropathy, 14.0 [13.0; 15.0], p = 0.00001 and 9.0 [8.0; 10.0], respectively, which could be accounted for by the contribution from pyramidal disorders and by the symptom complex of sensitive disorders. Thus, in the IS patients with signs of arthropathy it was identified in 19 (53% p= 0.005) of patients, and in IS patients without signs of arthropathy, only in 11 (31%) cases. Often this relates to the formation of a vicious circle of pathological interaction of motor, sensitive and cognitive disorders and ultimately may lead to decrease of motivation of patients to recover.

The investigation of the level of intellect and memory disorders on the MMSE scale in patients with arthropathy showed that among them, the most severe cognitive defects were registered at 15.8 [14.7; 17.0] points vs. patients without signs of artropathy at 20.3 [19.3; 22.1] points, p = 0.01.

The analysis of the structure of the rehabilitation routing scale showed that the degree of deterioration of self-care capacity in arthropathy patients was more severe as compared to the general sampling. Among patients with arthropathy, the RRS score of 5 points was twice as high (30 (80%, p

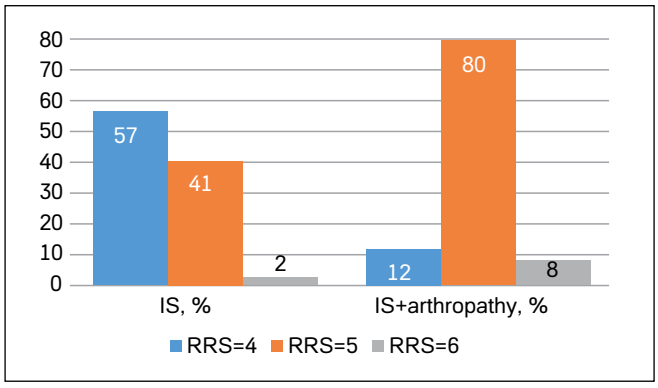

Figure 3. *The structure of the routing scale in stroke patients with upper limb arthropathy, %.*

Рисунок 3. *Структура ШРМ у больных ИИ с артропатией верхней конечности, %.*

=0.005)) vs. general group, and RRS score of 4 points only in 4 patients (12%, p = 0.04), RRS of 6 points, in 2 patients (8%). The data is shown in **Fig. 3**.

The evaluation of the degree of deterioration of self-care capacity in the IS patients in the course of dynamic follow-up (**Table 1**) among patients in the 1A group identified improvement of the neurosomatic status. This occurs not only due to prevalence of RRS of 4 points (31(60%, p = 0.004); the number of patients with RRS of 3 points also increased to 12 persons (23%). At the same time, among patients of the 1B group there still prevailed patients with RRS of 5 points: 25 persons (53%, p= 0.005).

As expected, follow-up assessment revealed a significant reduction in NIHSS scores to 6.1 [5.6; 7.0] points (p=0.04) among patients who received the second-stage comprehensive rehabilitation within the first 1–2 months after IS. In contrast, NIHSS scores in the group deprived of second-stage medical rehabilitation remained significantly higher at 9.0 [8.4; 9.8] points. Analysis of the dynamic severity structure of neurological deficit using the NIHSS revealed that while in the acute phase of IS, the main cohort of patients with RRS scores of 4-6 points consisted of individuals with moderate impairments (77 (79%, p=0.004)), and no cases of mild stroke manifestations were identified, the follow-up assessment showed a more favorable severity distribution. In Group 1A, patients with mild acute cerebrovascular events appeared (22 (42%, p=0.05)); consequently, the proportion of patients with a moderate course of ACVE significantly decreased (30 (58%, p=0.05)). However, in Group 1B, no significant dynamic changes were recorded, and patients with moderate impairments prevailed (44 (95%, p=0.004)). The data is presented in **Table 2**.

The incidence of arthropathy during follow-up was identified in 28 patients (28%). Among patients in Group 1A, it was found in only 8 individuals (16%), whereas in Group 1B it was 2.5 times more frequent, occurring in 20 patients (44%, p=0.04). Contracture of the affected upper limb had developed in 15 patients (15%). While it was present in only 3 patients (5%) from Group 1A, it was observed in 12 patients (26%) from Group 1B. This inevitably affected the cognitive status of the IS patients. Specifically, among patients without arthropathy, cognitive status showed significant recovery to 25.4 [23.4; 26.2] points (p=0.01), whereas among patients with established contracture, it remained significantly depressed at 19.4 [18.2; 22.1] points.

The identified pattern emphasizes the necessity of implementing early preventive diagnostic technologies for detecting and characterizing arthropathy in order to prevent contractures.

DISCUSSION

Recent scientific literature focused on evaluating the relationship between the severity of pyramidal tract impairments, the degree of limitations in self-care capacity and the extent of cognitive deficits. This is based on the concept that *barriers to rehabilitation can include cognitive disorders, 'higher-level' motor impairments, fall risk, depression, chronic fatigue, pain syndromes, and comorbidities* [13–16]. Our study identified a direct correlation between NIHSS and RRS scores (r=0.77), which supports this assertion.

Furthermore, we established that in patients with severe limitations in self-care capability, beyond assessing the degree of motor impairments, attention must be paid to the presence of upper limb arthropathy, which was recorded in over one-third (37%) of patients in the ischemic stroke cohort.

Presence of the shoulder joint arthropathy is related to the formation of deep paresis of the upper limbs (predominantly, 0-1 points on the MRS scale), and to the more manifested sensitive (19 (53%)) and cognitive disorders (15.8 [14.7; 17.0]), that constitute the prevailing criterion of disablement of ischemic stroke patients [12].

Analysis of the impact of timely implementation of treatment and rehabilitation measures for preventing severe disabling motor impairments in ischemic stroke patients showed that arthropathy during follow-up was observed in 8 patients (16%) in Group 1A, but 2.5 times more frequently in Group 1B, in 20 cases (44%, p=0.04). The contracture of the affected upper limb developed in half of the cases, 15 patients (15%), which is a marker of severe patient disability. The identified pattern emphasizes the necessity of implementing

RRS	Group 1 (n=98)	Group 1A (n=52)	Group 1B (n=46)
3 points		12 (23%)	2 (5%)
4 points	56 (57 %, p= 0.005)	31 (60 %, p= 0.004)	17 (38 %)
5 points	40 (41%)	9 (17 %, p = 0.004)	25 (53%, p= 0.005)
6 points	2 (2%)	–	2 (4%)

Note. Accuracy of variance between studied groups in dynamic follow-up: p ≤ 0.05.

Table 1. *Dynamic structure of the routing scale in stroke patients, abs. (%)*

Таблица 1. *Динамическая структура уровня ШРМ у больных ИИ, абс. (%)*

NIHSS	Group 1 (n=98)	Group 1A (n=52)	Group 1B (n=46)
0–4 points	–	22 (42%, p = 0.05)	2 (5%)
5–15 points	77 (79%)	30 (58%, p = 0.05)	44 (95%, p = 0.004)
≥16 points	21 (21%, p = 0.03)	–	–

Note. Accuracy of variance between studied groups in dynamic follow-up: p ≤ 0.05.

Table 2. *Dynamic structure of NIHSS in stroke patients, abs. (%)*

Таблица 2. *Динамическая структура уровня NIHSS у больных ИИ, абс. (%)*

early preventive diagnostic technologies for detecting and characterizing arthropathy to prevent contractures.

CONCLUSION

Development of novel preventive clinical and diagnostic technologies for identifying early markers of arthropathy necessitates the timely implementation of a recommended complex of therapeutic and rehabilitative measures to prevent contractures. Moreover, the early and active initiation of rehabilitation itself constitutes a crucial stage in preventing contractures as a significant factor contributing to disability in ischemic stroke patients, regardless of age.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
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Mild cognitive impairments in patients in the acute period of cardioembolic stroke

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Abstract

Aim – to study the features of moderate cognitive disorders in patients with acute ischemic stroke of the cardioembolic subtype during comprehensive neuropsychological testing in comparison with data on structural changes in brain tissue identified using visual semi-quantitative scales during magnetic resonance imaging of the brain.

Material and methods. The prospective observational study involved 60 patients (22 women and 38 men) diagnosed with cardioembolic stroke. The study participants were divided into two groups: patients with non-amnesic (neurodynamic) multifunctional type of moderate cognitive disorders (40 patients: 70% men, 30% women, mean age 64.3 years) and patients with amnestic multifunctional type (20 patients: 50% men, 50% women, mean age 76.1 years). All patients underwent a comprehensive neuropsychological examination and magnetic resonance imaging of the brain using standard magnetic resonance scales.

Results. Patients with non-amnestic multifunctional type of moderate cognitive disorders accounted for 67% of the examined patients (40 people), and 33% (20 people) were patients with amnestic multifunctional type. During the examination, neuropsychological features were identified in each group. 22% of patients (13 people) had infarctions in the "strategic" zones, and 45% of patients (27 people) had multiple focal ischemic strokes. In 90% of patients (54 people), there was a pronounced lesion of the white matter in the form of a hyper-intense signal from the periventricular and subcortical areas and a moderate widening of the cerebral sulci against the background of slight atrophy of the gyri.

Conclusion. The comprehensive diagnostic approach, including neuropsychological testing and assessment of structural changes in the brain using visual semi-quantitative magnetic resonance scales, allows for the detection of cognitive impairments at the pre-dementia stage and the initiation of therapy aimed at preventing the progression of these impairments.

Keywords: mild cognitive impairment, cardioembolic stroke, MRI scales, neurodegeneration, neuropsychological assessment, dysregulatory disorders.
Conflict of interest: nothing to disclose.

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Умеренные когнитивные нарушения у пациентов в остром периоде кардиоэмболического инсульта

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Аннотация

Цель – изучить характеристики умеренных когнитивных расстройств у пациентов в остром периоде ишемического инсульта кардиоэмболического подтипа в ходе комплексного нейропсихологического тестирования в сопоставлении с данными структурных изменений вещества головного мозга, выявляемых с помощью визуальных полуколичественных шкал при магнитно-резонансной томографии головного мозга.

Материал и методы. Проведено проспективное обсервационное исследование с включением 60 пациентов (22 женщины и 38 мужчин) с диагнозом «кардиоэмболический инсульт». Исследуемые разделены на две группы: пациенты с неамнестическим (нейродинамическим) мультифункциональным типом умеренных когнитивных расстройств (40 пациентов: 70% мужчин, 30% женщин, средний возраст составил 64,3 года) и больные с амнестическим мультифункциональным типом (20 пациентов: 50% мужчин, 50% женщин, средний возраст составил 76,1 года). Всем пациентам проведены комплексное нейропсихологическое обследование и магнитно-резонансная томография головного мозга с применением стандартных магнитно-резонансных шкал.

Результаты. Пациенты с неамнестическим мультифункциональным типом умеренных когнитивных расстройств составили 67% обследуемых (40 человек), а 33% (20 человек) – пациенты с амнестическим мультифункциональным типом. В ходе обследования были выявлены нейровизуализационные особенности в каждой группе. У 22% пациентов (13 человек) определялись инфаркты в области «стратегических» зон», у 45% пациентов (27 человек) был обнаружен многоочаговый ишемический инсульт. У 90% пациентов (54 человек) отмечалось выраженное поражение белого вещества в виде гиперинтенсивности сигнала от перивентрикулярных и субкортикальных областей и умеренное расширение борозд головного мозга на фоне незначительной атрофии извилин.

Выводы. Комплексный диагностический подход в виде нейропсихологического тестирования и оценки структурных изменений вещества головного мозга с применением визуальных полуколичественных магнитно-резонансных шкал позволяет выявить когнитивные нарушения на додементной стадии и инициировать терапию, направленную на профилактику прогрессирования данных нарушений.

Ключевые слова: умеренные когнитивные нарушения, кардиоэмболический инсульт, МР-шкалы, нейродегенерация, нейропсихологическое обследование, дизрегуляторные расстройства.
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Список сокращений
МРТ – магнитно-резонансная томография; УКР – умеренное когнитивное расстройство; нУКР – неамнестический (нейродинамический) мультифункциональный тип УКР; аУКР – амнестический мультифункциональный тип; FCSRT – тест ассоциированного селективного распознавания; MMSE – краткая шкала оценки психического статуса; MoCA – Монреальская шкала оценки когнитивных функций; FAB – батарея тестов лобной дисфункции; ШДМ – шкала деменции Маттиса; MTA – шкала атрофии медиальных отделов височной доли; GCA – шкала глобальной кортикальной атрофии; NIHSS – The National Institutes of Health Stroke Scale.

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INTRODUCTION

Cardioembolic stroke is one of the most prevalent subtypes of ischemic stroke. In its acute phase, some syndromes may develop that preclude effective rehabilitation. These include cognitive impairments that have a significant adverse effect on the quality of life and reduce the possibilities of social and household adaptation. At the same time, the clinical patterns of the higher cortical functions have not been fully identified to this day. In the diagnostic algorithm of acute cerebrovascular accidents (ACVA), magnetic resonance imaging (MRI) has an important role. Semi-quantitative visual scales were developed to improve quality of assessment of findings of structural MRI and objectification of the obtained data. However, comparison of results of changes of the brain matter identified using such scales with the developing cognitive disorders has not been carried out in to a sufficient extent. Identification of some correlations of these indicators would facilitate a better understanding of impairments of the higher cortical functions from the perspective of the theory on their dynamic localization, and would improve the quality of prediction of their condition in remote periods of ACVA.

The term “mild cognitive impairment” was first used by the American neurologist R.C. Petersen in 1997 to characterize an interim stage between the normal aging and dementia [1]. A mild cognitive impairment (MCI) is a clinically significant deterioration of cognitive functions (attention, memory, speech, perception, praxis, executive functions) that has not reached the degree of dementia [2]. At this level of impairment of higher cortical functions, complete maladaptation of patients and loss of independence in daily life are not observed. Prevalence of MCI among people aged 60 and above varies from 5.0 to 36.7% [3]. The rate of MCI progression to dementia is approx. 8-15% per year [4]. The following are identified as the major diagnostic criteria of MCI: deterioration of the higher cortical functions vs. individual baseline level, complaints of impairment of memory, attention and other cognitive functions that come both from the patient and from the informants (relative or a person close to the patient), or from the consulting physician. The functional impairment is confirmed by neuropsychological tests or other clinical measurement. The impairment may involve one or more cognitive spheres. Some independence in the daily life may remain but theme may be minor difficulties in the performance of complex tasks, however, the level of alterations observed is below the level of dementia. Besides, these impairments manifest on the background of a clear mind, lack of delirium and other psychic disorders [5–7].

In 2014, R.C. Petersen identified 4 types of MCI: amnestic mono-functional; amnestic multifunctional; non-amnestic (neuro-dynamic) mono-functional; non-amnestic multifunctional [8]. Prof. O.S. Levin, in his turn, suggested the amnestic type with memorizing impairment, neuro-dynamic-dysregulatory type with the development of a fronto-subcortical syndrome; the type predominated by visuospatial impairments; the type predominated by language impairments; and the combined type of observed MCI [9, 10].

According to the Russian studies, the most prevalent type of MCI is the non-amnestic multifunctional type [11]. It also follows from literature that 68% of MCIs stem from dyscirculatory encephalopathy or earlier ACVA [12]. It is to be noted that neuropsychological examination of cognitive functions that allows assessment of their different components, is the gold standard of determining the MCI type [13].

AIM

To study the features of moderate cognitive impairments in patients with acute ischemic stroke of the cardioembolic subtype during comprehensive neuropsychological testing in comparison with data on structural changes in brain tissue identified using visual semi-quantitative scales during magnetic resonance imaging of the brain.

MATERIAL AND METHODS

The prospective observation study conducted at the Almazov National Medical Research Centre included 60 patients (22 women and 38 men). Inclusion criteria: acute period of cardioembolic subtype ischemic stroke (diagnosed as per criteria established in the 2024 clinical recommendations); mild cognitive impairments as per diagnostic criteria of the National Institute of Aging and Alzheimer’s Association, ICD-11 criteria, DSM-5; normal consciousness; general stable condition, including compensated chronic diseases; informed consent to participate in the study. Exclusion criteria: known earlier diagnosis that could have been a possible cause of cognitive disorders (Alzheimer’s disease, dementia with Lewy bodies, Pick disease, frontotemporal dementia, Parkinson’s disease, Huntington’s disease, Wilson-Konovalov’s disease and other diseases); speech impairments including aphasia of varying severity; manifested dysarthria; presence of traumatic brain injury; history of alcoholism; surgery within one year prior to inclusion in the study (except emergency endovascular thrombectomy and thromboaspiration on admission); clinically manifested depression or anxiety.

To exclude the functional causes of cognitive disorders, a screening for anxiety and depression was performed using the Hamilton's scale. The finding of this test in the study group did not reach threshold values and matched the normal emotional background.

The study was performed on day 10-14 from the onset of stroke. The patients were divided in two groups. Group I: patients with non-anamnestic (neuro-dynamic) multifunctional MCI. Group II: patients with amnestic multifunctional type or multifunctional type with hippocampal-type memory impairments.

The division of patients into groups was performed based on complaints of memory impairments, particularly, disorders in memorizing new information, and on results of tests focusing on differential diagnostics of MCI types (the 5 word test, free and cued selective reminding test (FCSRT), verbal fluency test (phonetic and semantic associations), trail-making test.

All patients underwent the following assessments: collection of cognitive complaints, medical and life history; neurological examination; evaluation using clinical scales commonly applied in neurological practice to assess stroke severity, functional limitations, and post-stroke disability (National Institutes of Health Stroke Scale, Barthel Index, Modified Rankin Scale, Rivermead Mobility Index, Glasgow Outcome Scale); comprehensive neuropsychological testing; brain MRI with application of MR scales for assessing brain tissue condition.

The neuropsychological testing included a mini-mental scale examination (MMSE) Montreal cognitive assessment, frontal assessment battery test (FAB), clock drawing test, 5 word test, verbal fluency test (phonetic and semantic associations), Mattis dementia rating scale, digit span test, Hamilton anxiety and depression rating scales, symbol digit modalities test, Schulte table test, free and cued selective reminding test (FCSRT) [21–33].

The brain MRI identified the following: localization and volume of the focus of the ischemic stroke, lesion of the areas strategically important for the higher cortical functions, multi-focal lesion of the brain. To assess white matter changes, the Fazekas, Scheltens and Wahlund scales were used. The presence of selective cerebral atrophy or gray matter pathology was evaluated using the following scales: the medial temporal lobe atrophy (MTA) scale, the Koedam parietal atrophy scale and the global cortical atrophy (GCA) scale [34, 40].

Statistical processing of the data was performed in the RStudio integrated development environment. To describe the data, the following descriptive statistics methods were used: for the data with normal or near-normal distribution, mean value and standard deviation were calculated; for the data with distribution significantly different from normal, mean value and standard deviation were augmented with median and values of first and third quartiles (with bootstrapping). Distribution was assessed by constructing histograms. Histograms are presented for data with distributions significantly deviating from normality. For comparing values between MCI types, the two-sample Mann–Whitney U test with Holm's correction for multiple comparisons was applied. Boxplots were constructed for measures showing significant differences between types.

RESULTS

Clinical and neuropsychological characteristics

According to the patient history data, arterial hypertension and atrial fibrillation was found in all patients of the study sample. 28 patients (42%) had chronic heart failure, and 14 patients (21%) had type II diabetes mellitus. According to the lipid profile, 59 patients (89%) had dyslipidemia. According to the medical documents, 42 patients (64%) had been diagnosed with 'dyscirculatory encephalopathy' of various severity prior to the development of the stroke. The evaluation of the neurological status revealed the following: motor impairments, hemiparesis in 60 (91%) patients, sensory impairments in 29 (44%) patients, speech impairments such as dysarthria or volume disorders in 24 (36%) patients, dysfunction of cerebral nerves such as oculomotor disorders, asymmetry and sensory impairments of the face, dysphagia in 33 (50%) patients. The Doppler ultrasonic examination of the brachycephalic arteries and vessels of the head identified atherosclerotic lesion of the brachycephalic vessels (common and internal carotid arteries) in 66 patients (100%). At the same time, hemodynamically significant stenosis over 50% were not identified in the study sample.

The neurological examination found that the average score on the NIHSS scale matched that of mildly severe ischemic stroke. In the vast majority of cases, motor, sensory and coordination disorders were found. In the evaluation of mobility, degree of activity impairment and disability it was found that the patients were able to move about the hospital department without any aids, had mild to moderate activity impairments and were capable of taking care of themselves without assistance. The average score on the Hachinski scale shows that clinical signs of vascular cognitive disorders prevailed in the patients included in the study. Some individual cases demonstrated possible presence of a neurodegenerative component. In the evaluation of the patient mobility by the Rivermead index it was found, that mild impairment of mobility was prevalent in the studies cohort. The study of functional activity using the Barthel scale demonstrated mild to moderate dependence degrees. On the whole, these data matched the results of Rankin scale examination (mild to moderate activity impairments). The testing on the Glasgow outcome scale also correlated with these findings. The general values follow **in Table 1**.

In the evaluation of the neuropsychological status, 100% patients (n=60) came up with cognitive complaints. These included lowered attention focus, quick fatigue when performing cognitive tasks, easy distraction, abstraction, longer time needed to perform a specific action, forgetfulness, lowered thinking rate. The neurological tests identified the following cognitive disorders most often: lowered attention focus, some instability and exhaustion of attention, reduced verbal fluency, deterioration of constructive and dynamic praxis, lower quality of regulatory functions, executive skills, lowered psychomotor rate without impairment of thinking structure, deterioration of short-term memory,

Parameter	M±SD	Median (Q1–Q3)
Age	68,23 ± 11,24	-
NIHSS	3,33 ± 2,57	2,50 (2,00–4,00)
Rivermead	10,10 ± 3,85	11,00 (7,00–14,00)
Rankin	2,83 ± 0,81	-
Barthel	78,50 ± 23,87	90,00 (65,00–95,00)
Hachinski	9,83 ± 1,24	-
Glasgow outcome scale	4,20 ± 0,58	-

Notes: NIHSS – The National Institutes of Health Stroke Scale
Примечания: NIHSS – The National Institutes of Health Stroke Scale.

Table 1. *Clinical and neurological characteristics of patients with MCI in the acute period of cardioembolic stroke on days 10-14 (in points, M±SD, median (Q1–Q3))*

Таблица 1. *Клинико-неврологическая характеристика пациентов с УКР в остром периоде кардиоэмболического инсульта на 10–14 сутки (в баллах, M±SD, медиана (Q1–Q3))*

mild disorders of the visuospatial gnosis. The cumulative data of the results of neuropsychological examination follow **in Table 2**.

Based on the analysis of complaints, analysis of life and disease history, and data of complex neurological assessment, the patients were divided into two groups. The patients with non-amnestic (neuro-dynamic) multifunctional MCI (nMCI) comprised 67% of the patients (n=40); while 33% (20 patients) had amnestic multifunctional MCI (aMCI) or multifunctional MCI with hippocampal-type memory impairments. The data follow in **Table 3**.

Patients with amnestic multifunctional MCI performed worse in neuropsychological tests that assessed memory and memory-associated activities. The group comparison showed the following specifics: in patients with aMCI there were disorders in the information memorizing process, which manifested in difficulties in delayed recall of words. Cues were of little assistance. This group also showed deterioration of visuospatial functions, which manifested in disorders in the clock drawing test and methods involving copying of material. In patients with nMCI, the differences in the immediate and delayed recall of words were less

Test	M±SD	Median (Q1–Q3)
Mattis dementia rating scale (MDRS), total	121,72 ± 6,29	25,00 (25,00–26,25)
MDRS, initiation – perseveration	29,40 ± 3,60	-
MDRS, attention	31,22 ± 2,50	-
MDRS, constructive praxis	5,00 ± 0,71	-
MDRS, conceptualization	34,55 ± 1,78	-
MDRS, memory	21,47 ± 2,27	-
MMSE	25,52 ± 1,08	-
FAB	14,65 ± 1,78	-
Clock drawing test	9,48 ± 0,85	10,00 (9,00–10,00)
Digit span test	25,37 ± 8,84	-
MoCA	23,90 ± 1,87	24,00 (23,00–25,00)
Schulte table No.1	65,17 ± 10,22	-
Schulte table No.2	65,75 ± 10,37	-
Schulte table No.3	65,85 ± 11,14	-
Schulte table No.4	65,77 ± 10,83	-
Schulte table No.5	66,58 ± 10,64	-
Direct numbers	4,82 ± 0,39	5,00 (5,00–5,00)
Reverse numbers	3,80 ± 0,40	4,00 (4,00–4,00)
FCSRT (free reminding)	18,08 ± 3,72	-
FCSRT (cued reminding)	13,33 ± 3,94	-

Notes: MDRS – Mattis dementia rating scale, MMSE – mini-mental status evaluation, MoCA – Montreal scale of cognitive assessment, FAB – frontal dysfunction battery of tests.

Примечания: ШДМ – шкала деменции Маттиса, MMSE – краткая шкала оценки психического статуса, MoCA – Монреальская шкала оценки когнитивных функций, FAB – батарея тестов лобной дисфункции.

Table 2. *Results of neuropsychological examination of patients with MCI in the acute period of cardioembolic stroke (in points, M±SD, median (Q1–Q3))*

Таблица 2. *Результаты нейропсихологического обследования пациентов с УКР в остром периоде кардиоэмболического инсульта (в баллах, M±SD, медиана (Q1–Q3))*

manifested, and the semantic cue usually helped recall the stimulus material. The charts of value distribution in the study samples are shown in **Fig. 1**.

Test	Dysregulatory type		Amnestic type	
	M±SD	Median	M±SD	Median
5 word test (immediate recall)	(Q1–Q3)	4,50 (4,00–5,00)	(Q1–Q3)	4,00 (3,00–4,00)
5 word test (cued immediate recall)	4,70 ± 0,52	5,00 (4,00–5,00)	4,40 ± 0,68	4,50 (4,00–5,00)
5 word test (delayed recall)	3,17 ± 0,75***	3,00 (3.00–4,00)	1,85 ± 0,99	2,00 (1,75–2,25)
5 word test (cued delayed recall)	3,92 ± 0,76*	4,00 (3,00–4,00)	3,20 ± 0,95	3,00 (2,75–4,00)
Trail-making test, part A	64,42 ± 10,30	66,00 (59,50–69,75)	71,70 ± 10,31	70,50 (65,75–77,25)
Trail-making test, part B	65,90 ± 10,81	68,00 (61,00–72,00)	72,00 ± 10,50	72,00 (65,75–77,25)
Phonetic association test	9,57 ± 1,81*	10,00 (8,00–11,00)	8,00 ± 1,95	7,50 (7,00–9,00)
Semantic association test	12,62 ± 2,22*	12,50 (11,00–15,00)	10,45 ± 2,46	10,00 (9,00–12,00)
FCSRT (free reminding)	19,75 ± 2,73	20,00 (17,75–22,00)	14,75 ± 3,18	15,00 (11,75–17,25)
FCSRT (cued reminding)	15,05 ± 3,57	16,00 (13,00–18,00)	9,90 ± 1,86	10,00 (8,00–12,00)
FCSRT, total score	34,80 ± 4,16***	35,00 (31,75–38,00)	24,65 ± 3,18	25,00 (22,75–27,00)

*Notes: * – p<0.05, ** – p<0.01, *** – p<0.001, FCSRT – free and cued selective reminding test.*
*Примечания: * – p<0,05, ** – p<0,01, *** – p<0,001, FCSRT – тест ассоциированного селективного распознавания.*

Table 3. *Comparative analysis of neuropsychological test data in two groups (in points, M±SD, median (Q1–Q3))*

Таблица 3. *Сравнительный анализ данных нейропсихологического тестирования в двух группах (в баллах, M±SD, медиана (Q1–Q3))*

In 22% of patients (n=13) with mild cognitive impairments, infarctions were detected in some areas of the 'strategic' zones such as thalamus, striatum, hippocampus, prefrontal cortex, left temporo-parieto-occipital junction; in 45% of patients (n=27), multifocal brain lesions in the form of ischemic stroke were detected. This patient group is characterized by fairly pronounced white matter lesions appearing as hyperintensities in the periventricular and subcortical regions. These lesions are represented by numerous foci of varying diameters, typically distributed across all cerebral lobes, sometimes showing a tendency to coalesce. This group also exhibits moderate sulcal widening with mild gyral atrophy. When using the Fazekas scale, it was determined that 90% of patients (n=54) exhibited moderate white matter lesions, corresponding to a score of 3 or 4 points. This group was characterized by the presence of leukoaraiosis foci along the cerebral ventricles, as well as diffusely distributed gliosis areas appearing as hyperintense signals. These changes generally matched the data obtained in the analysis of MRI scans using the Wahlund scale, where the local alteration foci prevail sometimes showing a tendency to coalesce. The vast majority of these changes was localized in the frontal lobes, and, to a lesser degree, in the parietal and temporal lobes. At the same time, the use of the Scheltens scale demonstrated a more pronounced degree of white matter lesion, which reflects the specifics of interpretation of results on this scale and the emphasis on the quantitative assessment of foci. The analysis of results of parietal lobe lesions on the Koedam scale generally revealed moderate atrophy of the gyri of the lobes, accompanied with some widening of the sulci (1 point). In some cases, not changes were found. In individual cases, severe atrophy was identified that came up to 2 points. The analysis of alterations in the medial section of the temporal lobe using the MTA scale identified no pronounced alterations in any of the cases. In individual examinations, no significant atrophy was found. For the majority of patients, the characteristic features were the mild dilatation of the chorioidal fissure (1 point) or a minor reduction in the height of the hippocampus accompanied by slight enlargement of the temporal horns of the lateral ventricles (2 points). The assessment using the GCA scale revealed that for the majority of the examined patients a minor atrophy of the cerebral matter (10 points or less) was characteristic. The atrophies were represented with some widening of the sulci and ventricles and some loss of volume of the gyri. A small number of patients demonstrated moderate atrophic changes, ranging from 11 to 20 points on the applied scale. These changes primarily affected the frontal regions, to a lesser extent the temporal areas and the parieto-occipital regions. The overall data from the brain assessment using MR scales are presented in **Table 4**.

DISCUSSION

The neuropsychological assessment revealed that patients with MCI following cardioembolic stroke primarily develop neurodynamic and dysregulatory impairments. These deficits are associated with damage to

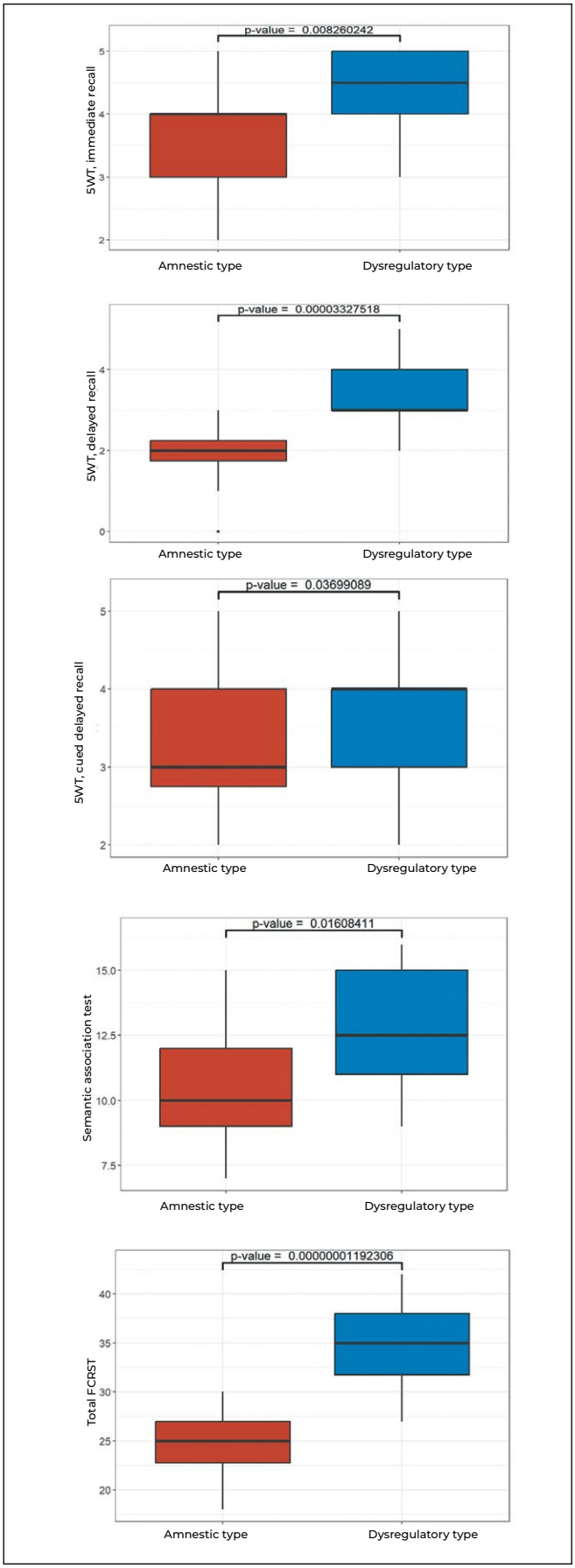

Figure 1. *Boxplots comparing the neuropsychological examination data of the two identified variants of MCI.*

Рисунок 1. *Диаграммы размаха сравнения данных нейропсихологического обследования двух выявленных вариантов УКР.*

MP scale	Average score
Fazekas	3,35
Scheltens	18,94
Wahlund	12,75
Medial Temporal lobe Atrophy (MTA)	1,41
Koedam	1,11
Global Cortical Atrophy (GCA)	7,65

Table 4. *MR scale data in the study group of patients with MCI*
Таблица 4. *Данные МР-шкал в исследуемой группе пациентов с УКР*

the 1st and 3rd structural-functional blocks, according to A.R. Luria's theory of higher cortical function organization [14]. Thic MCI type is usually represented with disorders in the programming, regulation and control over the progression of psychic activity, processes of formation of intentions, goals of psychic activity, regulation and control of actions including behavior, disorders of attention, motivation, decrease of speed of psychic processes with the development of bradyphrenia [15]. The development of these impairments is based on either a fronto-subcortical syndrome (primary or secondary frontal lobe pathology) or a disconnection phenomenon [8, 16]. Such cases may also demonstrate deterioration of short-term memory and formation of a nonspecific forgetfulness with preserved recognition and mediated memorizing [15, 17, 18]. For amnestic impairments, hippocampal-type memory dysfunctions, long-term memory, primary memorizing of new information (true amnesia) or recognition are characteristic [15, 18]. Such impairments stem from lesions of hippocampal structures and its connections [18–20]. This type of MCIs may indicate a pre-dementia (preclinical) stage of Alzheimer's disease [20]. The assessment of cerebral changes using visual MR scales, mildly pronounced atrophic changes of the white and the gray matter are observed. Al the same time, lesions of the frontal lobes prevail as well as those of subcortical structures, which also characterized the development of fronto-subcortical syndrome and aligns with findings of neuropsychological examination. In some cases, atrophic changes in the hippocampal area and in the mediobasal structures of temporal lobes were detected. In the clinical picture, they were combined with hippocampal-type memory impairments. This may indicate that these patients have a competing neurodegenerative process and formation of mixed cognitive disorders. Identification of atrophic changes in the parietal lobes was less frequent. Quite expectedly, according to fundamentals of functional neuroanatomy, these patients demonstrated formation of visuospatial impairments that was combined with neurodynamic and dysregulatory impairments.

CONCLUSION

A comprehensive diagnostic approach involving careful collection of complaints and history, neuropsychological testing and assessment of structural brain changes using visual semi-quantitative MR scales facilitates detection of cognitive impairments at the pre-dementia stage and identification of their potential anatomical substrate. This approach assists implementation of optimal therapeutic approaches to their treatment and prevention of progression to the stage of dementia. Determination of the amnestic type of MCI may indirectly indicate an alternative pathological process such as pre-dementia stage of the Alzheimer's disease, which enables direction of the patient for further examination to confirm or exclude this condition.

Thus, the identification of mild cognitive impairments (MCI) in patients during the acute phase of ischemic stroke enables neurologists to formulate appropriate recommendations for the subsequent rehabilitation period, with a focus on the correction of higher cortical function deficits.

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Оригинальность. При создании настоящей работы автором не использовались ранее опубликованные сведения (текст, иллюстрации, данные).	***Statement of originality.*** No previously published material (text, images, or data) was used in this work.
Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима.	***Data availability statement.*** The editorial policy regarding data sharing does not apply to this work.
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Possibilities of surgical treatment of pancreatic head neuroendocrine neoplasms with major venous invasion

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Abstract

Aim – to demonstrate the feasibility and relative safety of resection of the portal and/or superior mesenteric veins invaded by tumor during surgical treatment of the neuroendocrine neoplasm of the pancreatic head, as well as the feasibility of simultaneous resection of the liver for resectable metastases in patients with stage IV disease during primary surgery and at disease progression of any stage following surgical treatment.

Material and methods. Surgical treatment of 16 patients with neuroendocrine neoplasm of the pancreatic head with invasion of the superior mesenteric and/or portal veins of stages III-IV of high and moderate differentiation (G1 and G2) included a standard gastropancreoduodenal resection in 87.5% cases, extended gastropancreoduodenal resection with aortocaval lymph node dissection in 6.25% cases, and pancreatectomy in 6.25% cases. During the standard operation, in one female patient (6.25%) segmental resection of the liver was performed to remove the metastasis. The rate of portal vein resection was 6.25%, superior mesenteric vein, 50%, both major veins, 43.8%. Neoadjuvant treatment was not administered, while adjuvant XELOX treatment was administered to 3 (18.8%) patients. The statistic processing of the study results was performed in Statistica for Windows v.10 and SPSS v21. The obtained differences were deemed statistically significant at $p \leq 0.05$ (≥95% accuracy). In order to calculate the survival rate, the Kaplan-Meier method was used with log-rank test evaluation of significance of differences.

Results. The rate of R0 surgical treatment was 93.8%, the rate of complications of surgical treatment of Clavien-Dindo class III and above was 43.8% with the total rate of all complications of 75%. The main complications included gastric stasis (50.1%), arrosive hemorrhage (18.8%), acute gastrointestinal ulcer hemorrhage (18.8%), pneumonia (18.8%). The rate of postoperative thrombosis of the portal and/or superior mesenteric vein was 12.5%, leakage of the pancreato-digestive anastomosis was 12.5%, leakage of the bilio-digestive anastomosis, 6.3%, pancreatic fistula, 12.5%. Relaparotomy was performed in 2 (12.5%) patients who later died due to complications of surgical treatment (leakage of the pancreato-digestive anastomosis with arrosive hemorrhage). Disease progression was seen in 10 (62.5%) of the patients within 3 to 69.3 months, the median time before identification of progression being 39.7 [7.1; 52.8] months, and mortality from progression being 50%. Local recurrence developed in 12.5% patients, metastases in the retroperitoneal lymph nodes in 6.25%, metastases in the liver in 43.75%, in two cases, liver resection due to metastases was performed. In cases of progression, all patients received antineoplastic therapy with analogs of prolonged somatostatin. The median overall survival was 70.1 months, progression-free survival, 49.2 months, one-year survival was 81.2% and 78.6%, respectively, three-year survival, 68.2% and 63.5%, five-year, 68.2% and 36.3%, ten-year, 20.55% and 18.1%.

Conclusion. The outcomes of surgical treatment of patients with neuroendocrine neoplasm of the pancreatic head with invasion of the portal and/or superior mesenteric vein show the feasibility, relative safety and efficiency of resection of these major veins. In the majority of patients surgical treatment may be performed in the radical volume and extended by liver resection in the event of resectable metastases. Considering the relatively favorable prognosis of the disease, liver resection for resectable metastases and disease progression may be performed: it is safe, it improves quality of life of patients, and extends the period without tumor manifestations.

Keywords: neuroendocrine neoplasm of the pancreas, gastropancreoduodenal resection, resection of the portal vein, resection of the superior mesenteric vein, resection of the liver.

Conflict of interest: nothing to disclose.

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Возможности хирургического лечения нейроэндокринной неоплазии головки поджелудочной железы, инвазирующей магистральные вены

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Аннотация

Цель – показать возможность и относительную безопасность резекции инвазированных опухолью воротной и/или верхней брыжеечной вен во время хирургического лечения нейроэндокринной неоплазии головки поджелудочной железы, а также возможность симультанной резекции печени по поводу резектабельных метастазов у больных с IV стадией заболевания во время первичного оперативного вмешательства и при прогрессировании заболевания любой стадии после хирургического лечения.

Материал и методы. Хирургическое лечение 16 пациентов с нейроэндокринной неоплазией головки поджелудочной железы с инвазией верхней брыжеечной и/или воротной вен III–IV стадии высокой и умеренной степени дифференцировки (G1 и G2) включало стандартную гастропанкреатодуоденальную резекцию в 87,5% случаев, расширенную гастропанкреатодуоденальную резекцию с аортоковальной лимфодиссекцией – в 6,25% и панкреатэктомию – в 6,25%. Во время стандартной операции у одной больной (6,25%) провели сегментарную резекцию печени для удаления метастаза. Частота резекций воротной вены составила 6,25%, верхней брыжеечной вены – 50%, обеих магистральных вен – 43,8%. Неоадъювантную терапию не проводили, адъювантное лечение по схеме XELOX получили 3 (18,8%) человека. Статистическую обработку результатов исследования выполнили на основе статистического пакета программ Statistica for Windows v.10 и SPSS v21. Полученные различия считали статистически значимыми при уровне значимости $p \leq 0,05$ (≥95% точность). Для расчета выживаемости использовали метод Каплана – Мейера с оценкой достоверности различий по log-rank test.

Результаты. Частота хирургического лечения в объеме R0 составила 93,8%, частота осложнений оперативного вмешательства III и выше класса по шкале Clavien – Dindo – 43,8% при общей частоте всех осложнений – 75%. Основные осложнения – гастростаз (50,1%), аррозивное кровотечение (18,8%), кровотечение из острой язвы желудочно-кишечного тракта (18,8%), пневмония (18,8%). Частота послеоперационного тромбоза воротной и/или верхней брыжеечной вен – 12,5%, несостоятельности панкреатодигестивного анастомоза – 12,5%, несостоятельности билиодигестивного анастомоза – 6,3%, панкреатического свища – 12,5%. Релапаротомию выполнили 2 (12,5%) пациентам, которые впоследствии умерли от осложнений хирургического лечения в виде несостоятельности панкреатодигестивного анастомоза с аррозивным кровотечением. Прогрессирование болезни выявили у 10 (62,5%) человек в сроки от 3 до 69,3 месяца (медиана времени до выявления прогрессирования 39,7 [7,1; 52,8] месяца, летальность от прогрессирования – 50%. Местный рецидив развился у 12,5% больных, метастазы в забрюшинные лимфатические узлы – у 6,25%, метастазы в печень – у 43,75%, в двух случаях выполнена резекция печени по поводу метастазов. При прогрессировании все больные получали противоопухолевое лечение аналогами пролонгированного соматостатина. Медиана общей выживаемости составила 70,1 месяца, медиана выживаемости без признаков прогрессирования заболевания – 49,2 месяца, однолетние показатели выживаемости – соответственно 81,2% и 78,6%, трехлетние – 68,2% и 63,5%, пятилетние – 68,2% и 36,3%, десятилетние – 20,55% и 18,1%.

Заключение. Результаты хирургического лечения пациентов с нейроэндокринной неоплазией головки поджелудочной железы с инвазией воротной и/или верхней брыжеечной вен свидетельствуют о допустимости, относительной безопасности и эффективности резекций этих магистральных вен. У большинства пациентов хирургическое лечение можно провести в радикальном объеме, а также дополнить резекцией печени по поводу резектабельных метастазов. Учитывая относительно благоприятный прогноз заболевания, можно проводить резекцию печени по поводу резектабельных метастазов и при прогрессировании болезни: это безопасно, улучшает качество жизни пациентов и продлевает период без проявлений опухоли.

Ключевые слова: нейроэндокринная неоплазия поджелудочной железы, гастропанкреатодуоденальная резекция, резекция воротной вены, резекция верхней брыжеечной вены, резекция печени.

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НЭН – нейроэндокринная неоплазия; ПЖ – поджелудочная железа; ЖКТ – желудочно-кишечный тракт; ВВ – воротная вена; ВБВ – верхняя брыжеечная вена; ГПДР – гастропанкреатодуоденальная резекция.

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INTRODUCTION

Currently, there are relatively few publications in the literature addressing the frequency, characteristics, and outcomes of major venous resections in patients with locally advanced pancreatic neuroendocrine neoplasms (NENs) invading the portal and superior mesenteric veins. This may be explained by the low incidence of NENs (ca. 2% among oncological diseases of the pancreas and the gastrointestinal (GI) tract) [1, 2]; however, in the opinion of L.R. McKenna, B.H. Edil (2014) [3], one in every ten tumors of the pancreas is a neuroendocrine neoplasm. The Practical recommendations for drug treatment of neuroendocrine neoplasias of the gastrointestinal tract and pancreas", published in 2023, recommend that surgical treatment be recommended for resectable processes, still, there is no unified solution on neo- and adjuvant therapy, and personalized approach and discussion by a multidisciplinary team are required [4].

According to the publications of the last 10–15 years, the frequency of resection of major vessels in the course of surgical treatment of patients with locally advanced pancreatic NENs of high and moderate differentiation (G1 and G2) is multiple-values ranging from 5% to 25% [5]. Thus, S.-P. Haugvik et al. (2013) performed resection and reconstruction of vessels during resection of the pancreas in 7 (9.3%) out of 75 patients

with invasion into the portal vein (PV), splenic vein, or the common hepatic artery and the celiac trunk[6], whereas A.L. Titan et al. (2020), in 25.3% [7].

As far as the complications of vascular resections are concerned, they are comparable with the complications of similar surgical treatment of neoplasias of the pancreatic head without vascular resections. The study of S.-P. Haugvik et al. had no complications of grade III–IV on the Clavien – Dindo scale or lethal outcomes after the resection of major veins and arteries in 7 patients [6]. A.L. Titan et al. report that 30-day mortality after resections of NENs involving resection and reconstruction of invaded major veins was 2% [7]. In 2024, A. Nießen et al. published results of surgical treatment of NENs with resection of the portal vein and/or superior mesenteric vein (SMV) in 54 patients [8]. The incidence of complications of grade IIIb and above on the Clavien – Dindo scale was 27.8% and was similar to the outcomes surgeries without vascular resection (13%, p=0.071). The incidence rate of portal vein thrombosis was 19%, relaparotomy, 33%, 90-day mortality, 2%.

AIM

To demonstrate the feasibility and relative safety of resection of the portal and/or superior mesenteric veins invaded by tumor during surgical treatment of the neuroendocrine neoplasm of the pancreatic head, as well as the feasibility of simultaneous resection of the liver for resectable metastases in patients with stage IV disease during primary surgery and at disease progression of any stage following surgical treatment.

MATERIAL AND METHODS

In this retrospective analysis, we included the data of 16 with NEN of the pancreatic head invading into the PV and/or SMV, who were examined or treated at the N.N. Blokhin National Medical Research Center of Oncology in 2001–2023. The study included 5 (31.3%) men and 11 (68.7%) women, aged at the moment of hospitalization from 22 to 62 years (median age: 51 years). In all of the patients, the tumor had no clinical hormonal activity, the size varying from 2.5 to 7 cm (median size: 5.3 cm). Stage T2N1M0 was identified in 1 (6.25%) patient, T4N0M0 in 12 (75%), T4N1M0 in 2 (12.5%) and T4N1M1 in 1 (6.25%). In 3 (18.8%) cases, high degree of tumor differentiation (G1) was diagnosed, and in 13 (81.2%) cases, moderate degree (G2). The median level of Ki-67 was 8.5%, and in patients from the SMV+PV group the marker credibly was higher than in the SMV group (14% vs. 4.5%, p= 0.032). In 4 (25%) patients, tumor invasion was identified into the duodenum, and in 3 (18.8%), into the duodenum and the choledochus. In 9 (56.3%) patients jaundice was identified at the time of hospitalization, and it required biliary drainage; its progression in the SMV+PV group was observed credibly more frequently than in the SMV group (100% vs. 25%, p=0.006). Standard pancreatoduodenectomy (PD) was performed in 14 (87.5%) patients; a mesenteric approach was used in 1 (6.25%) case; extended PD with aortocaval lymph node dissection was performed in 1 (6.25%) patient; and pancreatectomy was performed in 1 (6.25%). During standard PD, one female patient (6.25%) underwent a segmental liver resection to remove a metastasis. Resection of the PV was performed in 1 (6.2%) patients, SMV, in 8 (50%) patients; resection of both major veins (SMV+PV), in 7 (43.8%) patients. In 14 (87.5%) patients, circular resection of major veins was performed with the length of 2 to 5 cm (median length: 3.5 cm). In 9 (56.3%) cases, end-to-end anastomosis was performed, and in 5 (31.3%) cases, reconstruction with synthetic Gore-Tex prosthesis was performed. Two patients (12.5%) underwent partial (wedge) venous wall resection of major veins with a length of 1 to 3 cm (median: 2.0 cm); the repair was performed using a running suture. The portal vein clamp time for constructing a direct end-to-end anastomosis was from 13 to 16 minutes, while in the case of using a synthetic graft, it ranged from 22 to 32 minutes. Temporary bypass shunts were not created. Neoadjuvant therapy was not administered; adjuvant XELOX chemotherapy was given to 3 (18.8%) patients.

Statistical processing of the study results was performed in Statistica for Windows v.10 and SPSS v21. The obtained differences were considered statistically significant at p≤0,05 (≥95% accuracy). In order to calculate survival, the Kaplan-Meier method was used with differences evaluated for reliability using the log-rank test.

RESULTS

Out of the 16 patients, 15 (93.8%) underwent R0 surgery, and 1 (6.2%) underwent R2 surgery due to NEN invasion of the superior mesenteric artery and surrounding adipose tissue. The median duration of surgeries was 305 [265; 360] minutes (from 210 to 600 min.), and median intraoperative blood loss was 3000 [2100; 4850] mL (from 600 to 6500 mL).

Complications of surgical treatment were observed in 12 (75%) out of 16 patients: 7 (43.8%) patients had complications of grade III and above on the Clavien – Dindo scale. The incidence of early complications was 62.5% (10/16), early and late, 12.5% (2/16). In 3 (18.8%) patients, one complication developed, in 2 (12.5%), two, in 4 (25%), three, and in 3 (18.7%), four and more. The most frequent complications included gastric stasis (50.1%), arrosive hemorrhage (18.8%), gastrointestinal ulcer hemorrhage (18.8%) and pneumonia (18.8%). The types and the incidence rate of complications depending on the volume of the venous resection follow in Table 1.

Two (12.5%) female patients underwent relaparotomy for leakage efrom pancreato-digestive anastomosis with arrosive hemorrhage; both patients died due to complications of surgery.

The histopathological study of surgical specimens in 13 (81.3%) out of 16 patients confirmed invasion of the NEN of the pancreatic head to the surrounding adipose tissue. Retroperitoneal extraorgan invasion was verified in 10 (62.5%) cases, and perineural invasion in 6 (37.5%); in 3 patients extrapancreatic lesion was identified, in 2, intrapancreatic, in one patient, extra- and intrapancreatic lesions. The frequency of histologic confirmation of deformation of PV and/or SMV as per Nakao classification was as follows: type A – 33.3%, type B – 87.5%, type C – 75%, type D – 100%.

The median follow-up period of 16 patients was 62.6 [17.7; 98.2] months, the follow-up terms varying from 0.5 to 172.0 months. Disease progression was found in 10 (62.5%) patients after 3 to 69.3 months (median time before progression was found was 39.7 [7.1; 52.8] months). Local relapse developed in 2 (12.5%) patients, metastases in the liver in 7 (43.75%)

Complication		Volume of major vein resection						Total (n=16)	
		PV (n=1)		SMV (n=8)		SMV+PV (n=7)			
		Abs.	%	Abs.	%	Abs.	%	Abs.	%
Bilio-digestive anastomosis leakage		-	-	1	12,5	-	-	1	6,3
Pancreato-digestive anastomosis leakage		-	-	1	12,5	1	14,3	2	12,5
Pancreatic fistula (type)	Total	-	-	1	12,5	1	14,3	2	12,5
	B	-	-	1	12,5	-	-	1	6,3
	C	-	-	-	-	1	14,3	1	6,3
Gastric stasis		-	-	5	62,5	3	42,9	8	50,1
Intestinal fistula		-	-	1	12,5	-	-	1	6,3
Peritoneal abscess		-	-	1	12,5	-	-	1	6,3
Cholangitis		-	-	-	-	1	14,3	1	6,3
Arrosive hemorrhage		-	-	1	12,5	2	28,6	3	18,8
Gastrointestinal ulcer hemorrhage		-	-	2	25,0	1	14,3	3	18,8
SMV and/or PV thrombosis		-	-	1	12,5	1	14,3	2	12,5
PATE									
Diarrhea		-	-	1	12,5	-	-	1	6,3
Pneumonia		-	-	1	12,5	2	28,6	3	18,8
Pleuritis									
Multi-organ failure		-	-	-	-	2	28,6	2	12,5
Sepsis		-	-	1	12,5	1	14,3	2	12,5

Table 1. *Types and incidence rate of complications depending on venous resection during surgical treatment of patients with neuroendocrine neoplasm of the pancreatic head with invasion of major veins*

Таблица 1. *Виды и частота осложнений в зависимости от объема венозной резекции во время хирургического лечения пациентов с НЭН головки ПЖ с инвазией магистральных вен*

patients, metastases in the retroperitoneal lymph nodes in one (6.25%) patients. In the event of progression all patients received antitumor therapy with analogs of slow-release somatostatin. As of the end of the study, eight patients were dead and two patients were alive.

It is to be mentioned that out of the 7 patients with metastases to the liver, two female patients underwent liver resection in the course of anti-tumor treatment with analogs of slow-release somatostatin, after which they lived without manifestations of disease for two years when secondary progression of the NEN (metastases to the liver) developed.

One of these female patients (age: 22) underwent surgical treatment of stage III NEN (T4N0M0G2) in the volume of standard radical pancreatoduodenectomy with wall resection of the SMV with repair performed using a running suture. The metastasis to the liver was diagnosed 53 months after the surgery. The patient received no additional antitumor therapy. The patient underwent resection of the metastasis to the liver and received anti-tumor treatment with analogs of slow-release somatostatin. 24 months later, recurrent progression of the NEN was diagnosed (metastases to the liver and retroperitoneal lymph nodes). The patient died 100.6 months after the surgery.

The second female patient (age: 51) underwent surgical treatment of stage III NEN (T4N0M0G2) in the volume of radical extended pancreatoduodenectomy with circular resection of the PV with end-to-end anastomosis formation. After 66 months, metastases to the liver were found. The metastases were resected, and anti-tumor treatment with analogs of slow-release somatostatin was administered. 23 months later, metastases in the liver developed recurrently. The death was certified 99.5 months after surgical treatment of the NEN.

The overall survival median of the 16 patients with NEN of the pancreatic head with invasion in the major veins was 70.1 [11.4; 100.1] months, recurrence-free survival was 49.2 [14; 66.7] months; one-year survival was 81.2±9.8% and 78.6±11.0%, respectively; three-year survival was 68.2±11.8% and 63.5±13.1%, five-year survival, 68.2±11.8% and 36.3±14.0%, ten-year survival, 20.5±12.5% and 18.1±11.5%.

No statistically significant differences of any of the represented indicators depending on the volume of vein resection were identified ($p>0.05$).

DISCUSSION

Our findings match the data of A. Nießen et al. [8]. It follows from literature that the complications after the vascular resections in patients with neuroendocrine neoplasias of the pancreas are characterized with an acceptable incidence rate and low level of mortality in comparison with similar surgeries without vascular resections [9–11].

In almost all studies, remote oncological outcomes of pancreatic head resection with vascular reconstruction in patients with highly and moderately differentiated neuroendocrine tumors confirm favorable prognosis, especially in R0 resections and lack of remote metastases [12–14]. E.g., D.J. Birnbaum et al. (2015) report that the median overall survival of patients with locally advanced forms of pancreatic NENs was 90 months, five-year overall survival was 66%, and five-year recurrence-free survival was 26% [15]. In the study of A. Nießen et al. [8], the overall five-year survival of patients with NEN who underwent PV resection was 66.7% for G1 tumors and 51.2% for G2 tumors ($p=0.0008$), with greater difference in the five-year recurrence-free survival, 66.7% and 22.8%, respectively. For the entire group of patients after vascular resection, three-year overall survival was 66.4%, five-year survival – 44.6%, and ten-year survival reached 41.2%.

The surgical treatment for patients with pancreatic head NENs involving the SMV and/or PV is feasible, relatively safe, and can be combined with liver resection for resectable metastases. The 5-year overall and recurrence-free survival rates reach high values, supporting the viability and efficacy of vascular resections in pancreatic head NENs, provided the tumors are well- to moderately differentiated and surgical treatment is radical.

CONCLUSION

The outcomes of surgical treatment for patients with highly differentiated to moderately differentiated (G1, G2) pancreatic head NENs invading the PV and/or SMV support the feasibility, relative safety and efficacy of resecting these major veins. For the majority of patients, surgeries can be performed radically and appended with liver resection for resectable metastases. Considering the relatively favorable prognosis of the disease, resection of resectable liver metastases can be performed even upon disease progression at any stage. This approach is safe, it improves the patients' quality of life and prolongs the symptom-free period.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical Approval Statement. The article was performed as part of the dissertation "Angioplasty operations in abdominal oncology" for the degree of Doctor of Medical Sciences. The thesis topic was approved by the Scientific Council of the Scientific Research Institute of Clinical Oncology n.a. Academician of the Russian Academy of Sciences and the Russian Academy of Medical Sciences N.N. Trapeznikov, Blokhin National Research Medical Center of Oncology.	***Этическая экспертиза.*** Статья выполнена в рамках диссертации «Ангиопластические операции в абдоминальной онкологии» на соискание ученой степени доктора медицинских наук. Тема диссертации утверждена на ученом совете НИИ Клинической онкологии имени академика РАН и РАМН Н.Н. Трапезникова ФГБУ НМИЦ онкологии имени Н.Н. Блохина Минздрава России.
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Contribution of individual authors. Abgaryan M.G., Berdnikov S.N., Avdyukhin I.G., Belozerskikh A.M.: data collection, analysis and interpretation, preparation of the text of the article. Abgaryan M.G., Kotelnikov A.G.: study concept and design. Peregorodiev I.N., Polyakov A.N.: 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.*** Абгарян М.Г., Бердников С.Н., Авдюхин И.Г., Белозерских А.М.: сбор, анализ и интерпретация данных, подготовка текста статьи. Абгарян М.Г., Котельников А.Г. – концепция и дизайн работы. Перегородиев И.Н., Поляков А.Н. – редактирование текста статьи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	***Доступ к данным.*** Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	***Генеративный искусственный интеллект.*** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
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Quality of life assessment in patients with prostate cancer using the FACT-P questionnaire: linguistic and cultural adaptation of the Russian version

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Abstract

Aim – to perform linguistic and cultural adaptation of the international FACT-P (Functional Assessment of Cancer Therapy – Prostate) questionnaire for Russian-speaking patients with prostate cancer and to evaluate its psychometric properties.

Material and methods. The adaptation process included forward and backward translation, expert review, pilot testing (n = 50), and psychometric validation. Internal consistency was assessed using Cronbach's alpha coefficient, test/retest reliability via intraclass correlation coefficient (ICC), and construct validity by factor analysis.

Results. The Russian version of FACT-P demonstrated high internal consistency across all subscales (α = 0.78–0.89), excellent test/retest reliability (ICC = 0.91), and construct validity confirmed by factor analysis. All five theoretically defined domains – physical, social, emotional, functional well-being, and prostate cancer-specific symptoms – were reliably reproduced in the sample. Most respondents noted the clarity of the wording and the relevance of the content.

Conclusion. The adapted Russian-language version of the FACT-P questionnaire is a reliable, valid, and clinically significant tool for assessing the quality of life in patients with prostate cancer. It is recommended for use in clinical practice and research.

Keywords: prostate cancer, quality of life, FACT-P, adaptation, validity, psychometrics.

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Оценка качества жизни больных раком предстательной железы с помощью опросника FACT-P: языковая и культурная адаптация русскоязычной версии

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Аннотация

Цель – провести языковую и культурную адаптацию международного опросника FACT-P (Functional Assessment of Cancer Therapy – Prostate) для русскоязычных пациентов с раком предстательной железы и оценить его психометрические характеристики.

Материал и методы. Процедура адаптации включала прямой и обратный перевод, экспертную оценку, пилотное тестирование (n = 50) и психометрическую валидацию. Внутренняя согласованность оценивалась по коэффициенту α Кронбаха, ретестовая надежность – по внутриклассовой корреляции (ICC), конструктивная валидность – с использованием факторного анализа.

Результаты. Русскоязычная версия FACT-P показала высокую внутреннюю согласованность по всем шкалам (α = 0,78–0,89), отличную ретестовую надежность (ICC = 0,91) и конструктивную валидность, подтвержденную факторным анализом. Все пять теоретически заложенных доменов – физическое, социальное, эмоциональное, функциональное благополучие и специфические симптомы рака предстательной железы – достоверно воспроизвелись в выборке. Большинство респондентов отметили ясность формулировок и релевантность содержания.

Выводы. Адаптированная русскоязычная версия опросника FACT-P является надежным, валидным и клинически значимым инструментом для оценки качества жизни пациентов с раком предстательной железы. Она рекомендована к применению в клинической практике и научных исследованиях.

Ключевые слова: рак предстательной железы, качество жизни, FACT-P, адаптация, валидность, психометрия.

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Список сокращений
РПЖ – рак предстательной железы; КЖ – качество жизни; FACT-P – опросник оценки функционального состояния при терапии рака простаты; PWB – физическое благополучие; SWB – социальное и семейное благополучие; EWB – эмоциональное благополучие; FWB – функциональное благополучие; PCS – шкала специфических симптомов при раке предстательной железы; ICC– внутриклассовая корреляция; FACIT – фонд оценки функционального состояния при терапии заболеваний.

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INTRODUCTION

Measurement of quality of life (QOL) of patients with prostate cancer (PC) becomes ever more important given the steady growth of morbidity and mortality from the disease [1]. Globally, in 2024 ca. 1.47 million new cases of PC were registered, i.e. approx. 29.4 cases per 100,000 men; and Russia ranked fourth in the absolute number of new cases (52,712), the indicator of standardized incidence rate being approx. 47.4 per 100,000 men. According to the analysis of dynamics in the Russian Federation, within the period from 1993 to 2019 the incidence rate increased from 9.7 to 44.2 per 100,000, reflecting both the ageing of population and better availability and quality of diagnostics [2, 3]. Modern concepts of medical aid in PC recognize importance of evaluation of subjective condition of patients, including physical, emotional and functional health and social well-being as integral components of treatment outcomes [4]. The FACT-P questionnaire (Functional Assessment of Cancer Therapy – Prostate) was designed specifically for PC patients. It is widely used in international clinical studies and practical monitoring [5].

Despite the recognition of FACT-P in English-language and international studies, the Russian medical community does not yet have an officially published, methodologically justified and psychometrically valid version of this tool, adapted with respect to linguistic and cultural specifics of Russian-speaking patients [6, 7]. The classic adaptation procedure involves direct and back translation, cognitive interviewing with native speakers, pilot testing and further statistical confirmation of reliability and validity (e.g., Cronbach's coefficient calculation, factor analysis) [7, 8]. Lack of such a version might result in a measurement of a biased or incomplete recognition of QOL in a cohort of male patients with PC [9, 10].

The advent of a validated Russian-language version of the FACT-P questionnaire will significantly improve the accuracy and reproducibility of scientific research related to assessment of QOL, and to integrate the results of Russian scientific research into international meta-analyses and clinical trials [11, 12]. Besides, this will create a background for customized approaches in clinical practice that will register clinically significant changes in the patients' condition, monitor the long-term effect of therapy and improve daily living and psychological well-being [13–16]. Thus, the language and cultural adaptation of the Russian-language version of the FACT-P questionnaire is not merely important but an indispensable component of follow-up of PC patients in the Russian-language community that will foster improvement of quality of medical aid and a deeper scientific understanding of therapeutic effect on prostate cancer.

AIM

To perform linguistic and cultural adaptation of the international FACT-P (Functional Assessment of Cancer Therapy – Prostate) questionnaire for Russian-speaking patients with prostate cancer and to evaluate its psychometric properties.

MATERIAL AND METHODS

The procedure complied with international recommendations on adaptation of questionnaires in the field of healthcare. It comprised the following consecutive stages: direct translation, approval, back translation, expert assessment, pilot testing and statistical testing of reliability and validity. The direct translation of the original English version of the FACT-P questionnaire was performed by two independent translators with professional competences in the area of medicine and psychology. Special attention was paid to preserve semantic and conceptual equivalence of wording, as well as to take into account the cultural context. Once the preliminary Russian version was complete, the approval stage took place that involved clinical experts; it produced a reconciled version respecting the idiomatic features of the Russian language. In the next step, the independent translators, native speakers of English, who had no access to the original, made a back translation. The comparison of the back translation with the original enabled rectification of the minor notional and stylistic discrepancies. The final version of the questionnaire was presented to the multidisciplinary expert commission that involved oncologists, a psychiatrist, a clinical psychologist and a linguist. The commission performed a comprehensive analysis of the translated statements with the concepts of the original tool and assessed the transparency, neutrality and cultural relevance of each item.

The adapted questionnaire was tested on a sample of 50 with a verified diagnosis of prostate cancer who were in various stages of treatment at the Granov Russian Research Center of Radiology and Surgical Technologies. The average age of respondents was 67.3 ± 6.2 years. All respondents were speakers of Russian, had no cognitive disorders, and provided an informed written consent for

the participation in the study. The participants filled out the questionnaire by themselves. After that, interviews were conducted to identify difficulties experienced by patients in understanding of individual statements. Based on the feedback, some editorial changes were made to the questionnaire. To assess the internal concordance of the adapted version, the Cronbach's α-coefficient was used. The α values for all subscales varied from 0.78 to 0.90, which indicates a high degree of reliability. The constructive validity was tested by expert assessment and comparison with clinical characteristics of patients. Focus was made on sensitivity of the instrument on the differences in the patients' condition, which allows its use in the dynamic follow-up and assessment of treatment efficacy. Re-test reliability was assessed by a repeated filling-up of the questionnaire after 7-10 days in a subgroup of patients; however, specific ICC indicators within this publication are not provided.

The study was performed in compliance with the principles of Helsinki declaration and was approved by the local ethical committee of the medical institution. All participants signed an informed consent for the participation in the study and processing of personal data.

RESULTS

The average time of questionnaire completion was 12.4 ± 3.1 minutes. The questionnaire included 39 statements grouped for the following subscales: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB) and prostate cancer subscale (PCS). Each statement was assessed on a 5-point scale from 0 ("not at all") to 4 ("very much").

The test of internal concordance using the Cronbach's α-coefficient yielded the following values: physical well-being (PWB): α = 0.83; social/family well-being (SWB): α = 0.81; emotional well-being (EWB): α = 0.78; functional well-being (FWB): α = 0.85; prostate cancer subscale (PCS): α = 0.88. The total internal concordance of the questionnaire was α = 0.89, which indicates the high reliability of the diagnostic tool. The values are within the range that is similar or exceeds the parameters of the original English version of the FACT-P tool.

Re-test reliability was analyzed on a subgroup of 20 patients who completed the questionnaire for a second time 7 days later. The in-class correlation coefficient (ICC) for the total score was 0.91 (95% CI: 0.86–0.96), which shows the high re-test reliability.

Following the results of the testing, after completing the questionnaire 92% of participants reported that the questionnaire was quite clear, 86% noted that it reflected their current condition, 74% commented that completion of the questionnaire helped them structure their own sensations and complaints. None of the participants refused from completing the questionnaire. The values of the Cronbach's α-coefficient in all scales exceed the threshold value of 0.70, which confirms the high internal concordance of the Russian version of the FACT-P questionnaire. The values in the prostate cancer subscale (PCS) and functional well-being (FWB) subscales are especially high, which emphasizes their stability and informative value in the assessment of the clinical condition of the patients.

To assess the constructive validity of the Russian version of the FACT-P questionnaire, a factor analysis by method of main components with Varimax rotation was performed. It included 15 statements representative for each of the five scales of the original instrument. In the end, five factors were identified that matched the theoretically justifies structure of the questionnaire. Taken together, they explained 66.4% of the total dispersion (**Table 1**).

F1, physical well-being (PWB), brings together the statements on the somatic symptoms of the patient including fatigue, pain, and necessity of staying in bed. The most typical statements were: "I have a lack of energy" (PWB1), "I have nausea" (PWB2), "Because of my physical condition, I have trouble meeting the needs of my family" (PWB3). The high factor loads (0.75 to 0.81) indicate a preserved physical status, whereas the low ones indicate the manifested somatic symptoms that lower the quality of life.

F2, social and family well-being (SWB), includes the statements that evaluate support from friends and family, degree of satisfaction with social interactions and role

Statement	Factor 1 (PWB)	Factor 2 (SWB)	Factor 3 (EWB)	Factor 4 (FWB)	Factor 5 (PCS)
PWB1	0,78	0,10	0,09	0,12	0,08
PWB2	0,75	0,10	0,09	0,12	0,08
PWB3	0,81	0,10	0,09	0,12	0,08
SWB1	0,12	0,82	0,09	0,12	0,08
SWB2	0,12	0,79	0,09	0,12	0,08
SWB3	0,12	0,77	0,09	0,12	0,08
EWB1	0,09	0,11	0,80	0,11	0,08
EWB2	0,09	0,11	0,78	0,11	0,08
EWB3	0,09	0,11	0,76	0,11	0,08
FWB1	0,11	0,11	0,10	0,85	0,08
FWB2	0,11	0,11	0,10	0,82	0,08
FWB3	0,11	0,11	0,10	0,83	0,08
PCS1	0,09	0,09	0,08	0,09	0,79
PCS2	0,09	0,09	0,08	0,09	0,82
PCS3	0,09	0,09	0,08	0,09	0,81

Notes: *the abbreviations stand for scales and statements within the structure of the FACT-P (Functional Assessment of Cancer Therapy – Prostate) questionnaire: PWB – Physical Well-Being; SWB – Social/Family Well-Being; EWB – Emotional Well-Being; FWB – Functional Well-Being ; PCS – Prostate Cancer Subscale. The figures (1–3) after each abbreviation designate specific statements included in the analysis for each of the scales, e.g. PWB1 stands for the first statement in the Physical Well-being scale.*

Примечания: *сокращения отражают шкалы и утверждения, входящие в структуру опросника FACT-P (Functional Assessment of Cancer Therapy – Prostate): PWB – Physical Well-Being / Физическое благополучие; SWB – Social/Family Well-Being / Социальное и семейное благополучие; EWB – Emotional Well-Being / Эмоциональное благополучие; FWB – Functional Well-Being / Функциональное благополучие; PCS – Prostate Cancer Subscale / Специфические симптомы при раке предстательной железы. Цифры (1–3) после каждой аббревиатуры обозначают отдельные утверждения, включенные в анализ по каждой шкале. Например, PWB1 – первое утверждение шкалы физического благополучия.*

Таблица 1. *Факторная нагрузка утверждений опросника FACT-P по шкалам (вариант адаптации)*

Table 1. *Factor Loadings of FACT-P Questionnaire Items by Subscales (Adapted Version)*

№	Statement	0	1	2	3	4
	Physical well-being					
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
	Social/family well-being:					
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section*					
GS7	I am satisfied with my sex life	0	1	2	3	4
	Emotional well-being					
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
	Functional well-being					
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4
	Other concerns					
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Notes: 0 – "Not at all", 1 – "A little bit", 2 – "Somewhat", 3 – "Quite a bit", 4 – "Very much"
Примечания: 0 – «Нет», 1 – «Немного (слабо)», 2 – «Время от времени (не сильно)», 3 – «Периодически (довольно сильно)», 4 – «Очень часто (очень сильно)».

Table 2. *Russian-language version of FACT-P*
Таблица 2. *Бланк русскоязычной версии опросника FACT-P*

of interpersonal relations. It has the following typical statements: "I get emotional support from my family" (SWB2), "I get support from my friends" (SWB3). The range of factor loads is from 0.77 to 0.82. This component reflects the role of social support as a factor of adaptation to the disease, the high values showing the availability of the emotional and social resource of the patient.

F3, the patient's emotional well-being (EWB), describes the emotional reactions to the disease, including anxiety, depression, fear of progression and confidence in getting over the disease, and includes the following statements: "I feel sad" (EWB1), "I am losing hope in the fight against my illness" (EWB3). The factor loads vary from 0.76 to 0.80, the high scores showing the patient's emotional stability, and the low scores showing the presence of manifestations of depression and anxiety.

F4, the functional well-being (FWB), includes statements that assess the patient's capability of performing daily actions, to work, and to enjoy life: "I am able to work" (FWB1), "I am able to enjoy life" (FWB3). The variability of factor loads is within the range of 0.82 to 0.85 and reflects the degree of preserved activity and independence of the patient. Low scores indicate functional limitations.

F5, the prostate cancer subscale (PCS), comprises the symptoms characteristic of the prostate cancer specifically, such as dysuric disorders, pelvic pain, decrease of the sexual function. The typical statements include "I feel difficulty urinating" (PCS3), "I am able to feel like a man" (PCS5). The factor loads vary from 0.79 to 0.82. The high scores show good coping with specific symptoms, and the low scores reflect the manifested effect of the disease on the urogenital function and the patient's self-sentiment.

The results of the factor analysis confirm the theoretically expected structure of the FACT-P questionnaire matching its original model. A clear distribution of statements into components shows the high constructive validity of the Russian version of the tool. This facilitates its use both in scientific research and in routine clinical practice for a complex assessment of various aspects of quality of life of patients with prostate cancer.

Once the linguistic and cultural adaptation of the FACT-P questionnaire was completed and the psychometric properties of the tool were validated, the final version of the questionnaire was compiled (**Table 2**).

CONCLUSION

The linguistic and cultural adaptation of the FACT-P questionnaire for the Russian-speaking prostate cancer patients was performed in compliance with international standards and methodological recommendations of FACIT.org. In the course of the study, it was possible to create a relevant, semantically precise and psychometrically justified version of the document suitable for use in the Russian clinical and scientific practice. The obtained results confirm the high internal concordance of the scales (Cronbach's α from 0.78 to 0.89), excellent re-test capability (ICC = 0.91), as well as constructive validity confirmed by a factor analysis. All five specified factors (physical, family/social, emotional and functional well-being) and specific symptoms of the prostate cancer aligned with the original structure of the questionnaire and reliably reflected the stated domains of the quality of life. Besides, we confirmed the sensitivity of this instrument towards clinical differences between the patients.

The Russian version of FACT-P was praised by the patients and medical professionals as a clear, informative and clinically useful instrument. It may be used for dynamic follow-up of quality of life, monitoring of side effects of therapy and assessment of efficacy of oncological treatment from the patient's perspective.

The validated Russian version of FACT-P may be recommended for wide use in practical oncourology as well as in multi-center studies including Russian-speaking respondents. This will improve the quality of diagnostics, rehabilitation and personalized oncological assistance in Russia and Russian-speaking countries.

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Original study article | Оригинальное исследование
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Transmesenteric approach in the surgical treatment of left kidney cancer with venous tumor thrombus of Mayo levels 0–I

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Abstract

Aim – to evaluate the efficacy and safety an original transmesenteric approach for laparoscopic nephrectomy with thrombectomy in patients with left kidney cancer and venous tumor thrombus (levels 0–I according to the Mayo classification).

Material and methods. The study included 19 patients with histologically verified left kidney cancer who underwent laparoscopic nephrectomy with thrombectomy using a transmesenteric approach. Eleven patients had renal vein thrombus (Mayo level 0), and eight patients had thrombus extending into the inferior vena cava up to 2 cm from the renal vein orifice (Mayo level I). The following parameters were assessed: age, body mass index, operative time, intraoperative blood loss, hospital stay, and postoperative complications.

Results. All procedures were completed laparoscopically without conversion. The mean operative time was 125.8 ± 11.4 min, and the mean blood loss was 152.6 ± 62.9 ml. The mean hospital stay was 7.4 ± 0.6 days. No early or late complications were recorded. Operative time and blood loss were significantly lower compared to previously published series of laparoscopic and open procedures. Conclusion. The transmesenteric approach minimizes surgical trauma, reduces operative time and blood loss, and lowers the risk of complications while maintaining oncological radicality. The method can be recommended for widespread use in onco-urological practice.

Keywords: renal cell carcinoma; venous tumor thrombus; laparoscopic nephrectomy; thrombectomy; transmesenteric approach.
Conflict of interest: nothing to disclose.

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Трансмезентериальный доступ в хирургическом лечении рака левой почки с опухолевым венозным тромбозом 0–I уровня

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Аннотация

Цель – оценить эффективность и безопасность оригинального трансмезентериального доступа при лапароскопической нефрэктомии с тромбэктомией у пациентов с раком левой почки и опухолевым венозным тромбозом 0–I уровня по классификации Mayo.

Материал и методы. В исследование включены 19 пациентов с верифицированным раком левой почки, которым выполнена лапароскопическая нефрэктомия с тромбэктомией трансмезентериальным доступом. У 11 больных выявлен тромб, ограниченный почечной веной (0 уровень по Mayo), у 8 – распространение тромба в нижнюю полую вену до 2 см от устья почечной вены (I уровень). Оценивались возраст, индекс массы тела, продолжительность операции, объем кровопотери, длительность госпитализации, наличие осложнений.

Результаты. Все вмешательства завершены лапароскопически, конверсий не потребовалось. Средняя продолжительность операции составила 125,8 ± 11,4 мин, средний объем кровопотери – 152,6 ± 62,9 мл. Средняя длительность госпитализации составила 7,4 ± 0,6 суток. Ранних и поздних осложнений в исследуемой группе не зарегистрировано. Показатели длительности операции и кровопотери были достоверно ниже, чем в опубликованных сериях лапароскопических и открытых операций.

Заключение. Трансмезентериальный доступ позволяет минимизировать травматичность вмешательства, сократить продолжительность операции, снизить кровопотерю и риск осложнений при сохранении онкологической радикальности. Методика может быть рекомендована для широкого применения в онкоурологической практике.

Ключевые слова: почечно-клеточный рак; опухолевый венозный тромбоз; лапароскопическая нефрэктомия; тромбэктомия; трансмезентериальный доступ.
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ПКР – почечно-клеточный рак; НПВ – нижняя полая вена; ИМТ – индекс массы тела.

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INTRODUCTION

Renal cell cancer (RCC) remains a significant oncological problem in many countries [1]. According to the GLOBOCAN report, a total of 434,480 new cases of renal cancer were registered worldwide in 2022, and there is a tendency for the morbidity rate to grow (considering improved visualization techniques, demographic changes and such risk factors as obesity and arterial hypertension) [2]. In Russia, every year approx. 25,000 new cases of renal cancer are registered [3]. Epidemiologic data show that the age-standardized incidence rate in the Russian Federation is ca. 13-14 cases per 100,000 population for both men and women [4]. One of the characteristic features of RCC is the venous extension of the tumor: the venous tumor thrombus (VTT) is found in approx. 10% patients with RCC [5]. The growth of the thrombus level complicates the surgical approach, increases the risk of complications and impacts the prognosis [6].

To describe the incidence rate of the VTT, the Mayo classification is widely used (also known as the Mayo grading, or Mayo levels). Accordingly, the following levels are identified: 0 – tumor thrombus is limited to the renal vein; I – tumor thrombus extends to the inferior vena cava (IVC), apex < 2 cm from the venous entry; II – tumor thrombus extends into the IVC more than 2 cm above the entry but below the hepatic veins; III – tumor thrombus extends above the level of hepatic veins but below the diaphragm; IV – tumor thrombus extends above the diaphragm and may extend to the right atrium [7, 8].

The survival of RCC patients largely depends on the level of VTT and the presence of metastases, condition of lymph nodes and attendant characteristics of the tumor [9, 10]. In the Mayo Clinic experiment that analyzed 540 RCC patients and tumor thrombus over three decades, the five-year specific survival at thrombus level 0 was ca. 49.1%, while with the involvement of the IVC (levels I–II–III–IV), it was significantly lower (e.g., level I, ~31,7%, level II, ~26,3%) [11].

The study of Z. Chen *et al.* (2021), including 121 patients, demonstrated higher values of overall survival (OS) in thrombus levels 0 and I: 3-year OS was approx. 59%, 5-year OS, approx. 47%, in higher thrombus levels, 5-year OS lowered to ~32% [12]. In patients with thrombus levels 0–II, 5-year survival was approx. 46.7% [13]. Russian literary sources also report an increase in the diagnosing of the renal cancer, including that of early stages [14].

However, the data on the prevalence of the venous thrombosis, especially on levels 0–I, as well as detailed survival values for such patients in the Russian practice remain insufficient and fragmentary [15].

While the treatment standard of the renal cancer with venous tumor thrombus is the radical nephrectomy with thrombectomy, the technical aspects of the surgery remain a subject of discussion [16]. In order to adequately mobilize the left kidney, the traditional laparoscopic access requires dissection of the lienocolic and splenophrenic ligaments, as well as mobilization of the descending colon [14]. This increases the duration of the operation and involves risk of damaging the wall of the colon and of the spleen, which might result in serious intra- and postoperative complications.

Another problem is the necessity of mobilization of the ascending colon to ensure access to retroperitoneal space if the tumor thrombus has extended into the inferior vena cava [17]. Such manipulations involve the risk of injuring the liver and increase the probability of development of postoperative peritoneal adhesions and intestinal obstruction [18]. This necessitates development of new surgical methods that enable minimization of injury and improve results of surgery while preserving its radicality.

The designed method of laparoscopic mesenteric approach to the left kidney covered by the Russian Federation patent No.2803686 (dated 19.09.2023) enables minimization of the risks of the standard approach[1]. The access is achieved through the mesentery of the sigmoid colon, which excludes the necessity of mobilization of the mobilization of the descending colon and dissection of the lienocolic and splenophrenic ligaments. The method lowers the risk of injury of the colon and the spleen, reduces surgery time and increases its safety while providing an adequate approach to the inferior vena cava without a large-scale mobilization of the ascending colon. This reduces the probability of injuring the liver as well as the risk of postoperative adhesions. The surgery is performed with the patient in the supine position, ergonomically optimal both for the team of surgeons and anesthesiologists and for the patient. Lack of necessity of changing the body position during the operation further decreases the risks of implantation metastases and of the loss of sterility of the surgical area. Transmesenteric approach combines minimized injury, comfort of the patient's and the surgeon's positioning, as well as reproducibility, which allows regarding the method as an alternative to the standard laparoscopic approach.

[1] Мирзабеков М.К., Богомолов О.А., Школьник М.И. Патент РФ «Способ лапароскопической радикальной левосторонней нефрэктомии с тромбэктомией из нижней полой вены». Доступно по: https://patents.google.com/patent/RU2803686C1/ru

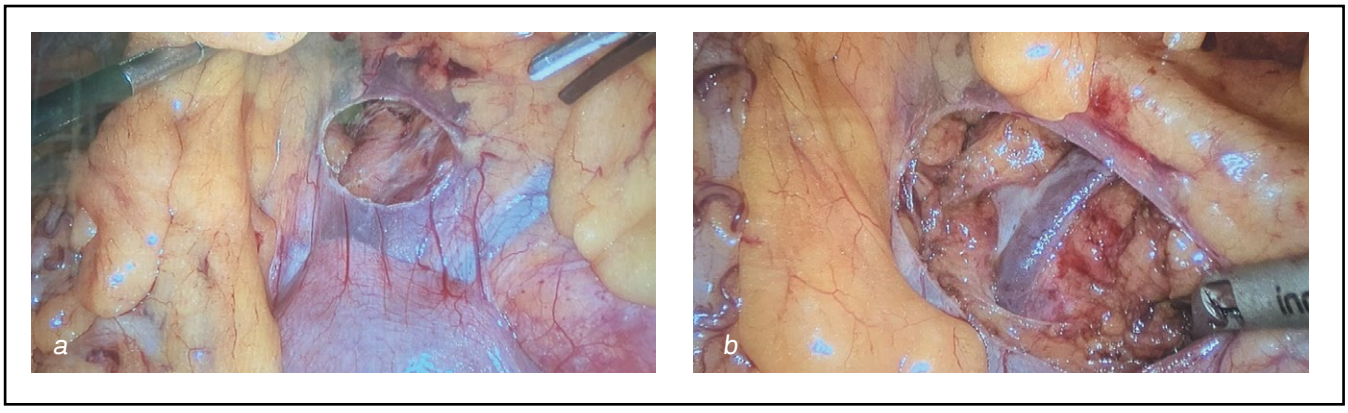

Figure 1. *Stages of transmesenteric approach formation: a – creation of a window in the mesentery of the descending colon; b – completed access to the left kidney, left renal vein with tumor thrombus in its lumen.*

Рисунок 1. *Этапы формирования трансмезентериального доступа: a – формирование «окна» в брыжейке нисходящей ободочной кишки; b – сформированный доступ к левой почке, левая почечная вена с опухолевым тромбом в ее просвете.*

AIM

To evaluate the efficacy and safety of using the original transmesenteric approach for laparoscopic nephrectomy with thrombectomy in patients with left kidney cancer and venous tumor thrombus (levels 0-I according to the Mayo classification).

MATERIAL AND METHODS

The study included 19 patients with histologically verified left kidney cancer with venous tumor thrombus who underwent laparoscopic nephrectomy with thrombectomy using a transmesenteric approach. Eleven patients had renal vein thrombus (Mayo level 0), and eight patients had thrombus extending into the inferior vena cava up to 2 cm from the renal vein orifice (Mayo level I).

Inclusion criteria: patients with left kidney cancer and venous tumor thrombus of levels 0-I as per Mayo classification, no remote metastases, ECOG 0-2 somatic status.

Exclusion criteria: identification of level II-IV thrombus, bilateral damage, severe comorbidities precluding the feasibility of laparoscopic intervention.

The surgical technique is illustrated with intraoperative images: formation of a 'window' in the mesentery of the descending colon and the final formed tramsmesenteric approach to the left kidney with visualization of the left renal vein (**Fig. 1**).

Study design: prospective single-center study.

Assessed parameters: age, body mass index (BMI), duration of the surgery, blood loss, duration of hospital stay, status of early (less than 30 days) and ate complications. The efficacy of the method was assessed with the feasibility of radical surgery without the need of conversion, level of blood loss and duration of the surgery. The safety was assessed with the aid of frequency of complications and specific features of the postoperative period.

Statistical processing of data was performed in the standard software suites (MedCalc; Microsoft Excel 2019). Quantitative indicators were described using mean values (M), standard deviation (SD), median (Me), minimum and maximum values, as well as 95% of confidence intervals (95% CI). The normality of quantitative data distribution was assessed using the Shapiro-Wilk test. For variables with approximately normal distribution, the single-sample Student's t-test was used. In cases of deviation from normality, the Wilcoxon signed-rank test was additionally applied. All comparisons were conducted using two-tailed tests at a statistical significance level of $p < 0.05$. For visual representation of the results, graphical visualization methods were used: histograms were constructed for the distribution of age, BMI, blood loss volume, duration of the surgery, and length of hospital stay (bed-days).

RESULTS

Out of the 19 patients with left kidney cancer, in 11 (57.9%) patients the thrombus was in the renal vein (level 0); in 8 (42.1%) patients, the thrombus extended to the inferior vena cava up to 2 from the renal vein orifice (level I).

The age of the patients varied from 54 to 76 years, the average age being 64.5 ± 5.6 years, median: 65 years (95% CI 61.8–67.2). **Fig. 2** shows patient distribution by age matching the symmetric normal distribution.

The mean BMI values was 26.0 ± 1.8 kg/m^2 (23.7 to 30.1 kg/m^2), median: 25.7 kg/m^2. The majority of patients had a normal or moderately elevated BMI, which is characteristic of the general distribution for individuals of this age group (**Fig. 3**).

The mean duration of hospital stay was 7.4 ± 0.6 days (7 to 9), median: 7 days (**Fig. 4**).

The majority of patients were discharged within the first week after the operation, which reflects the relatively low

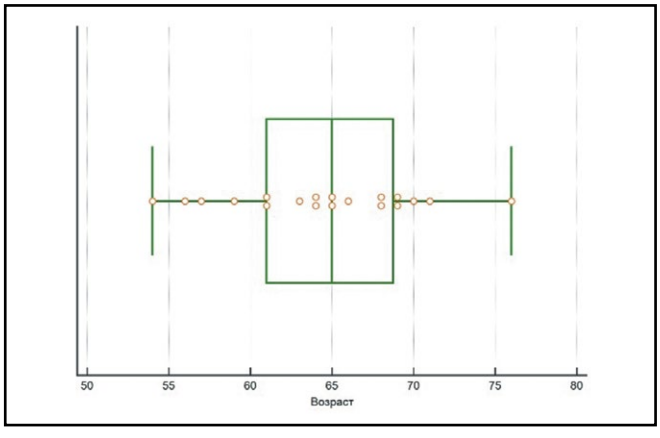

Figure 2. *Distribution of patient age in the study cohort (n = 19).*

Рисунок 2. *Распределение возраста пациентов, включенных в исследование (n = 19).*

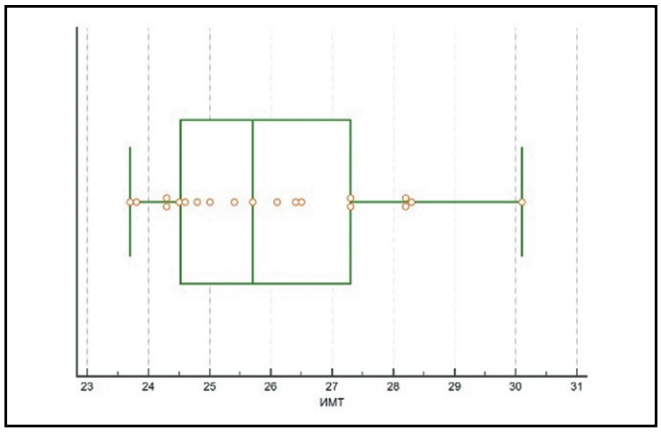

Figure 3. *Distribution of body mass index (BMI) in the study cohort (n = 19).*

Рисунок 3. *Распределение индекса массы тела (ИМТ) пациентов, включенных в исследование (n = 19).*

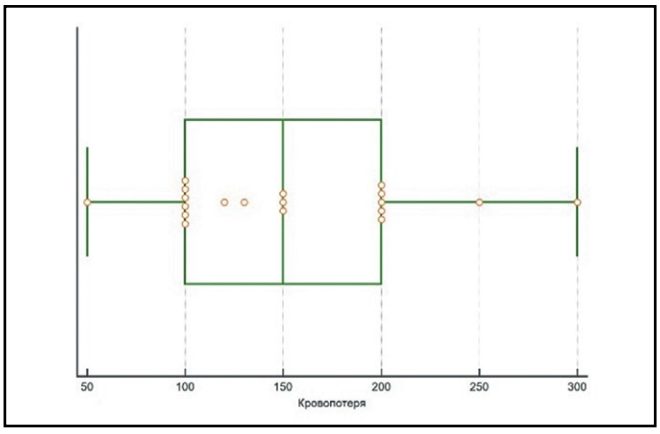

Figure 5. *Distribution of intraoperative blood loss in the study cohort (n = 19).*

Рисунок 5. *Распределение объема интраоперационной кровопотери у пациентов, включенных в исследование (n = 19).*

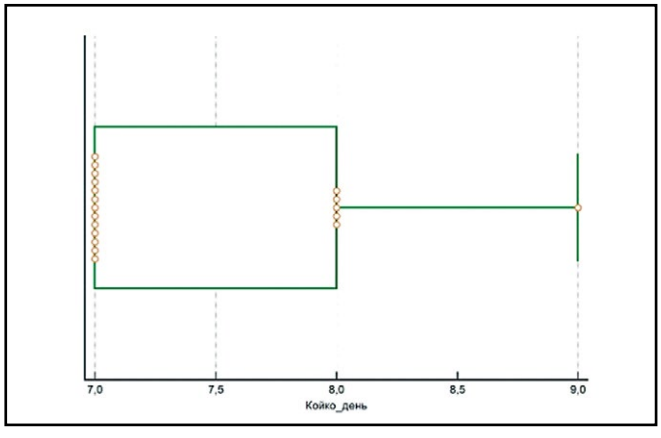

Figure 4. *Distribution of hospital stay (bed-days) in the study cohort (n = 19).*

Рисунок 4. *Распределение длительности госпитализации (койко-день) у пациентов, включенных в исследование (n = 19).*

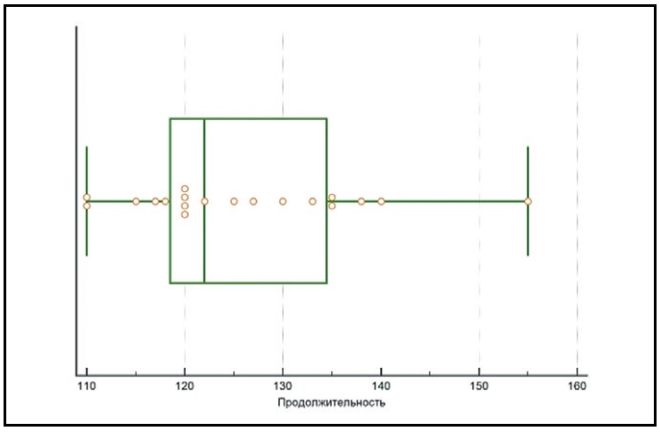

Figure 6. *Distribution of operative time in the study cohort (n = 19).*

Рисунок 6. *Распределение продолжительности операций у пациентов, включенных в исследование (n = 19).*

surgical injury of the operation and the favorable progression of the postoperative period.

The mean volume of intraoperative blood loss was 152.6 ± 62.9 mL (from 50 to 300 mL), median: 150 mL. In the majority of patients, the blood loss volume did not exceed 200 mL, confirming low surgical injury and sufficient visualization of the surgical area when using the transmesenteric approach (**Fig. 5**).

The mean duration of the laparoscopic nephrectomy with thrombectomy using a transmesenteric approach was 125.8 ± 11.4 minutes (110 to 155 min.), median: 122 minutes. The majority of surgeries lasted from 2 to 2.5 hours which is either comparable or less than series using the standard laparoscopic approach (**Fig. 6**).

DISCUSSION

The obtained results indicate that the use of the transmesenteric approach in laparoscopic nephrectomy with thrombectomy in patients with Mayo level 0-I tumor thrombus enables high efficacy and safety. When comparing it with the literature data, our findings were more favorable: in the studies of P. Dell'Oglio et al. (2024), the average duration of such surgeries was 180–240 min., and the volume of blood loss often exceeded 500 mL [19]; in the retrospective series of Z. Chen *et al.* (2021), the average blood loss reached 400 mL, with complications observed in 15-20% of patients [12]. Thus, the transmesenteric approach allowed for a substantial minimization of the surgical trauma and ensure a high level of safety. The average duration of the surgery was 125.8 min., average blood loss was 152.6 mL, average duration of the hospital stay was 7.4 days; no complications or conversions to an open surgery were reported. These indicators are either comparable or superior to the data found in literature for standard laparoscopic surgeries [20].

The major advantage of the transmesenteric approach described in the Russian Federation patent No. 2803686 (2023) is lack of necessity to mobilize the descending colon and dissection of the splenic ligaments when approaching the left kidney. The additional factor favorable for the outcomes is the possibility of accessing the IVC without mobilization of the ascending colon, lowering the probability of liver injury and the risk of adhesion complications.

A significant advantage is the performance of the surgery with the patient in the supine position, which ensures ergonomics for the surgical team and optimal conditions for anesthetic management. The absence of the need for patient repositioning reduces surgery time, decreases the likelihood of compromised sterility, and lowers the risks of tumor migration

and implantation metastasis. Combined, these factors demonstrate the suggested approach as a safer, physiological alternative to the standard laparoscopic approach in cases of renal cancer with low-level thrombosis.

The limitations of this study are the low size of the sample and the single-center character of observation, which precludes extrapolation of the obtained data to a wider cohort. Besides, the study assessed only the early results without the analysis of the remote oncological outcomes. Nevertheless, the obtained data confirm the prospects and the reproducibility of the method forming the foundation for its further use in clinical practice.

The presented results show that the transmesenteric approach offers a number of advantages, making it potentially applicable not only in laparoscopic surgery but also in the context of robot-assisted interventions. The ergonomics of access with the patient in the supine position fully meets the capabilities of robotic complexes, and the excluded need for mobilization of the colon simplifies the dissection stages and reduces operative time, which is especially important in the conditions of operating space and necessity of least invasive manipulations with the vessels.

A promising direction is the expansion of indications for the use of the transmesenteric approach in Mayo level II venous tumor thrombus. With this level of IVC involvement, a much wider surgical access is required, which is associated with an increased risk of complications. At the same time, the anatomic specifics of transmesenteric approach allow for a direct adequate view of vascular structures, which could theoretically improve the safety of operations for this category of patients. The final verification of these advantages requires studies on larger cohorts of patients including both laparoscopic and robot-assisted operations, as well as analysis of oncological outcomes in the long term. The proposed method not only expands the capabilities of laparoscopic surgery in renal cancer with low-level venous tumor thrombus but also opens prospects of integration with contemporary minimally invasive technologies.

CONCLUSION

Implementation of transmesenteric approach into clinical practice allows for a significant increase in safety and reproducibility of laparoscopic nephrectomy with thrombectomy in patients with level 0-I venous tumor thrombus. The use of this technique reduces operative time, decreases the extent of organ mobilization and the risk of their injury, and minimizes the likelihood of postoperative complications. This method can be recommended for widespread adoption in oncourology centers and is considered promising for adaptation to robot-assisted surgery platforms.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethics approval. The study was approved by the LEC of Granov Russian Research Center of Radiology and Surgical Technologies (extract from protocol № 03-11/2021 dated 18.11.2021).	***Этическая экспертиза.*** Проведение исследования одобрено ЛЭК ФГБУ «РНЦРХТ им. ак. А.М. Гранова» (выписка из протокола № 03-11/2021 от 18.11.2021).
Consent for publication: All patients signed a written informed consent form.	***Согласие на публикацию.*** Все пациенты подписывали добровольное информированное согласие.
Study funding. The study was 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. Mirzabekov M.K.: concept development, statistical analysis, text preparation. Shkolnik M.I., Bogomolov O.A.: text editing and approval. 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.*** Мирзабеков М.К. – разработка концепции, проведение статистического анализа, подготовка текста. Школьник М.И., Богомолов О.А. – редактирование и утверждение текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	***Доступ к данным.*** Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	***Генеративный искусственный интеллект.*** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	***Рассмотрение и рецензирование.*** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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Cochlear implantation in patients with chronic otitis media

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Abstract

Cochlear implantation is a highly technological method of rehabilitation for patients with profound sensorineural hearing loss. In most cases, cochlear implantation follows a standard technique, but there are cases that require meticulous attention in the selection of tactics. Recently, chronic otitis media was considered as a contraindication for cochlear implantation due to the risk of developing a number of complications. Despite these potential problems, cochlear implantation is the only solution to help patients with chronic otitis media and stage IV sensorineural hearing loss. There are various methods for managing the above-mentioned group of patients. Some authors describe performance of cochlear implantation with middle ear surgery in one stage, while other authors, in several stages. The issue of cochlear implantation in patients suffering from chronic suppurative otitis media has always aroused discussions among otosurgeons.

In this article, we analyzed a series of clinical cases (10 patients) with chronic otitis media who underwent middle ear sanation surgery and cochlear implantation. In our opinion, a single-stage cochlear implantation together with a sanation intervention on the middle ear can be considered as a technique that allows to accelerate the auditory-speech rehabilitation of patients with stage IV sensorineural hearing loss and epitympanitis. This is especially important for patients with acquired pathology of the inner ear and the risk of ossification of the cochlea spiral canal.

Keywords: cochlear implantation, epitympanitis, chronic otitis media, radical surgery of the middle ear, profound sensorineural hearing loss.
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Кохлеарная имплантация у пациентов с эпитимпанитом

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Аннотация

Кохлеарная имплантация представляет собой высокотехнологичный метод реабилитации лиц, страдающих сенсоневральной тугоухостью высокой степени и глухотой. Чаще всего кохлеарная имплантация проводится по стандартной методике, однако нередко встречаются неординарные случаи, требующие более тщательного подбора тактики ведения пациентов. В прошлом хронический гнойный средний отит считался противопоказанием к кохлеарной имплантации из-за риска развития ряда осложнений. Несмотря на эти потенциальные проблемы, выполнение кохлеарной имплантации является единственным вариантом помощи пациентам с эпитимпанитом и двусторонней хронической сенсоневральной тугоухостью IV степени. Существуют различные методики ведения вышеуказанной группы пациентов. Одни авторы описывают проведение кохлеарной имплантации с санирующими операциями на среднем ухе в один этап, другие – в несколько этапов. Проблема кохлеарной имплантации у пациентов, страдающих хроническим гнойным средним отитом, остается предметом дискуссии среди лор-хирургов.

В статье мы проанализировали серию клинических случаев (10 пациентов) с эпитимпанитом, которым была проведена санирующая операция на среднем ухе и кохлеарная имплантация. На наш взгляд, одноэтапное проведение кохлеарной имплантации совместно с санирующим вмешательством на среднем ухе может рассматриваться как методика, позволяющая ускорить слухоречевую реабилитацию пациентов с двусторонней хронической сенсоневральной тугоухостью IV степени и эпитимпанитом. Это особенно актуально для пациентов с приобретенной патологией внутреннего уха и риском оссификации спирального канала улитки.

Ключевые слова: кохлеарная имплантация, эпитимпанит, хронический средний отит, радикальная операция на среднем ухе, двусторонняя хроническая сенсоневральная тугоухость IV степени.
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Список сокращений
ДХСНТ – двусторонняя хроническая сенсоневральная тугоухость;
КИ – кохлеарная имплантация; КТ – компьютерная томография;
НСП – наружный слуховой проход; СНТ – сенсоневральная тугоухость;
СП – субтотальная петрозэктомия; ХГСО – хронический гнойный средний отит.

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BACKGROUND

Chronic suppurative otitis media (CSOM) is one of the frequent medical conditions in otorhinolaryngology. Its rate of incidence is 4.76 cases (1.7 to 9.4) per 1,000 population (ca. 31 million cases per year), 22.6% of cases occur in children below 5 years old. The prevalence of this pathology among children and adults worldwide is from 0.3% to 15%, and 60% of patients suffer from a significant loss of hearing [1].

Often, epitympanitis results in complications that might cause deafness and that require cochlear implantation (CI). Today, CI is the most efficient and technological method of rehabilitation and social adaptation of people suffering from deafness and profound sensorineural haring loss [2–4]. Lack of a unified tactics of management of patients with epitympanitis makes the problem of CI a subject of ongoing debate among ENT surgeons.

Epitympanitis used to be regarded as a contraindication for CI due to the 'portal of entry' of infection which undoubtedly increases the risk of development of meningitis, relapsing choleteastoma and electrode extrusion to the cavity after the radical surgery in the middle ear due to damage to the fine epidermal lining [2, 5, 6]. Moreover, development of otitis media after the implantation might bring about intracranial complications, extrusion of the device or necessitate removal of the implant. Despite these potential problems, CI remains the only solution in assistance to patients with epitympanitis [7, 8].

Patients with a severe hearing loss due to CSOM are candidates for CI. However, they need close attention from respective specialists [9].

DESCRIPTION OF THE CLINICAL SERIES

The study included ten (10) patients who underwent surgeries at the Saint Petersburg Research Institute of Ear, Throat, Nose and Speech of the Ministry of Health of the Russian Federation from 2019 to 2025. The patients had grade IV bilateral chronic sensorineural loss of hearing and epitympanitis. There were 2 children and 8 adults among the patients. Within the specified period, 7 patients underwent single-stage surgery and 3 patients, two-stage surgery. Two patients had no ear surgeries prior to CI, 5 patients had a history of a radical surgery on the implanted ear. One patient had had antromastoidotomy on the implanted ear, and 3 patients had had tympanoplasty on the implanted ear.

Technique of Cochlear Implantation

Patient with epitympanitis and a history of antromastoidectomy on the implanted ear. CI was performed simultaneously with revision of the mastoid cavity. In the course of the operation, during harvesting of the soft tissue, a choleteastoma was visualized in the antromastoid cavity (**Fig. 1, 2**).

Using a burr, the antromastoid cavity was extended to the mastoid apex. Cholesteatoma matrices lined the plates of the middle and posterior cranial fossae, as well as the sigmoid sinus. They spread to the cells of the sinodural angle and to the area of the anterior semicircular canal. All the pathological mass was removed. The incus and malleus were eroded, their remnants covered with cholesteatoma tissue, which was removed. The tendon of the tensor tympani muscle was represented by a stump, and the chorda tympani was absent. Cholesteatoma tissue covered the tympanic section of the facial nerve, whose bony canal was partially eroded, and extended to the attic. Partial atticitomy and extended posterior tympanotomy were performed to the level of the bulb of the jugular vein. The pathological mass was removed. Cholesteatoma tissue was identified within the Eustachian tube and was also removed. At the transition between the mastoid and tympanic segments of the facial nerve, a herniation of the mastoid segment was observed, which was decompressed using a burr. The overhang over the cochlear window was removed with a burr, revealing a fibrosed membrane of the cochlear window with an area of fibrous obliteration. Diamond burs were used to drill out the fibrous obliteration of the descending cochlear turn, which extended approx. 7 mm. In the region of the basal turn, fibrous obliteration was identified and drilled through. A sponge soaked in dexamethasone was placed adjacent to the mastoid segment of the facial nerve. The implant was positioned and secured in its bed, with its active electrode fully inserted into the cochlea via the mastoid cavity and posterior tympanotomy. The excess electrode was covered along its entire course with autologous cartilage strips and a single fascial graft. The external auditory canal was packed with a MEROCEL hemostatic sponge.

One year after the surgery the patient presented a computed tomography (CT) scan of the temporal bones (**Fig. 3**). The postoperative cavity is clean with no pathological mass. No relapse of the choleteastoma or electrode extrusion were identified.

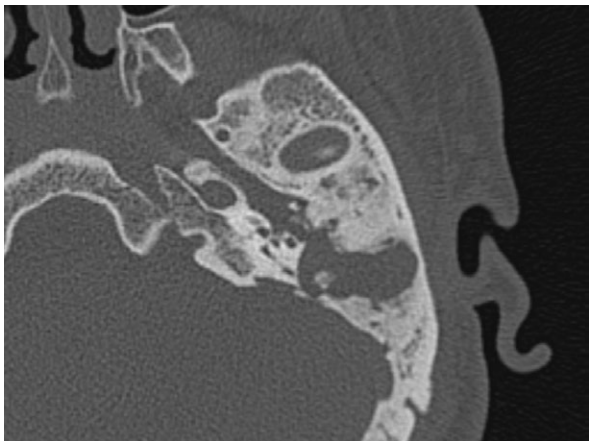

Figure 1. *CT of the left temporal bone of the patient before surgical intervention. The postoperative cavity after antromastoidotomy is totally filled with cholesteatomic masses, the labyrinth fistula is present, the tympanic segment of the facial nerve is exposed.*

Рисунок 1. *КТ левой височной кости пациента до проведения оперативного вмешательства. Послеоперационная полость после антромастоидотомии тотально заполнена холестеатомными массами, наличие фистулы лабиринта, обнажение барабанного сегмента лицевого нерва.*

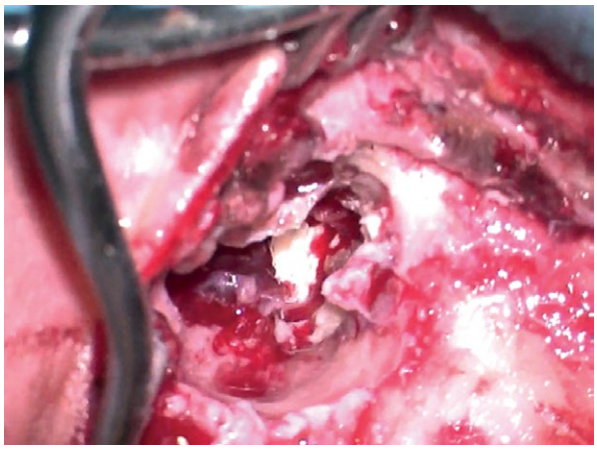

Figure 2. *Intraoperative photo of the patient with the exposed antromastoid cavity on the left, where a fragment of a cholesteatoma is visualized.*

Рисунок 2. *Интраоперационное фото пациента со вскрытой антромастоидальной полостью слева, где визуализируется фрагмент холестеатомы.*

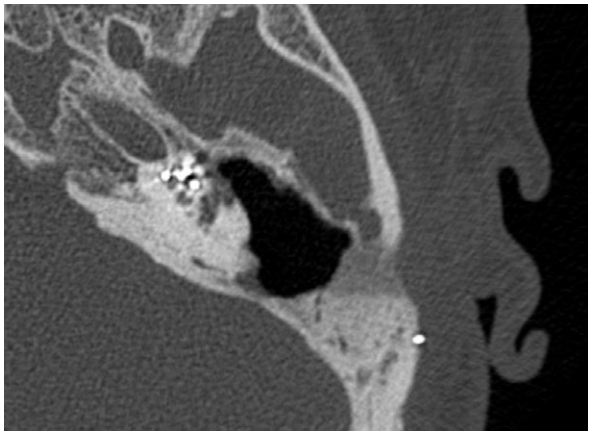

Figure 3. *CT of the left temporal bone of the patient 12 months after the surgery. The postoperative cavity is without pathological contents. There are no signs of recurrence of cholesteatoma and electrode extrusion.*

Рисунок 3. *КТ левой височной кости пациента через 12 месяцев после проведения оперативного вмешательства. Послеоперационная полость без патологического содержимого. Признаки рецидива холестеатомы и экструзии электрода отсутствуют.*

Patient with epitympanitis without history of surgical intervention on the implanted ear. CI was performed in two stages: Stage I, radical surgery with sanation of the infection focus; Stage II, six months after the radical surgery.

During Stage I, cholesteatomic masses were found that engulfed the eroded malleus and incus. The stapedial superstructure was absent, and partial destruction of the posterior wall of the external auditory canal was noted. A radical mastoidectomy was performed with removal of pathological contents from the tympanic cavity, eradication of the chronic infectious focus, and closure of the tympanic membrane defect. A distinctive feature of the procedure was the preservation of a slightly prominent 'spur' in the inferior part of the tympanic cavity to support the electrode over the mastoid segment of the facial nerve during the subsequent stage.

Six months later, during the CI, the burr cavity was opened and expanded, and bored were used to prepare the implant bed, the groove for the positioning of the electrode in the mastoid segment of the burr cavity, and the tunnel in the 'spur'. The implant was positioned and stabilized in the bed, the active electrode being fully inserted in the cochlea via mastoid cavity, groove above the 'spur' and the secondary tympanic membrane opened earlier. The excess electrode was covered along its entire course with autologous cartilage strips and fascial grafts. The packing of the external auditory canal was done with a silicone protector and "Belkozin" hemostatic sponge.

Recurrence of the cholesteatoma was not observed in the patients with a prior radical surgery on the implanted ear. The difficulty of the CI was in the positioning and stabilization of the active electrode in the mastoid and tympanic segments to prevent its extrusion. For that purpose, the electrode was covered with autologous cartilage and fascial grafts. In five patients, an allograft cartilage was used (**Fig. 4**). Throughout the entire follow-up period, extrusion of the electrode was not observed.

Patient with grade IV bilateral chronic sensorineural loss of hearing and history of antromastoidoectomy. CT scans of the temporal areas visualize cholesteatoma completely filling the antromastoid cavity. A decision was made to perform a simultaneous sanation surgery on the middle ear and cochlear implantation. In the course of the operation, cholesteatomic masses were found that extended in the entire antromastoid cavity and penetrated into the attic. Atticotomy was performed with preservation of the posterior wall of the external auditory canal. The cholesteatomic masses were removed. Following the posterior tympanotomy and opening of the secondary membrane of the cochlea, the electrode grid was placed in the *scala timpani*. The preservation of posterior wall of the external auditory canal excluded the necessity of additional

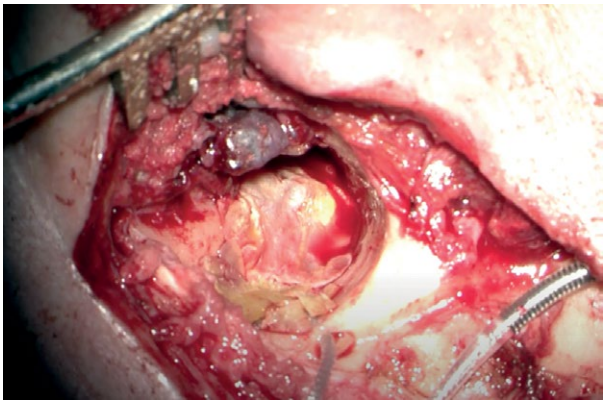

Figure 4. *Intraoperative photo of the electrode being covered with autofasciation and allogeneic cartilage during cochlear implantation after radical surgery of the left ear.*

Рисунок 4. *Интраоперационное фото укрытия электрода аутофасцией и аллогенным хрящом при проведении кохлеарной имплантации после радикальной операции на левом ухе.*

coverage of the electrode and reduced the risk of its extrusion in the postoperative period.

The cholesteatoma was found intraoperatively in three patients: 1) the patient with a history of antromastoidotomy on the implanted ear, 2) the patient with a history of separate atticoantrotomy and 3) the patient with no history of ear surgeries (in case of the latter, the CI was performed in two stages).

The posterior wall of the external auditory canal had to be removed in two patients.

All patients underwent planned postoperative otomicroscopy 1 month and 6 months, during their rehabilitation course. No postoperative complications were observed in any of the patients. The results of hearing and speech rehabilitations were similar to those in patients of the respective age groups who had no epitympanitis.

DISCUSSION

Contemporary literature presents extensive data on methods of treatment and tactics of management of patients with epitympanitis who underwent or are planning to undergo CI. At the same time, the views of specialists on the surgical tactics differ, especially with respect to staging of surgeries.

Thus, J. T. F. Postelmans *et al*. (2009) believe that cochlear implantation is to be performed in stages for patients with signs of active chronic suppurative otitis media. CSOM patients with a cavity after a radical surgery without any pathological changes may benefit from a single stage CI. It is generally accepted that CI would be safe for patients with non-acute epitympanitis. At the same time, their results show that there is still a possibility of serious complications with subsequent replacement of the cochlear implant [10].

In the study of P. Canzi *et al*. (2023) that included data of patients who underwent surgeries from 2005 to 2022, the single-stage surgery was demonstrated to be the optimal tactic. Multiple-stage surgeries are mainly recommended in the event of presence of cholesteatomic masses, but not in an active inflammatory process [11].

As early as in 2009, C.A. Hellingman and E.A. Dunnebier analyzed literature data and came to the conclusion that the patients with cholesteatoma would benefit from separate atticoantrotomy or a radical surgery of the middle ear with subsequent CI in stage II using a non-obliterative technique. IF a cavity remains after a radical surgery, a non-obliterative procedure is recommended after the mastoidectomy (revision mastoidectomy) to prepare the ear for the implantation and to ensure protection of the electrodes, preferably without closure of the external auditory canal, which simplifies control in the follow-up period [12].

The problem of CI in CSOM is analyzed in detail in the retrospective study of A. Vashishth *et al*. (2018) including 35 patients. In 31 cases, the implantation was performed simultaneously with the sanation operation, and in 5 cases, in two stages. The average follow-up period was 7 years. Explantation was required in 4 patients (11%) due to electrode extrusion and infection; in three patients, recurrent implantation was performed. No relapse of choleasteotoma was observed. The authors concluded that CI was possible in this category of patients, and the simultaneous tactics was possible when there was no active inflammation, yet the risk of explantation was higher than in the cases of conventional implantation [13].

Young Hoon Yoon *et al*. (2020) assessed remote outcomes of different tactics of CI in CSOM. The average follow-up period was 3 years (ranging from 0.5 to 9 years). One patient with a staged CI in the cavity after a radical surgery experienced electrode extrusion. The treatment of this complication involved subtotal petrosectomy (SP) and obliteration of the cavity. No significant differences were observed in the outcomes of the hearing and speech rehabilitation between single- and multiple-stage CI [14].

S. Lee *et al*. (2020) conducted a retrospective study of 31 patients with simultaneous CI and subtotal petrosectomy. Significant improvement of results of hearing and speech rehabilitation was seen in all patients, as compared to preoperative observations. Complications developed in three patients (9.6%). One patient had a defect of closure of the external auditory canal, and two more had migration of the transceiver of the cochlear implant. The migrations occurred despite stabilization of the device in the temporo-parietal area. Migrated implants were returned into position in a revision surgery. The authors concluded that simultaneous CI with SP was an effective and safe surgical method with a relatively low incidence of complications [15].

CONCLUSION

Single-stage cochlear implantation with sanation on the middle ear may be regarded as a method facilitating faster hearing and speech rehabilitation of patients with grade IV of bilateral chronic sensorineural loss of hearing with epitympanitis. This is even more important for patients with an acquired pathology of the middle ear and the risk of ossification of the spiral canal of the cochlea.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
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Contribution of individual authors. Lilenko A.S., Sugarova S.B., Kuzovkov V.E.: concept and design of the article, editing of the article. Lilenko A.S., Kharitonova P.R., Timofeeva P.R.: writing of the text. Korneva Yu.S., Timofeeva P.R.: collection and processing of material. 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.*** Лиленко А.С., Сугарова С.Б., Кузовков В.Е. – концепция и дизайн статьи, ее редактирование. Лиленко А.С., Харитонова П.Р., Тимофеева П.Р. – написание текста. Корнева Ю.С., Тимофеева П.Р. – сбор и 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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Rhizarthrosis: treatment approaches in modern orthopedics

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Abstract

Rhizarthrosis is an osteoarthritis of the trapezium-metacarpal joint, a common condition mainly affecting postmenopausal women, which has a significant impact on the quality of life and functionality of the hand. The thumb is critical for grasping and strength of the entire hand, and functional impairment of the thumb mobility in rhizarthrosis reduces hand function significantly. Despite its high prevalence and risk of disability, therapeutic options for rhizarthrosis remain limited. Treatment usually requires a multidisciplinary approach using a combination of non-pharmacological, pharmacological and surgical strategies. The literature review observes various surgical treatment options for rhizarthrosis, such as ligament reconstruction, tendon interposition, resection arthroplasty and joint replacement or arthrodesis.

Keywords: rhizarthrosis, orthopedics, trapezium-metacarpal joint, surgical treatment, hand joints, biomechanics, joint replacement.
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Ризартроз: особенности лечения в современной ортопедии

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Аннотация

Ризартроз, или остеоартроз трапециевидно-пястного сустава, – распространенное заболевание, в основном поражающее женщин в постменопаузе и оказывающее значительное влияние на качество жизни человека. Первый (большой) палец определяет силу хвата всей руки, поэтому нарушение его подвижности при ризартрозе значительно снижает функционал кисти. Несмотря на высокую распространенность и риск развития инвалидности, терапевтические возможности лечения ризартроза по-прежнему ограничены. Лечение обычно требует междисциплинарного подхода с использованием комбинации нефармакологических, фармакологических и хирургических методик. Литературный обзор посвящен анализу таких хирургических методов лечения ризартроза, как реконструкция связок, интерпозиция сухожилий, резекционная артропластика, эндопротезирование или артродезирование сустава.

Ключевые слова: ризартроз, ортопедия, трапециевидно-пястный сустав, хирургическое лечение, суставы кисти, биомеханика, протезирование сустава.
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РзА – ризартроз, CMCJ – пястно-запястный сустав (carpometacarpal joint).

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INTRODUCTION

Rhizarthrosis (RzA), or trapeziometacarpal osteoarthritis, is an arthritic degenerative process that affects the first joint of the thumb [1]. The thumb having the leading function in the biomechanics of the hand, the loss of that function results in 40 to 50 per cent deterioration of the function of the hand [2]. RzA manifests as pain in the base of the thumb, restricting the force of the grip and making performance of daily tasks complicated. The pain sets on in certain movements and can progress to permanent sense of discomfort over time. Chronic RzA leads co joint contractures, visual deformations (Z-shaped thumb), and muscular atrophy [3].

Functional disorder of the thumb that determines the grip and the force of the hand decreases a person's capability of performing everyday activities, such as writing, opening of jars, turning keys or handling small objects [4]. The anatomic configuration of the joint surfaces of the carpometacarpal joint (CMCJ) of the thumb is complex. The base of the metacarpal bone is concave dorsovolarly and convex radioulnarly. Conversely, the trapezoid concave arc is radioulnar, and the convex arc is dorsovolar. The trapezoid and the metacarpal joint surfaces have incommensurable curvature radii that match only in the extreme positions of the movement. The concave-convex saddle-shaped structure of the CMCJ is involved in the flexion/extension and abduction/adduction. Pronation and supination is a complex rotation and translation of the joint. The concavity of each articular surface is shallow, and the bone and cartilage component ensures minor internal stability of the CMCJ. The ligaments and muscles play an important role in the stability of this complex joint [5].

The biomechanics of CMCJ is characterized with multidimensional mobility [6]. The high mobility of the human CMCJ has developed in the course of evolution. The evolutionary requirements for gripping and manipulative activity of the upper limbs developed simultaneously with upright posture [7, 8]. The functional paradox of the CMCJ is in the combination of stability and high mobility. The thumb needs a wide range of motion to perform tasks only characteristic of humans, from a strong grip to a fine pinch [5].

WP 3rd Cooney and EY Chao (1977) used the method of biomechanical analysis to calculate the internal forces in the joints and soft tissues of the thumb during the pinch and the grip. It was found that the tendons of the intrinsic and extrinsic of the thumb withstand from 10 to 30 kg during the pinch exerting a force of 5 kg on the tip of the thumb, and up to 50 kg during the grip. The force of contraction (contact) of the joint on average is 3 kg in the phalangeal joints, 5.4 in the metacarpophalangeal joints and 12.0 kg in the carpometacarpal joint (CMCJ) in the simple pinch (applied force of one kg). Gripping forces up to 120 kg may develop in the CMCJ in a strong grip [9]. Since the skeletal architecture of CMCJ provides rather mild internal bone stability, the ligaments are critically important to withstand the natural tendency for incomplete dislocation in the compression and gripping [5]. CMCJ copes with extreme forces created by such movements since it is stabilized with a complex system of ligaments and muscles. Without that stability, the incomplete dislocation of the thumb could occur under loads of grip and compression, and the gripping would be incomplete. The understanding of the character of such interaction occurring in the CMCJ is important for the adequate treatment of pathology of this joint [10].

H. Hafiz et al. (2024) developed a biomechanical model of CMCJ to study the contribution of tendons, ligaments and other soft tissues in the passive forces during distraction. Five fresh autopsied specimens were tested with a distractor in order to measure the applied forces during gradual distraction of the non-damaged joint. The next step included positioning of a sensor into the articular capsule through a minor incision for a precise measurement of the main intra-articular forces while maintaining integrity of tendons and ligaments. Prior to the separation of the bones the forces exerted by the tendons and ligaments were relatively low in comparison to the force of the capsule that was approx. 92% from the total applied force. The contribution from the tendons and ligaments increased with further distraction. The passive contribution of the tendon force in distraction for 2 mm was less than 11% while that of the tendons it was 74%. Thus, the 'ligament-capsule' complex plays a significant role in the passive forces of the CMCJ during distraction [11]. The thumb is responsible for over 40% of the hand functions for its gripping and compressing capacity is inefficient without its opposition and gripping capability [12]. Therefore, degeneration of the CMCJ may lead to disability [3].

Traditionally, RzA is seen as an endemic women's disease in the post-menopausal period. Demographic radiographic studies show that incidence ratio of CMCJ in women and men is 6:1; however, the ratio decreases over age, and the incidence rate in women and men at the age of 75 is 40% and 25%, respectively [5]. The clinical prevalence of RzA is

twice as high in women than in men (affecting 25% women in the post-menopause), while its radiographic prevalence is even higher, from 45% to 60% [13, 14]. In women aged 70 and above the risk of the disease is double than that in women after the menopause [15]. The high susceptibility of women towards RzA is related to the lower congruence of the articular surfaces: the concavity of the metacarpal surface and the convexity of the trapezoid surface in women are less pronounced than in men [16].

The diagnosis of RzA is basd on a clinical examination. The major symptoms are pain localized in the basis of the thumb, stiffness, loss of range of motion and significant impairment of the function of the hand. The pain is often diffuse, originates in the anatomical snuffbox, and follows a waxing-and-waning pattern [4]. Radiographic findings are commonly used to stage the disease, even in the absence of a clear correlation between clinical symptoms and the severity of imaging changes [17].

In 1973, Richard Eaton and William Littler described four progressive radiographic stages of RzA, which were later modified to include scaphotrapezial arthritis. The modified Eaton-Littler classification is currently the most widely used radiographic staging system for basal arthrosis of the first digit of the hand.

Stage I: minor expansion of the CMC joint gap. Stage II: minor narrowing of the CMC joint gap, sclerosis and cystic alterations with osteophytes or loose bodies < 2 mm. Stage III: considerable narrowing of the CMC joint gap, sclerosis and cystic alterations with osteophytes or loose bodies > 2 мм. Stage IV стадия: arthritic alterations in the CMCJ similar to Stage III with scaphotrapezial arthritis [18, 19].

Despite the advanced developments in the therapy of the hand, conservative options of RzA treatment are still limited. Usually, treatment required a multidisciplinary approach utilizing a combination of non-pharmacological, pharmacological and surgical methods [20]. Non-pharmacological measures include rest, changes in the physical activity, immobilization with braces or controls, exercise and physiotherapy [21]. Pharmacological treatment includes analgesics, local or oral non-steroid anti-inflammatory drugs, and injections of gluco-corticosteroids or hyaluronic acid [4, 22]. Intra-articular injections may be administered with ultrasonic control [23]. Intra-articular injection therapy is usually applied to alleviate the symptoms of the disease since it may circumvent the systemic effect and potential side effects of oral drugs [14, 24]. Other injections may include corticosteroids, platelet-rich plasma, and stem cells; there were trial methods of treatment with Infliximab, □-interferon, botulinum toxin [25] and oxygen and nitrogen mixture [26].

Conservative methods of RzA may ensure symptomatic relief in early stages, while later stages require surgical treatment [27].

The aim of this review is to describe and analyze the surgical methods of RzA treatment. The topic of surgical treatment of RzA being in development for a considerable time, we used the sources from the 1940s describing the classic methods, to the present time. The analysis of literature data was performed using scientifica databases: Pubmed, Healio Orthopedics, Medline, Scirus. The literary sources were selected using the following keywords: ризартроз, ортопедия, трапециевидно-пястный сустав, хирургическое лечение, суставы кисти, биомеханика, протезирование сустава, rhizarthrosis, orthopedics, trapezium-metacarpal joint, surgical treatment, hand joints, biomechanics, joint replacement.

SURGICAL METHODS OF RHIZARTHROSIS TREATMENT

Resection of the trapezoid bone

Resection of the trapezoid bone, or trapeziectomy, was first described by W.H. Gervis in 1940s as an option of surgical treatment of RzA. The surgeon performed a simple resection of the trapezoid bone to remove the source of the 'bone-to-bone' pain originating from the metacarpal bone articulating with the trapezoid bone. The author reported good initial results in the series of 18 resections of the trapezoid bone [28]. To date, simple trapeziectomy remains the most popular method of surgical treatment of RzA. The method provides mitigation of the pain syndrome and relatively high mobility of the thumb [29].

Later, many technical modifications stemmed from trapeziectomy: these were aimed at prevention of shortening of the thumb than caused recurrent pain and loss of strength in mid-term perspective [30].

T.F.M. Yeoman *et al*. (2019) demonstrated significant and stable improvement of thumb function after the simple trapeziectomy. 205 patients filled the quick questionnaire on disablement of arm, shoulder and hand (QuickDASH) and five-dimensional EuroQoL questionnaire (EQ-5D), on average 8.2 (3.5…17.0) years after the simple trapeziectomy. The average QuickDASH score of the post-surgery group was 37±17, and the average EQ-5D score was 0.56±0.31. The average QuickDASH score in the pre-surgery group was 54.0±17.0. The mean difference in the QuickDASH score between the pre- and post-surgery groups was 17 points (95% CI 8–26, p = 0.0003) [31].

N. Janakiramanan *et al*. (2021) saw that trapeziectomy could restore the functions of the thumb with positive mid-term and long-term results, yet the defect in the area of resected bone caused pain, especially in the first two or three months [32]. The simple trapeziectomy could also bring about some complications such as shortening of the thumb, decrease of grip strength, cramping of the distal part of the scaphoid bone [30]. In 1960, A.H. Murley analyzed outcomes of 39 trapeziectomies and concluded that the grip strength and the range of motion in abduction decrease, which is important for men performing hard work [33]. The study of A. Weilby showed that 5 out of 17 patients after trapeziectomy experienced weakness of the hand, painful spasms and difficulties in holding objects [34].

Such results of simple trapeziectomies fostered development of methods of stabilization and restoration of CMCJ surface to ensure a physiological reconstruction [5].

K. Van Royen *et al*. (2021) studied the possibility of arthrodesis of the scaphoid-metacarpal joint (SMC) with a structural bone graft for multiply operated patients. All patients demonstrated symptomatic instability of the basis of the thumb, and they had undergone three to four surgeries including arthrodesis. Three patients underwent SMC

arthrodesis using structural bone graft from the iliac crest. All patients were satisfied with the results. The average grip strength increased from 3.5 to 10.5 kg, and the average pinch strength, from 1.5 to 2.5 kg. The arthrodesis was confirmed in all patients. We believe that the SMC arthrodesis with structural bone autograft is the operation of choice that significantly preserves the thumb opposition and restores stability [35].

Tendon and Ligament Reconstruction

Researchers emphasized importance of reconstruction of ligament reconstruction tendon interposition (LRTI), or tendon suspension technique of the *abductor pollicis longus* (APL), allograft and other methods of interposition, implantation arthroplasty, unloading osteotomy and arthrodesis [36]. A.I. Froimson (1970) identified the problem of metacarpal subsidence and weakness following trapeziectomy and recommended the interposition of a tendon spacer between the metacarpal and scaphoid bones [37].

Other researchers maintained the approach of stabilizing the metacarpal bone by reconstructing the ligaments that would bind the basis of the first metacarpal bone with the neighboring metacarpal bone of the second finger. The aim of the intervention was to prevent development of incomplete dislocation and sinking of the metacarpal bone with the absence of the entire trapezoid bone or part thereof and to secure the ratio of the first metacarpal bone to the second [5].

R.G. Eaton, J.W. Littler (1973) reported that after the simple trapeziectomy the hypermobility of the thumb caused pain and predisposed the joint to progressive degeneration. They developed a method of reconstruction of the palmar carpal ligament using a half of the distal tendon of the radial flexor of the wrist (*flexor carpi radialis*, FCR), that would be passed through the palmar dorsal aperture at the base of the metacarpal bone of the thumb. The tendon is tensioned and sutured to the adjacent periosteum. After fixation, the graft is passed through the abductor tendon of the first digit and re-sutured to the proximal portion of the FCR. It was supposed that the reconstruction restores the function of the weak palmar ligament and strengthens the thin radial capsule. This reconstruction supports the joint in two planes making it more stable that a single-plane reconstruction [38].

In 1973, R.G. Eaton and J.W. Littler used the reconstruction of the palmar ligament to treat patients with all four stages of disease of basal joints. The authors reported good or excellent results in 16 out of 18 patients and two satisfactory results in patients with stage IV of basal joint disease [38]. In 1984, results of a long-term follow-up were published: of the 38 patients who were followed up for 7 years, 32 (84%) had good or excellent results, and 6 (16%) patients had satisfactory results [39].

Today LRTI is the most frequent method of RzA treatment. The LRTI technique involves interposition of the tendon not used for reconstruction to a space created after the trapezoid excision. Alternative LRTI procedures use different redirection paths for the FCR tendon (with or without bone tunnels) or use various tendons to suspend the first metacarpal to the second metacarpal [5].

R.I. Burton and V.D. Jr. Pellegrini (1986) performed LRTI by expanding the reconstruction of the palmar ligaments to combine it with partial and total trapeziectomy. The concept is similar to the reconstruction of palmar ligaments with the exception that the tendon is directed diagonally via the base of the metacarpal bone of the thumb and exits dorsally approx. 1 cm distally to the joint surface, perpendicularly to the plane of the thumb. The remaining tissue is folded and inserted into the space created after the trapezoid excision. The reconstruction is stabilized with the Kirschner wire [40]. Initially, a split FCR tendon was used for reconstruction, but recent practice employs the entire tendon, thereby providing more tissue for interposition. A two-year postoperative follow-up by D.M. Freedman *et al*. (2000) of 25 patients after LRTI showed that the first metacarpal subsided proximally by 11% of the arthroplasty space, and subluxation was limited to 7%. Pain relief was observed in 92% of patients, who were satisfied with the outcomes [41]. In a 9-year study of 24 patients, M.M. Tomaino *et al*. (1995) reported a minor change in the subsidence of the metacarpal (13%) and subluxation (11%), as well as pain relief (95%). The strength improved as did the grip by 93%, the key pinch improved by 34%, and the pinch grip by 65% [42].

Suspensionplasty utilizes a portion of the *abductor pollicis longus* (APL) tendon to stabilize the first metacarpal. The method was proposed by J.S. Thompson (1989) as reoperative treatment after unsatisfactory arthroplasty of the CMCJ osteoarthritis. Considering its marked positive outcome, the indications were extended to include primary treatment of Stage II-IV of CMCJ disease. During the procedure, a portion of the APL tendon is split distal to the myotendinous junction, mobilized from proximal to distal, and left attached to the dorsal base of the first metacarpal. An oblique tunnel is created at the base of the first metacarpal, similar to the one used in LRTI. The tunnel originates dorsally, approximately 1 cm distal to the articular surface, and exits proximally, slightly volar to the center of the metacarpal base. A second tunnel is drilled in a dorsal-to-volar direction, 1 cm distal to the base of the second metacarpal. Using suture materials or a tendon passer, the APL graft is passed through the base of the first metacarpal and then in a volar-to-dorsal direction through the base of the second metacarpal. After appropriate tension is set, the APL graft is secured dorsally by suturing it to the adjacent tendon of the *extensor carpi radialis longus* (ECRL) [43].

O. Soejima et al. (2006) reported on 18 patients (21 cases) after suspensionplasty who were followed up for on average of 33 months. No pain was registered in 13 cases; 5 patients experienced mild pain under vigorous physical activity, and 3 patients reported minor pain under mild activity. The subsistence of the metacarpal was 15% from the arthroplasty space. Radial and volar abduction were 56 degrees [44]. These findings match with results of LRTI reported by R.I. Burton and V.D. Jr. Pellegrini (1986) [40].

The systematic review by M. Saab and G. Chick (2021) described long-term outcomes and complications of trapeziectomy after a five-year follow-up. It included 22 studies involving 728 patients. All studies reported good outcomes with respect to pain and range of motion in the follow-up of patients for 8.3 years (from 5 to 22 years); the average level of satisfaction with treatment was 91% (from 84% to 100%). The force of the key pinch returned

to pre-operative level, whereas the pinch grip had a slight improvement (+14%), the grip force increasing by 25%. The complications were related to tendons or nerves involved in the course of additional procedures for the stabilization of the joint (11.6%; n = 56). Mechanical complications included symptomatic impingement of the scaphoid M1 (3.1%; n = 15/580), which led to nine surgical revisions of 581 trapeziectomies [30].

Interpositional Implants

The construction of interpositional implants provides for filling of the empty space remaining after trapeziectomy thereby preserving the length of the thumb, the grip strength and preventing the joint of the first metacarpal and the scaphoid bones. Implants of the first generation appeared in 1970s and were silicone liners stabilized with a pin inserted in the first metacarpal [29]. Some retrospective studies showed positive long-term outcomes with high patient satisfaction in a 10-25 years follow-up.

H.P. Bezwada et al. (2002) analyzed long-term outcomes of silicone arthroplasty of CMCJ. From 1975 to 1990, 85 patients with RzA received 90 silicone implants. 62 implants in 58 patients were available for subsequent analysis for an average of 16.4 years (10–25 years). In 84% cases satisfactory results with positive outcomes were achieved that were characterized with reduced pain and preserved function of the thumb. Strength in power grip, key pinch and tip pinch increased. The ability to touch the base of the fifth finger with the tip of the first finger improved. Subluxation was observed in 19% of patients but was not clinically significant. Implant failure occurred in 6% of patients, requiring revision surgery. Out of 62 cases reviewed, none developed silicone synovitis [45].

At the same time, other authors reported high numbers of remote complications with silicone synovitis, failure of the implant and subluxation [46, 47]. Thus, A. Minami et al. (2005) published a review of 12 surgeries on 10 patients who underwent partial trapeziectomy and interpositional arthroplasty using silicone implants. The follow-up period was 15 years, on average. The surgery provided patients with early pain relief, however, subsequent follow-ups registered its strengthening. The dislocation of the implant was observed in two cases, and its failure, in five. Periprosthetic osteolysis was found in four patients [46]. The study of J.C. MacDermid et al. (2003) showed that out of the 26 operated patients, periprosthetic and wrist osteolysis was seen in 90% patients. Six patients (20%) required revision surgeries (three in the early and three in the later stages), including one patient with a pathological fracture of the scaphoid bone [47].

In order to prevent failure of the silicone implant and development of synovitis, the implants began to be manufactured from solid materials. An example of these is the titanium basal implant CMJ Swanson (Wright Medical) for cement-free fixation. Data published on its application are not abundant but literary sources report about 20% revisions 2 years after the surgery [48]. A similar structure was developed by BioPro: it uses a Cobalt-chromium prosthetic with modular head sizes. The pin is covered with a layer of titanium to promote osseointegration [29]. Pin-free interpositional implants are also manufactured from ceramics and pyrolytic carbon. The analysis of their use revealed such problems as instability, subsistence, fracture of the trapezoid bone, and revision surgeries were quite frequent [49–51].

Porous materials, such as polyurethane-urea mesh graft (Artelon), were also used for implantation following partial trapezium resection; however, a significant number of complications in the early postoperative period was reported [52].

Pyrocardan, the pyrolytic carbon disk, is used in interpositional arthroplasty. S. Russo *et al*. (2016) reported that its use required revision surgeries in 6% of the cases over three years [53]. The Pyrocardan implant for trapeziometacarpal interposition is a free-floating intra-articular spacer composed of pyrocarbon. This biconcave resurfacing implant, which preserves both ligaments and bone stock, is indicated for use in early and moderate stages of RzA. Post-surgery findings after implantation with Pyrocardan are comparable with those after surgeries for ligament reconstruction and tendon interposition (LRTI), the robustness being higher than in LRTI [54]. J. Logan *et al*. (2020) published a prospective cohort study of mid-term outcomes of the use of the Pyrocardan implant. 40 Pyrocardan implants were implanted in 37 patients. The median age of patients was 58 (46–71) years. The patients were examined before the surgery and 3 months, 6 months, 1 year and 2 years after the surgery. There were no significant complications or revision surgeries after the implantation. The average follow-up period was 29 months (from 12 months to 7 years). The average grip strength after 2 years was 30 kg vs. 19.6 kg in the group of patients of the same age after trapeziectomy [54].

The PyroDisk implant has a central aperture enabling stabilization of soft tissues. F. Smeraglia *et al*. (2020) conducted a retrospective study to evaluate 8-year outcomes of surgical treatment of 46 patients who underwent arthroplasty using the PyroDisk implant. The average follow-up interval was 9.5 years (median of 113 months with the range of 97–144 months). The study showed that interpositional arthroplasty with PyroDisk provided considerable relief of pain and high satisfaction of patients. All patients demonstrated lowering of the DASH score by an average of 30 points. PyroDisk demonstrated good longevity and stability after the surgery; however, the functional results achieved with its use were not above the results of trapeziectomy with or without ligamentoplasty. The authors concluded that implantation with PyroDisk is a reliable operation without any additional advantages over the simpler methods of surgery [55].

Thus, the outcomes of interposition arthroplasty vary. Convincing evidence that interposition is superior to trapeziectomy was not established.

Arthroplasty of CMCJ

Arthroplasty of CMCJ aims to provide pain-free movement of the thumb while preserving its stability. The normal anatomical saddle joint is replaced by a spherical prosthesis. Designs that preserved the anatomical features inherent to the joint were used in clinical practice [29], but without positive outcomes, which was associated with the required capsular release and subsequent instability of the components due to anatomical constraints [56]. Some authors also reported impaired osseointegration and subsequent instability of the prosthetic components [57].

Currently, the spherical prosthesis is the most common design for CMCJ arthroplasty. The first trapeziometacarpal joint prosthesis was developed in the early 1970s by J.Y. de la Caffiniere.

In 1979, JY de la Caffiniere and P.C. Aucouturier published a scientific article on the use of the developed prosthesis. The authors implanted a total of 34 full trapeziometacarpal joint prostheses. 28 were followed up for over 6 months (max. 5 years) allowing for a reliable evaluation of results. Two thirds of cases demonstrated positive outcomes. In 5 cases, weakening of the trapezoid cup was observed due to intraoperative errors [58]. E.T. Skyttä *et al.* (2005) analyzed the outcomes of implantation with the de la Caffiniere implants in patients with inflammatory arthropathy affecting the CMCJ. A total of 57 procedures were performed for rheumatoid arthritis (41 cases), juvenile chronic arthritis (10 cases), psoriatic arthritis (4 cases), and other inflammatory joint diseases (2 cases). During follow-up, 5 cases of prosthetic component instability and 2 cases of recurrent prosthetic component dislocation requiring reoperation were observed. The survival rate of the prosthesis based on revision surgeries was 87% (95% CI 73–94) over 10 years, and the total rate of component instability as per radiographic data was 15% (95% CI 7–29) over 10 years [59]. P. Johnston *et al*. (2012) analyzed long-term outcomes in 71 patients (93 procedures) who had the de la Caffiniere prosthesis implanted from 1980 to 1989. 26 patients were followed up for an average of 19 years (from 16 to 26 years). The patients reported satisfactory strength and mobility of the thumb [60].

Despite predominantly positive outcomes, isolated cases of cup instability were reported [61]. To address this problem, a cementless fixation method was developed. However, due to the constrained anatomical space and the biomechanical characteristics of the joint, a metal-on-metal bearing couple was utilized [29]. P.J. Regnard (2006) analyzed results of implantation of 100 cementless fixation "Elektra" prostheses made from titanium and chrome-cobalt steel. The key advantage of the prosthesis was its 9 mm cup diameter, which could be accommodated within the small trapezial bone. The mean follow-up period was 54 (36 to 78) months. Studies assessing pain intensity, range of motion, and dynamometry were conducted, with positive results reported in 83 cases. The most prevalent complication was lack of osseointegration of the trapezoid component of the prosthesis (15 cases). In two cases, sinking of the distal pin into the metacarpal bone was reported. Other complications were observed, too: metal allergy (one case), fracture after direct injury of the thumb (one case) and osteoarthritis of the scapho-trapezoid joint with an acute pain syndrome (one case) [62]. Negative aspects of the intervention are the consequences of using the chosen metal-on-metal bearing couple, which were complicated by metallosis. [63, 64]. According to C. Frølich and T.B. Hansen (2015), abnormal reactions to prostheses with metal-on-metal construction are well known from replacement arthroplasty: elevated level of chromium or cobalt in the blood, pain and formation of a pseudo-tumor [63]. Increased concentration of chromium and cobalt ions after such surgeries was reported by other researchers [64, 65]. At present, metal-on-metal bearing prostheses are used much less frequently [29].

Cementless Prostheses with a Metal-on-polyethylene Bearing Couple

Arthroplasty of the CMCJ may restore the length of the thumb and the metacarpal arch. Correction of adduction of the thumb and the compensatory hyperextension of the metacarpophalangeal joint may be achieved in most patients [66–68]. Based on the studies of prior designs, a new line of CMCJ prostheses was developed. Cementless fixation reduces the risk of instability of the cup component, and the bearing surface minimizes wear and causes no adverse reactions seen in the metal-on-metal designs [65].

What causes problems from the perspective of stability of the system is the cup of the prosthesis. The load exerted on the trapezial cup during pinching and gripping is a combination of both shear and axial forces, resulting in an oblique vector that can predispose the cup to instability. Therefore, the trapezoid component is vulnerable in terms of instability, especially in the early postoperative phase before the osseointegration occurs. To minimize the possible instability of the component the manufacturers use two principal geometric shapes of the cup, the conical and the hemispherical [29]. The cup shapes differ in distribution of the potential force, but there are no clinical or empirical proof that one design is superior towards the other. Both demonstrate promising results in the stability of components in the follow-up for over 5 years [66, 69–71] or even ten years [72, 73].

Another issue with spherical joint designs is dislocation. Consequently, a dual-mobility system was developed, well-known since the early 1980s and based on the principles of total hip arthroplasty [74]. In the standard design, the metallic head of the metacarpal component articulates with a polyethylene liner that is rigidly fixed within the metallic shell of the trapezoid cup, creating an articulation between the metallic head and the polyethylene liner. In the dual-mobility design, the metallic head is housed within a larger polyethylene head, which in turn articulates with a smooth metallic cup fixed within the trapezium. Thus, there are two articulations: one between the metallic head and the polyethylene head, and another between the polyethylene head and the cup. The polyethylene head acts as a mobile liner constrained by the metallic head. The larger head reduces the risk of dislocation by increasing the range of motion arc and enlarging the "jump distance" required for dislocation to occur [29].

Considering the range of motion of the thumb, the "jump distance" is clinically more important than the increased motion arc before the impact. The double mobility design decreased the incidence rate of dislocations and replaced the prostheses of the second generation. The early short-term results of implantation of this kind of prostheses showed some good dynamics [66, 69, 75, 76]. The double mobility design is used in the following products: Maia (Groupe Lepine, France), Moovis (Stryker, Pusignan, France) and Touch (Keri Medical, Switzerland). Although this design is intended to reduce the likelihood of dislocations, there is a risk of intraprosthetic dislocation (between the metallic head and the mobile polyethylene liner) and polyethylene liner wear due to increased loads.

J. Glaser *et al*. (2025) studied the scapho-metacarpal joint prosthesis with double-mobility design for patients with

persisting pain symptom and functional disorder after the surgery. The study involved 11 patients (with 13 surgeries), who demonstrated no positive dynamics after previous surgeries. They underwent underwent bilateral arthroplasty of the scapho-metacarpal joint. All patients demonstrated considerable improvement of the thumb function. Dynamometry results showed average restoration of up to 80–90% of the force of the contralateral side. Radiography showed good osseointegration of implants with no signs of instability or dislocation. The complications included one case of persistent mild hypesthesia of the superficial branch of the radial nerve, which did not impair the function, and one case of fracture of the scaphoid bone 4 weeks after the arthroplasty, during immobilization [77]. The characteristics of the double-mobility prosthesis clearly depend on the type of polyethylene used. The wear of polyethylene largely depends on its molecular composition, shape, vendor and technological process [29].

CONCLUSION

Trapeziectomy usually yields positive outcomes in RzA, relieving the pain and restoring the mobility of the thumb. At the same time the shortening of the thumb may result in a decreased grip and compression strength. Scientists focus on developing alternative methods of treatment. One of surgical methods of treatment is arthroplasty. However, it will take additional studies before it can be viewed as the "golden standard", like the trapeziectomy. The same applies to cementless total CMCJ prostheses that are instrumental in achieving fast rehabilitation, pain relief and restoration of grip force and movement freedom. Over time, these factors will render total CMCJ arthroplasty a full-fledged alternative to trapeziectomy.

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