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ИММУННЫЕ И МЕТАБОЛИЧЕСКИЕ МЕХАНИЗМЫ РАЗВИТИЯ И СОВРЕМЕННЫЕ ПОДХОДЫ К ТЕРАПИИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С ВИЧ-ИНФЕКЦИЕЙ

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Immune And Metabolic Mechanisms of Development and Modern Approaches to The Treatment of Heart Failure in Patients with HIV Infection

Резюме

Сердечная недостаточность (СН) остаётся одной из ключевых причин заболеваемости и смертности у пациентов с ВИЧ-инфекцией. За последние десятилетия фенотипы СН у данной популяции претерпели значительные изменения: если ранее доминировала сердечная недостаточность со сниженной фракцией выброса (СНнФВ), то в настоящее время всё большую клиническую значимость приобретает сердечная недостаточность с сохранённой фракцией выброса (СНсФВ). Патогенез этих состояний имеет мультифакторный характер и определяется взаимодействием вирус-ассоциированных механизмов, хронического воспаления, дисрегуляции иммунной системы, кардиометаболических нарушений и побочных эффектов антиретровирусной терапии (АРТ). Для СНнФВ характерны процессы, связанные с хроническим воспалением, активацией моноцитов и макрофагов, ускоренным развитием атеросклероза, ишемической болезни сердца и патологическим ремоделированием миокарда. СНсФВ, напротив, ассоциируется преимущественно с системными метаболическими нарушениями — ожирением, инсулинорезистентностью, дислипидемией, нарушением регуляции кишечного барьера и дисфункцией жировой ткани, что ведёт

к формированию фенотипа кардиометаболической СН. Особую роль в этих процессах играют метаболическое воспаление и специфическое воздействие АРТ (ингибиторов интегразы, нуклеозидных и ненуклеозидных ингибиторов обратной транскрипции). Понимание иммунных и метаболических механизмов ВИЧ-ассоциированной СН открывает перспективы для разработки новых терапевтических подходов, включающих иммуномодуляцию, коррекцию метаболических нарушений, использование статинов, ингибиторов SGLT2 и агонистов GLP-1. Дальнейшие исследования, направленные на стратификацию пациентов и оценку клинических исходов, имеют решающее значение для оптимизации ведения данной сложной категории больных.

Ключевые слова: *сердечная недостаточность; ВИЧ-инфекция; сердечная недостаточность со сниженной фракцией выброса; сердечная недостаточность с сохранённой фракцией выброса; иммунное воспаление; метаболические нарушения; антиретровирусная терапия*

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Abstract

Heart failure (HF) remains one of the leading causes of morbidity and mortality among patients with HIV infection. Over the past decades, the phenotypes of HF in this population have shifted substantially: while heart failure with reduced ejection fraction (HFrEF) was historically predominant, heart failure with preserved ejection fraction (HFpEF) has emerged as an increasingly important clinical manifestation. The pathogenesis of these conditions is multifactorial, driven by virus-related mechanisms, chronic inflammation, immune dysregulation, cardiometabolic disturbances, and adverse effects of antiretroviral therapy (ART). HFrEF in HIV-infected individuals is primarily associated with chronic inflammation, monocyte–macrophage activation, accelerated atherosclerosis, ischemic heart disease, and pathological myocardial remodeling. By contrast, HFpEF is linked to systemic metabolic abnormalities such as obesity, insulin resistance, dyslipidemia, gut barrier dysfunction, and adipose tissue dysregulation, ultimately leading to the cardiometabolic HF phenotype. A central role in this process is played by metabolic inflammation and the impact of ART (including integrase inhibitors, nucleoside and non-nucleoside reverse transcriptase inhibitors). Understanding the immune and metabolic mechanisms of HIV-associated HF opens new opportunities for therapeutic development. Promising approaches include immunomodulation, metabolic correction, and the use of statins, SGLT2 inhibitors, and GLP-1 receptor agonists. Future studies focusing on patient stratification and clinical outcomes are essential for optimizing the management of this complex patient group.

Key words: *heart failure, HIV infection, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, immune inflammation, metabolic disorders, antiretroviral therapy*

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ART — antiretroviral therapy, HIV — human immunodeficiency virus, BMI — body mass index, IL — interleukin, LV — left ventricle, HDLP — high-density lipoproteins, LDLP — low-density lipoproteins, MRI — magnetic resonance imaging, RR — relative risk, HF — heart failure, HFrEF — heart failure with reduced ejection fraction, HFpEF — heart failure with preserved ejection fraction, CRP — C-reactive protein, FMT — faecal microbiota transplantation, EF — ejection fraction, ECG — electrocardiography, AIDS — acquired immune deficiency syndrome, IL-1β — interleukin-1β, IL-6 — interleukin-6, NLRP3 — NOD-like receptor protein 3, TLR — Toll-like receptor, SGLT2 — sodium-glucose linked transporter 2, GLP-1 — glucagon-like peptide-1, INSTI — integrase inhibitors, NRTI — nucleoside reverse transcriptase inhibitors, NNRTI — non-nucleoside reverse transcriptase inhibitors, TMAO — trimethylamine N-oxide, MACE — major adverse cardiovascular events

Introduction

Heart failure (HF) has been regarded for several decades as one of the most unfavourable clinical outcomes in patients living with HIV infection; however, its characteristics have changed substantially over the past forty years [1]. Before the advent of antiretroviral therapy (ART), HF in HIV-infected patients was predominantly associated with complications of acquired immunodeficiency syndrome (AIDS), including severe uncontrolled viremia, opportunistic infections, and the related dilated cardiomyopathies [2].

With the introduction and widespread use of ART, the life expectancy of patients with HIV has increased significantly, leading to a shift in the pattern of morbidity,

with cardiovascular diseases emerging as a major concern in this population [3, 4]. Despite the overall progress in reducing mortality achieved through ART, HIV-positive patients continue to have a significantly higher risk of developing HF compared with the general population [5, 6].

It should be emphasised that, in contemporary clinical practice, HF and associated cardiovascular diseases in patients with HIV are only partially explained by traditional risk factors observed in the general population. Mechanisms specific to chronic HIV infection continue to play a substantial role, including persistent systemic inflammation, immune dysregulation, and the consequences of prolonged viral persistence, all of which contribute to both the development and progression of HF [7].

The clinical spectrum of HF in this patient population is heterogeneous and is determined by the interplay of multiple etiological factors. The most widely used approach to classifying HF remains stratification according to left ventricular ejection fraction (LVEF). This classification distinguishes heart failure with reduced ejection fraction (HFrEF), which is predominantly associated with systolic dysfunction, from heart failure with preserved ejection fraction (HFpEF), which is characterised by diastolic dysfunction and a high prevalence of systemic comorbid conditions in the absence of a marked reduction in LVEF [8].

Importantly, therapeutic strategies for HFrEF and HFpEF differ and require the implementation of distinct management algorithms [8]. In recent years, there has been growing recognition that these phenotypes represent heterogeneous clinical pathophysiological subpopulations characterised by unique mechanisms underlying disease development and progression. This has opened new avenues for the development of individualised therapeutic approaches.

People living with HIV exhibit an increased risk of both HF overall and the development of the HF phenotype with HFpEF. In this context, understanding the precise pathophysiological mechanisms underlying the various forms of HF in this population is of fundamental importance for optimising therapeutic strategies and selecting individualised approaches [9–11]. This review examines the key mechanisms through which HIV infection may exert both direct and indirect effects on the development of different HF subtypes and clinical manifestations, including HFrEF and HFpEF.

The purpose of this review is to systematise and critically analyse the present knowledge of the immune and metabolic mechanisms of heart failure in patients with HIV infection; and to evaluate the impact of antiretroviral therapy and the possibility of using novel therapeutic strategies to correct these conditions.

Methods of study search

A literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science and eLibrary for the period from January 2000 to March 2024. The following keywords and keyword combinations were used for the search: “HIV infection”, “heart failure”, “HFrEF”, “HFpEF”, “immune mechanisms”, “immune dysregulation”, “metabolic disorders”, “metabolic inflammation”, “antiretroviral therapy”. At the first stage, all publications containing the specified keywords in the title or abstract were considered. At the second stage, sources were filtered by publication type; the analysis included original studies, systematic reviews, meta-analyses, clinical practice guidelines, and expert statements issued by relevant professional associations. At the third stage, articles without full-text access, duplicate publications, and studies in which heart failure in HIV-infected individuals was addressed only indirectly were excluded. The final set of publications was established following an independent assessment of relevance by two authors. As a result of the selection process, 67 publications that most comprehensively reflect the current state of knowledge on the subject were included in this review.

Epidemiology of HIV and heart failure

Over the past decades, a substantial body of evidence has accumulated demonstrating an increased incidence and prevalence of HF among people living with HIV infection compared with the general population [9]. The risk of HF in HIV-infected patients is 1.5-2 times higher than in non-infected population [12]. A large cohort study of veteran ageing, which included the US national data for 2003–2016, demonstrated that in HIV patients the risk of HF was significantly higher than in individuals living without HIV (RR 1,6), despite regular ART [9].

Similar results were reported in a national study based on the Taiwanese databases, where it was demonstrated that ART reduces the risk of HF; however, even in patients undergoing treatment, the probability of HF remains 1.5 times higher than in non-HIV patients [10]. In a single-centre study conducted within an urban healthcare system between 2000 and 2016, the risk of HF among people living with HIV and pulmonary hypertension was found to be more than twice as high as that among patients without HIV infection [6].

It is important to emphasise that many early studies demonstrating an increased risk of HF among people living with HIV included cohorts in which access to ART was limited. Nevertheless, even in contemporary studies focusing exclusively on patients receiving ART, the prevalence of HF remains high. For example, one recent multicentre study reported a prevalence of HFrEF of 2.4 % [13]. Furthermore, individuals with HIV continue to have an intrinsically elevated risk of developing HF compared not

only with the general population but also with patients affected by other chronic inflammatory diseases [14].

Recent observations demonstrate that the HFpEF phenotype prevails in the structure of HF in HIV-positive patients. For instance, HEART with HIV study showed that in individuals living with HIV, the risk of both HFrEF and HFpEF is higher than in people without HIV, and the relative risk of HFpEF turns out to be more pronounced [5]. Imaging studies have shown that the prevalence of diastolic dysfunction among middle-aged patients may range from 22 % to 37 % [11, 13, 17–19].

Data from a meta-analysis of 54 studies encompassing North America, Europe, Africa, and Asia further underscore the global nature of this problem: the prevalence of left ventricular systolic dysfunction was 12.3 %, whereas the prevalence of diastolic dysfunction reached 29.3 % [11]. Although the exact relationship between subclinical abnormalities and the development of clinically overt HF remains incompletely understood, the observed differences in the prevalence of diastolic and systolic dysfunction suggest a potential shift in the disease spectrum toward a higher prevalence of HFpEF among HIV-infected patients [15, 16]. This emphasises the need in further prospective studies in order to clarify pathogenetic mechanisms and predict long-term outcomes.

Clinical presentation of heart failure in patients living with HIV infection depends to a greater extent on the stage of the infectious process. During the acute phase of HIV infection, cases of heart failure are observed predominantly in the setting of myocarditis and transient myocardial dysfunction associated with high viral load and marked immune activation. During the chronic (latent) stage, persistent systemic inflammation, immune dysregulation, and metabolic disturbances become the predominant factors, creating the conditions for the development of heart failure with preserved ejection fraction. In contrast, during disease progression and the development of AIDS, severe forms of heart failure with reduced ejection fraction are more commonly encountered, resulting from direct cardiomyocyte injury, opportunistic infections, and dilated cardiomyopathy. Thus, the clinical course of HF in HIV infection reflects both the stage of the infectious process and the interplay among virus-related, immune-mediated, and metabolic mechanisms.

Heart failure with reduced ejection fraction in HIV: phenotypes and pathogenetic mechanisms

Traditionally, heart failure with reduced ejection fraction in HIV-infected population is associated with cardiomyocyte death, structural remodelling, and formation of fibrosis resulting in reduced systolic function of the left ventricle [20]. During the early years of the HIV/AIDS epidemic, HF frequently developed as a consequence of direct myocardial injury, including infection of cardiomyocytes and immune cells by the virus, the toxic effects of HIV proteins, and opportunistic infections, all of which contributed to the development of dilated cardiomyopathy [21]. Although such an etiology has become less common in the era of highly effective ART, it remains relevant among populations with limited access to treatment [11].

Modern mechanisms of CFrEF

At present, chronic inflammation and immune dysregulation, which persist even in the setting of successful ART, play a central role [22]. In most patients, residual viremia persists, promoting sustained activation of innate immune cells, particularly monocytes and macrophages [23]. Specifically, the proportion of non-classical proinflammatory monocytes (CD16+) in individuals with HIV may account for up to 40 % of circulating mononuclear cells, compared with 5–10 % in HIV-negative individuals [24]. These cells produce cytokines and chemokines that maintain a chronic inflammatory state within the myocardium [25].

Dysregulated monocyte-macrophage activation contributes to the accelerated development of atherosclerosis, coronary artery disease, and myocardial infarction in patients with HIV infection. These effects are mediated through enhanced production of reactive oxygen species, increased expression of adhesion molecules and chemokines, foam cell formation, and accelerated progression of atherosclerotic plaques [26]. Subsequent myocardial infarctions, accompanied by replacement of damaged myocardium with scar tissue, lead to ischemic cardiomyopathy and HFrEF [27, 28].

Role of epidemiological factors

In addition to biological mechanisms, social and behavioural factors have substantial significance. Smoking is substantially more prevalent among patients with HIV infection than in the general population [29], thereby contributing to the development of atherosclerosis and HFrEF. Similarly, the higher prevalence of methamphetamine use among people living with HIV [30] has been associated with an increased risk of toxic cardiomyopathies and HFrEF [31]. Although the available data regarding this association are inconsistent, further studies are needed to clarify its role in the spectrum of HF among patients with HIV [32].

Cardiac fibrosis and chronic inflammation

Profibrotic effect of chronic inflammation is of particular significance. HIV-infected monocytes and macrophages produce excessive IL-1β, which activate inflammasome NLRP3 and resident immunocytes in the heart, causing enhanced myocyte apoptosis, collagen synthesis, and scarring [33,34]. In addition, HIV proteins activate

TLR-receptors, thereby amplifying inflammatory signalling cascades [35]. Dysfunction of regulatory T cells promotes the overproduction of transforming growth factor-β1 (TGF-β1) and the activation of myofibroblasts [36].

Impaired intestinal barrier as a factor of HFrEF

Acute HIV-infection is associated with destruction of CD4+ T cells in the intestine and epithelial integrity damage, resulting in translocated microbial products and activation of TLR/NLRP3-inflammasome [37]. In addition, HIV-infected individuals exhibit enhanced production of intestinal metabolites, including trimethylamine N-oxide (TMAO), which is associated with development of cardiac fibrosis [38]. These alterations persist even with successful ART, thereby maintaining a sustained risk of HFrEF progression [39].

Thus, HFrEF in people living with HIV results from a combination of conventional factors, such as coronary artery disease and toxic insults, and mechanisms unique to this population, including chronic inflammation, profibrotic signalling pathways, and disruption of the intestinal barrier. Even in the era of highly effective ART, these processes continue to drive myocardial remodelling and the progression of heart failure.

Therapeutic approaches to heart failure with reduced ejection fraction in HIV-infected patients

Core principles

Regardless of HIV status, the cornerstone of treatment for HFrEF remains guideline-directed medical therapy, including β-blockers, inhibitors of the renin-angiotensin-aldosterone system, mineralocorticoid receptor antagonists, and SGLT2 inhibitors; treatment selection and dose titration are performed according to the general management algorithms for HFrEF [8]. Against this background, additional strategies (primarily anti-inflammatory and immunomodulatory approaches) are being explored in HIV-infected individuals as potential adjunctive therapies for patients with a persistent inflammatory phenotype of myocardial remodelling.

IL-1β inhibition

In pilot studies involving HIV-infected individuals, canakinumab, a monoclonal antibody targeting IL-1β, has been shown to reduce systemic inflammation and signs of atherosclerotic disease, making the IL-1β-inflammasome axis an attractive therapeutic target in the subgroup of patients with residual inflammatory activity despite virologic suppression [40]. However, evidence regarding their impact on major cardiovascular outcomes in HIV-infected patients with HFrEF remains insufficient.

IL-6 blockage and inflammasome targeting

Approaches aimed at suppressing the cytokine cascade are currently being investigated, including the use of tocilizumab, an IL-6 receptor inhibitor, as well as direct targeting of the NLRP3 inflammasome with experimental antagonists of its subunits [40]. These strategies are pathophysiologically justified, given the role of IL-6-mediated myeloid cell activation and the central involvement of NLRP3 in fibrogenesis. However, they require rigorous evaluation of their safety profile in patients with HIV infection, particularly with regard to the risk of opportunistic infections and potential drug interactions with ART.

TLR signalling modulation

In order to inhibit the innate immune activation, the use of 4-aminoquinoline (hydroxychloroquine) for regulation of TLR-mediated signalling has been studied [41]. Correct positioning of such devices is possible only within the scope of clinical studies among thoroughly selected patients having the signs of the inflammatory phenotype of remodelling.

Intestinal barrier and microbiota

Given the contribution of HIV-associated intestinal barrier dysfunction to the maintenance of systemic inflammation and profibrotic signalling pathways, including TLR- and NLRP3-mediated activation, interventions aimed at restoring enterocyte integrity and the composition of the gut microbiota are currently being investigated. These include probiotics and faecal microbiota transplantation (FMT) [41, 42]. Although the pathogenetic rationale for these approaches is compelling, randomised trials with clinically relevant endpoints in patients with HFrEF are still required.

Clinical significance and patient selection criteria

At the present stage, immunomodulatory therapy in HIV-infected patients with HFrEF should be regarded solely as an adjunct to guideline-directed medical therapy and optimised ART, and should be implemented exclusively within the framework of clinical protocols. Such approaches should incorporate targeted stratification based on biomarkers of residual inflammation (e.g., high-sensitivity C-reactive protein, IL-6, sCD14, and sCD163), evidence of myocardial fibrosis (as assessed by cardiac MRI with T1/ECV mapping), and the presence of stable virologic suppression. Key endpoints should include reverse left ventricular remodelling, heart failure-related hospitalisations, and composite major adverse cardiovascular events (MACEs). Careful assessment of safety and potential interactions with ART is mandatory, particularly with respect to CYP-mediated mechanisms and effects involving P-gp substrates.

Limitations and safety

The majority of the above-mentioned approaches (IL-1β/IL-6 inhibitors, anti-NLRP3, FMT) does not have a confirmed advantage in clinical outcomes in HIV-infected patients with HFrEF and has not been included in the standards of care. Risks of immune suppression, latent infection reactivation and the impact on the vaccine-mediated response require thorough evaluation within the scope of clinical trials [40–42].

Heart failure with preserved ejection fraction in HIV-infected individuals

Whereas HFrEF was the predominant HF phenotype during the early years of the HIV epidemic, contemporary trends indicate an increasing prevalence of HFpEF [8]. In contrast to HFrEF, which is characterised by cardiomyocyte loss and replacement fibrosis, HFpEF is driven predominantly by systemic comorbidities and cardiomyocyte dysfunction in the absence of substantial cytolytic cell death [15, 43]. Traditionally, HFpEF has been regarded as a consequence of hypertensive heart disease, occurring mainly in elderly patients in whom increased myocardial stiffness limits diastolic relaxation [44].

In HIV-infected individuals, chronic activation of innate immune cells (monocytes and macrophages) is associated with systemic inflammation, stiff aorta and increased vascular rigidity, which is pathophysiologically similar to the mechanisms of hypertensive disease [45]. The mechanisms of pathological fibrosis formation, which were previously discussed for HFrEF, can manifest as the HFpEF phenotype even before systolic dysfunction develops [46]. Numerous studies in patients with HIV have demonstrated increased activity of the monocyte-macrophage compartment, including peripheral monocytosis and enhanced production of chemokines and cytokines involved in chemotaxis and the maintenance of chronic inflammation [47]. Taken together, these factors create a milieu that predisposes HIV-infected individuals to an increased susceptibility to the development of HFpEF.

Cardiometabolic dysfunction and metabolic inflammation

Although arterial hypertension remains one of the most important risk factors of HFpEF, the data for the last 15 years demonstrate that cardiometabolic dysfunction plays an equally important role [48]. Obesity and metabolic syndrome are associated with increased secretion of inflammatory cytokines, including IL-6, which promotes the so-called metabolic inflammation. This process both initiates and worsens HFpEF [49].

Experimental models have demonstrated that systemic inflammation induces tissue hypoxia, which metabolically reprograms both innate and adaptive immune cells, shifting their energy metabolism from mitochondrial respiration to anaerobic glycolysis [50]. This state of energetic stress disrupts the transcription of regulatory genes, promotes dysfunction of resident myocardial immune cells, diminishes their cardioprotective capacity, and impairs the processes responsible for the resolution of inflammation [51]. As a consequence, chronic diastolic dysfunction develops in the absence of overt cardiomyocyte death [52]. With the increasing prevalence of obesity, this cardiometabolic phenotype of HFpEF is becoming increasingly important, including among younger patients [43].

The role of retroviral therapy

A significant risk factor of metabolic disorders in HIV patients is the side effects of ART. Early regimens that included protease inhibitors were associated with pronounced disturbances in lipid metabolism, lipodystrophy, and obesity [53]. Although these agents have largely been replaced, even contemporary ART regimens, including integrase strand transfer inhibitors (INSTIs), nucleoside reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs), have been associated with weight gain and alterations in body fat distribution [54, 55].

Recent pre-clinical studies demonstrated that the widely used first-line agents, such as Dolutegravir and Bictegravir, stimulate adipogenesis, adipocyte hypertrophy and facilitate obesity [56]. Moreover, INSTIs may disrupt the physiological processes of adipose tissue accumulation, thereby inducing adipocyte hypoxia, oxidative stress, and insulin resistance [57]. Thus, despite the undeniable benefits of ART in reducing mortality, its metabolic adverse effects contribute additionally to the increasing prevalence of HFpEF among patients living with HIV.

Dysregulation of intestinal barrier and adipose tissue

An important component of pathogenesis is disrupted intestinal barrier in HIV infection. Loss of enterocyte layer integrity and the translocation of lipopolysaccharides into the bloodstream lead to activation of inflammatory cascades, reduced efficiency of reverse cholesterol transport, and impaired HDLP function [58]. These processes exacerbate dyslipidemia and metabolic stress, thereby increasing the risk of atherosclerosis and metabolic inflammation.

In addition, some HIV-associated proteins have been shown to inhibit preadipocyte differentiation even in the presence of low-level viremia. This results in adipocyte hypertrophy, hyperglycemia, and organ steatosis, even in individuals with a normal body mass index [59]. HIV infection is also associated with impaired function of dicer-RNAse and white fat dysfunction [60]. In the adipose tissue of HIV-infected individuals, increased infiltration by CD8+ T cells has been observed even in those with

a normal BMI, resembling the pattern seen in obese individuals without HIV infection [59, 61]. Such infiltration amplifies adipocyte inflammation and promotes the development of insulin resistance and metabolic syndrome.

HFpEF in HIV-infected individuals represents a multifactorial phenotype driven by the interplay among chronic inflammation, metabolic disturbances, adverse effects of ART, and dysfunction of the intestinal barrier and adipose tissue. These processes confer an increased predisposition to the cardiometabolic form of HF, even in patients without traditional risk factors such as obesity and hypertension. Consequently, HFpEF is emerging as the predominant clinical phenotype of heart failure in the population of patients living with HIV infection.

Therapeutic approaches to heart failure with preserved ejection fraction in HIV-infected patients

Given the increasing prevalence of cardiometabolic heart failure in both the general population and among people living with HIV, as well as the particular susceptibility of this patient group to cardiometabolic disturbances, optimisation of therapeutic strategies aimed at reducing metabolic inflammation has become of paramount importance. These strategies encompass both non-pharmacological approaches, such as lifestyle modification, and pharmacological interventions.

Statins and dyslipidemia

One of the most extensively studied strategies is the use of statins for the management of dyslipidemia. Their efficacy in lowering cholesterol levels and preventing cardiovascular complications has long been established in the general population. The latest European guidelines on the management of dyslipidemias recommend statin therapy for individuals aged 40 years and older living with HIV for primary prevention, regardless of estimated cardiovascular risk or LDLP levels, in order to reduce the risk of cardiovascular events; the choice of statin should be guided by the potential for drug-drug interactions [62]. Available evidence indicates that statins also possess substantial preventive potential with respect to cardiovascular events in people living with HIV [41, 43, 63]. Of particular importance are the findings of the large REPRIEVE trial, in which pitavastatin significantly reduced the 5-year risk of major adverse cardiovascular events in patients with HIV infection, underscoring the role of this strategy in the prevention of cardiometabolic heart failure [64].

SGLT2 inhibitors

Beyond lipid-lowering therapy, there is growing interest in conventional heart failure treatments that exert anti-inflammatory and metabolically modulating effects. In the EMPEROR-Preserved trial, treatment with empagliflozin was associated with a reduction in heart failure-related hospitalisations among patients with HFpEF. Additional biomarker analyses suggest that the cardioprotective effects of this SGLT2 inhibitor may be mediated, at least in part, by improvements in mitochondrial function and reductions in oxidative stress [65, 66].

GLP-1 receptor agonists

Another promising strategy is the use of GLP-1 receptor agonists. In the STEP-HFpEF trial, treatment with semaglutide in patients with obesity resulted in significant improvements in HF symptoms and functional status, as well as a 43.5 % reduction in C-reactive protein levels [67]. Moreover, data from a phase IIb clinical trial involving HIV-infected individuals receiving ART demonstrated that semaglutide promotes weight loss, reduces waist circumference, and improves markers of metabolic dysfunction-associated liver disease associated with an inflammatory phenotype [68].

The role of metabolic inflammation as a therapeutic target

Taken together, these findings suggest that metabolic inflammation may represent a viable therapeutic target in cardiometabolic HFpEF among patients living with HIV infection. However, further studies are needed to determine the optimal combinations of anti-inflammatory and metabolic therapies and to assess the extent to which modulation of metabolic inflammation can improve long-term outcomes in HFpEF.

Conclusion

The evidence discussed above highlights the numerous and diverse mechanisms through which HIV infection contributes to the development of both HFrEF and HFpEF. Regardless of the clinical phenotype, whether characterised by enhanced myocardial fibrosis, increased susceptibility to atherosclerotic disease, disruption of myocardial immune cell organisation, or alterations in cardiomyocyte metabolism, the central pathophysiological theme remains dysregulation of the innate and adaptive immune systems, resulting in chronic pathological inflammation.

In recent years, the concept of metabolic inflammation as a driving force underlying the cardiometabolic phenotype of HF has attracted particular interest. This concept opens new therapeutic opportunities, including strategies aimed at immunomodulation and the correction of metabolic disturbances.

Given that the prevalence of cardiometabolic HF is increasing both in the general population and among people living with HIV, future research should focus on elucidating the interplay among immune dysregulation, chronic inflammation, and altered metabolism. A deeper understanding of these interactions is crucial for the development of targeted therapeutic strategies capable of improving outcomes in patients with HIV infection.

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НЕИНВАЗИВНАЯ ВАГУСНАЯ НЕЙРОСТИМУЛЯЦИЯ (НВНС): ОБЗОР ИССЛЕДОВАНИЙ ПРИ ГОЛОВНОЙ БОЛИ, ТИННИТУСЕ, НАРУШЕНИЯХ СНА И ТРЕВОГЕ

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Noninvasive Vagus Nerve Stimulation (NVNS): A Review of Research on Headache, Tinnitus, Sleep Disorders and Anxiety

Резюме

Неинвазивная вагусная нейростимуляция (нВНС) — перспективный метод лечения, который изучается и показывает положительные результаты при большом спектре заболеваний. Стимуляция осуществляется через поверхностные электроды в проекции шейной части или ушной (аурикулярной) ветви блуждающего нерва. Возрастающий интерес к нВНС обусловлен простотой, доступностью, безопасностью и хорошей переносимостью, однако до настоящего времени в России данный метод не нашел широкого применения. В данном обзоре представлены основные параметры, используемые для стимуляции аурикулярной ветви и шейной части блуждающего нерва, а также результаты клинических исследований по использованию нВНС при головной боли, тиннитусе, нарушениях сна и тревоге. Обсуждены рекомендации FDA по применению стимулятора шейного отдела блуждающего нерва при головной боли, а также вопросы, необходимые для повышения уровня доказательной базы нВНС при различных нозологиях. Обозначена востребованность и перспективность разработки отечественного устройства для стимуляции периферической ветви вагуса, с целью более широкого внедрения методики в практику и накопления опыта его амбулаторного применения.

Ключевые слова: *неинвазивная стимуляция блуждающего нерва, вагус, головная боль, мигрень, тиннитус, бессонница*

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Abstract

Non-invasive vagus nerve stimulation (nVNS) is a promising treatment showing positive results for a wide range of diseases and is currently under active investigation. Surface electrodes are used to stimulate the cervical or auricular branch of the vagus nerve. The growing interest in nVNS is driven by its simplicity, accessibility, safety, and good tolerability. However, to date, this method has not been widely adopted in Russia. This review

covers the main stimulation parameters for auricular and cervical vagus nerve targets and the clinical evidence supporting nVNS use in managing headache, tinnitus, sleep disorders, and anxiety. We discuss FDA guidance on cervical VNS for headache and the research gaps that need to be filled to advance the evidence for nVNS in various conditions. We emphasize the necessity and prospects for a domestic (Russian) peripheral vagus nerve stimulation device, which would promote wider clinical integration and data collection on outpatient use.

Key words: *noninvasive vagus nerve stimulation, vagus, headache, migraine, tinnitus, insomnia*

Conflict of interests

Co-author of the article Suponeva N.A. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Suponeva N.A. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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CBT — cognitive behavioural therapy, nVNS — non-invasive vagus nerve stimulation, PSQI — Pittsburgh Sleep Quality Index, FDA — Food and Drug Administration

Introduction

Over the past several decades, neuromodulation techniques have been increasingly employed in the treatment of neurological disorders. One such approach is invasive vagus nerve stimulation (VNS), which has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of epilepsy and depression in patients older than 12 years of age [1]. Despite being considered minimally invasive, the procedure is associated with a risk of implantation-related complications, including bradyarrhythmias, peritracheal hematoma due to the close anatomical relationship between the vagus nerve and the carotid artery, and respiratory complications such as vocal cord dysfunction and dyspnoea [2]. Rare cases of late-onset bradyarrhythmias and severe asystole have also been reported in patients with implanted devices [3]. These concerns continue to limit the widespread adoption and broader implementation of invasive vagus nerve stimulation.

A promising alternative that avoids the limitations associated with invasive stimulation is non-invasive vagus nerve stimulation (nVNS). In nVNS, stimulation is delivered through surface electrodes placed over the cervical portion of the vagus nerve or the auricular branch of the vagus nerve [2, 4]. The neurophysiological mechanisms underlying this technique have been extensively investigated at the preclinical level. Briefly, vagus nerve stimulation transmits afferent signals to the nucleus tractus solitarius, which in turn activates the locus coeruleus and promotes the release of norepinephrine. Increased norepinephrine levels subsequently stimulate the dorsal raphe nucleus, leading to enhanced serotonin release, a process associated with increased synaptic plasticity and neurogenesis. In addition, vagus nerve stimulation activates the basal nucleus, thereby modulating the cholinergic system, which plays a crucial role in neuroplasticity, including through mechanisms of long-term potentiation [5].

The therapeutic potential of nVNS extends beyond the treatment of depression and epilepsy. This approach is currently being investigated in a wide range of neurological disorders, including headache, tinnitus, insomnia, pain syndromes, restless legs syndrome, Parkinson's disease, and others [4, 5]. Adverse effects associated with nVNS are generally mild and include skin irritation at the stimulation site; less commonly, patients report headache, dizziness, nausea, nasopharyngitis, and other symptoms [6]. To date, non-invasive vagus nerve stimulation has not been widely adopted in Russia.

The aim of this review is to summarise and systematise the available evidence regarding the use of nVNS in the treatment of headaches, tinnitus, sleep disturbances, and anxiety.

A literature search was conducted using the PubMed (including MEDLINE) and Web of Science databases, as well as the Russian scientific electronic libraries CyberLeninka and eLibrary.Ru. The following keywords were used: "non-invasive vagus nerve stimulation", "vagus", "headache", "migraine", "tinnitus", and "insomnia".

Use of nVNS in headache, tinnitus, sleep disturbances, and anxiety

A brief overview of studies investigating the efficacy of nVNS is presented in Table 1.

Table 1. *Brief description of studies of the effectiveness of nVNS in headache, tinnitus, sleep disorders and anxiety*

Author, year, reference	Nosology (number of patients)	Stimulation site (side)	Stimulation parameters: 1. pulse width 2. intensity 3. frequency	Treatment regimen	Result
P.J. Goadsby et al, 2014 [8]	episodic migraine (30)	neck (R)	1. NS 2. NS 3. NS	– 2 x 90s doses (15 min apart) after the onset of the headache – follow-up period — 6 weeks	2 hours after onset of headache: – with moderate and severe attack — no pain in 21 % (first attack)/22 % (all attacks) – with mild attack — 63 % pain free (first attack)/38 % pain free (all attacks)
P. Barbanti et al, 2015 [9]	chronic migraine (50)	neck (R)	1. NS 2. NS 3. NS	– 2 x 120s doses (3 min apart) within 20 min of the onset of mild or moderate headache – follow-up period — 2 weeks	48 patients: – after 1 hour: ≥ 50 % reduction in VAS in 56,3 % of patients, VAS = 0 in 35,4 % of patients – after 2 hours: ≥ 50 % reduction in VAS in 64,6 % of patients, VAS = 0 in 39,6 % of patients 131 migraine attacks: – after 1 hour: ≥ 50 % reduction in VAS in 38,2 % of attacks, VAS = 0 in 17,6 % of attacks – after 2 hours: ≥ 50 % reduction in VAS in 51,1 % of attacks, VAS = 0 in 22,9 % of attacks
T.M. Kinfe et al., 2015 [10]	treatment-refractory migraine and sleep disturbance (20)	neck (L, R)	1. 1 ms 2. up to 24 V 3. 25 Hz	– for treatment — 120s on each side – for prevention — 120s on each side, 2 times a day, 3 months	– decreased frequency (p <0,01), intensity (p <0,0001) and duration (p <0,002) of migraine attacks – improvement in performance, sleep quality and depressive symptoms (p <0,05)
L. Grazzi et al., 2016 [11]	menstrual /menstrually related migraine (51)	neck (L, R)	1. 0,2 ms 2. up to 60 mA 3. 25 Hz	– 120s on each side, 3 times a day – from –3 days before estimated onset of menstruation through +3 days after the end of menstruation during each cycle of the 12-week treatment period	reduction in the number of menstrual migraine/ menstrually related migraine days and analgesic use (p <0,001)
C. Tassorelli et al, 2018 [12]	episodic migraine (120)	neck (L, R)	1. 0,2 ms 2. 60 mA 3. 25 Hz	120s on each side within 20 min of the onset of headache	nVNS is superior to placebo for pain freedom at 30 minutes and 60 minutes after the onset of the attack (p <0,01), increases the probability of having mild pain or being pain-free 2 hours poststimulation
S.D. Silberstein et al, 2016 [13]	chronic migraine (59)	neck (R)	1. NS 2. up to 60 mA 3. NS	– 2 x 120s doses (5-10 min apart), 3 times a day – follow-up period — 8 months	reduction in the number of headache days compared to baseline (p <0,01)
C. Gaul et al., 2016 [14]	chronic cluster headache (45)	neck (R)	1. NS 2. 60 mA 3. 25 Hz	3 x 120s doses, 2 times a day	a greater reduction in the number of headache attacks per week compared with the control group (p = 0,02)

Table 1. (Continued)

Author, year, reference	Nosology (number of patients)	Stimulation site (side)	Stimulation parameters: 1. pulse width 2. intensity 3. frequency	Treatment regimen	Result
S.D. Silberstein et al, 2016 [15]	episodic and chronic cluster headache (150)	neck (R)	1. 0,2 ms 2. up to 60 mA 3. 25 Hz	3 x 120s doses (1 min apart)	in the nVNS group, more patients with episodic cluster headache responded to treatment (VAS = 0 or 1 after 15 minutes) (p =0,008)
P.J. Goadsby et al, 2018 [16]	episodic and chronic cluster headache (48)	neck (on the attack side)	1. 0,2 ms 2. up to 24 V 3. 5 kHz	3 x 120s doses	in the nVNS group, a higher proportion of episodic cluster headache attacks achieved pain-free status within 15 minutes (p <0,01)
A. Straube et al, 2015 [19]	chronic migraine (46)	ear, concha (L)	1. 0,25 ms 2. below pain threshold 3. 1 Hz or 25 Hz	4h a day, 12 weeks	stimulation with a frequency of 1 Hz leads to a greater reduction in headache days over a 28-day period compared to stimulation with a frequency of 25 Hz (p =0,035)
J. Lehtimäki et al, 2013 [26]	tinnitus (10)	ear, tragus (L)	1. NS 2. above sensory threshold (about 0,8 mA) 3. 25 Hz	7 sessions x 45/60 min	decreased severity of tinnitus symptoms (THI and mini-TQ questionnaires), improved mood (WHO-5 questionnaire); no statistical verification was performed
P.M. Kreuzer et al, 2014 [31]	tinnitus (50)	NS	1. NS 2. 0,1-10 mA 3. 25 Hz	– phase I: 6h a day – phase II: 4h a day – follow-up period — 24 weeks	– phase I (terminated prematurely due to two cardiac events) — decreased TQ scores (p =0,036) – phase II — insignificant decrease in TQ scores (p =0,146)
Z. Mei et al, 2014 [27]	tinnitus (32)	ear, concha (NS)	1. 1 ms 2. 1 mA 3. 20 Hz	– 20 min, 2 times a day – daily for 8 weeks	higher efficacy (THI and TDI questionnaires) in the main group (nVNS + sound therapy) compared with the control group after 8 weeks (p <0,05)
H.J. Shim et al, 2015 [28]	tinnitus (30)	ear, concha (L)	1. 0,2 ms 2. 1-10 mA (below pain threshold) 3. 25 Hz	10 sessions x 30 min	– insignificant decrease in THI scores (p =0,339) – decrease in tinnitus loudness (p =0,005) and tinnitus awareness (p =0,020)
W.C. Suk et al, 2018 [29]	tinnitus (24)	ear (cavum, cymba and tragus) (NS)	1. 0,2 ms 2. below pain threshold 3. 30 Hz	4 sessions x 12 min (each site for 4 min) for 2 weeks (day 1-3-8-10)	1 month after the end of the sessions: – reduction of tinnitus characteristics (loudness, awareness, annoyance and effect on life) (p <0,05) – decrease in THI scores (p <0,001) – decrease in BDI scores (p =0,004)
T.Yu. Vladimirova et al, 2023 [30]	tinnitus (25)	ear, cymba (L)	1. NS 2. 10 mA 3. 1-30 Hz	14 sessions x 10 min	patients of the main group (nVNS + medications) were 60 % more likely to have a positive effect from treatment in the following indicators: the assessment of the strength of subjective ear noise, the tone of the autonomic nervous system, the results of the THI questionnaire, the qualitative hearing characteristics

Table 1. *(The end)*

Author, year, reference	Nosology (number of patients)	Stimulation site (side)	Stimulation parameters: 1. pulse width 2. intensity 3. frequency	Treatment regimen	Result
M. Luo et al, 2017 [40]	primary insomnia (35)	no data	no data	– 30 min, 2 times a day – 5 days a week, for 4 weeks	– decrease in PSQI scores at the end of the 2nd week (p <0,05) – decrease in HAMD and HAMA scores at the end of weeks 4 and 6 (p <0,05)
Y. Jiao et al, 2020 [41]	insomnia (31)	ear, concha (on both sides)	1. NS 2. adjusted by participants 3. 20 Hz — 10 s, 4 Hz — 5 s	– 30 min, 2 times a day – 5 consecutive days a week, for 4 weeks	significant decrease in PSQI score in the main group (nVNS) at week 4, with no significant difference compared to the control group (sham nVNS)
Y. Wu et al, 2022 [42]	insomnia (15)	ear, concha (on both sides)	1. 0,2 ms 2. 1 mA 3. 20 Hz	– 20 min, 2 times a day – 1 month	a more significant decrease in PSQI scores in the main group (nVNS) compared with the control group (sham nVNS) (p =0,027)
L. Zhang et al, 2023 [43]	altitude insomnia (33)	ear, tragus (L)	1. 0,5 ms 2. NS 3. 25 Hz	– 45 min x once a day – 5 consecutive days a week, for 4 weeks	– significant decrease in PSQI, ISI and GAD-7 scores in the main group (nVNS) and the CBT group – the effectiveness of nVNS at 4 and 8 weeks after treatment is higher than that of CBT
S. Zhang et al, 2024 [45]	insomnia (36)	ear, cymba and cavum (on both sides)	1. 0,2 ms ±30 % 2. 0,8-1,5 mA (below pain threshold) 3. 20 Hz — 10 s, 4 Hz — 5 s	– 30 min, 2 times a day – 5 consecutive days a week, for 8 weeks – follow-up period — 20 weeks	– a more significant decrease in PSQI, ISI, HAMD, HAMA and FFS scores after 8 weeks in the main group (nVNS) compared with the control group (sham nVNS) (p <0,001) – the advantage of nVNS persisted during the 20-week follow-up period
J.W. Yeom et al, 2025 [44]	insomnia (no data)	no data	no data	30 min daily for 6 weeks	– a more significant decrease in PSQI (p =0,009) and ISI (p = 0,023) scores in the main group (nVNS) compared with the control group (sham nVNS) – increased total sleep time (p =0,019) and improved quality of life in the nVNS group (p =0,047)
V. Srinivasan et al, 2024 [46]	anxiety (no data)	no data	no data	– 30 min – 4 days a week, for 4 weeks	a more significant decrease in anxiety symptoms (GAD-7 questionnaire) and salivary cortisol levels in the main group (nVNS) compared with the control group (Jacobson's PMR)
V. Srinivasan et al, 2024 [47]	anxiety and sleep disturbances (no data)	no data	no data	– 30 min – 3 days a week, for 4 weeks	significant improvement in sleep quality and anxiety reduction at 4 weeks (p = 0,001)

Note. BDI — Beck Depression Inventory; CBT — Cognitive behavioral therapy; FFS — Flinders Fatigue Scale; GAD-7 — Generalized Anxiety Disorder-7; HAMA — Hamilton Anxiety Rating Scale; HAMD — Hamilton Rating Scale for Depression; ISI — Insomnia Severity Index; L — left; NS — not stated; nVNS — noninvasive Vagus Nerve Stimulation; PMR — Progressive Muscle Relaxation; PSQI — Pittsburgh Sleep Quality Index; R — right; TDI — Tinnitus Dysphoria Inventory; THI — Tinnitus Handicap Inventory; TQ — Tinnitus Questionnaire; VAS — Visual Analogue Scale; WHO-5 — World Health Organization-Five Well-Being Index

Table 2. *Treatment recommendations for using the gammaCore Sapphire stimulator [Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf21/K211856.pdf (accessed date on 03.08.2025)]*

Indication	Treatment recommendations
The preventive treatment of migraine headache in adolescent (aged 12 and older) and adult patients	120-second stimulation cycle, 2 consecutive stimulations on either side of the neck as follows: • First daily treatment: within 1 hour of waking • Second daily treatment: 4-6 hours after the first daily treatment • Third daily treatment: within 1 hour before going to sleep
The acute treatment of pain associated with migraine headache in adolescents (aged 12 and older) and adult patients	120-second stimulation cycle, 2 bilateral stimulations up to 3 times a day
Adjunctive use for the preventive treatment of cluster headache in adult patients	120-second stimulation cycle, 3 consecutive stimulations on either side of the neck as follows: • First daily treatment: within 1 hour of waking • Second daily treatment: 7-10 hours after the first daily treatment
The acute treatment of pain associated with episodic cluster headache in adult patients	120-second stimulation cycle, 3 consecutive stimulations up to 8 times a day
Treatment of hemicrania continua in adults in adolescents (aged 12 and older) and adult patients	120-second stimulation cycle, 2 stimulations ipsilateral to the side of pain up to 3 times a day
Treatment of paroxysmal hemicrania in in adolescents (aged 12 and older) and adult patients	120-second stimulation cycle, 2 stimulations ipsilateral to the side of pain up to 3 times a day

nVNS and headache management

Electrical neuromodulation techniques, including nVNS, occupy a distinct niche among non-pharmacological approaches to the management of primary headache disorders [7].

The first device designed for cervical vagus nerve stimulation was the gammaCore system (electroCore, Inc., USA). Results of the pilot study by P.J. Goadsby et al., published in 2014, demonstrated the efficacy and favourable tolerability of cervical nVNS for the acute treatment of episodic migraine attacks [8]. Subsequent studies confirmed these findings, showing that nVNS significantly reduced the frequency, intensity, and duration of migraine attacks, decreased analgesic consumption, and alleviated associated functional impairment, sleep disturbances, and depressive symptoms [9–12]. According to the results of the double-blind, randomised, controlled PRESTO trial, the efficacy of nVNS for the acute treatment of episodic migraine corresponds to a level of evidence of 1b [12]. In addition, the preventive effect of nVNS in chronic migraine, manifested by a reduction in the number of headache days, was demonstrated in a study by S.D. Silberstein et al., published in 2016, with a level of evidence of 2b [13]. In addition to migraine, nVNS may alleviate pain attacks in patients with trigeminal autonomic cephalalgias [14–17], with the most compelling evidence (level of evidence 1b) reported for episodic cluster headache [15, 16]. The gammaCore Sapphire cervical vagus nerve stimulator has received FDA approval for the treatment of several headache disorders, including migraine, cluster headache, hemicrania continua, and paroxysmal hemicrania [18] (Table 2).

The NEMOS device (Cerbomed, Germany) is designed to stimulate the auricular branch of the vagus nerve. In a study by A. Straube et al., 46 patients with migraine underwent stimulation with the NEMOS device for 4 hours daily over a period of three months. The results demonstrated the safety of nVNS and showed that stimulation at a frequency of 1 Hz was more effective than stimulation at 25 Hz for the prevention of chronic migraine. In the 1 Hz stimulation group, approximately one-third of patients experienced a reduction of more than 50 % in the number of headache days (level of evidence 2b) [19]. Currently, functional MRI is being used to investigate the pathophysiological mechanisms underlying the effects of electrical stimulation [20, 21], as well as to identify predictors of [22] response to auricular nVNS in patients with migraine.

nVNS and tinnitus management

Subjective tinnitus represents a significant medical and social problem, as it can substantially impair quality of life by affecting both social interactions and work performance. Episodic tinnitus is experienced by 30–45 % of the adult population, approximately 8 % of individuals perceive it constantly, and in about 1 % of cases it has a considerable impact on daily functioning [23]. Individuals of working age, particularly those between 40 and 60 years old, are most commonly affected. The development of tinnitus is associated with a variety of factors, including overweight and obesity, comorbid conditions such as hypertension and diabetes mellitus, the use of certain medications (aminoglycosides, furosemide, cisplatin, and some nonsteroidal anti-inflammatory drugs or antidepressants), as well as otologic disorders resulting in hearing loss. In addition, an important role is attributed to an individual's premorbid psychological status, particularly the level of anxiety [24].

Because the development of tinnitus is often unrelated to structural abnormalities of the auditory conduction system, objective registration of the symptom is generally not possible. As all currently available assessment methods are subjective, the patient's own description of the tinnitus characteristics plays a pivotal role in the diagnostic process [24].

Current treatment approaches aimed at alleviating tinnitus are diverse and include psychotherapy, tinnitus maskers and sound therapy, biofeedback, pharmacological treatment, various neuromodulation techniques (such as transcranial magnetic stimulation, deep brain stimulation, and different forms of peripheral nerve stimulation), as well as acupuncture. These approaches differ considerably in terms of availability, efficacy, cost, and degree of invasiveness [25].

The results of a pilot study evaluating nVNS combined with sound therapy in 10 patients with tinnitus were published in 2013. The sound therapy consisted of specially selected classical music from which one octave corresponding to each patient's tinnitus frequency had been removed. After seven sessions of left tragus stimulation, most participants reported improvements in mood, as assessed by the WHO-5 questionnaire, as well as a reduction in tinnitus severity, reflected by decreases in scores on the Tinnitus Handicap Inventory (THI) and the Mini-Tinnitus Questionnaire (mini-TQ). One patient experienced no change in tinnitus characteristics, while another reported only minimal symptom improvement [26]. The beneficial effects of nVNS, both in combination with sound therapy and as a standalone intervention, have also been demonstrated in other studies [27–30]. However, the second phase of the study conducted by P.M. Kreuzer et al. failed to show a significant reduction in the total Tinnitus Questionnaire (TQ) score after 24 weeks of nVNS treatment [31]. It should be noted that the vast majority of published studies have been characterised by low or very low methodological quality [26, 28–31]. Moderate evidence supporting the efficacy of combined therapy (nVNS plus tinnitus sound masking), corresponding to a level of evidence of 2b, was provided only by the study of Z. Mei et al. published in 2014 [27].

In a systematic review published in 2021, the authors analysed studies investigating both invasive and non-invasive vagus nerve stimulation and concluded that, due to methodological limitations and the poor reporting quality of the included studies, the effects of these interventions on tinnitus remain uncertain [32]. Therefore, the efficacy of nVNS for the treatment of tinnitus, including its use as a standalone intervention without concomitant sound therapy, requires confirmation in larger and methodologically rigorous studies [33].

nVNS and sleep disturbances and anxiety

Insomnia is a common sleep disorder characterised by persistent difficulties with sleep initiation and/or sleep maintenance, resulting in insufficient sleep duration [34]. Currently, insomnia is classified as acute (symptoms lasting less than 3 months), chronic (symptoms occurring at least three times per week for at least 3 months), or unspecified [35].

Epidemiological studies have shown that insomnia affects up to 10 % of adults worldwide [36] and up to 50 % of patients seeking primary care [34], with a higher prevalence observed among women [37]. Insomnia has a substantial negative impact on quality of life and work productivity and is recognised as an important risk factor for cardiovascular disease, type 2 diabetes mellitus, cognitive impairment, and psychiatric disorders [35].

Cognitive behavioural therapy (CBT) is considered the cornerstone of treatment for chronic insomnia; however, a shortage of qualified specialists limits the widespread implementation of this therapeutic approach [35]. Although pharmacotherapy demonstrates efficacy comparable to CBT in the management of acute sleep disturbances, its effectiveness in chronic insomnia is reduced because of a substantial decline in the durability of the therapeutic effect [38]. Consequently, alternative treatment strategies, particularly non-invasive vagus nerve stimulation, have attracted growing interest. Owing to its targeted modulation of the auricular branches of the vagus nerve, nVNS is generally well tolerated [39]. In addition, the user-friendly interface of stimulation devices makes them suitable for self-administration in the outpatient setting.

In an analysis of the nVNS effects in 35 patients with insomnia and affective disorders, M. Luo et al. [40]

observed a significant reduction in Pittsburgh Sleep Quality Index (PSQI) scores by the end of the second week of treatment ($p < 0.05$), as well as significant decreases in Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) scores by the fourth and sixth weeks of therapy ($p < 0.05$). Based on these findings, the authors concluded that nVNS may improve sleep quality and alleviate symptoms of anxiety and depression. However, the absence of a control group in this study limits the interpretation of the results.

Subsequently, studies with a higher level of evidence (1b) were conducted. For instance, Y. Jiao et al. [41] reported a significant reduction in PSQI scores after four weeks of treatment in both the active nVNS group and the sham stimulation group, with no statistically significant difference between them. However, superior efficacy of nVNS compared with sham stimulation in the treatment of insomnia was demonstrated in several other studies [42–44]. Moreover, in a study by L. Zhang et al. [43], which analysed the effects of stimulation in 100 men living at high altitude, nVNS not only showed efficacy comparable to that of CBT, but also outperformed CBT with respect to several outcome measures.

In a recent randomised clinical trial [45], the duration of nVNS therapy was extended to eight weeks for the first time. Patients in the active treatment group demonstrated a significant reduction in PSQI scores, indicating the clinical efficacy of nVNS in chronic insomnia, with superiority over sham stimulation persisting for up to 20 weeks. In addition, vagus nerve stimulation exerted significantly greater effects on reducing symptoms of depression and anxiety, as well as daytime fatigue, in patients with insomnia.

The effects of nVNS on anxiety symptoms during and after the COVID-19 pandemic were investigated by V. Srinivasan et al. [46, 47]. These studies demonstrated significant reductions in Generalised Anxiety Disorder-7 (GAD-7) scores and salivary cortisol levels after four weeks of nVNS. Furthermore, nVNS was shown to be superior to Jacobson's progressive muscle relaxation technique [46] and was associated with significant improvements in sleep quality [47].

The findings of a recent systematic review and meta-analysis suggest that nVNS represents a promising, safe, and non-invasive therapeutic option for insomnia [48]. The simultaneous improvement in sleep quality and anxiety symptoms is particularly relevant for patients with comorbid disorders. To enhance the reproducibility of findings and optimise the application of this approach across broader populations, standardisation of nVNS protocols is required.

Devices based on nVNS technology are not yet available on the Russian market, creating opportunities for the development of domestic systems. A key priority in this process is the identification of optimal stimulation parameters for both the auricular branch and the cervical portion of the vagus nerve.

Stimulation parameters of the auricular branch of the vagus nerve

In 2024, a review of 109 studies investigating auricular nVNS was published, including an analysis of the stimulation parameters used across studies [5]. The authors noted that only three studies provided a complete description.

Stimulation *intensity* ranged from 0.5 to 50 mA; however, in 77 % of the studies reporting this parameter, the average intensity did not exceed 6 mA. In 68 % of the studies, the intensity of auricular nVNS was individually adjusted to a level between the participant's sensory and pain thresholds. Pulse *frequency* was specified in most studies, with frequencies of 20 or 25 Hz being used in 74 % of cases. Three studies reported the use of a combination of two frequencies, namely 4 and 20 Hz. In the vast majority of studies, the *wavelength* ranged from 0.05 to 1.0 ms, with values of 0.20 or 0.25 ms being employed in 51 % of the reports. The *side* of stimulation was specified in 84 studies; among these, left-sided stimulation was used most frequently (62 %). Bilateral stimulation was applied in 27 % of studies, whereas right-sided stimulation was employed in 11 %. The stimulation *site* was largely determined by electrode geometry, with electrodes most commonly attached to the cymba conchae (31 studies), the concha (27 studies), or the tragus (21 studies) of the auricle. Information regarding the *duty cycle (the ratio between stimulation and pause periods)* was reported in only 32 studies (29 %), with a 30 s on/30 s off pattern being used in 14 of them. The *duration and number of stimulation sessions* varied considerably both within studies investigating the same condition and across different indications. Therefore, the optimal parameters for transcutaneous stimulation of the auricular branch of the vagus nerve have yet to be established [5].

Stimulation parameters of the cervical vagus nerve

The vast majority of studies employing cervical vagus nerve stimulation have been conducted in patients with headache disorders [2]. In addition, a case report published in 2011 described the resolution of intractable hiccups following transcutaneous stimulation of the phrenic nerve and the cervical vagus nerve [49], while a study published in 2016 evaluated the effects of cervical nVNS on inflammatory cytokine levels in healthy volunteers [50].

The stimulating surface of the nVNS device is positioned over the sternocleidomastoid muscle on either the right or left side of the neck, or sequentially on both sides. Stimulation *intensity* is individually adjusted, with maximum values reaching 24 V and 60 mA. In the majority of studies, a pulse *frequency* of 25 Hz was used, whereas one study [49] employed a frequency of 1 Hz. *Wavelength* was set at either 0.2 ms or 1 ms. The *duration* of individual stimulation cycles ranged from 30 to 120 seconds [2]. Treatment can be safely administered several times per day. The FDA recommendations regarding the use of the gammaCore Sapphire cervical stimulator for headache disorders are summarised in Table 2.

Conclusion

The growing interest in nVNS is driven by the simplicity, accessibility, safety, and favourable tolerability of this approach. The development of a domestic device implementing nVNS techniques therefore represents an important and timely objective. The number of studies investigating nVNS continues to increase, accompanied by a broadening range of clinical conditions in which its efficacy is being evaluated. The results obtained with the gammaCore cervical vagus nerve stimulator formed the basis for the FDA approval of its use for the preventive and acute treatment of cluster headache and for the acute treatment of episodic migraine. Subsequently, the indications were expanded to include migraine prevention, as well as the treatment of cluster headache and hemicrania continua. With regard to non-invasive stimulation of the auricular branch of the vagus nerve, despite encouraging results in headache disorders, tinnitus, insomnia, and anxiety, further high-quality studies are required to strengthen the evidence base. Such studies should include larger sample sizes, standardised stimulation protocols or detailed descriptions thereof, and appropriate randomisation and blinding procedures.

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НАРУШЕНИЯ СИСТЕМЫ ГЕМОСТАЗА КАК ПРЕДИКТОР НЕБЛАГОПРИЯТНОГО ИСХОДА COVID-19

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Disorders Of the Hemostatic System as A Predictor of Adverse Outcome In COVID-19

Резюме

Инфекция COVID-19 ассоциирована с высоким риском тромботических осложнений, определяющих тяжесть течения и исход заболевания. Выявление ключевых предикторов неблагоприятного исхода среди параметров системы гемостаза остается важной задачей. **Цель.** Оценить значимость показателей системы гемостаза в качестве предикторов неблагоприятного исхода у пациентов с COVID-19. **Материалы и методы.** Проведено одноцентровое ретроспективное когортное исследование, включившее 9256 пациентов с подтвержденным COVID-19. В зависимости от исхода (неблагоприятный/благоприятный) пациенты были разделены на группы. При поступлении оценивались показатели коагулограммы (активированное частичное тромбопластиновое врермя, протромбиновый индекс, тромбиновое время, фибриноген, D-димер, антитромбин III). Статистический анализ выполнялся с использованием U-критерия Манна-Уитни. Для описания количественных показателей использовались медиана, 25-й и 75-й процентили. **Результаты.** У пациентов с неблагоприятным исходом зафиксированы статистически значимые различия по сравнению с выжившими: значительное повышение уровня D-димера (медиана 464,5 нг/мл [Q25–Q75: 245,0–1120,0] нг/мл против 198,0 [110,0–350,0] нг/мл; p<0,0001) и фибриногена (5,62 [4,70–6,80] г/л против 5,03 [4,30–5,90] г/л; p<0,0001), снижение активности антитромбина III (81,0 % [73,0–89,0] против 99,0 % [90,0–108,0]; p=0,0001) и протромбинового индекса (83,0 % [77,0–90,0] против 93,0 % [88,0–98,0]; p<0,0001), а также удлинение тромбинового времени (15,4 с [14,5–16,5] против 14,9 с [14,2–15,8]; p=0,0001). Показатель АЧТВ значимо не отличался между группами (p=0,95). **Заключение.** У пациентов с неблагоприятным исходом COVID-19 выявлена выраженная гиперкоагуляция с признаками коагулопатии потребления, характеризующаяся резким повышением D-димера и фибриногена на фоне снижения антитромбина III и протромбинового индекса. Мониторинг этих показателей, особенно D-димера и антитромбина III, обладает высокой прогностической ценностью для стратификации риска и своевременной коррекции терапии.

Ключевые слова: *COVID-19, система гемостаза, коагулопатия, D-димер, антитромбин III, фибриноген, летальность, прогноз*

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Abstract

COVID-19 is associated with a high risk of thrombotic complications, which determine the severity and outcome of the disease. Identifying key predictors of adverse outcomes among hemostatic system parameters remains an important task. **Aime.** To assess the significance of hemostatic system parameters as predictors of adverse outcomes in patients with COVID-19. **Materials and methods.** A single-center retrospective cohort study

was conducted, including 9256 patients with confirmed COVID-19. Depending on the outcome (adverse/favorable), patients were divided into groups. Upon admission, coagulogram parameters (APTT, prothrombin index, thrombin time, fibrinogen, D-dimer, antithrombin III) were assessed using an ACL TOP 750 analyzer. Statistical analysis was performed using the Mann-Whitney U test. For the description of quantitative indicators, the median, the 25th and 75th percentiles were used. **Results.** Statistically significant differences were recorded in patients with adverse outcome compared to survivors: a significant increase in D-dimer level (median 464.5 [Q25–Q75: 245.0–1120.0] ng/mL vs. 198.0 [110.0–350.0] ng/mL; p<0.0001) and fibrinogen (5.62 [4.70–6.80] g/L vs. 5.03 [4.30–5.90] g/L; p<0.0001), a decrease in antithrombin III activity (81.0 % [73.0–89.0] vs. 99.0 % [90.0–108.0]; p=0.0001) and prothrombin index (83.0 % [77.0–90.0] vs. 93.0 % [88.0–98.0]; p<0.0001), as well as a prolongation of thrombin time (15.4 s [14.5–16.5] vs. 14.9 s [14.2–15.8]; p=0.0001). The APTT parameter did not differ significantly between the groups (p=0.95). **Conclusion.** Patients with adverse COVID-19 outcomes exhibited marked hypercoagulation with signs of consumption coagulopathy, characterized by a sharp increase in D-dimer and fibrinogen against a background of decreased antithrombin III and prothrombin index. Monitoring these parameters, especially D-dimer and antithrombin III, has high prognostic value for risk stratification and timely therapy adjustment.

Key words: *COVID-19, hemostatic system, coagulopathy, D-dimer, antithrombin III, fibrinogen, mortality, prognosis*

Conflict of interests

Co-author of the article Karpov I.A. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Karpov I.A. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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ACE2 — angiotensin-converting enzyme 2, aPPT — activated partial thromboplastin time, DIC — disseminated intravascular coagulation, PTI — prothrombin index

Introduction

Since the beginning of the COVID-19 pandemic, compelling evidence has been gathered indicating that SARS-CoV-2 causes not merely a respiratory infection, but a systemic disease characterised primarily by vascular injury (vasculopathy) and thromboinflammation [1]. A key mechanism initiating these processes is the interaction of the viral S-protein with the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed on the surface of endothelial cells, type II pneumocytes, enterocytes, and cells of other organs [2]. This interraction triggers a cascade of reactions leading to direct endothelial dysfunction, massive release of proinflammatory cytokines (the so-called "cytokine storm"), and subsequent activation of both the plasma and cellular components of the hemostatic system, resulting in a state of hypercoagulability [3].

The resulting phenomenon, which is often described as COVID-19-associated blood-clotting disorder, differs from the classic sepsis-associated DIC-syndrome [4, 5]. Marked hypercoagulability is characteristic of COVID-19 and, in the early phase, is manifested by a significant increase in D-dimer and fibrinogen levels — an acute-phase protein and substrate for blood clot formation, accompanied by only mild prolongation of standard coagulation tests, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), and by a relatively preserved or even elevated platelet count during the early stages of the disease [6]. This pattern reflects intensive blood clotting, primarily in the microcirculatory bloodstream, associated with generalised endothelial activation and inflammation.

Numerous prospective and retrospective studies conducted in different countries confirmed that the D-dimer level upon admission is a powerful independent prognostic marker of disease severity and mortality. Tang et al. (2020) demonstrated that in non-survivors, D-dimer levels were significantly higher than those observed in surviving subjects, and values > 1.0 μg/mL were associated with a high risk of mortality [7]. These data were later confirmed by large-scale meta-analyses where higher D-dimer levels were associated with 3–4-fold increase in the risk of death [8, 9].

However, optimal threshold values of this marker for risk ranking; they can vary considerably depending on the study population, test method, and disease characteristics. Moreover, the prognostic value of an isolated measurement of D-dimer at hospital admission may be insufficient. Researchers emphasise a set of changes in hemostasis. Progressive thrombocytopenia during the course of the disease is an independent adverse prognostic factor, likely reflecting platelet consumption during blood clotting formation and the severity of endothelial injury [10].

Evaluation of the activity of the natural anticoagulant systems is of particular interest. Reduced activity of antithrombin III, the key physiological inhibitor of thrombin and other serine proteases, may indicate its consumption under conditions of extensive blood clot formation and/or impaired hepatic synthetic function, thereby exacerbating the procoagulant shift [5]. At the same time, higher levels of von Willebrand factor and soluble thrombomodulin have been studied as markers of endothelial trauma and activation [11]. Another feature of COVID-19-associated coagulopathy is the frequent detection of lupus anticoagulant, which may contribute to the pathophysiology, although its direct role in thrombogenesis and its impact on clinical outcomes require further clarification [12].

Thus, a comprehensive, multiparametric evaluation of hemostatic status extending beyond the scope of the routine coagulation profile appears to be of critical importance. Such an approach may not only enable highly accurate prediction of adverse outcomes but also facilitate the identification of patients who may benefit from intensified anticoagulant therapy, which is currently the subject of ongoing clinical investigations [13].

Study objective: To perform a comprehensive analysis of clinical and laboratory parameters of the hemostatic system in patients with COVID-19 of various severity in order to identify the independent predictors of adverse outcomes.

Materials and Methods

A single-centre retrospective cohort study was conducted. The study included 9,256 patients (3,980 men and 5,276 women; mean age: 61 ± 16.5 years) with confirmed COVID-19 (based on a positive nasopharyngeal swab PCR test) who were admitted at the Minsk City Clinical Infectious Diseases Hospital between March 2020 and December 2023. Inclusion criteria: age 18 years old and over; hospital admission during the study; laboratory-confirmed SARS-CoV-2 infection by polymerase chain reaction; and the availability of written informed consent provided by the patient or their legal representative for participation in the study and the use of anonymised medical data for scientific purposes, including publication. Exclusion criteria: age below 18 years old; congenital coagulation disorders, the use of therapeutic-dose anticoagulants prior to hospitalisation; and the absence of data on key hemostatic parameters at the time of admission.

Subjects were divided into two groups, depending on the outcome: the study group (patients with adverse outcome, n = 375) and the comparison group (patients with favourable outcome, n = 8,881). For certain laboratory parameters, the size of the analysed subgroups varied depending on the availability of examination data, as reflected in the results table (Table 1).

Venous blood samples were collected upon hospital admission before the initiation of anticoagulant therapy. Standard hemostatic parameters were determined using an ACL TOP 750 automated analyser (Werfen, Spain) with HemosIL reagent kits (Werfen, Spain) in accordance with the manufacturer's instructions. The following parameters were assessed: activated partial thromboplastin time (aPTT), s; antithrombin III, %; D-dimer, ng/mL; prothrombin index (PTI), %; thrombin time, s; and fibrinogen, g/L.

Statistical analysis was performed using R software version 4.2.1. Quantitative variables with non-normal distributions (assessed using the Shapiro-Wilk test) were described using the median (Me) and the 25th and 75th percentiles (Q25–Q75). Comparisons between the two independent groups (favourable and adverse outcomes) were performed using the nonparametric Mann-Whitney U test. Differences were considered statistically significant at $p < 0.05$. Due to the retrospective nature of the study and the lack of data regarding the exact timing of events, Kaplan-Meier survival analysis was not performed.

Results and Discussion

The comparative analysis of hemostatic parameters between patients with adverse and favourable outcomes revealed statistically significant differences in the majority of the variables studied (see table).

The most notable differences were observed in D-dimer levels. The median value of this marker in patients with adverse outcome (464.5 ng/mL) was more than two times higher than in patients with favourable outcome (198.0 ng/mL) ($p < 0.0001$) (Fig.1). A significant elevation in D-dimer levels strongly indicates marked activation of fibrinolysis and intense blood clot formation in patients with an unfavourable prognosis, which is consistent with numerous studies confirming the role of D-dimer as a key predictor of adverse outcomes in COVID-19 patients [7–9]. However, it is worth noting that D-dimer threshold values proposed in literature vary; and in this study, the median value in patients with adverse outcomes was 464.5 ng/mL, which is below the threshold value of 1000 ng/mL, but is significantly above the levels in the comparison group, emphasising the importance of the relative elevation and follow-up [14]. The data are consistent with the meta-analysis results generated by Lippi G. and Favaloro E.J. (2020), who noted that the absolute D-dimer value upon hospital admission is a reliable marker of disease severity; however, the optimal threshold can vary depending on the population and methods used [8]. Moreover, the findings of our study, i.e., a more than twofold increase in

the median D-dimer level in the adverse outcome group, are quantitatively consistent with the results reported by Tang N. et al. (2020), who observed a similar difference between survivors and non-survivors [7].

Significantly lower antithrombin III activity (median value 81.0 % vs 99.0 % in survivors, p = 0.0001) in patients with adverse outcome of COVID-19 infection points at depletion of the most important natural anticoagulant mechanism. This reduction may result from consumption during blood clot formation and/or impaired hepatic synthetic function, thereby contributing to the prothrombotic state (Figure 2), and is consistent with findings from other studies describing decreased antithrombin III levels as a marker of severe consumptive coagulopathy in COVID-19 [15]. The results confirm the findings by White D. et al. (2021), who reported significantly lower antithrombin III activity in patients with severe COVID-19, associated with higher consumption during generalised coagulation activation [15]. This represents an important distinction from classical sepsis-associated disseminated intravascular coagulation (DIC), in which antithrombin III levels also decline, but typically at later stages, whereas in COVID-19 this feature may be observed earlier in the disease course [4, 5].

Table 1. *Alterations of hemostatic parameters in COVID-19 patients based on clinical outcome.*

Parameter	Group	N	Median (Q25-Q75)	p
APTT, sec	Adverse outcome	375	32.8 (29.5–36.2)	0.95
	Favorable outcome	8881	32.2 (29.0–36.0)	
Antithrombin III, %	Adverse outcome	38	81.0 (73.0–89.0)	0.0001
	Favorable outcome	90	99.0 (90.0–108.0)	
D-dimer, ng/mL	Adverse outcome	372	464.5 (245.0–1120.0)	0.0000
	Favorable outcome	9367	198.0 (110.0–350.0)	
Prothrombin Index, %	Adverse outcome	255	83.0 (77.0–90.0)	0.0000
	Favorable outcome	5189	93.0 (88.0–98.0)	
Thrombin Time, sec	Adverse outcome	189	15.4 (14.5–16.5)	0.0001
	Favorable outcome	3214	14.9 (14.2–15.8)	
Fibrinogen, g/L	Adverse outcome	364	5.62 (4.70–6.80)	0.0000
	Favorable outcome	9019	5.03 (4.30–5.90)	

Note: APTT — activated partial thromboplastin time; N — number of observations; Q25–Q75 — 25th and 75th percentiles (interquartile range); p — level of statistical significance of differences between groups (Mann-Whitney test)

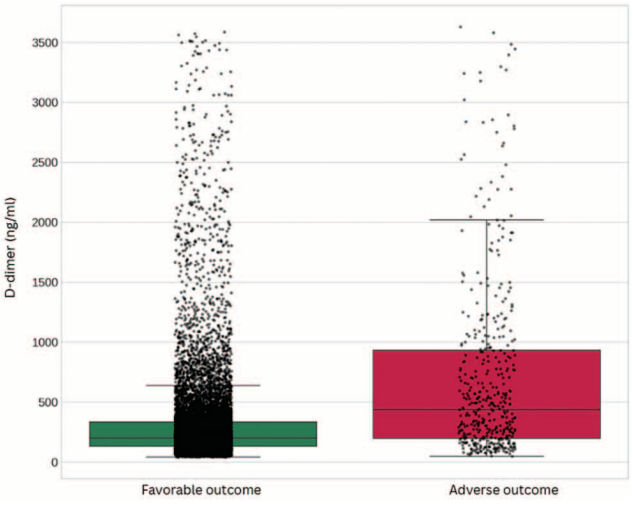

Figure 1. *Distribution of COVID-19 infection disease outcomes depending on the level of D-dimers at hospital admission*

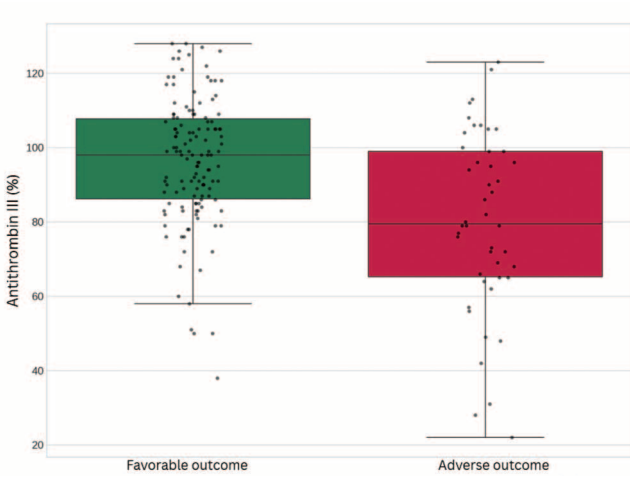

Figure 2. *Distribution of COVID-19 infection outcomes depending on antithrombin III level upon hospital admission*

Statistically significant reduction in prothrombin index (median value 83.0 % vs 93.0 %, $p < 0.0001$) in patients with adverse outcome reflects impaired extrinsic blood coagulation, which is likely to be associated with more marked hepatic damage or vitamin K deficiency in patients with severe disease. Similar changes were described in articles about blood-clotting disorder in COVID-19 patients, where prolonged prothrombin time (and lower PTI) was associated with poorer outcomes [7]. It can be caused both by direct viral damage to hepatic cells, expressing ACE2 receptor, and hypoxia or use of medications in critically ill patients [2].

Fibrinogen concentration was significantly higher in patients with adverse outcome of COVID-19 infection (median value 5.62 g/L vs 5.03 g/L, $p < 0.0001$). Elevated fibrinogen levels, as an acute-phase protein, may reflect the intensity of the systemic inflammatory response (hypercytokinemia), which is directly associated with activation of the coagulation system [3, 11]. Although the trend toward increased fibrinogen levels in patients with severe disease or fatal outcomes was statistically significant, it was less pronounced in our study than that observed for D-dimer. This finding is consistent with the observations of Iba T. et al. (2020), who reported that COVID-19 is characterised by elevated or normal fibrinogen levels even in the presence of overt thrombosis, distinguishing it from other forms of consumptive blood-clotting disorder and underscoring the role of hyperinflammation in the pathogenesis of thrombosis [4]. Therefore, significantly higher, but not extreme fibrinogen levels, in this study contributes to hypercoagulation and inflammation.

A slight but statistically significant prolongation of thrombin time (median value 15.4 s vs 14.9 s, $p = 0.0001$) in patients with adverse outcomes may indicate qualitative alterations in fibrinogen or the presence of coagulation inhibitors in the plasma, which may also reflect severe metabolic disturbances. These slight changes in standard global tests in marked hypercoagulability are a characteristic feature of COVID-19-induced coagulopathy [6].

In contrast, activated partial thromboplastin time (aPTT) did not differ significantly between the groups ($p = 0.95$), suggesting that the intrinsic coagulation pathway is less involved in the pathological process or that its alterations are compensated by other factors. This pattern is characteristic of COVID-19-induced coagulopathy and distinguishes it from classical disseminated intravascular coagulation (DIC) [4, 6]. These findings are fully consistent with the international guidelines developed by ISTH (Thachil J. et al., 2020), where it is emphasised that normal or slightly altered aPTT values in the presence of elevated D-dimer and fibrinogen levels is a typical laboratory finding in COVID-19 and should alert clinicians to the risk of thrombosis [6].

Therefore, the combination of the observed alterations (marked elevation of D-dimer, moderate increase in fibrinogen levels, reduced antithrombin III activity and PTI, together with unchanged aPTT) constitutes a laboratory profile characteristic of COVID-19-induced coagulopathy, with features of consumptive coagulopathy in the setting of pronounced hypercoagulability and inflammation. This profile is qualitatively consistent with the findings reported in most contemporary studies [4, 5, 6, 15], while the quantitative values obtained in the present study cohort further expand the existing body of evidence by providing a more detailed characterisation of these parameter changes in this patient population.

Conclusion

Patients with adverse outcomes of COVID-19 infection demonstrate marked hypercoagulation, characterised by significantly higher D-dimer and fibrinogen levels, as well as depleted anticoagulant potential (reduced antithrombin III concentration) and impaired procoagulant synthesis by the liver (reduced PTI). These changes give rise to a pattern of COVID-19-induced coagulopathy characterised by features of both a procoagulant shift and consumption of coagulation factors. Monitoring of these parameters, especially of D-dimer and antithrombin III levels, has high predictive value for timely therapy adjustment and improvement of disease outcomes.

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Anisko L.A. — conceptualization and study design, data collection and processing, statistical data analysis, writing and editing the article

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АКТИВНОСТЬ ЗАБОЛЕВАНИЯ КАК ФАКТОР РИСКА ПОВЫШЕНИЯ АРТЕРИАЛЬНОЙ ЖЕСТКОСТИ У ПАЦИЕНТОВ С ЯЗВЕННЫМ КОЛИТОМ

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Disease Activity as A Risk Factor for Increased Arterial Stiffness in Patients with Ulcerative Colitis

Резюме

Цель исследования. Изучить показатели артериальной жесткости и ее вариабельности при суточном мониторировании в зависимости от клинической и эндоскопической активности язвенного колита. **Материалы и методы.** В поперечном ретроспективном исследовании участвовали 100 пациентов с язвенным колитом (средний возраст 40 [33; 49] лет, 38 (38 %) мужчин, длительность заболевания — >1 года, без сопутствующих сердечно-сосудистых и метаболических нарушений) и 50 здоровых лиц контрольной группы. Параметры артериальной жесткости оценивались с помощью суточного мониторирования артериального давления с использованием технологии Vasotens. Пациенты были разделены на 3 группы по активности язвенного колита: 1-я группа включала 30 пациентов с клинической и эндоскопической ремиссией, 2-я группа — 22 пациента с клинической ремиссией и эндоскопической активностью, 3-я группа — 48 человек с клиническим и эндоскопическим обострением. Статистическая обработка полученных данных проводилась с помощью пакета компьютерных программ «IBM SPSS Statistics Version 25.0». **Результаты.** У 67 (67 %) пациентов с язвенным колитом выявлена повышенная артериальная жёсткость (скорость распространения пульсовой волны в аорте (PWVao) >10 м/с), что значимо чаще, чем в контрольной группе (OR=4,74; p <0,001). Наиболее выраженные изменения отмечены в группе с клинико-эндоскопическим обострением: повышены скорость распространения пульсовой волны в аорте, приведенная к систолическому артериальному давлению (САД)=100 мм рт.ст. и частоте сердечных сокращений (ЧСС)=60 уд/мин ($PWVao_{100\text{-}60)}$) (p=0,003), индекс аугментации при ЧСС=75 уд/мин (AIx75) (p <0,001) и вариабельность PWVao (p=0,002). При эндоскопической активности без клинических симптомов величины AIx75, $PWVao_{100\text{-}60}$ и вариабельность скорости нарастания артериального давления в аорте (dP/dt вар.) были значимо выше, чем в группе контроля. При регрессионном логистическом анализе выявлено, что возраст старше 40 лет (p=0,001; 95 % ДИ: 2,045 — 15,309), активность язвенного колита (p=0,025; 95 % ДИ: 1,151 — 8,200), отягощенная наследственность по сердечно-сосудистым заболеваниям (p=0,033; 95 % ДИ: 1,131 — 17,312) являются предикторами повышения артериальной жесткости у пациентов с язвенным колитом. Модель демонстрирует хорошую прогностическую способность: площадь под ROC-кривой (AUC) = 0,76 ± 0,051 [95 % ДИ: 0,66 — 0,86], чувствительность — 0,851, специфичность — 0,638, точность — 0,747 (p <0,001). **Заключение.** У пациентов с язвенным колитом наблюдается значимое повышение артериальной жёсткости, коррелирующее с активностью воспалительного процесса. Эндоскопическое обострение в отсутствии симптомов язвенного колита уже ассоциировано с неблагоприятными сосудистыми изменениями. Разработанная модель прогнозирования повышенной артериальной жесткости на основе трёх клинических критериев (возраст >40 лет, обострение язвенного колита, наследственность) может быть внедрена в практику для раннего выявления пациентов с высоким сердечно-сосудистым риском.

Ключевые слова: *язвенный колит, артериальная жёсткость, скорость пульсовой волны, индекс аугментации, суточная вариабельность, сердечно-сосудистый риск*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Objective. We aimed to study the parameters of arterial stiffness and its variability during 24-hour monitoring in relation to the clinical and endoscopic activity of ulcerative colitis. **Materials and methods.** This cross-sectional retrospective study involved 100 patients with ulcerative colitis (mean age 40 [33; 49] years, 38 (38 %) men, disease duration >1 year, without concomitant cardiovascular diseases or metabolic disorders) and 50 healthy control subjects. Arterial stiffness parameters were assessed via 24-hour ambulatory blood pressure monitoring with Vasotens technology. Based on disease activity patients were divided into 3 groups: Group 1 included 30 patients in clinical and endoscopic remission; Group 2 consisted of 22 patients in clinical remission with endoscopic activity; Group 3 included 48 patients with both clinical and endoscopic exacerbation. Statistical analysis was performed using the software package "IBM SPSS Statistics Version 25.0". **Results**. Increased arterial stiffness (aortic pulse wave velocity (PWVao) >10 m/s) was detected in 67 (67 %) of ulcerative colitis patients, which was significantly higher than in the control group (OR = 4.74; p<0.001). The most pronounced alterations were observed in the group with clinical-endoscopic exacerbation, which showed increased aortic pulse wave velocity at systolic blood pressure (SBP)=100 mmHg and heart rate (HR)=60 bpm (PWVao 100-60) (p=0.003), augmentation index adjusted for HR=75 bpm (AIx75) (p<0.001), and PWVao variability (p=0.002). In endoscopically active disease without clinical symptoms, AIx75, PWVao100-60, and variability of the rate of increase in blood pressure in the aorta (dP/dt var.) were significantly higher compared to controls. Logistic regression analysis identified age >40 years (p=0.001; 95 % CI: 2.045 to 15.309), disease activity of ulcerative colitis (p=0.025; 95 % CI: 1.151 to 8.200), and a positive family history of cardiovascular disease (p=0.033; 95 % CI: 1.131 to 17.312) as independent predictors of increased arterial stiffness in patients with ulcerative colitis. The prediction model demonstrated good performance: area under the ROC curve (AUC) = 0.76 ± 0.051 (95 % CI: 0.66–0.86), sensitivity 0.851, specificity 0.638, and accuracy 0.747 (p <0.001) and can be implemented in practice for the early identification of patients with high cardiovascular risk. **Conclusion**. Patients with ulcerative colitis exhibit a significant increase in arterial stiffness, which correlates with the degree of inflammatory activity. Endoscopic activity, even in the absence of clinical symptoms, is associated with adverse vascular changes. The developed predictive model, based on three clinical criteria (age >40 years, active ulcerative colitis, and positive family history), could be implemented clinically for the early identification of high cardiovascular risk in this patient population.

Key words: *ulcerative colitis, arterial stiffness, pulse wave velocity, augmentation index, 24-hour variability, cardiovascular risk*

Conflict of Interest

The authors declare that this work, its topic, subject matter, and content do not affect any competing interests.

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Compliance with the principles of ethics

The study was approved by the local ethics committee of Chita State Medical Academy (protocol no. № 125 dated November 23, 2022). Written consent was obtained from the patients for publication of relevant medical information and all of accompanying images within the manuscript.

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AH — arterial hypertension, BP — blood pressure, IBD — inflammatory bowel diseases, SBP — systolic blood pressure, ABPM — 24-hour ambulatory blood pressure monitoring, CVD — cardiovascular diseases, PWV — pulse wave velocity, HR — heart rate, UC — ulcerative colitis

Introduction

Over recent decades, it has become increasingly evident that the systemic inflammation underlying ulcerative colitis (UC) is associated with an increased risk of cardiovascular disease (CVD) [1–3]. At the same time, conventional cardiovascular risk assessment tools have proven to be insufficiently effective in patients with inflammatory bowel disease (IBD), as they tend to underestimate the true risk of cardiovascular events in this population [4].

Arterial stiffness is an early, independent, and powerful predictor of cardiovascular events and may be used to predict CVD risk [5]. Proinflammatory cytokines, oxidative stress, and endothelial dysfunction are the main factors influencing arterial stiffness and contributing to the development of premature atherosclerosis in patients with UC [4, 6]. Recent studies have demonstrated that increased arterial stiffness is associated with both disease duration and the frequency of UC exacerbations [7, 8]. Specifically, the principal marker of arterial stiffness, that is pulse wave velocity (PWV), has been shown to increase by 0.205 m/s for each additional year of IBD duration [9]. In a multicentre prospective study, Zanoli et al. (2019) found that patients with IBD had higher PWV values vs. controls and that indices of arterial stiffness could decrease following long-term treatment with tumour necrosis factor-α (TNF-α) antagonists and with the achievement of remission [10].

Assessment of cardiovascular risk should also take into account increased variability in vascular wall stiffness, which itself has prognostic significance. For example, in patients with hypertension, the greatest variability in arterial stiffness has been observed among those at high and very high cardiovascular risk [11]. According to the available literature, variability in arterial stiffness has not previously been evaluated in patients with UC.

Investigation of arterial stiffness parameters and their variability according to the degree of UC activity may facilitate the identification of clinical predictors of early cardiovascular disease in this patient population.

Aim

The aim of the study was to investigate arterial stiffness parameters and their variability during 24-hour ambulatory monitoring in relation to the clinical and endoscopic activity of UC.

Materials and methods

A cross-sectional, retrospective study of arterial stiffness parameters was conducted in 100 patients with UC (median age 40 [33–49] years; 38 (38 %) were men). The inclusion criteria were age between 20 and 50 years, a duration of UC greater than 1 year (diagnosed in accordance with the 2024 Ulcerative Colitis Clinical Guidelines issued by the Russian Gastroenterological Association and the Russian Association of Coloproctologists) [12], and provision of informed consent to participate in the study. The exclusion criteria included severe UC exacerbation; systemic diseases and malignancies of any localisation, haematologic disorders, endocrine diseases, pregnancy and lactation; grade 2–3 arterial hypertension and other cardiovascular diseases; class II–III alimentary-constitutional obesity; a history of colectomy or proctocolectomy; treatment with glucocorticoids, antihypertensive agents, or lipid-lowering drugs; severe renal or hepatic insufficiency; and other chronic diseases in the stage of exacerbation. The control group consisted of 50 healthy individuals matched to the study group with respect to age and sex. All subjects provided informed written consent. The study protocol (No. 125) was approved by the Local Ethics Committee of the Chita State Medical Academy of the Ministry of Health of the Russian Federation on November 23, 2022. All participants underwent a comprehensive clinical evaluation, including assessment of medical history and physical status, lipid profile analysis, 24-hour ambulatory blood pressure monitoring (ABPM), and video ileocolonoscopy. Cardiovascular risk was assessed using the relative risk charts for individuals younger than 40 years and the SCORE2 scale for those aged 40 years and older. Patients with UC and controls had similar clinical characteristics (Table 1). During ABPM, patients with UC exhibited higher mean 24-hour systolic blood pressure values compared with the control group ($p < 0.05$). It should be noted that, according to medical history data, none of the study participants had a prior diagnosis of arterial hypertension (AH). Labile grade 1 hypertension, characterised by episodic BP elevations during ambulatory monitoring despite normal mean 24-hour blood pressure values, was detected significantly more frequently in patients with UC than in the control group (OR 4.04; 95 % CI: 1.46–11.17; $p = 0.005$). This finding is consistent with previous reports indicating an increased risk of AH in patients with UC [13]. No significant differences were observed between the groups with respect to the magnitude or prevalence of other cardiovascular risk factors.

The higher prevalence of chronic gastrointestinal diseases (including gastritis, cholecystitis, pancreatitis, gastroesophageal reflux disease, peptic ulcer disease, Gilbert syndrome, and cholelithiasis) observed among patients with UC is likely attributable to more intensive and regular follow-up by gastroenterologists, which facilitates the detection of concomitant gastrointestinal pathology.

Patients with UC had various courses of the disease: continuous course was reported in 22 % (22/100), recurrent — in 48 % (48/100), and remission lasting for over one year — in 30 % (30/100). All patients received continuous anti-inflammatory therapy: 57 % (57/100) were treated with 5-aminosalicylic acid derivatives, 20 % (20/100) — with immunosuppressive agents (azathioprine or 6-mercaptopurine), and 23 % (23/100) — with biologic therapies.

Arterial stiffness parameters were assessed using the results of ABPM performed with the BPLabWin device (Petr Telegin LLC, Nizhny Novgorod, Russia) and the Vasotens 24 software package. The following 24-hour indices of arterial stiffness were analysed: mean aortic pulse wave velocity and its variability (PWVao, PWVao var.), ambulatory arterial stiffness index (AASI), augmentation index and its variability (AIx, AIx var.), mean pulse pressure and its variability (mean PP, PP var.), and mean rate of blood pressure rise and its variability (dP/dt, dP/dt var.). Since vascular stiffness parameters are strongly influenced by the current blood pressure (BP) level and heart rate (HR), the analysis used values normalised to a systolic blood pressure (SBP) of 100 mm Hg and a heart rate of 60 beats/min, namely RWTT100-60 and PWVao100-60. In addition, the augmentation index was adjusted to a heart rate of 75 beats/min (AIx75).

Statistical processing of the data was performed using the IBM SPSS Statistics software, version 25.0 (International Business Machines Cation, USA). The distributions of the variables were tested for normality using

the Kolmogorov-Smirnov test (for comparisons between groups) and the Shapiro-Wilk test (for comparisons between subgroups). As the quantitative variables were not normally distributed, they were expressed as the median and interquartile range (Me [Q_1; Q_3]). Comparisons of continuous variables between the ulcerative colitis and control groups were performed using the Mann-Whitney U test, whereas comparisons among multiple groups were conducted using the Kruskal-Wallis H test. To address the issue of multiple comparisons, pairwise comparisons were subsequently performed using the Bonferroni correction, with a significance threshold of p = 0.0083. Qualitative attributes are presented as absolute numbers and percentages (%). Comparisons of qualitative attributes were performed using Pearson's χ^2 test, and, for small sample sizes, the likelihood ratio correction was applied. The significance of differences was assessed using odds ratios (ORs) with corresponding 95 % confidence intervals (95 % CI). Differences were considered statistically significant at $p < 0.05$.

Table 1. *Clinical Characteristics of the Study Participants*

Parameter	Patients with UC (n=100)	Control (n=50)	Test Statistics
Age, years	40 [33; 49]	40[35; 46]	U=2285,0, p=0,391.
Sex male/female, n (%)	38/62 (38/62)	12/38 (24/76)	χ^2=2,94, df=1, p=0,09.
SBP, mm Hg	116 [109; 121]	111 [103; 115]	**U=1835,0, p=0,008.**
DBP, mm Hg	74 [69; 79]	72,5 [67; 77]	U=2123,5, p=0,133.
Labile AG 1st grade, n (%)	31 (31 %)	5 (10 %)	**χ^2=8,059, df=1, p=0,005**
BMI, kg/m²	23,8 [21,0; 27,1]	23,2 [21,0; 24,3]	U=2100,0, p=0,110.
WC, cm	84 [78; 90]	83 [78; 86]	U=2208,5, p=0,244.
Smoking, n (%)	8 (8 %)	6 (12 %)	χ^2=0,20, df=1, p=0,65
FH of CVD, n (%)	27 (27 %)	11 (22 %)	χ^2=0,49, df=1, p=0,49
TC, mmol/L	5,0 [4,2; 5,7]	5,1 [4,3; 5,9]	U=1420,5, p=0,885.
LDL-C, mmol/L	3,2 [2,7; 3,8]	3,5 [2,8; 3,9]	U=1273,5, p=0,934
HDL-C, mmol/L	1,3 [1,1; 1,6]	1,3 [1,2; 1,5]	U=1134,0, p=0,226.
VLDL-C, mmol/L	0,5 [0,3; 0,6]	0,6 [0,3; 0,7]]	U=752,5, p=0,356.
TG, mmol/L	1,0 [0,7; 1,3]	1,2 [0,7;1,6]	U=1150,0, p=0,599.
Cardiovascular risk:			
– Low, n (%)	55 (55 %)	32(64 %)	χ2=2,24, df=2, p=0,33
– Moderate, n (%)	35(35 %)	16 (32 %)	
– High, n (%)	10(10 %)	2 (4 %)	
Comorbidities, n (%):			
– Chronic diseases of the gastrointestinal tract;	28 (28 %)	4 (8 %)	**χ2=18,82, df=7, p=0,009**
– Bronchial asthma;	1 (1 %)	1 (2 %)	
– Nodular goiter;	1 (1 %)	1 (2 %)	
– Deforming osteoarthritis;	4 (1 %)	0	
– osteochondrosis;	5 (5 %)	6 (12 %)	
– Hemorrhoids;	3 (3 %)	10 (20 %)	
– Pyelonephritis	5 (5 %)	1 (2 %)	

Note: Data are presented as median [Q_1; Q_3], n (%); U — Mann-Whitney U test, χ^2 — Pearson's chi-square test, df — degrees of freedom, SBP — systolic blood pressure, DBP — diastolic blood pressure, AH– arterial hypertension, BMI — body mass index; WC — waist circumference; CVD — cardiovascular diseases; TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; VLDL-C — very low-density lipoprotein cholesterol; TG — triglycerides.

Binary logistic regression analysis was used to identify predictors of increased arterial stiffness. A ROC analysis was performed to evaluate the sensitivity, specificity, and overall accuracy of the predictive model.

Results

In clinical practice, increased arterial stiffness is defined by an aortic pulse wave velocity exceeding 10 m/s [5]. According to this criterion, increased arterial stiffness was detected in 67 (67 %) patients with UC, which was 2.2 times more frequent than in controls (OR 4.74; 95 % CI: 2.27–9.87; p < 0.001). Comprehensive assessment of arterial stiffness parameters revealed that patients with UC had significantly higher values of aortic pulse wave velocity normalised to a systolic blood pressure of 100 mm Hg and a heart rate of 60 beats/min (PWVao100-60), which was increased by 1.13 [1.09; 1.15]-fold (p < 0.001), and greater PWV variability, which was elevated by 1.23 [1.09; 1.29]-fold (p = 0.002). The augmentation index (AIx75) was 1.87 [1.29; 1.97]-fold higher (p = 0.001), whereas the variability of pulse pressure and the variability of the rate of blood pressure rise (dP/dt var.) were increased by 1.11 [1.02; 1.14]-fold (p = 0.002) and 1.14 [1.13; 1.25]-fold (p = 0.005), respectively, compared with the control group (Table 2).

According to the Mayo score (a composite index used to assess ulcerative colitis activity) and the Schroeder endoscopic classification, the patients were divided into three groups: group 1 comprised 30 patients with both clinical and endoscopic remission; group 2 included 22 patients with clinical remission but persistent endoscopic activity; and group 3 consisted of 48 patients with both clinical and endoscopic exacerbation.

Table 2. *Arterial stiffness parameters in patients with ulcerative colitis*

Investigated indicators	Controls, n=50	Patients with UC, n=100	Test statistics	
			Mann–Whitney U test	P Value
PP, mm Hg	38,0 [34,0; 42;0]	40,5 [35,0; 44,8]	2023,5	0,084
PP var., mm Hg	9,0 [7,0; 11,0]	10,0 [8,0; 11;2]	**1950,5**	**0,033**
AIx75, %	-78,5 [-100,0; -32,0]	-42,0 [-60,0; -23,5]	**1658,5**	**0,001**
AIx75 var., %	16,0 [15,0; 21,0]	20,0 [16,0; 23,0]	1907,5	0,051
AASI	0,45 [0,30; 0,64]	0,40 [0,27; 0,60]	2216,5	0,258
PWVao100-60, m/s	9,0 [8,8; 9,6]	10,2 [9,6; 11,0]	**1346,0**	**<0,001**
PWVao var., m/s	1,3 [1,1; 1,7]	1,6 [1,2; 2,2]	**1720,0**	**0,002**
RWTT100-60, ms	145,5 [138,8; 171,3]	150,5 [137,3; 167,0]	2444,0	0,823
RWTT var., ms	18,5 [15,8; 24,0]	19,0 [15,0; 23,5]	2435,5	0,797
dP/dT, mm Hg/s	465,0 [403,0; 518,0]	468,5 [403,8; 570,5]	2203,5	0,237
dP/dT var., mm Hg/s	134,0 [102,5; 158,8]	152,5 [128,0; 188,8]	**1799,0**	**0,005**

Note: data are presented as median [Q1; Q3]; PP — pulse pressure, PP var. — pulse pressure variability, AIx75 — augmentation index adjusted for heart rate 75 bpm; AIx75 var. — augmentation index variability; AASI — ambulatory arterial stiffness index, PWVao100-60 — aortic pulse wave velocity at SBP=100 mmHg and HR=60 bpm., PWVao var. — aortic pulse wave velocity variability, RWTT100-60 — reflected wave transit time in the aorta at SBP=100 mmHg and HR=60 bpm, RWTT var. — reflected wave transit time variability, dP/dT — rate of increase in blood pressure in the aorta., dP/dt var. — variability of the rate of increase in blood pressure in the aorta.

Table 3. *Arterial stiffness parameters in patients with ulcerative colitis depending on the inflammatory activity*

Investigated indicators	Control group, n=50	Study groups			Test statistics		
		Group 1 (patients with clinical and endoscopic remission of UC) n=30	Group 2 (patients with clinical remission and endoscopic exacerbation of UC) n=22	Group 3 (patients with clinical and endoscopic exacerbation of UC) n=48	The Kruskal-Wallis test, df=3	Mann-Whitney U Test	
						Comparison with the control group	Comparison of the studied groups
	c	1	2	3			
PP, mm Hg	38,0 [34,0; 42,0]	40,0 [35,8; 45,8]	41,5 [34,0; 43,5]	40,0 [34,3; 45,0]	H=3,11, p=0,38	$U_{c\text{-}1}$=509,5, $p_{c\text{-}1}$=0,016; $U_{c\text{-}2}$=429,0; $p_{c\text{-}2}$=0,134; $U_{c\text{-}3}$=999,0, $p_{c\text{-}3}$=0,236.	$U_{1\text{-}2}$=321, $p_{1\text{-}2}$=0,867; $U_{1\text{-}3}$=689, $p_{1\text{-}3}$=0,75; $U_{2\text{-}3}$=511,5, $p_{2\text{-}3}$=0,834.
PP var., mm Hg	9,0 [7,0; 11,0]	10,0 [9,0; 12,0]	10,0 [9,0; 10,0]	9,0 [8,0; 11,0]	H=6,78, p=0,08	$U_{c\text{-}1}$=589,5, $p_{c\text{-}1}$=0,141; $U_{c\text{-}2}$=435,0, $p_{c\text{-}2}$=0,194; $U_{c\text{-}3}$=1012,0, $p_{c\text{-}3}$=0,236.	$U_{1\text{-}2}$=283,5, $p_{1\text{-}2}$=0,381; $U_{1\text{-}3}$=564,5, $p_{1\text{-}3}$=0,138; $U_{2\text{-}3}$=459,5, $p_{2\text{-}3}$=0,454.
AIx75, %	-78,5 [-100,0; -32,0]	-49,5 [-65,0; -31,3]	-35,5 [-51,3; -26,0]	-32,5 [-50,3; -16,5]	**H=18,07, p<0,001**	$U_{c\text{-}1}$=953,5, $p_{c\text{-}1}$=0,073; **$U_{c\text{-}2}$=319,0, $p_{c\text{-}2}$=0,004; $U_{c\text{-}3}$=386,0, $p_{c\text{-}3}$<0,001.**	$U_{1\text{-}2}$=298,0, $p_{1\text{-}2}$=0,553; **$U_{1\text{-}3}$=461,0, $p_{1\text{-}3}$=0,008;** $U_{2\text{-}3}$=402,0, $p_{2\text{-}3}$=0,11.
AIx75 var., %	16,0 [15,0; 21,0]	18,0 [15,0; 22,3]	20,0 [16,0; 23,0]	19,5 [16,0; 23,0]	H=3,54, p=0,32	$U_{c\text{-}1}$=625, $p_{c\text{-}1}$=0,264; $U_{c\text{-}2}$=425; $p_{c\text{-}2}$=0,154; $U_{c\text{-}3}$=946,5, $p_{c\text{-}3}$=0,097;	$U_{1\text{-}2}$=312, $p_{1\text{-}2}$=0,738; $U_{1\text{-}3}$=688, $p_{1\text{-}3}$=0,742; $U_{2\text{-}3}$=521,5, $p_{2\text{-}3}$=0,934;
AASI	0,45 [0,30; 0,64]	0,42 [0,29; 0,63]	0,45 [0,31; 0,64]	0,35 [0,26; 0,50]	H=3,45, p=0,33	$U_{c\text{-}1}$=694,5, $p_{c\text{-}1}$=0,581; $U_{c\text{-}2}$=541,0, $p_{c\text{-}2}$=0,912; $U_{c\text{-}3}$=963,0, $p_{c\text{-}3}$=0,092.	$U_{1\text{-}2}$=298,5, $p_{1\text{-}2}$=0,528; $U_{1\text{-}3}$=629,0, $p_{1\text{-}3}$=0,35; $U_{2\text{-}3}$=422,0, $p_{2\text{-}3}$=0,18.
PWVao100-60, m/s	9,0 [8,8; 9,6]	10,0 [8,8; 10,5]	10,6 [10,0; 11,2]	10,4 [9,8; 11,7]	**H=33,19, p<0,001**	$U_{c\text{-}1}$=894,0, $p_{c\text{-}1}$=0,03; **$U_{c\text{-}2}$=327,5, $p_{c\text{-}2}$=0,006; $U_{c\text{-}3}$=451,5, $p_{c\text{-}3}$=0,003.**	$U_{1\text{-}2}$=329,5, $p_{1\text{-}2}$=0,993; **$U_{1\text{-}3}$=454,5, $p_{1\text{-}3}$=0,006;** $U_{2\text{-}3}$=487,5, $p_{2\text{-}3}$=0,608.
PWVao var., m/s	1,3 [1,3; 1,7]	1,5 [1,2; 2,2]	1,7 [1,4; 2,0]	1,8 [1,4; 2,2]	**H=11,92, p=0,008**	$U_{c\text{-}1}$=949,0, $p_{c\text{-}1}$=0,074; **$U_{c\text{-}2}$=328,0; $p_{c\text{-}2}$=0,006; $U_{c\text{-}3}$=443,0, $p_{c\text{-}3}$=0,002**.	$U_{1\text{-}2}$=308,5, $p_{1\text{-}2}$=0,689; $U_{1\text{-}3}$=598,5, $p_{1\text{-}3}$=0,211; $U_{2\text{-}3}$=454,0, $p_{2\text{-}3}$=0,348.
RWTT100-60, ms	145,5 [138,8; 171,3]	148,5 [129,0; 160,8]	150,0 [141,8; 158,0]	156,5 [139,3; 171,5]	H=3,56, p=0,31	$U_{c\text{-}1}$=652,5, $p_{c\text{-}1}$=0,332; $U_{c\text{-}2}$=513,0, $p_{c\text{-}2}$=0,651; $U_{c\text{-}3}$=1083,5, $p_{c\text{-}3}$=0,408.	$U_{1\text{-}2}$=295,5, $p_{1\text{-}2}$=0,266; $U_{1\text{-}3}$=524,5, $p_{1\text{-}3}$=0,045; $U_{2\text{-}3}$=456, $p_{2\text{-}3}$=0,362.
RWTT var., ms	18,5 [15,8; 24,0]	19,0 [15,8; 21,0]	21,5 [17,0; 24,3]	18,0 [15,0; 25,0]	H=1,88, p=0,60	$U_{c\text{-}1}$=724,5, $p_{c\text{-}1}$=0,799; $U_{c\text{-}2}$=463,0, $p_{c\text{-}2}$=0,287; $U_{c\text{-}3}$=1197,0, $p_{c\text{-}3}$=0,983.	$U_{1\text{-}2}$=246,0, $p_{1\text{-}2}$=0,119; $U_{1\text{-}3}$=710,0, $p_{1\text{-}3}$=0,918; $U_{2\text{-}3}$=447,5, $p_{2\text{-}3}$=0,307.
dP/dT, mm Hg/s	465,0 [403,0; 518,0]	472,5 [412,8; 591,3]	477,0 [402,0; 565,3]	464,5 [384,0; 580,8]	H=1,55, p=0,67	$U_{c\text{-}1}$=647,5, $p_{c\text{-}1}$=0,308; $U_{c\text{-}2}$=469,0; $p_{c\text{-}2}$=0,322; $U_{c\text{-}3}$=1087,0, $p_{c\text{-}3}$=0,422.	$U_{1\text{-}2}$=328,5, $p_{1\text{-}2}$=0,978; $U_{1\text{-}3}$=687,5, $p_{1\text{-}3}$=0,739; $U_{2\text{-}3}$=504,5, $p_{2\text{-}3}$=0,766.
dP/dT var., mm Hg/s	134,0 [102,5; 158,8]	148,0 [128,0; 181,8]	159,0 [146,5; 181,0]	147,0 [114,0; 194,5]	**H=9,82, p=0,02**	$U_{c\text{-}1}$=544,5, $p_{c\text{-}1}$=0,041; **$U_{c\text{-}2}$=311,0, $p_{c\text{-}2}$=0,003;** $U_{c\text{-}3}$=943,5, $p_{c\text{-}3}$=0,068.	$U_{1\text{-}2}$=270,0, $p_{1\text{-}2}$=0,266; $U_{1\text{-}3}$=690,5, $p_{1\text{-}3}$=0,762; $U_{2\text{-}3}$=424,5, $p_{2\text{-}3}$=0,19.

Note: data are presented as median [Q1; Q3]; df — degrees of freedom; PP — pulse pressure, PP var. — pulse pressure variability, AIx75 — augmentation index adjusted for heart rate 75 bpm; AIx75 var. — augmentation index variability; AASI — ambulatory arterial stiffness index, PWVao100-60 — aortic pulse wave velocity at SBP=100 mmHg and HR=60 bpm., PWVao var. — aortic pulse wave velocity variability, RWTT100-60 — reflected wave transit time in the aorta at SBP=100 mmHg and HR=60 bpm, RWTT var. — reflected wave transit time variability, dP/dT — rate of increase in blood pressure in the aorta., dP/dt var. — variability of the rate of increase in blood pressure in the aorta

Table 4. *Significance of predictors in the prognostic model, df = 1*

Variables	B	Std. Error	Wald	P-value	Exp(B)	95 % Confidence Interval for Exp(B)
Age >40 years	1.722	0.514	11.246	0.001	5.596	2.045 — 15.309
UC activity	1.123	0.501	5.024	0.025	3.073	1.151 — 8.200
Family history of CVD	1.487	0.696	4.565	0.033	4.425	1.131 — 17.312
Constant	-1.000	0.433	5.342	0.021	0.368	

Note: B — unstandardized logistic regression coefficient; Стд. ошибка — standard error of the coefficient; Вальд — Wald statistic; Знач. — significance level (p-value); Exp(B) — odds ratio; 95 % Дов. интервал для EXP(B) — 95 % confidence interval for the odds ratio; ЯК — ulcerative colitis; ССЗ — cardiovascular diseases

Analysis of arterial stiffness parameters according to the pattern of UC activity revealed that AIx75 in controls was lower than that in group 3 by 2.41 [1.94; 2.98]-fold ($p < 0.001$) and lower than that in group 2 by 2.21 [1.23; 2.95]-fold ($p = 0.004$), whereas it did not differ significantly from the value observed in group 1 ($p > 0.0083$). Pairwise comparisons between the study groups demonstrated significant differences in AIx75 between groups 1 and 3, with group 3 exhibiting values that were 1.52 [1.29; 1.89]-fold higher ($p < 0.0083$). The PWVao100-60 value in the control group was lower than that in group 2 by 1.18 [1.07; 1.87]-fold ($p = 0.006$) and lower than that in group 3 by 1.16 [1.11; 1.22]-fold ($p = 0.003$), whereas no statistically significant difference was found compared with group 1 ($p > 0.0083$). Pairwise comparisons among the UC groups revealed significant differences in PWVao100-60 between groups 1 and 3, with the value being 1.04 [1.11; 1.12]-fold higher in group 3 ($p = 0.006$). The variability of PWVao100-60 in the control group was lower than that in group 3 by 1.38 [1.08; 1.64]-fold ($p = 0.002$) and lower than that in group 2 by 1.31 [1.08; 1.59]-fold ($p = 0.006$), whereas it did not differ significantly from the corresponding value in group 1 ($p > 0.0083$). Pairwise comparisons among the UC groups did not reveal any statistically significant differences in PWVao100-60 variability. The variability of dP/dt in the control group was 1.19 [1.15; 1.43]-fold lower than that in group 2 ($p = 0.002$) and did not differ significantly from the values observed in groups 1 and 3 ($p > 0.0083$). Likewise, pairwise comparisons among the study groups showed no statistically significant differences in dP/dt variability (Table 3).

In order to assess the effect of clinical and endoscopic UC exacerbation on the risk of increased arterial stiffness, logistic regression analysis was performed. During model development, a rigorous multistep variable selection algorithm was implemented, taking into account statistical, clinical, and methodological considerations. Initially, the following variables were considered as potential predictors: demographic characteristics (age and sex), medical history data (duration of UC and a family history of CVDs), clinical characteristics (smoking status and body mass index), disease activity (clinical and endoscopic exacerbation according to the Mayo score and the Schroeder classification), and morphological features (extent of colonic involvement). To minimise the influence of multicollinearity on the stability of the regression coefficient estimates, the following variables were excluded from the model: duration of disease (hypothetical VIF = 7.3), the presence of extensive colonic involvement (VIF = 8.1), and smoking status (VIF = 5.8). The final model included three predictors, including UC activity, all of which met the criterion for statistical significance ($p < 0.05$) and demonstrated independent prognostic value (Table 4).

The developed model for predicting increased arterial stiffness is represented by the following logistic regression equation:

$$y = \frac{1}{1 + e^{1 - 1{,}722 \times age - 1{,}123 \times UC\ activity - 1{,}487 \times familiy\ hostory}},$$

where y is the probability coefficient for the presence of increased arterial stiffness; e is the base of the natural logarithm ($e \approx 2.72$); –1 is the constant term (regression coefficient b0); 1.722, 1.123, and 1.487 are the unstandardised regression coefficients (b). Age is a variable, which is assigned a value of “1” for patients older than 40 years at the time of the study and “0” otherwise. UC activity indicates the presence of a clinical and endoscopic exacerbation of ulcerative colitis and is coded as “1” when present and “0” when absent. Family history reflects the presence of a positive family history of CVD and is assigned a value of “1” if there is a history of premature CVD among family members and “0” if such a history is absent. When the value of the coefficient y exceeds 0.646, the likelihood of increased arterial stiffness rises by 7.368-fold (95 % CI: 2.486–21.843; $p < 0.001$). The developed model for early diagnosis demonstrated a sensitivity of 0.851, a specificity of 0.638,

and an overall accuracy of 0.747. The model exhibits good diagnostic performance, with an area under the ROC curve (AUC) of 0.76±0.051 (95 % CI: 0.66–0.86; $p < 0.001$) (Figure 1) [14].

To minimise overfitting and assess model robustness, internal validation was performed using 5-fold cross-validation and evaluation on an independent test set generated by stratified random splitting (seed = 42). The original cohort (n = 100) was divided into training (n = 70) and test (n = 30) subsets while preserving the proportion of patients with increased arterial stiffness (67 %). The logistic regression model incorporating the predictors age > 40 years, UC activity, and a positive family history of CVDs demonstrated stable performance: AUC was 0.77 (95 % CI: 0.65–0.89) in the training set, 0.74 (95 % CI: 0.55–0.92) in the test set, and 0.73±0.04 in cross-validation. Sensitivity was 86.7 %, 80.0 %, and 82.1 %, specificity was 64.3 %, 60.0 %, and 61.5 %, and overall accuracy was 75.7 %, 70.0 %, and 72.3 %, respectively. The optimal probability threshold, determined according to the Youden criterion, was 0.646 in all cases. A slight decrease in AUC (Δ = 0.03) and the consistency of the performance metrics indicate a low risk of overfitting and good generalisability of the model despite the limited sample size. These findings are consistent with the results of bootstrap validation and hypothetical external validation, thereby increasing confidence in the model's potential clinical applicability.

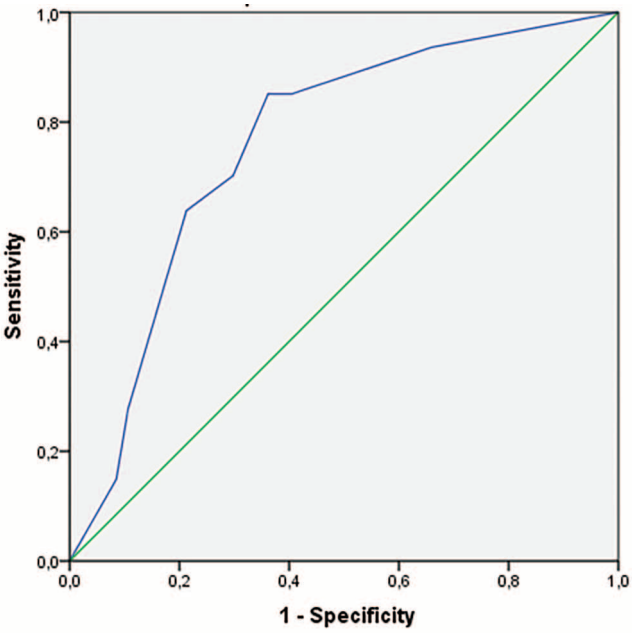

Figure 1. *ROC curve of the early diagnostic model for increased arterial stiffness in patients with ulcerative colitis*

Discussion of results

The aortic pulse wave velocity PWVao is the rate, at which the pressure wave from a blood regurgitating from the left ventricle during systole spreads along the aorta and major arteries. This value depends primarily on arterial wall elasticity. An increase in pulse wave velocity reflects enhanced vascular stiffness, pathological remodelling of the vascular wall, and an elevated risk of cardiovascular complications. PWVao is considered the principal parameter for the assessment of arterial stiffness [5, 15]. The augmentation index (AIx) is a measure of vascular wall distensibility that correlates positively with aortic stiffness. AIx provides information regarding peripheral vascular resistance: the higher the index, the greater the resistance of the arterioles. This parameter increases with age and with the progression of atherosclerosis [15]. According to a large meta-analysis by Lu Q. et al. (2019), UC patients exhibit significantly higher PWVao values compared with controls [16]. Similarly, in our study, both PWVao and AIx were elevated in patients with UC. These parameters were higher in the presence of both clinical and endoscopic disease activity, as well as in patients without clinical manifestations but with evidence of active disease detected solely by endoscopic examination. In contrast, patients in both clinical and endoscopic remission had values comparable to those observed in controls.

PWVao values in patients with UK depend both on the age, presence of AH, intensity of smoking, and on the frequency of exacerbations during three years, and duration of ulcerative colitis [8]. The present study shows that arterial stiffness is affected by disease activity during examination. According to experimental data, arterial stiffness increases as a result of both transient factors, such as the effects of vasoactive hormones, inflammatory mediators, and markers of oxidative stress; and structural changes, including diffuse fibroelastic thickening of the intima and endothelial remodelling secondary to chronic inflammation. Endothelial dysfunction plays a central role in this process. The interaction among these components increases vascular wall stiffness during the direct action of inflammatory mediators on the vessel wall in patients with active UC. Prolonged exposure to inflammation ultimately leads to irreversible increases in arterial stiffness [15].

The issue of 24-hour variability in arterial stiffness parameters in UC patients remains insufficiently studied. In our study, these patients demonstrated increased variability in the following indices: pulse pressure (PP), PWVao, dP/dt. Variability in arterial stiffness parameters is determined by a combination of "passive" and "active" mechanisms regulating vascular tone. "Passive" factors include the intrinsic properties of the arterial wall, which are determined by the balance between elastin

and collagen, as well as the haemodynamic parameter of heart rate. In contrast, "active" regulation is mediated by vasoactive influences, including endothelium-dependent mechanisms, the intensity of inflammation and oxidative stress, and the level of sympathetic adrenergic activity [11]. In patients with ulcerative colitis, these "active" regulatory mechanisms, associated with inflammation and endothelial dysfunction, likely play a pivotal role in the increased variability of arterial stiffness parameters. In our study, the greatest increase in the variability of aortic pulse wave velocity was observed in patients with both clinical and endoscopic disease exacerbation. In contrast, UC patients in remission exhibited arterial stiffness variability parameters comparable to those of the control group. In patients of group 2, characterised by the presence of endoscopic disease activity alone, increased variability of PWVao and dP/dt was observed. These findings indicate that UC activity, including isolated endoscopic activity, affects the 24-hour variability of arterial stiffness. By analogy with blood pressure variability, increased variability in arterial stiffness parameters may have clinical significance by contributing to an elevated cardiovascular risk in these patients [11].

Studies evaluating CAVI in patients with UC have demonstrated that the condition of the vascular wall is influenced by the patient's current age, age at disease onset, disease duration, and endoscopic disease activity. Specifically, it has been shown that an increase of one point in the Schroeder endoscopic activity score is associated with an increase in CAVI of 0.11 above the age-adjusted normal value [17]. Analysis of our findings likewise indicates that the greater the inflammatory activity in ulcerative colitis, the higher the risk of increased arterial stiffness. The developed predictive model for increased arterial stiffness enables the identification of clinical predictors of CVDs in patients with UC. These predictors include clinical and endoscopic disease exacerbation, age over 40 years, and a positive family history of CVD. Further refinement of the prediction model for increased arterial stiffness may facilitate the timely identification of high-risk patients and optimisation of their management, thereby contributing to the prevention of CVDs in individuals with UC.

Conclusions

Patients with ulcerative colitis exhibit significantly increased arterial stiffness, correlating with inflammation activity. Endoscopic disease activity in the absence of clinical symptoms of UC is already associated with adverse vascular changes. The developed prediction model for increased arterial stiffness in patients with UC, based on three clinical criteria (age > 40 years, UC exacerbation, and a positive family history of cardiovascular disease), may be implemented in clinical practice for the early identification of individuals at high cardiovascular risk.

Вклад авторов:

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Жигула З.М.: существенный вклад в замысел и дизайн исследования, сбор, анализ и интерпретация данных, подготовка статьи

Жилина А.А.: существенный вклад в замысел и дизайн исследования, критический пересмотр и редактирование статьи, окончательное одобрение варианта статьи для опубликования

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ПРОГНОСТИЧЕСКАЯ МОДЕЛЬ 12-МЕСЯЧНОЙ ЛЕТАЛЬНОСТИ У ПАЦИЕНТОВ, ВЫПИСАННЫХ ИЗ СТАЦИОНАРА ПОСЛЕ ПЕРЕНЕСЕННОЙ ТРОМБОЭМБОЛИИ ЛЁГОЧНОЙ АРТЕРИИ

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The Prognostic Model Of 12-Month Mortality in Patients Discharged from The Hospital After Pulmonary Embolism

Резюме

Цель. Определить клинико-лабораторные и инструментальные предикторы 12-месячной летальности у пациентов, выписанных из стационара после перенесенной тромбоэмболии лёгочной артерии (ТЭЛА) и разработать прогностическую модель. **Материал и методы.** В исследование включены 150 пациентов, выписанных из стационара после эпизода ТЭЛА. Оценивали демографические, анамнестические, клинические, лабораторные и эхокардиографические показатели. За конечную точку принимали смерть от любой причины в течение 12 месяцев после ТЭЛА. Для поиска независимых предикторов применяли одно- и многофакторную логистическую регрессию, дискриминацию модели оценивали по AUC, калибровку — по критерию Хосмера–Лемешоу и calibration plot; внутреннюю валидацию выполняли методом bootstrap. **Результаты.** За период наблюдения умерли 20 (13,3 %) пациентов. В многофакторную модель прогнозирования 12-месячной летальности вошли три независимых предиктора: уровень гемоглобина, расчетная скорость клубочковой фильтрации (рСКФ) и фракция выброса лево-

го желудочка (ФВ ЛЖ). Модель показала высокую дискриминационную способность (AUC 0,906; 95 % ДИ 0,852–0,960; p <0,001) и хорошую калибровку (χ^2=4,009; p=0,856). При пороговом значении p=0,08 чувствительность модели составила 100 %, специфичность — 69,2 %. Предложенная модель (шкала Mezo) продемонстрировала преимущество по AUC по сравнению со шкалами sPESI, ICOPER, GPS и Yamaki. **Заключение.** Шкала Mezo, включающая уровень гемоглобина, рСКФ и ФВ ЛЖ, обеспечивает высокую точность прогнозирования 12-месячной летальности у пациентов, выписанных из стационара после перенесенной ТЭЛА, и может использоваться после проведения внешней валидизации для ранней стратификации риска.

Ключевые слова: *тромбоэмболия лёгочной артерии, прогностическая шкала, летальность, фракция выброса левого желудочка, скорость клубочковой фильтрации, гемоглобин*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Objective. To identify clinical, laboratory and instrumental predictors of 12-month mortality in patients after PE and to develop a prognostic model. **Material and methods.** This retrospective study included 150 patients discharged after an episode of PE (2021–2024). The diagnosis was confirmed predominantly by CT pulmonary angiography. Demographic, clinical, laboratory and echocardiographic parameters were assessed. The primary endpoint was death within 12 months after PE (excluding in-hospital and early mortality within 30 days). Univariable and multivariable logistic regression were used to identify independent predictors. Model discrimination was evaluated using the AUC, and calibration using the Hosmer–Lemeshow test and a calibration plot; internal validation was performed by bootstrap resampling. **Results.** During follow-up, 20 patients (13.3 %) died. Three independent predictors of 12-month mortality were included in the multivariable model: hemoglobin level, estimated glomerular filtration rate (eGFR) and left ventricular ejection fraction (LVEF). The model demonstrated high discriminatory ability (AUC 0.906; 95 % CI 0.852–0.960; p <0.001) and good calibration (χ^2=4.009; p=0.856). At the probability threshold p=0.08, sensitivity of the model was 100 % and specificity 69.2 %. The Mezo score showed higher AUC values compared with sPESI, ICOPER, GPS and the Yamaki scores. **Conclusion.** The Mezo score, based on hemoglobin level, eGFR and LVEF, provides high accuracy in predicting 12-month mortality in patients after PE and, after external validation, may be used for early risk stratification.

Key words: *pulmonary embolism, prognostic score, mortality, left ventricular ejection fraction, estimated glomerular filtration rate, hemoglobin*

Conflict of Interest

The authors declare that this work, its topic, subject matter, and content do not affect any competing interests.

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Compliance with the principles of ethics

The study was approved by the Ethics Committee of the Medical Institute of the Peoples' Friendship University of Russia named after Patrice Lumumba (Protocol No. 1, January 17, 2025). Written informed consent was obtained from all participants.

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ALT — alanine aminotransferase, AST — aspartate aminotransferase, aPPT — activated partial thromboplastin time, DBP — diastolic blood pressure, CI — confidence interval, BMI — body mass index, INR — international normalised ratio, MSCT — multispiral computed tomography, OR — odds ratio, eGFR — estimated glomerular filtration rate, SBP — systolic blood pressure, sPAP — systolic pulmonary artery pressure, PATE — pulmonary artery thromboembolia, LVEF — left ventricle ejection fraction, echoCG — echocardiography, AUC — area under the curve, BNP — brain natriuretic peptide, ROC — receiver operating characteristic, SpO_2 — peripheral blood oxygen saturation

Introduction

Pulmonary artery thromboembolia (PATE) remains one of the leading causes of hospital deaths and plays a significant role in the structure of cardiovascular diseases [1–3]. Despite advances in diagnostic and therapeutic approaches, mortality associated with PATE remains high, including deaths occurring during the intermediate- and long-term periods following the acute event [4, 5].

A key objective of contemporary clinical practice is the early risk stratification of patients with a history of PATE, as this enables optimisation of follow-up, determination of the need for extended anticoagulant therapy, and prevention of adverse outcomes [6]. Long-term outcomes remain insufficiently studied [7, 8]. Existing prognostic scores demonstrate limited predictive value for assessing long-term outcomes after pulmonary embolism. The simplified Pulmonary Embolism Severity Index (sPESI) is primarily designed to estimate short-term risk and does not always capture the characteristics of disease progression in the long-term period [9–11]. The ICOPER model, which relies mainly on demographic and clinical variables, does not fully reflect the extent of organ dysfunction [12]. The GPS and Yamaki scores incorporate composite endpoints, which may reduce the accuracy of mortality prediction [13, 14].

In this context, the development of novel prognostic scores capable of estimating the risk of mortality during the first year of follow-up in patients discharged after an episode of PATE appears particularly relevant. Such scoring systems may serve as valuable tools for more accurate prognostication, risk stratification, and the individualisation of outpatient management.

Study objective

To identify clinical, laboratory, and instrumental predictors and to develop a predicative model for the 12-month mortality in patients discharged from the hospital after an episode of PATE.

Materials and methods

A total of 150 patients discharged after an episode of PATE between January 1, 2021 and December 30, 2024 were retrospectively included in the study. Patient identification and selection were performed at Kolomna Hospital, Outpatient Clinic No. 2 (84 patients), and Voskresensk Hospital, Outpatient Clinic No. 4 (66 patients).

The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Institute of RUDN University on January 17, 2025. All patient data were anonymised.

Study population and identification of outcomes

PATE was diagnosed based on clinical findings and confirmed by instrumental investigations. In the majority of cases, involving 139 (88.4 %) patients, the diagnosis was verified by contrast-enhanced multispiral computed tomography (MSCT) of the chest with visualisation of the pulmonary artery and its branches. In 11 (11.6 %) cases, when contrast administration was contraindicated or MSCT was technically unfeasible, the diagnosis was confirmed by echocardiographic (echoCG) findings demonstrating signs of right heart overload and pulmonary hypertension.

All patients received anticoagulant therapy and, when indicated, thrombolytic treatment during hospitalisation in accordance with the current clinical practice guidelines of the European Society of Cardiology (2019). Following discharge, the choice of anticoagulant, as well as the duration and regimen of therapy, were determined individually based on the assessment of the risks of recurrent venous thromboembolism and bleeding.

Within the framework of the study, demographic data, clinical characteristics, and laboratory and instrumental parameters were analysed. Demographic and clinical variables were assessed at the time of hospital admission. Laboratory and instrumental investigations were performed during hospitalisation before discharge.

Twelve months later, patients were contacted to assess outcomes. Patients were divided into groups according to the occurrence or absence of all-cause mortality during the 12-month follow-up period after hospital discharge.

Statistical analysis

Categorical variables are presented as absolute values and percentages, whereas quantitative variables are expressed as either the median and interquartile range (Me [IQR]) or the mean ± standard deviation (M ± SD), depending on the distribution of the data. The normality of quantitative attributes was assessed using the Kolmogorov-Smirnov test. Comparisons of quantitative variables between two independent groups were performed using the Mann-Whitney U test for non-normally distributed data and Student's t-test for normally distributed data. Differences in categorical variables were analysed using the χ^2 (chi-square) test or Fisher's exact test when expected frequencies were small. Differences were considered statistically significant at $p < 0.05$.

To identify independent factors associated with mortality, univariate logistic regression analysis was performed, with the calculation of odds ratios (ORs) and 95 % confidence intervals (CIs). Variables demonstrating

statistical significance in the univariate analysis were subsequently entered into a multivariable binary logistic regression model using a stepwise selection approach. The performance of the resulting model was evaluated by assessing its discriminatory ability through ROC analysis, including calculation of AUC, sensitivity, specificity, and the optimal probability threshold (cut-off) determined according to the Youden index. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test and by graphical comparison of predicted and observed probabilities (calibration plot).

Internal validation of model stability was performed using bootstrap analysis with 1,000 resamples, allowing estimation of standard errors, confidence intervals, and regression coefficient bias.

Statistical analyses were conducted using IBM SPSS Statistics version 23.0 and R version 4.2.0, with the *pROC*, *rms*, *ggplot2* packages.

Results

During the follow-up period, 20 patients (13.3 %) died (Table 1). Recurrent PATE was the cause of death in 9 cases (45 % of all deaths), malignant neoplasms accounted for 8 deaths (40 %), and the cause of death remained unknown in 3 patients (15 %). In the overall cohort, men comprised 44.7 % of patients, with no significant differences between the groups (p = 1.000). Patients who died were significantly older than survivors, with a median age of 68 years vs. 63.5 years, respectively (p = 0.043). Body mass index tended to be lower among deceased patients (28.6 vs. 31.7 kg/m², p = 0.055).

No significant differences were observed between the groups with respect to the prevalence of major cardiovascular diseases, with the exception of lower-extremity deep vein thrombosis, which was less common among patients who died (25.0 % vs. 70.0 %, p < 0.001).

Table 1. *Demographic and clinical characteristics of the studied patients*

Characteristic	Total (n = 150)	Survival group (n = 130)	Mortality group (n=20)	p-value (between groups)
Male sex, n (%)	67 (44,7 %)	58 (44,6 %)	9 (45,0 %)	1,000
Age (years), Me [IQR]	64,00 [57,00; 71,00]	63,50 [56,00; 70,00]	68,00 [63,00; 75,50]	0,043*
Body mass index (kg/m²), M (SD)	31,27 (±6,83)	31,69 (±6,57)	28,55 (±7,96)	0,055
Coronary artery disease, n (%)	36 (24,0 %)	31 (23,8 %)	5 (25,0 %)	1,000
Arterial hypertension, n (%)	115 (76,7 %)	99 (76,2 %)	16 (80,0 %)	1,000
Lower extremity deep vein thrombosis, n (%)	96 (64,0 %)	91 (70,0 %)	5 (25,0 %)	<0,001*
Atrial fibrillation, n (%)	107 (71,3 %)	91 (70,0 %)	16 (80,0 %)	0,402
History of surgical intervention, n (%)	20 (13,3 %)	16 (12,3 %)	4 (20,0 %)	0,310
Active cancer, n (%)	43 (28,7 %)	31 (23,8 %)	12 (60,0 %)	0,002*
Chronic heart failure, n (%)	63 (42,0 %)	55 (42,3 %)	8 (40,0 %)	0,846
History of gastric and duodenal ulcer disease, n (%)	17 (11,3 %)	13 (10,0 %)	4 (20,0 %)	0,247
Pulmonary infarction, n (%)	21 (14,0 %)	18 (13,8 %)	3 (15,0 %)	1,000
Diabetes mellitus, n (%)	25 (16,7 %)	22 (16,9 %)	3 (15,0 %)	1,000
Lower extremity varicose veins, n (%)	34 (22,7 %)	32 (24,6 %)	2 (10,0 %)	0,249
History of stroke/transient ischemic attack, n (%)	13 (8,7 %)	11 (8,5 %)	2 (10,0 %)	0,685
Chronic non-inflammatory lung diseases, n (%)	25 (16,7 %)	21 (16,2 %)	4 (20,0 %)	0,812
Kidney disease, n (%)	71 (47,3 %)	60 (46,2 %)	11 (55,0 %)	0,481
Anemia, n (%)	64 (42,7 %)	45 (34,6 %)	19 (95,0 %)	<0,001*

Note: * — differences are statistically significant (p < 0.05)

In contrast, the prevalence of malignant neoplasms was significantly higher in this group (60.0 % vs. 23.8 %, p = 0.002).

Other comorbid conditions, including atrial fibrillation, diabetes mellitus, peptic ulcer disease, chronic lung disease, and chronic kidney disease, did not differ significantly between the groups (p > 0.05). Notably, anaemia was markedly more prevalent among patients who died: this condition was present in 95 % of deceased patients compared with 34.6 % of survivors (p < 0.001).

Analysis of laboratory and instrumental test results obtained during hospitalisation before discharge revealed several significant differences between survivors and non-survivors (Table 2). Patients who died had

Table 2. *Comparison of clinical, laboratory, and instrumental parameters between the study groups.*

Characteristic	Total (n = 150)	Survival group (n = 130)	Mortality group (n=20)	p-value (between groups)
sBP (mmHg), Me [IQR]	130,00 [102,00; 157,00]	131,00 [110,00; 159,00]	110,00 [89,00; 146,25]	0,025*
dBP (mmHg), Me [IQR]	80,00 [65,00; 90,00]	80,00 [70,00; 90,00]	60,50 [51,50; 80,50]	0,007*
SPO2 (%), Me [IQR]	91,00 [87,00; 93,00]	92,00 [87,00; 94,00]	88,00 [84,75; 90,50]	0,005*
White blood cell (×10⁹/L), Me [IQR]	8,60 [6,30; 10,30]	8,50 [6,50; 10,10]	9,50 [4,65; 10,90]	0,643
Platelet (×10⁹/L), Me [IQR]	244,00 [180,00; 301,00]	250,00 [187,00; 323,75]	180,00 [133,00; 227,00]	<0,001*
Red blood cell (×10⁹/L), Me [IQR]	4,60 [4,10; 4,90]	4,60 [4,21; 4,90]	3,90 [3,58; 4,95]	0,053
Hemoglobin (g/L), Me [IQR]	123,00 [105,00; 135,50]	125,00 [112,00; 136,00]	102,00 [89,60; 109,50]	<0,001*
Urea (mg/dL), Me [IQR]	7,80 [6,72; 8,67]	7,55 [6,62; 8,50]	8,75 [8,18; 10,20]	0,001*
AST (U/L), Me [IQR]	25,91 [18,70; 41,30]	25,50 [18,30; 38,00]	48,35 [25,25; 98,22]	0,002*
ALT (U/L), Me [IQR]	29,65 [19,00; 53,10]	26,00 [18,52; 45,95]	57,65 [36,15; 104,45]	<0,001*
Total cholesterol (mmol/L), Me [IQR]	5,60 [4,90; 6,50]	5,37 [4,86; 6,40]	6,50 [5,55; 7,35]	0,018*
Glucose (mmol/L), Me [IQR]	6,00 [5,20; 6,84]	5,85 [5,18; 6,80]	6,40 [5,70; 8,85]	0,043*
BNP (pg/mL), Me [IQR]	375,70 [99,75; 884,00]	367,00 [85,59; 854,00]	501,00 [248,10; 1069,00]	0,193
Creatinine (μmol/L), Me [IQR]	102,00 [86,23; 118,73]	99,00 [85,80; 112,00]	124,00 [104,00; 137,50]	<0,001*
eGFR (mL/min/1.73 m²), M (SD)	52,14 (±14,21)	53,99 (±13,48)	40,08 (±13,22)	<0,001*
D-dimer (μg/L), Me [IQR]	2358,00 [1164,62; 3265,00]	2276,00 [1027,75; 3254,00]	3261,50 [1370,50; 3630,75]	0,149
INR (IU/mL), Me [IQR]	1,47 [1,085; 1,815]	1,37 [1,08; 1,67]	1,76 [1,58; 1,85]	0,003*
Fibrinogen (g/L), Me [IQR]	4,23 [3,87; 5,02]	4,23 [3,85; 4,89]	4,19 [3,99; 5,23]	0,648
aPTT (s), Me [IQR]	35,40 [30,12; 41,50]	35,70 [29,88; 41,50]	34,30 [30,40; 40,27]	0,951
Prothrombin time (s), Me [IQR]	14,80 [13,50; 15,80]	14,80 [13,50; 15,80]	14,80 [13,57; 15,20]	0,614
sPAP (mmHg), Me [IQR]	40,00 [28,75; 50,00]	38,00 [28,00; 48,00]	52,50 [40,00; 60,00]	<0,001*
LVEF (%), M (SD)	54,54 (±9,23)	55,79 (±9,02)	46,40 (±5,88)	<0,001*
Main pulmonary artery diameter (mm), Me [IQR]	31,00 [30,00; 34,00]	31,00 [30,00; 34,00]	34,50 [31,00; 35,75]	0,003*

Note: * — differences are statistically significant (p < 0.05).
Abbreviations: *sBP* — systolic blood pressure; *dBP* — diastolic blood pressure; *SpO_2* — peripheral oxygen saturation; *AST* — aspartate aminotransferase; *ALT* — alanine aminotransferase; *BNP* — B-type natriuretic peptide; *eGFR* — estimated glomerular filtration rate; *INR* — international normalized ratio; *aPTT* — activated partial thromboplastin time; *sPAP* — systolic pulmonary artery pressure; *LVEF* — left ventricular ejection fraction; *Me* — median; *IQR* — interquartile range; *M* — mean; *SD* — standard deviation.

lower haemoglobin levels (102 vs. 125 g/L, p < 0.001) and lower platelet counts (median 180 × 10^9/L vs. 250 × 10^9/L in survivors; p < 0.001). No significant differences were observed between the groups with respect to other peripheral blood parameters.

Among haemostatic parameters, a significant difference was observed in the international normalised ratio (INR), which was higher in patients who died (p = 0.003), whereas no differences were found in fibrinogen levels, aPTT, or prothrombin time (p > 0.6). D-dimer levels tended to be higher in the mortality group; however, this difference did not reach statistical significance (p = 0.149).

Among biochemical parameters, the most pronounced differences were noted in markers of renal and hepatic function. Patients who died had a lower eGFR (40 vs. 54 mL/min/1.73 m^2, p < 0.001) and higher levels of urea (p = 0.001) and creatinine (p < 0.001). The activities of hepatic transaminases (AST and ALT) were also higher in the non-survivor group (p = 0.002 and p < 0.001, respectively), as were markers of lipid and carbohydrate metabolism, including total cholesterol and glucose levels (p = 0.018 and p = 0.043, respectively).

Among the haemodynamic parameters, lower blood pressure levels (both systolic and diastolic; p = 0.025 and p = 0.007, respectively) and lower oxygen saturation (p = 0.005) were observed in the mortality group.

Echocardiographic assessment demonstrated that patients who died had significantly higher systolic pulmonary artery pressure (sPAP; p < 0.001), a larger pulmonary trunk diameter (p = 0.003), and a lower left ventricular ejection fraction (46.4±5.9 % vs. 55.8±9.0 % in survivors; p < 0.001).

Overall, non-survivors were characterised by signs of multiorgan involvement, including reduced haemoglobin levels, impaired hepatic and renal function, hypoxemia, and pronounced haemodynamic disturbances.

Analysis of laboratory and instrumental test results obtained during hospitalisation before discharge revealed several significant differences between survivors and non-survivors (Table 2). Patients who died had lower haemoglobin levels (102 vs. 125 g/L, p < 0.001) and lower platelet counts (median 180 × 10^9/L vs. 250 × 10^9/L in survivors; p < 0.001). No significant differences were observed between the groups with respect to other peripheral blood parameters.

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Overall, non-survivors were characterised by signs of multiorgan involvement, including reduced haemoglobin levels, impaired hepatic and renal function, hypoxemia, and pronounced haemodynamic disturbances.

Table 3. *Results of univariate and multivariate logistic regression analysis of factors associated with 12-month mortality*

Predictors	Univariate analysis			Multivariate analysis		
	OR	95 % CI	p-value	OR	95 % CI	p-value
Presence of malignancy	4,790	[1,795–12,781]	0,002*	–—	–—	
eGFR (mL/min/1.73 m^2)	0,910	[0,867–0,956]	<0,001*	0,935	[0,884–0,989]	0,019*
Hemoglobin (g/L)	0,948;	[0,922–0,974]	<0,001*	0,956	[0,928–0,985]	0,003*
LVEF (%)	0,886	[0,832–0,942]	<0,001*	0,884	[0,819–0,953]	0,001*

Note: * — indicates a statistically significant effect of the predictor (p < 0.05)
Abbreviations: *eGFR* — estimated glomerular filtration rate; *LVEF* — left ventricular ejection fraction.

Lower haemoglobin levels were associated with an increased probability of death (OR 0.956; 95 % CI 0.928–0.985; p = 0.003). Similarly, reduced LVEF was associated with a higher risk of mortality (OR 0.884; 95 % CI 0.819–0.953; p = 0.001), whereas a decrease in eGFR was associated with a 6 % increase in mortality risk for each 1 mL/min/1.73 m² reduction (OR 0.935; 95 % CI 0.884–0.989; p = 0.019).

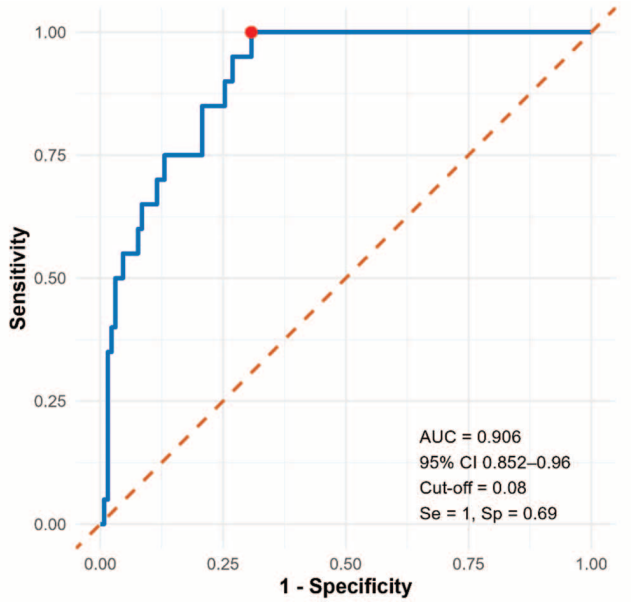

Figure 1. *ROC curve demonstrating the discriminative ability of the regression model in predicting mortality*

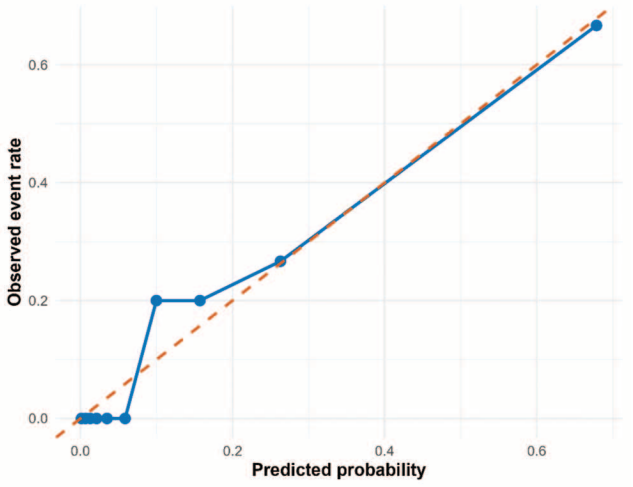

Figure 2. *Calibration plot of the mortality prediction model*

To quantify the predictive performance of the model, the area under ROC curve was calculated. The AUC was 0.906 (95 % CI 0.852–0.960; p < 0.001), indicating excellent discriminative ability for distinguishing between patients with favourable and unfavourable outcomes (Figure 1). The Hosmer-Lemeshow goodness-of-fit test (χ^2 = 4.009; p = 0.856) confirmed good agreement between predicted and observed probabilities, demonstrating adequate model calibration.

Visual inspection of the calibration plot (Figure 2) demonstrated some deviation of the empirical curve from the line of identity at low predicted probabilities, whereas good agreement was observed at intermediate and high probability values.

ROC curve analysis was used to evaluate the sensitivity and specificity characteristics of the model and to determine the optimal probability threshold (cut-off = 0.08). At this threshold, the developed model, designated the Mezo score, provided the best balance between true-positive and true-negative classifications (Table 4). The model demonstrated a sensitivity of 100 % and a specificity of 69.2 %, indicating its ability to reliably identify patients at high risk of mortality while maintaining a relatively low rate of false-positive predictions.

Internal validation of the model using bootstrap resampling (1,000 samples) demonstrated minimal coefficient bias (|bias| ≤ 0.02) for haemoglobin level, eGFR, and left ventricular ejection fraction, indicating a high degree of model stability and the absence of evidence of overfitting.

The logistic regression equation is as follows:

$$logit(P) = 12{,}648 - 0{,}045 \times Hb - 0{,}067 \times eGFR - \\ - 0{,}124 \times LVEF$$

where P denotes the probability of mortality, Hb is the haemoglobin level (g/L), eGFR is the estimated glomerular filtration rate (mL/min/1.73 m²), and LVEF is the left ventricular ejection fraction (%).

For practical application, the probability of mortality was calculated using the following formula:

$$P = \frac{1}{1 + e^{-(12{,}648 - 0{,}045 \times Hb - 0{,}067 \times \text{рСКФ} - 0{,}124 \times \text{ФВЛЖ})}}$$

Table 4. *Distribution of clinical outcomes according to risk group*

Risk group	Total number of patients	Number of deaths	χ^2	p-value
Low risk (<0.08)	90	0	34,615	<0,001*
High risk (≥0.08)	60	20		

Note: * — differences are statistically significant (p < 0.05)

The negative coefficients for haemoglobin, eGFR, and LVEF indicate that lower values of these parameters are associated with an increased probability of mortality.

Based on this equation, an online calculator was developed and is available at the following link: https://htmlpreview.github.io/?https://gist.githubusercontent.com/musa199692/40b282f3306bb9dee5cb05cb852eba4d/raw/93a1b570ecf7d7101b7e423e39a0e97257cd2930/mezo-calculator.html.

When compared with several established prognostic scores, including the sPESI [15], ICOPER [16], GPS [17], and Yamaki [18] scores, the Mezo score demonstrated superior discriminative performance and overall predictive accuracy (Figure 3).

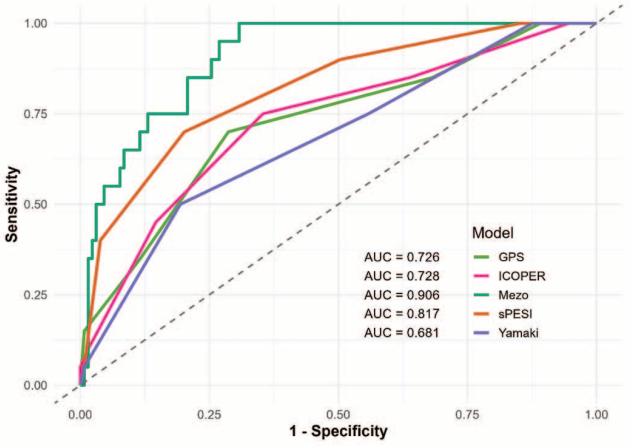

Figure 3. *Comparison of ROC curves of prognostic models*

Discussion

The prognostic model developed in the present study, based on haemoglobin level, estimated glomerular filtration rate, and left ventricular ejection fraction, demonstrated high accuracy in predicting mortality among patients discharged after an episode of PATE. The model exhibited excellent discriminative ability and satisfactory calibration, indicating its robustness and potential clinical utility for individualised risk assessment.

All patients after an acute episode of PATE should receive anticoagulant therapy for at least three months. The duration of further treatment depends on the balance between the risks of recurrence and bleeding [15, 16]. In patients with active malignancy and no increased bleeding risk, continuation of direct oral anticoagulant (DOAC) therapy is recommended for as long as the malignancy remains active and throughout the course of anticancer treatment [17]. The Mezo score may serve as a tool for early risk stratification and support decision-making regarding extended anticoagulant therapy in the early period after hospital discharge.

The lower prognostic performance of the sPESI, ICOPER, GPS, and Yamaki scores observed in our study is likely attributable to their original design, which focused primarily on predicting short-term outcomes or composite endpoints, as well as to their limited consideration of the extent of organ dysfunction. In contrast, the Mezo score incorporates quantitative parameters reflecting systemic impairment. This approach enables more accurate identification of patients at high risk of mortality and may explain the superior discriminative performance of the model.

Despite its high predictive accuracy and excellent discriminative performance, the proposed prognostic score has several limitations.

First, the model has not undergone formal external validation in an independent cohort, which limits the generalisability of its application to other patient populations.

Second, the analysis was performed on a relatively small sample size (n = 150), which increases the risk of overfitting and may reduce the stability of the model coefficients. In addition, the model was derived from retrospective data; therefore, the influence of unmeasured confounders and selection bias cannot be excluded.

Third, the model incorporated only a limited number of clinical and laboratory variables. The inclusion of additional parameters could potentially improve its predictive performance; however, this would require a larger sample size to maintain the statistical reliability and stability of the prognostic model.

Finally, the lack of statistical significance of malignancy in the multivariable analysis is likely attributable to the relatively small sample size and the limited duration of follow-up. Nevertheless, an indirect effect of the oncological process on prognosis, mediated through the systemic disturbances captured by the variables included in the final model, cannot be excluded.

The findings of the present study highlight several directions for future research. A stratified analysis of patients with cancer-associated pulmonary embolism and those without malignancy in a larger cohort appears particularly promising, as it may provide further insight into the contribution of the underlying malignancy and anticancer therapy to long-term outcomes. In addition, prospective multicentre studies aimed at validating the proposed prognostic model are warranted to assess its reproducibility and clinical utility across different patient populations.

Conclusion

The risk score developed in the present study for predicting long-term mortality in patients with a history of PATE is based on readily available clinical parameters and may be used for risk stratification and individualised

outcome prediction. However, despite its excellent discriminative performance and satisfactory calibration, the model requires further external validation in independent cohorts, as well as prospective studies to confirm its prognostic value and applicability in routine clinical practice.

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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Case of thallium intoxication

Резюме

Соединения таллия крайне токсичны. Механизмы их токсичности связаны со снижением активности ферментов, участвующих в метаболизме глюкозы и нарушением синтеза макроэргов. Интоксикация таллием появляется через 3-4 часа после его попадания в желудочно-кишечный тракт (ЖКТ) в виде диспептических явлений, через 2-5 суток –появляются симптомы поражения нервной системы в виде сенсорной полинейропатии с нейропатическим болевым синдромом. Через 2-3 недели развиваются дерматологические осложнения: алопеция, ангидроз, глоссит. Антидотом является гексацианоферрат калия.

Представляем собственное клинической наблюдение. Женщина, 38 лет, поступила в стационар с подострой сенсорно-моторной полинейропатией, гепатитом и алопецией. Лабораторные исследования продемонстрировали незначительное повышение уровня печеночных ферментов и тенденцию к снижению уровня калия в крови. Стимуляционная электронейромиография выявила сенсорно-моторную полинейропатию по типу аксонопатии. Учитывая полисистемность поражения, проводилась дифференциальная диагностика между аутоиммунными заболеваниями и острой интоксикацией. Анализ крови на маркеры системных заболеваний соединительной ткани дал отрицательный результат. Токсикологическое исследование сыворотки и мочи выявили резкое повышение уровня таллия. Введение гексацианоферрата калия дало положительный результат. Осмотр пациентки через год показал полное разрешение моторных и сенсорных симптомов, возобновление роста волос.

Интоксикации таллием в настоящее время встречаются крайне редко и представляют трудности для своевременной диагностики. При токсических полинейропатиях необходимо проводить дифференциальную диагностику с интоксикациями другими тяжелыми металлами (свинец, ртуть, кадмий), а также аутоиммунными процессами. Своевременное введение антидота позволяет вывести соединения таллия из организма и получить выраженным положительный клинический эффект.

Ключевые слова: *таллий, интоксикация, полинейропатия, алопеция*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Thallium compounds are extremely toxic. Their mechanisms of toxicity are associated with reduced activity of enzymes involved in glucose metabolism and impaired synthesis of high-energy compounds. Symptoms of thallium intoxication appear 3-4 hours after its ingestion in the form of dyspeptic phenomena. Within 2-5 days, symptoms of nervous system damage appear in the form of sensory polyneuropathy with neuropathic pain syndrome. After 2-3 weeks, dermatological complications develop: alopecia, anhidrosis, glossitis. The antidote is potassium hexacyanoferrate.

Clinical case. A 38-year-old woman was admitted to the hospital with subacute sensorimotor polyneuropathy, hepatitis, and alopecia. Laboratory tests showed a slight increase in liver enzyme levels and a tendency towards decreased blood potassium levels. Stimulatory electroneuromyography revealed sensorimotor polyneuropathy of the axonal type. Given the multisystem involvement, a differential diagnosis was conducted between autoimmune diseases and acute intoxication. A blood test for markers of systemic connective tissue diseases was negative. Toxicological analysis of serum and urine revealed a sharp increase in thallium levels. Administration of potassium hexacyanoferrate yielded a positive result. A follow-up examination of the patient one year later showed complete resolution of motor and sensory symptoms and regrowth of hair.

Thallium intoxications are currently extremely rare and present challenges for timely diagnosis. In cases of toxic polyneuropathies, differential diagnosis should include intoxication with other heavy metals (lead, mercury, cadmium) as well as autoimmune processes. Timely administration of the antidote facilitates the elimination of thallium compounds from the body and yields a pronounced positive clinical effect.

Key words: *thallium, intoxication, polyneuropathy, alopecia*

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GIT — gastrointestinal tract, ATP — adenosine triphosphate, ENMG — electroneuromyography, ECG — electrocardiography, VAS — visual analogue scale, BP — blood pressure, HR — heart rate, RR — respiratory rate, MRI — magnetic resonance imaging, SCTD — systemic connective tissue disorders

Introduction

Thallium is a heavy metal, which is a component of over 20 rare minerals. Thallium does not occur in nature in its pure form; however, synthetically produced thallium salts were previously used in some countries in agriculture as components of pesticides, as well as in medicine and cosmetology. The widespread use of thallium compounds stopped in mid-1970s; however, there are still clinical cases of thallium intoxication [1]. The literature even contains reports of mass thallium poisoning [2].

Thallium salts are highly toxic compounds, which are colourless and odourless. They can penetrate the body during direct skin contact, by inhalation (via lungs), and as a result of swallowing (via gastrointestinal tract (GIT)). Nowadays, poisoning with thallium compounds can occur as a part of occupational intoxication of chemical lab staff, with thallium-contaminated food or biologically active supplements, as well as in case of intentional malicious thallium poisoning [3].

The mechanisms of thallium toxicity are associated with reduced activity of enzymes involved in glucose metabolism and impaired synthesis of adenosine triphosphate (ATP) and other high-energy compounds. It causes impaired ATP-dependent Na/K-ion channel functioning and oedema, swelling and death of excitable tissues. Thallium also modifies riboflavin bioavailability and impairs ATP synthesis. Other mechanisms of thallium toxicity include disruption of the protein keratin through cleavage of cysteine-mediated disulphide bonds; inhibition of protein synthesis due to ribosomal damage, particularly involving the 60S subunit; and demyelination of nerve fibres in both the central and peripheral nervous systems [4].

Clinical manifestations of thallium poisoning can be seen 3–4 hours after swallowing as dyspepsia. Two to five days later, symptoms of nervous system damage appear: sensory polyneuropathy with neuropathic pain syndrome, ataxy, trembling; and the pathological process often involves cranial nerves. Two to three weeks later, dermatological complications develop: hair loss, anhidrosis, glossitis. Examination can reveal Aldrich-Mees lines on nails. Other signs of thallium intoxication include sleep disturbances, acute symptomatic cramps, and headache. Severe cases can result in a coma [5].

Diagnosis is established if thallium is found in body fluids, mostly in urine, and also in hair. In addition, a standard panel of laboratory tests is performed, along with electrocardiography (ECG) and stimulation electroneuromyography (ENMG) [5].

If ingested, thallium intoxication is treated with potassium hexacyanoferrate (Berlin blue), while activated carbon is less efficient. Haemodialysis helps reducing thallium concentration in blood [5].

At present, thallium poisoning is extremely rare, and healthcare professionals often have a low index of suspicion for this condition. This slows down diagnosis and targeted therapy, resulting in severe complications

and even death. Below is a case study of severe thallium intoxication with predominant peripheral nervous system involvement.

Case Study

Female patient U., 38 years old, with higher education, employed, was admitted to the Neurology Ward of G. G. Kuvatov Republican Clinical Hospital (Ufa) on December 5, 2023.

The patient complained of marked leg pain (anteroexternal thigh area, back of shins, and bottom of feet), 7–8 points on the visual analogue scale (VAS); leg weakness, making it difficult to walk; massive hair loss; recurrent abdominal heaviness; unstable stool; tearfulness; sleep disturbances.

She felt ill two weeks ago, when she noticed thigh pain; next day, pain spread to shins and feet; at the same time, she felt stabbing pain in her heart and lump in the throat. One week later, she noticed intensive hair loss.

She was diagnosed with autonomic instability and underwent outpatient treatment at the place of her residence. Since pain in her legs was worsening, the patient was hospitalised to the local district hospital with lumbosacral osteochondrosis (muscular irritation syndrome, attack phase). The therapy (non-steroidal anti-inflammatory drugs, muscle relaxants, vitamins B) was not efficient, and the patient was referred to G. G. Kuvatov Republican Clinical Hospital (Ufa).

The patient denied any chronic diseases.

Upon admission, the patient had hardly any hair left on the hairy part of her head. Positive hair pull test. Growth of the eyebrows and axillary hair was preserved. The skin was pale, with no rashes. The patient had an asthenic body build; body mass index: 17.95 kg/m2; blood pressure (BP): 110/70 mm Hg; heart rate (HR): 85 beats per minute. Cardiac rhythm was regular, heart sounds were normal, and no murmurs were detected. Vesicular breath sounds were present throughout all lung fields, with a respiratory rate of 18 breaths per minute. The abdomen was soft, with moderate tenderness on palpation in the epigastric and pylorobulbar regions. The liver and spleen were not enlarged.

Assessment of neurological status: cranial nerves are intact. A fine postural tremor of the hands was present. Arm muscle strength: 5 points; leg muscle strength: 3 points (proximal), 4 points (distal). Muscular hypotonia in legs was observed. Deep tendon reflexes in the upper extremities were brisk and symmetrical. In the lower extremities, patellar reflexes were absent, and Achilles tendon reflexes were diminished, more prominently on the left. Marked hyperesthesia of the feet was noted. Thigh and shin muscles were painful on palpation. Deep sensation was moderately diminished in lower extremities. No pathological reflexes were observed. There was no bladder or bowel dysfunction. The straight leg raise (Lasegue) test was positive at 60° bilaterally. The patient was emotionally labile.

Bloodwork showed slightly elevated erythrocyte sedimentation rate of 24 mm/h (reference value for women is up to 20 mm/h), CRP — 29.75 mg/L (up to 5 mg/L), ALT — 169.2 U/L, AST — 59.8 U/L (up to 31 U/L). Potassium and sodium levels were at the lower level of reference values: 3.62 and 138 mmol/L, respectively. Thyroid hormone levels were unremarkable. Urinalysis demonstrated leukocyturia (15 cells/μL). Spinal fluid composition was unchanged.

ECG showed sinus rhythm, HR 85 beats per minute; diffuse abnormalities in myocardium repolarisation were observed. Abdomen ultrasound revealed diffuse changes in the liver and deformed gall bladder. Magnetic resonance imaging (MRI) of thoracic and lumbar spine demonstrated degenerative-dystrophic changes, which could not be explained by the present neurological symptoms. Stimulation electroneuromyography showed signs of polyneuropathy, mostly with axonal involvement.

Since the patient had sensorimotor polyneuropathy syndrome, hair loss and liver involvement, differential diagnosis included systemic connective tissue disorder (SCTD) and intoxication with an unknown substance.

The patient was examined by a rheumatologist; her blood was tested for antibodies against double-stranded DNA, C3 and C4 component of the compliment, antinuclear antibody, and anti-mitochondria antibodies. Clinical and laboratory test results ruled out autoimmune diseases.

Biomaterials were tested for toxic microelements: thallium (hair) 1947.58 μg/kg (reference value: below 5 μg/kg), thallium (serum) 127.24 μg/L (below 0.05 μg/L), thallium (urine) 2020.98 μg/L (below 1 μg/L), thallium (nails) 12018.89 μg/kg (below 5 μg/kg). Concentrations of other microelements were within the normal range.

Given the clinical representation and results of toxic microelement tests, thallium intoxication was established. The patient was transferred to Acute Intoxication Ward at another medical institution. Therapy included sodium thiosulfate, unitiol, potassium hexacyanoferrate. Once potassium hexacyanoferrate was administered, the patient noted significant improvement of her condition.

At the 3-month follow-up examination, the patient's condition had improved, with resolution of the pain syndrome, improved gait (she no longer required assistance for walking), and restoration of scalp hair growth. The patient still complained of her leg muscles getting tired very quickly when walking for long distances; numb feeling in her feet; and emotional instability. Clinically,

Figure 1. *Mee's lines on finger nails in 3 months after intoxication*

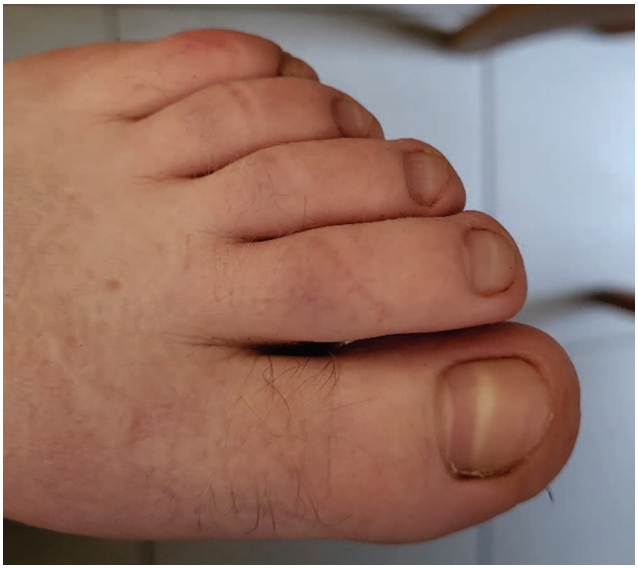

Figure 2. *Mee's lines on toe nails in 3 months after intoxication*

reduced muscle strength in the feet persisted, graded as 4/5, along with autonomic disturbances involving the skin of the feet (increased sweating and coldness to the touch). White transverse lines on the nails of fingers and toes (Aldrich-Mees lines, see Fig. 1 and 2) are worth noting.

Assessment using the Hospital Anxiety and Depression Scale (HADS) revealed subclinical anxiety (score: 10 points). Cognitive functions were normal, as demonstrated by Montreal Cognitive Assessment (29 points). Repeat measurement of thallium levels performed 1.5 months after admission showed concentrations of 10.99 μg/L in urine and 0.509 μg/L in blood serum. Following specific antidote therapy, thallium blood and urine concentrations dropped approximately 180–250 times, but remained 10 times the reference value.

At the 1-year follow-up examination, signs of peripheral autonomic dysfunction in the lower extremities persisted, along with increased emotional lability. A daytime anti-anxiety medication was prescribed, resulting in a favourable clinical response. Sensorimotor polyneuropathy resolved. Aldrich-Mees lines disappeared. The route by which thallium entered the patient's body is still unknown.

Discussion

At present, thallium compounds are hardly used in domestic settings, therefore thallium intoxication is extremely rare. In this clinical case, the patient exhibited multisystem manifestations at the time of hospital admission, and the differential diagnosis primarily included systemic connective tissue diseases and toxic exposures; accordingly, investigations were performed as part of a toxicological screening workup. Toxic polyneuropathy and hair loss are more common for patients undergoing chemotherapy; in this patient, this option was ruled out. Accordingly, it was decided to assess biological specimens for the presence and concentrations of toxic trace elements.

Toxic polyneuropathy can develop after intoxication with heavy metals — lead, arsenic, cadmium, and thallium. Lead-mediated polyneuropathy is characterised by asymmetrical involvement of motor fibres, as well as kidney damage and microcytic anaemia. In earlier years, this polyneuropathy was common; however, abandonment of lead compounds from industrial and domestic use resulted in drastic reduction in incidence of this condition. Arsenic poisoning is primarily characterised by gastrointestinal manifestations, followed by the development of polyneuropathy resembling acute inflammatory demyelinating polyneuropathy. Cadmium poisoning is characterised by polyneuropathy together with internal organ damage, encephalopathy and anosmia (Table 1) [7].

A retrospective analysis demonstrated that the patient had symptoms of acute thallium poisoning. The most common clinical signs are axonal polyneuropathy with pain syndrome and hair loss. Laboratory test results revealed moderate liver damage, as well as tendency to hypokalemia, which is also typical of thallium intoxication. Specific antidote therapy resulted in prompt favourable effect.

Figure 3 shows a diagnostic and therapy algorithm for thallium poisoning.

Table 1. *Differential diagnosis of toxic polyneuropathies caused by heavy metal poisoning*

	Lead Poisoning	Arsenic Poisoning	Cadmium Poisoning	Thallium Poisoning
Source of Exposure	Battery production, lead dust, old paint.	Semiconductors, pesticides, contaminated water/soil.	Battery production, pigments, soldering.	Electronics manufacturing, in the past — pesticides, rodenticides.
Type of Polyneuropathy	Predominantly **motor**. Primarily affects wrist extensors ("wrist drop"). Chronic, slowly progressive.	Predominantly **sensorimotor with neuropathic pain**. Acute or subacute course.	Predominantly **sensory or sensorimotor**.	Severe **sensorimotor polyneuropathy with neuropathic pain**. Rapid progression.
Pathognomonic Signs	Lead line on gums (Burton's line). Microcytic anemia with basophilic stippling. Abdominal pain («lead colic»), constipation.	Mees' lines (leukonychia) — white transverse stripes on nails. Skin manifestations (hyperkeratosis, melanosis). GI involvement resembling cholera (vomiting, diarrhea).	Proteinuria (renal tubular damage). Emphysema, osteomalacia. Olfactory disturbances.	**Hair loss (alopecia)** 2-3 weeks after poisoning. Mental disorders.
Laboratory Diagnostics	Blood (lead in whole blood).	Urine (24-hour urine for arsenic). Hair/nails (in chronic poisoning).	Urine (cadmium in urine). Blood (reflects recent exposure).	Urine (thallium in urine). Blood (in acute phase).
Antidotes	Ethylenediaminetetraacetic acid (EDTA); D-penicillamine	Unithiol; D-penicillamine	Ethylenediaminetetraacetic acid (EDTA)	Potassium hexacyanoferrate (II) («Prussian blue»)

Comparison with previously published reports of thallium poisoning showed that the clinical case presented here is representative of the typical manifestations of this condition. However, unlike cases of more severe poisoning, this patient did not have any signs of cranial nerve involvement manifesting as visual and oculomotor disorders, nystagmus. The patient did not have clear manifestations of nephropathy, whereas high thallium concentrations in the body cause acute kidney damage, which leads to poor outcomes [4].

Conclusion

This clinical case demonstrates the importance of timely diagnosis of thallium intoxication. Acute multisystem involvement affecting the peripheral nervous system, the skin and its appendages, as well as the liver and kidneys, should prompt screening for thallium intoxication, even in the absence of a history of exposure to chemical agents. Once thallium intoxication has been confirmed, immediate therapy with potassium hexacyanoferrate should be initiated.

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

Akhmadullina R.F.: Data collection and analysis, preparation and writing of the article text

Kutlubaev M.A.: Conceptualization and design of the article, editing, final approval of the manuscript

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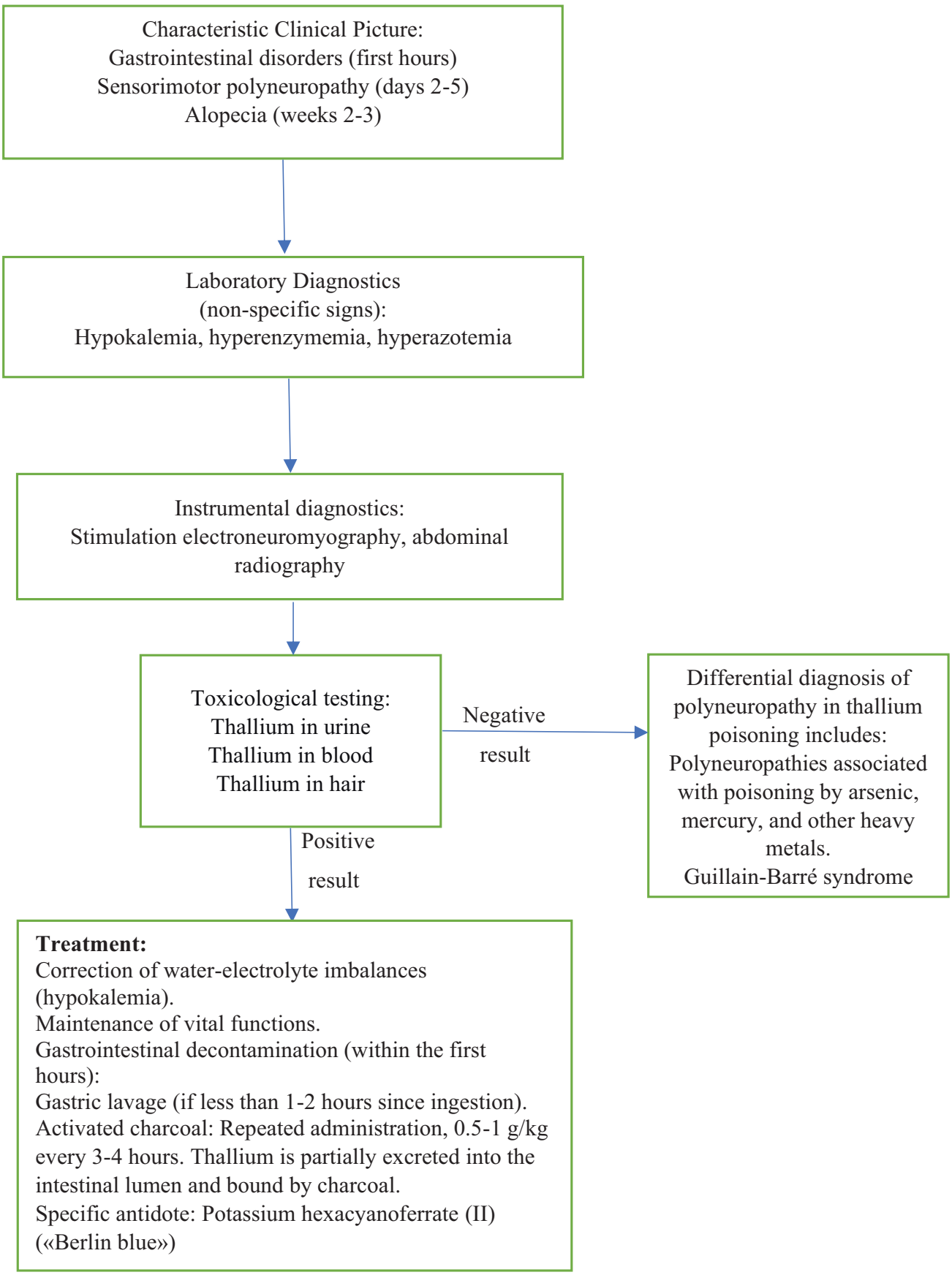

Figure 3. *Diagnostic and Treatment Algorithm for Thallium Poisoning*

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OVERLAP-СИНДРОМ — РЕДКОЕ СОЧЕТАНИЕ ТРЕХ АУТОИММУННЫХ ПАТОЛОГИЙ

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Overlap-Syndrome — A Rare Combination of Three Autoimmune Pathologies

Резюме

Совершенствование методов диагностики и возможностей современной медицины обуславливают более глубокое изучение аутоиммунной патологии. В клинической практике всё чаще стали встречаться случаи сочетанного течения двух и более иммунологических заболеваний, что называют термином «overlap-синдром» или «синдром перекрёста». До сих пор отсутствуют данные о конкретных причинах развития overlap-синдрома, среди наиболее вероятных версий является сочетание генетических изменений, в том числе разнообразия аллелей human leukocyte antigen (HLA), с триггерными факторами извне. Особенности данного синдрома заключаются в трудностях дифференциально-диагностического поиска из-за многообразия симптомов. Несвоевременная верификация диагноза приводит к позднему назначению лечения и менее благоприятному отдалённому прогнозу. В клинической практике наиболее часто встречается сочетание системной склеродермии или системной красной волчанки с ревматоидным артритом. В данной статье приводится пример overlap-синдрома у пациентки 69 лет с тремя аутоиммунными патологиями — системная склеродермия, синдром Шегрена (СШ) и первичный билиарный холангит с полиорганным поражением (лёгкие, кожа, желудочно-кишечный тракт, слюнные железы, сосуды, нервная система). Пациентка имела длительный анамнез синдрома Рейно, а также первичного билиарного холангита. За 2 года до обращения у пациентки был диагностирован синдром Шегрена, в 2025 году — лимитированная форма системной склеродермии. Таким образом, у пациентки в течение жизни развились сразу 3 аутоиммунные патологии, включенные в overlap-синдром. Специалистам следует проявлять повышенное внимание к пациентам с длительным анамнезом ревматологического заболевания для своевременного выявления других аутоиммунных патологий и начала своевременного лечения для предотвращения развития осложнений.

Ключевые слова: *overlap-синдром, синдром перекреста, системная склеродермия, синдром Шегрена, первичный билиарный холангит, прогрессирующий системный склероз*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

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Abstract

The improvement of diagnostic methods and the possibilities of modern medicine lead to a deeper study of autoimmune pathology. In clinical practice, cases of a combined course of two or more immunological diseases have become increasingly common, which is called the term "overlap-syndrome" or "crossroads syndrome". There is still no data on the specific causes of the overlap-syndrome, among the most likely versions is a combination of genetic changes, including the diversity of human leukocyte antigen (HLA) alleles, with external trigger factors. The features of this syndrome are the difficulties of differential diagnostic search due to the variety of symptoms. Untimely verification of the diagnosis leads to a late appointment of treatment and a less favorable long-term prognosis. In clinical practice, a combination of systemic scleroderma or systemic lupus erythematosus

with rheumatoid arthritis is most common. This article provides an example of the overlap-syndrome in a 69–year-old patient with three autoimmune pathologies — systemic scleroderma, CABG, and primary biliary cholangitis with multiple organ damage (lungs, skin, gastrointestinal tract, salivary glands, blood vessels, and nervous system). The patient had a long history of Raynaud's syndrome, as well as primary biliary cholangitis. Two years before the treatment, the patient was diagnosed with Sjogren's syndrome, and in 2025, a limited form of systemic scleroderma. Thus, during her lifetime, the patient developed 3 autoimmune pathologies included in the overlap-syndrome. Specialists should pay increased attention to patients with a long history of rheumatological disease in order to detect other autoimmune pathologies in a timely manner and initiate timely treatment to prevent the development of complications.

Key words: *overlap-syndrome, systemic scleroderma, Sjogren's syndrome, primary biliary cholangitis, progressive systemic sclerosis*

Conflict of interests
The authors declare no conflict of interests

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Conformity with the principles of ethics
The patient consented to the publication of laboratory and instrumental research data in the article « Overlap-Syndrome — A Rare Combination of Three Autoimmune Pathologies» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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AMA — antimitochondrial antibodies, ANA — antinuclear antibodies, ACA — anticentromere antibodies, RA — rheumatoid arthritis, SSD — systemic scleroderma, SLI — systemic lupus erythematosus, SS — Sjögren's syndrome, PBC — primary biliary cholangitis

Introduction

Overlap syndrome refers to a group of diseases and clinical conditions that fulfill the classification criteria of two or more immune-mediated inflammatory rheumatic diseases [1]. The development of these systemic autoimmune rheumatic diseases may occur either simultaneously or sequentially, and characteristic immunological abnormalities are not invariably present [2]. The term was first introduced to describe patients with a combined and difficult-to-differentiate clinical presentation of rheumatoid arthritis (RA) together with systemic lupus erythematosus (SLE) or systemic scleroderma (SSD) [3]. The exact cause of the coexistence of multiple rheumatic diseases remains unknown; however, most investigators suggest that overlap syndrome arises from a genetic predisposition triggered by environmental factors. Several studies have highlighted the role of genes within the human leukocyte antigen (HLA) system in the pathogenesis of overlap phenotypes [2]. A characteristic feature of overlap syndrome is the subtle and often attenuated presentation of symptoms, which may result in delayed diagnosis and initiation of treatment, thereby adversely affecting long-term prognosis.

It is important to distinguish overlap syndrome from mixed connective tissue disease. Mixed connective tissue disease is an autoimmune disorder characterised by clinical features of several systemic autoimmune rheumatic diseases in combination with high titers of antibodies directed against soluble nuclear ribonucleoprotein [2]. In clinical practice, however, the differential diagnosis between these conditions may be challenging. Cases of overlap syndromes have been described not only in rheumatology. Well-recognised examples include overlap between respiratory diseases, such as bronchial asthma and chronic obstructive pulmonary disease, as well as gastrointestinal disorders, including autoimmune hepatitis and primary biliary cirrhosis. The true prevalence of overlap syndrome remains uncertain; however, it is estimated to account for up to 20 % of rheumatic diseases [2]. At present, no specific management guidelines exist for this group of patients, and treatment is primarily based on controlling the manifestations driven by the underlying autoimmune process.

Systemic sclerodermas (SSc), also known as progressive systemic sclerosis, is a chronic multisystem disease characterised by a staged course and by vasospastic vascular reactions resembling Raynaud's phenomenon, as well as an obliterative vasculopathy associated with ischaemic tissue injury. The disease is accompanied by specific autoimmune abnormalities that promote fibroblast activation and excessive collagen deposition in tissues, ultimately leading to progressive fibrosis and organ involvement [4]. SSD is associated with the highest mortality among rheumatic diseases [5, 6]. Despite this, early diagnosis of SSD remains challenging because of its highly heterogeneous clinical presentation. Consequently, the correct diagnosis is often established only at advanced stages of the disease, when patients have already developed severe and sometimes life-threatening complications [7]. Antinuclear antibodies (ANA), which are detected in 90–95 % of patients, are commonly used

as diagnostic markers of SSD; however, these antibodies are not disease-specific and may also be present in a variety of other pathological conditions. Less specific markers include anticentromere antibodies (ACA) and anti-topoisomerase I antibodies (anti-Scl-70), which are detected in approximately 60 % of patients, particularly among those with cardiopulmonary complications. Antibodies against RNA polymerase III are identified less frequently, mainly in patients with diffuse systemic scleroderma, and are associated with the development of scleroderma renal crisis, a form of acute kidney injury [8]. In addition, several autoantibodies have been described in approximately 10 % of patients who are seronegative for the classical markers. These include anti-eIF2B antibodies, the anti-RuvBL1/2 complex, anti-U11/U12 RNP antibodies, and anti-BICD2 antibodies [9].

Sjögren's syndrome (SS) is an autoimmune disease of unknown etiology characterised predominantly by involvement of the salivary and lacrimal glands, resulting in dry mouth (xerostomia) and dry eyes (xerophthalmia), with possible involvement of the respiratory tract, gastrointestinal tract, and vagina. SS can be primary or secondary. Primary SS develops independently and is not associated with other diseases, whereas secondary SS occurs in patients with an underlying rheumatic disorder, such as SLI, RA or SSD [9]. The association between SS and SSD is thought to be related to the presence of anticentromere antibodies. In such cases, Raynaud's phenomenon is a common manifestation of SS [10].

Primary biliary cholangitis (PBC) is a rare chronic autoimmune cholestatic liver disease characterised by T-lymphocyte-mediated injury of the intrahepatic biliary epithelial cells, which may ultimately lead to liver cirrhosis. A distinctive feature of PBC is its frequent association with other autoimmune diseases and syndromes [11]. Detection of antimitochondrial antibodies (AMA), directed against the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2) located on mitochondrial membranes, represents a highly specific diagnostic marker of the disease [11]. PBC most commonly coexists with autoimmune hepatitis, whereas the prevalence of concomitant PBC and SSD occurs in only 2–4 % of cases [12].

A search of the PubMed database covering the period from 1993 to 2025 using the terms "systemic scleroderma, Sjögren's syndrome, primary biliary cholangitis overlap syndrome" yielded 14 records. However, none of the retrieved publications described cases involving the coexistence of all three conditions simultaneously. In the present article, we describe a clinical case of a patient with an overlap syndrome comprising the coexistence of all three aforementioned conditions, i.e., systemic scleroderma, Sjögren's syndrome, and primary biliary cholangitis with multisystem organ involvement.

Clinical Case Report

A 69-year-old woman was admitted to the rheumatology department in May 2025 with complaints of dry mouth and dry eyes, skin dryness, pruritus, muscle cramps affecting both the upper and lower extremities, and dysphagia manifested by difficulty swallowing dry food. In addition, the patient had recently begun to experience exertional dyspnea of mixed origin and an occasional dry cough during routine physical activity. Two days prior to admission, she reported a single episode of hemoptysis and the appearance of black stools.

On admission, the patient was in a moderately severe condition. The skin was of normal colour but appeared indurated on palpation, with excoriations present on both the upper and lower extremities and reduced skin turgor. Physical examination revealed bilateral Dupuytren's contractures, characteristic perioral tightening with a "purse-string" appearance of the mouth, palmar capillaritis, and telangiectasias on the anterior chest wall. The modified G.P. Rodnan skin score was 2 points, indicating moderate skin thickening, with the skin being difficult to lift into a fold. Pulmonary examination revealed harsh breath sounds with a respiratory rate of 18 breaths per minute and SpO_2 saturation of 98 %. Breath sounds were present throughout both lungs, and fine inspiratory crackles were auscultated bilaterally at the lung bases up to the level of the inferior angles of the scapulae. Heart sounds were muffled, rhythm was regular, and no murmurs were detected. Blood pressure was 120/80 mm Hg, and heart rate was 68 beats per minute. The tongue was dry and moderately coated with a yellowish deposit at the root. The abdomen was soft and non-tender on palpation, with no signs of peritoneal irritation. On percussion, the liver did not extend below the costal margin; however, palpation revealed a nodular, firm, and painless lower liver edge.

According to the medical history, Raynaud's phenomenon was diagnosed in 1984. In 2023, following the onset of xerostomia and xerophthalmia, the patient underwent further evaluation and was diagnosed with Sjögren's syndrome by a rheumatologist. The diagnosis was based on characteristic symptoms, a positive ANA test, elevated anti-LA/SS-B antibody levels (>200 U/mL; reference range 0–15 U/mL), as well as findings from sialography, sialometry, and salivary gland biopsy. The patient also had a confirmed diagnosis of PBC, which had progressed to Child-Pugh class B subcompensated liver cirrhosis. AMA were positive in February 2025. The disease was complicated by intrahepatic portal hypertension with esophageal and gastric varices and recurrent episodes of upper gastrointestinal bleeding. The patient has been receiving long-term therapy with calcium and vitamin D supplements, denosumab according to the prescribed regimen, spironolactone 50 mg daily, ursodeoxycholic acid 500 mg twice daily, L-ornithine

L-aspartate 3 g daily, and methylprednisolone 4 mg daily. The patient repeatedly refused treatment with hydroxychloroquine. A timeline of the patient's medical history is presented in Figure 1.

Laboratory investigations performed during hospitalisation revealed normochromic normocytic anaemia, with a haemoglobin level of 72 g/L (reference range: 120–140 g/L), decreased hematocrit of 28.1 % (35–47 %), thrombocytopenia with a platelet count of 135 × 10^9/L (180–320 × 10^9/L), whereas the white blood cell count was within the normal range at 7.64 × 10^9/L (5–9 × 10^9/L). Liver transaminase levels were within the reference range. Immunological testing demonstrated a positive antinuclear factor (ANF) titer of 1:640 (reference value <1:160) and positive ACA.

Computed tomography (CT) of the chest showed signs of bronchiolitis. Echocardiography revealed normal systolic and mean pulmonary artery pressures.

Abdominal ultrasonography demonstrated a moderate amount of free intraperitoneal fluid, diffuse cirrhotic changes of the liver, reactive oedema of the perivesicular tissue, and diffuse changes of the pancreas.

Ultrasonography of the parotid and submandibular salivary glands demonstrated diffuse changes characterised by moderately heterogeneous glandular architecture and reduced vascularisation of the parenchyma.

Esophagogastroduodenoscopy (EGD) revealed grade III esophageal varices according to the Sherzinger classification, as well as gastric varices (GOV1/GOV2 according to the Sarin classification). In addition, erosive reflux esophagitis was observed, with edematous esophageal mucosa and linear erosions covered with fibrin deposits involving all walls of the esophagus. Multiple flat erosions measuring up to 0.3 cm in diameter and covered with fibrin were present throughout the antrum of the stomach, while flat elevated hyperplastic lesions were identified in the gastric fundus. Liver elastography demonstrated stage F4 fibrosis according to the METAVIR scoring system.

Given the long-standing history of Raynaud's phenomenon, capillaroscopy was performed. The examination revealed an irregular arrangement of capillaries with dilated loops, reduced capillary density, and extensive avascular areas.

Thus, taking into account the presence of bronchiolitis, Raynaud's phenomenon, and cutaneous manifestations (indurative skin edema and a characteristic "purse-string" appearance of the mouth), together with positive immunological markers, the patient was diagnosed with SSD within the framework of an overlap syndrome comprising systemic scleroderma, primary biliary cholangitis, and Sjögren's syndrome (SSD + PBC + SS).

The diagnosis of SSD was established according to the current classification criteria (Table 1) of ACR/EULAR (American College of Rheumatology/European League Against Rheumatism Systemic Sclerosis classification criteria).

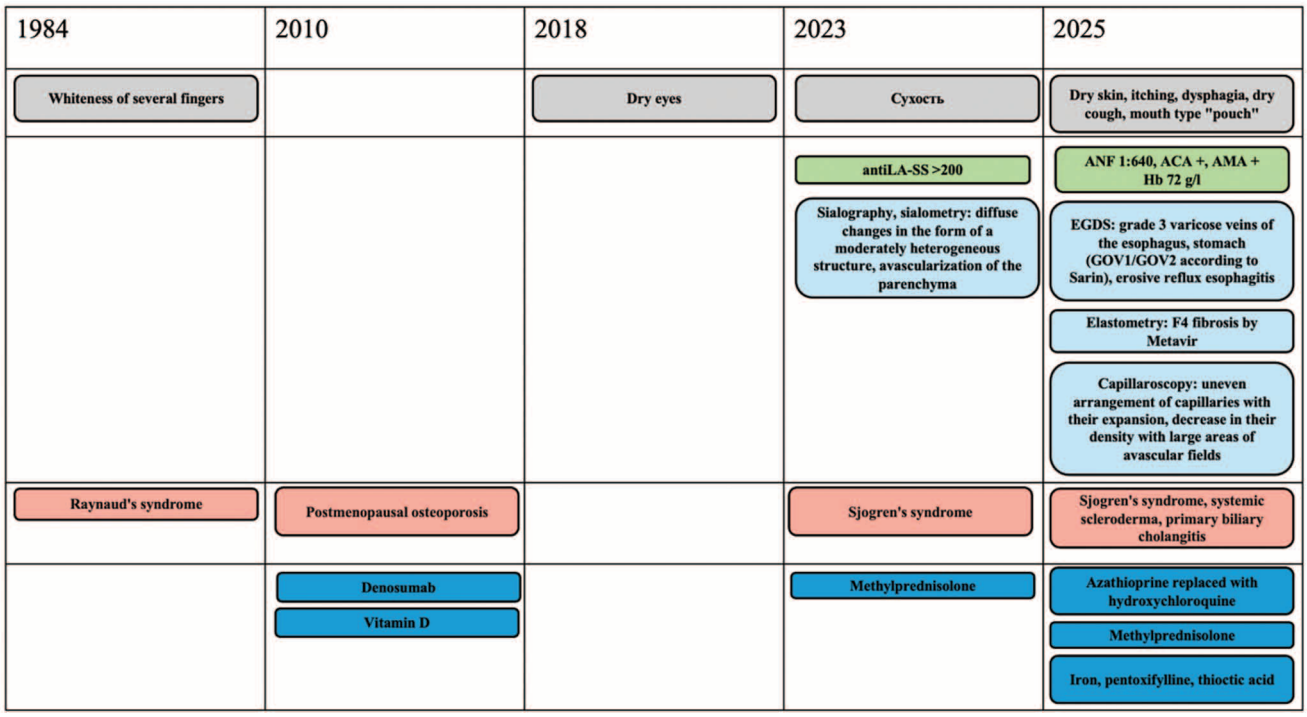

Figure 1. *Medical history of the patient*

Abbreviations shown in the figure: ANF — antinuclear factor, ACA — anticenter antibodies, AMA — antimitochondrial antibodies, EGDS — esophagogastroduodenoscopy, Hb — hemoglobin

Table 1. *Classification criteria of the 2013 ACR/EULAR SSD*

Parameter	Signs	Scores
Thickening of the skin of the fingers of both hands, extending proximally to the metacarpal joints (sufficient criterion)	-	9
Thickening of the skin of the fingers (only the maximum score is taken into account)	Dense swelling of the fingers	2
	Sclerodactyly (distal to the metacarpophalangeal joints)	4
Fingertip changes (only the maximum score is taken into account)	Ulcers of the fingertips	2
	Scarring on the fingertips	3
Telangiectasia	-	2
Changes in capillaries of the footbed	-	2
Pulmonary arterial hypertension and/or interstitial lung disease	Increased pressure in the pulmonary artery according to EchoCG data	2
	Signs of interstitial lung damage according to CT	2
The Raynaud phenomenon	-	3
Autoantibodies characteristic of SSD	Anti-centromeric	3
	Antibodies to topoisomerase I	3
	Antibodies to RNA polymerase III	3
Total		23 из 30

Note. 9 points or more is a diagnosis of reliable SSD. The criteria available to this patient are highlighted in color.
Abbreviations in the table: EchoCG- echocardiography, CT — computed tomography, RNA — ribonucleic acid, SSD — systemic scleroderma

Clinical diagnosis:

Primary diagnosis: overlap syndrome. Limited systemic scleroderma, chronic course, with involvement of the lungs (bronchiolitis), vasculature (Raynaud's phenomenon, capillaroscopic abnormalities, telangiectasias), gastrointestinal tract (esophageal hypomotility), skin (sclerodactyly with puffy fingers; modified G.P. Rodnan skin score of 2 points), nervous system (polyneuropathy), and immunological abnormalities (positive ANF and ACA). Sjögren's syndrome with involvement of the lacrimal glands (xerophthalmia, dry keratoconjunctivitis), salivary glands (chronic parenchymal parotitis, grade 3 xerostomia), and immunological abnormalities (positive ANF). Primary biliary cholangitis with progression to liver cirrhosis, Child-Pugh class B, with positive AMA-M2.

Complications: portal hypertension; grade III esophageal varices according to the Sherzinger classification; gastric varices (GOV1/GOV2 according to the Sarin classification); portal hypertensive gastropathy; hypersplenism syndrome with latent thrombocytopenia; grade I hepatic encephalopathy; and moderate normochromic normocytic anemia.

Comorbidities: chronic non-atrophic Helicobacter pylori-negative gastritis; gallbladder polyp; hepatic cyst; postmenopausal osteoporosis (T-score = −3.1), with a 10-year probability of osteoporotic fractures of 11.6% according to the FRAX tool.

Given the coexistence of three autoimmune diseases, initiation of azathioprine therapy at a dose of 50 mg/day with subsequent dose titration was recommended. Continuation of methylprednisolone at a dose of 4 mg/day was advised, together with the addition of iron supplementation, thioctic acid, and pentoxifylline.

In June 2025, azathioprine was replaced with hydroxychloroquine at a dose of 200 mg/day because of generalised weakness and loss of appetite. At follow-up in September 2025, the patient reported satisfactory well-being, with regression of muscle cramps, pruritus, and dyspnea. Biochemical blood tests performed in September 2025 demonstrated a slight elevation of alanine aminotransferase to 40.5 U/L (reference range 0–34 U/L), aspartate aminotransferase to 34.5 U/L, and gamma-glutamyl transferase to 56.4 U/L.

Discussion

Despite the fact that the diagnosis of autoimmune diseases has been greatly facilitated by the availability of serological testing for a wide range of autoantibodies, the identification of overlap syndromes remains challenging because of the distinctive features of their onset and clinical course.

The pathogenic mechanisms underlying the coexistence of multiple autoimmune diseases are not fully understood. It has been suggested that defects in immune regulation associated with genetic polymorphisms and environmental factors play a key role in their development.

SS is frequently associated with other rheumatic diseases. According to a retrospective study, among 1,119 patients with SS, 308 (27.5 %) were diagnosed with PBC [13].

The coexistence of three autoimmune diseases is uncommon. Date K. et al. reported a case of acute phlegmonous esophagitis caused by Candida spp. in a patient with SS, primary biliary cholangitis, and autoimmune hepatitis [14]. This case highlighted the importance of close monitoring of patients with multiple autoimmune disorders and regular assessment of laboratory parameters to prevent infectious complications, which may arise due to immune dysfunction.

Han H.S. et al. described a patient with PBC and autoimmune hepatitis who subsequently developed SSD. The authors emphasised the common pathogenetic background shared by these diseases [15].

Iikuni N. et al. reported a patient with SSD and SS who later developed primary biliary cirrhosis and Graves' disease [16]. In contrast to the present case, our patient initially developed SS and PBC, with manifestations of SSD appearing later in the disease course. No previous reports describing the coexistence of these three autoimmune diseases have been published. This observation further underscores the importance of extending the diagnostic workup in patients with an already established autoimmune disease, particularly when new clinical manifestations emerge.

Conclusion

A distinctive feature of overlap syndrome is the ability of each autoimmune disease to modify the clinical manifestations of the others, which considerably complicates timely diagnosis and appropriate treatment. Therefore, clinicians should remain aware of the heterogeneous nature of autoimmune disorders and consider the possibility of an overlap syndrome in patients.

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Яровой М.Д.: написание статьи, анализ клинического случая, обзор литературы, перевод на английский язык

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Шеменкова В.С.: написание статьи, редактирование текста

Резник Е.В.: идея, руководство, организация работы, редактирование рукописи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Iarovoi M.D.: article writing, literature review, case study analysis, translation into English

Khachirova E.A.: case study selection, selection and processing of the visual materials, text editing.

V.S. Shemenkova: article writing, text editing

Reznik E.V.: idea, leadership, work organization, edition

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ОТ СИНДРОМА ШЕГРЕНА К СИСТЕМНОЙ СКЛЕРОДЕРМИИ: КЛИНИЧЕСКИЙ СЛУЧАЙ МАНИФЕСТАЦИИ ЗАБОЛЕВАНИЯ С ТЯЖЕЛОЙ ЛЕГОЧНОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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From Sjogrens' Syndrome to Systemic Scleroderma: A Clinical Case of Disease Manifestation with Severe Pulmonary Arterial Hypertension

Резюме

Своевременное распознавание и лечение такого опасного осложнения системных заболеваний соединительной ткани как легочная артериальная гипертензия имеет крайне важное значение, так как данные пациенты имеют неблагоприятный прогноз.

В данной статье врачи-кардиологи демонстрируют клинический случай развития тяжелой легочной артериальной гипертензии высокого функционального класса и перикардиального выпота у пациентки 60 лет с подозрением на синдром Шегрена. Была проведена оценка клинического состояния и аутоиммунных маркеров, выполнены эхокардиография, компьютерная и магнитно-резонансная томографии, коронароангиография и зондирование правых отделов сердца, офтальмологическое тестирование, а также биопсия, ультразвуковое исследование и сцинтиграфия слюнных желез. В последующем верифицированы синдром Рейно и склередема, а также специфические иммунологические нарушения, что позволило установить диагноз лимитированной формы системной склеродермии, назначить иммуносупрессивную терапию и установить вторичный характер синдрома Шегрена.

Результаты проведенной диагностики, подтвержденные заключениями курирующих врачей, могут быть обсуждены медицинским сообществом и носят полезный прикладной характер для врачей-кардиологов, которые редко встречаются с ревматологическими заболеваниями в рутинной практике.

Ключевые слова: *Синдром Шегрена, системная склеродермия, CREST-синдром, легочная артериальная гипертензия, диагностика, клинический случай*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Пациентка дала согласие на опубликование данных лабораторных и инструментальных исследований в статье «ОТ СИНДРОМА ШЕГРЕНА К СИСТЕМНОЙ СКЛЕРОДЕРМИИ: КЛИНИЧЕСКИЙ СЛУЧАЙ МАНИФЕСТАЦИИ ЗАБОЛЕВАНИЯ С ТЯЖЕЛОЙ ЛЕГОЧНОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ» для журнала «Архивъ внутренней медицины», подписав информированное согласие

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Abstract

Timely recognition and treatment of pulmonary arterial hypertension, a dangerous complication of systemic connective tissue diseases, is extremely important, as these patients have a poor prognosis.

In this article, cardiologists present a clinical case of a diagnostic search for the cause of severe pulmonary arterial hypertension of high functional class and pericardial effusion in a 60-year-old female patient with suspected Sjögren's syndrome. An assessment of the clinical status and autoimmune markers was performed, echocardiography, computed tomography and magnetic resonance imaging, coronary angiography and right heart catheterization, ophthalmological testing, as well as biopsy, ultrasound examination and salivary gland scintigraphy were performed. Subsequently, Raynaud's syndrome and scleredema, as well as specific immunological disorders, were verified, which made it possible to diagnose a limited form of systemic scleroderma, prescribe immunosuppressive therapy, and establish the secondary nature of Sjögren's syndrome.

The diagnostic results, supported by the opinions of the supervising doctors, can be discussed by the medical community and are of practical use for cardiologists, who rarely encounter rheumatological diseases in their routine practice.

Key words: *Sjögren's syndrome, systemic sclerosis, CREST syndrome, pulmonary arterial hypertension, diagnostics, clinical case*

Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

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BP — blood pressure, CTD — connective tissue disorder, IFN — interferon, CAG — coronary arteriography, PAH — pulmonary artery hypertension, MSCT — multispiral computed tomography, SLI — systemic lupus erythematosus, SSD — systemic scleroderma, SS — Sjögren's syndrome, PATE — pulmonary artery thromboembolia

Introduction

Sjögren's syndrome (SS) is a chronic systemic autoimmune inflammatory disease, characterised by T-cell-mediated B-cell hyperactivity and cytokine production, the clinical presentation of which includes oral and ocular dryness, caused by local lymphocyte infiltration, sometimes with joint paint and fatigue. The disease can progress from asymptomatic adenopathy to systemic manifestations or even lymphoma. More often, clinical cases (up to 80 %) present with very dry mucous membranes, especially in the mouth and eyes; however, the disease may involve skin, nose, throat, and vagina. SS may present without significant involvement of the salivary glands, instead affecting other exocrine glands or systemic organs. This condition is called extraglandular SS; it has been described in literature sources and is reported in up to 20 % of patients with primary SS [1].

Historically, SS was classified into two categories: where symptoms appear independently (primary SS); and where symptoms go together with other systemic autoimmune diseases (secondary SS). The most common SS-associated conditions are rheumatoid arthritis, systemic lupus erythematosus (SLE) and systemic scleroderma (SSD) [2]. Currently, clinical studies aim mostly at primary SS [3]. Based on the most robust evidence from large population-based studies, the prevalence of primary SS is estimated to range from 0.01 % to 0.05 %. This condition affects primarily women; the women-to-men ratio varies from 9:1 to 28:1. Disease onset typically occurs between 40 and 50 years of age; in cases where the diagnosis is established in younger patients, at around 35 years of age, the disease often presents with fever and lymphadenopathy [4]. The majority of non-HLA genetic variants related to susceptibility to primary SS are associated with interferon (IFN) pathways or IFN-stimulated genes. Recent studies show that the long non-coding RNA XIST (X-inactive specific transcript), which is specific to women, is a unique and abundant source of ligands of Toll-like receptor (TLR) 7 and IFN activator in SLE patients. This gender-related difference can be the cause of gender-based predisposition not only to SLE, but also to primary SS [5].

Pulmonary artery hypertension (PAH) is a rare manifestation of SS and is a significant cause of death in such cases. SS patients have a higher risk of PAH, which is likely to be associated with chronic inflammation, vascular dysfunction and immune-mediated endothelial damage, which can contribute to higher pressure in the pulmonary artery and right ventricular overload [6]. By the time the classical symptoms of PAH become apparent, it is often already too late, as morphological and structural changes in the pulmonary vasculature have already occurred.

Clinical Case Report

Patient N., 60 years of age, was admitted to the hospital with suspected pulmonary artery thromboembolia (PATE). The patient complained of shortness of breath at minimal physical activity and at rest, with shortness of breath getting worse when lying on her left side; edematic lower extremities; constricting, pressing retrosternal pain at minor physical activity; dry mouth.

Her medical history did not show any neurological or rheumatologic diseases, cramps or head injuries. The family history did not indicate any autoimmune diseases. Also, there were no data on the use of any anticholinergic medications. The patient denied a history of mucosal ulcers, fever, arthralgia, photosensitivity, thrombosis or thrombophlebitis, and miscarriages.

Her medical history included an adenoma of the right thyroid lobe, cardia insufficiency, cardia-fundal prolapse, a sliding hiatal hernia, and chronic antral gastritis. In 2006, she underwent cholecystectomy due to an exacerbation of calculous cholecystitis. The patient had also been diagnosed with arterial hypertension (AH), with blood pressure values reaching up to 160/100 mm Hg. She did not take antihypertensive medications regularly. Since April 2025, the patient had been having episodes of pronounced shortness of breath. Subsequently, she noted decreased exercise tolerance and shortness of breath during walking at a usual pace. On 19 August 2025, she was evaluated by a local cardiologist, and ischaemic heart disease was suspected. The patient was advised to undergo coronary arteriography (CAG), and the following medications were prescribed: Torasemide 10 mg, Lisinopril 5 mg, Ivabradine 2.5 mf twice daily, isosorbide mononitrate 40 mg twice daily. Later, amlodipine and trimetazidine were added. The patient did not notice any improvement from the therapy.

In September 2025, the patient noted progressive worsening of shortness of breath, which began to occur after walking approximately 10 steps at a slow pace, as well as a marked decline in exercise tolerance, lower extremity oedema, and pressing, constricting retrosternal pain. The patient reported improvement in her shortness of breath and chest pain when lying in the prone position or on her right side. On September 27, 2025, multispiral computed tomography (MSCT) of the chest was performed, revealing signs of moderate hydropericardium (pericardial effusion up to 15 mm). Areas of ground-glass opacification within the lung parenchyma could not be excluded, although assessment of the pulmonary parenchyma was limited. During the outpatient visit, an ambulance was called, and the patient was transported to Regional Clinical Hospital No. 1 in Tyumen.

Objective findings: the patient's consciousness was clear. The body mass index was 28 kg/m2. The body temperature was 36.4 °C. The oral mucosa was clean, pink, and dry, with no defects. The skin was clean, pale. Marked peripheral oedema involving the feet and lower legs extending up to the knees was present. Respiratory rate was 20 breaths per minute. Oxygen saturation was 94 % while receiving supplemental oxygen. Breath sounds were vesicular but diminished at the lung bases. No crackles or wheezes were auscultated. Shortness of breath was mixed at rest. The heart rate was 96 beats per minute. The pulse was rhythmical. Blood pressure measured in the left arm was 170/90 mm Hg. Heart sounds were regular and muffled, with an accentuated second heart sound over the pulmonary artery. No cardiac murmurs were auscultated. The tongue was dry and uniformly coated with a thin film. The abdomen was soft and non-tender. The liver edge was palpable at the costal margin. Bowel and bladder function were unremarkable.

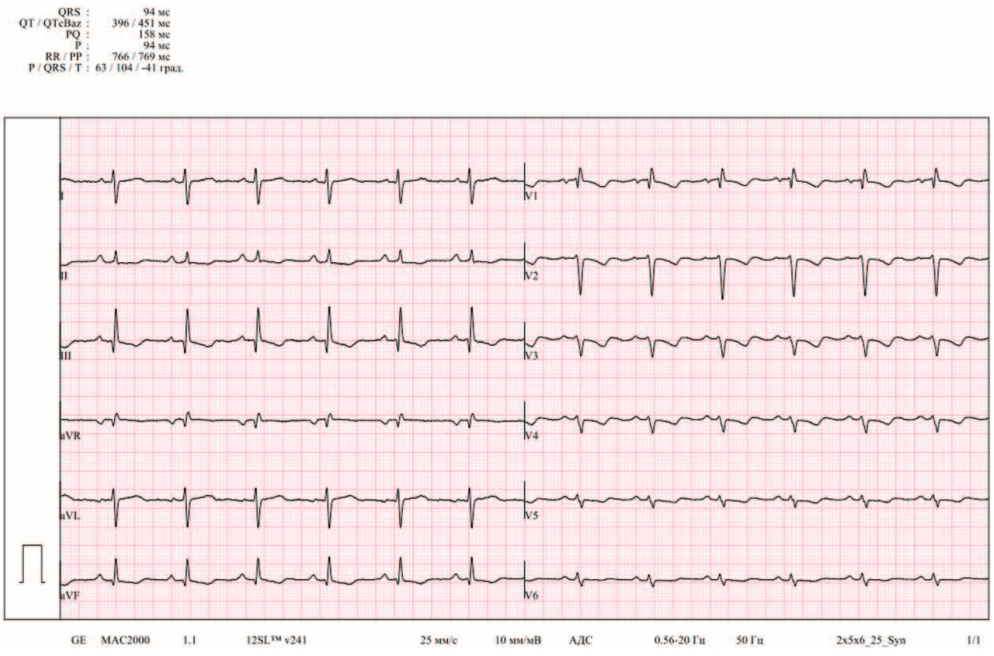


Figure 1. *Electrocardiogram from October 1, 2025.*

The patient had not undergone gynaecological examination; however, she denied vaginal dryness.

Given the elevated troponin levels (troponin I, 121 ng/L; reference range, 0.1–20.3 ng/L), a diagnostic CAG was performed to further assess the coronary anatomy. CAG dated September 30, 2025 did not reveal any visible pathology of the coronary arteries. Electrocardiography demonstrated sinus rhythm, a vertical electrical axis of the heart, incomplete right bundle branch block, low QRS voltage in the precordial leads, an S-wave pattern in the chest leads, and diffuse repolarisation abnormalities (Figure 1).

Table 1. *Patient's blood parameters from October 1, 2025.*

Test	Meaning	Reference
Sodium uretic peptide	3,298 pg/ml	0.00–464.20 pg/mL
Procalcitonin	1.1 ng/ml	0.000–2.000 ng/mL
C-reactive protein	0.657 mg/dl	< 0.5 mg/dL
Free thyroxine	12.6 pmol/l	9–22 pmol/L
Thyroid-stimulating hormone	0.455 µIU/ml	0.350–5.100 µIU/mL
CA 125	17.9 U/ml	0.0–35.0 U/mL
CA 19-9	14.11 units/ml	0.00–40.00 U/mL
Carcinoembryonic antigen	1.5 ng/ml	Non-smokers 0–5 ng/mL Smokers 0–10 ng/mL

CA 125 — cancer antigen 125, CA 19-9 — cancer antigen 19-9.

Table 2. *Immunological examination of the patient from October 9, 2025.*

Test	Meaning	Reference
Rheumatoid factor	5.9 IU/ml	0.1–14.0 IU/ml
Antinuclear antibody screening (ANA)	2.979 Positive	< 0.9 — Negative (normal)
Anti-double-stranded DNA antibodies	9.62 IU/ml	0.00–25.00 IU/ml
Anti-SS-A 52 antibodies	10 IU/ml Borderline (+)	<10 IU/ml
Anti-nucleosome antibodies	0.00 IU/ml Not detected	Absence
Anti-Scl-70 antibodies	0.00 IU/ml Not detected	Absence
Antibodies to the SS-A/Ro family	0.00 IU/ml Not detected	Absence
Antibodies to SS-B (La) antigens	147 IU/ml Strongly positive (+++)	Absence
Antibodies to RNP (ribonucleoproteins)	0.00 IU/ml Not detected	Absence
Antibodies to the Jo-1 (histidine) antigen	0.00 IU/ml Not detected	Absence
Anticentromere antibodies CENT-B	0.00 IU/ml Not detected	Absence
Anti-Sm (Smith)	0.00 IU/ml Not detected	Absence
Anti-histone antibodies (Histone)	0.00 IU/ml Not detected	Absence
Antibodies to ribosomal protein P	0.00 IU/ml Not detected	Absence

Because of her severe condition, the patient was admitted to the ICU. Complete blood count revealed mild chronic iron deficiency anaemia (haemoglobin, 99 g/L). Serological tests for HIV, viral hepatitis, and respiratory viruses were negative. The blood test results most relevant to the differential diagnosis are presented in Table 1. Thyroid and renal function tests, as well as urinalysis and stool studies, were within normal limits.

A direct Coombs test was performed and yielded a positive result. The patient was subsequently evaluated by a rheumatologist and underwent testing for additional autoimmune markers, which revealed positive antinuclear antibodies (ANA) and anti-La (SSB) antibodies. In contrast, rheumatoid factor, anti-double-stranded DNA antibodies, anti-ribosomal P protein antibodies, anticentromere antibodies, anti-Scl-70 antibodies, and anti-ribonucleoprotein antibodies were negative (Table 2).

Table 3. *Echocardiography dated from September 30, 2025.*

Parameters	Value
Mitral valve:	Thin leaflets, mitral valve annulus 2.6 cm. Regurgitation (+): Grade 1.
Ascending aorta:	Walls are thickened; Aortic base size: 1.9 cm; Ascending aorta size: 3.6 cm.
Aortic valve:	Thick leaflets, pressure gradient 4.5 mmHg.
Tricuspid valve:	Thin leaflets, PGr TR — 60 mmHg; Regurgitation (++-+++): Grade 2-3, central;
Pulmonary artery size:	3.0 cm
Pulmonary valve: Estimated PASP:	The valves are thin; 75 mmHg
Left atrium in M mode:	4.5 cm
LA volume in B mode:	65 ml
LVIDd:	3.9 cm
LVIDs:	2.6 cm
ESV:	64 ml
EDV:	26 ml
SV:	38 ml
Simpson ejection fraction:	60 %
IVS thickness in diastole:	0.9 cm
LV posterior wall thickness:	0.8 cm
Presence of pericardial effusion:	circular — up to 16-18 mm
PSV:	8 mm
RA area:	26.0 cm^2
IRAV:	55 ml/m^2
RV/LV ratio:	1.3
Shape index (eccentricity) EL:	1.9
TAPSE/e PASP:	0.15 mm/mmHg
RVOT acceleration time:	65 ms
IVC diameter:	2.3 cm, decreases less than 30 %

Note: EDV — end-diastolic volume; ESV — end-systolic volume; IRAV — indexed right atrial volum; IVC — inferior vena cava; IVS — interventricular septum; LA — left atrium; LV — left ventricle; LVIDd — left ventricular internal dimension in diastole; LVIDs — left ventricular internal dimension in systole; PASP — pulmonary artery systolic pressure; PSV — peak systolic velocity; RA — right atrium; RV — right ventricle; RVOT — right ventricular outflow tract; SV — stroke volume; TAPSE/ePASP — tricuspid annular plane systolic excursion/ estimated pulmonary artery systolic pressure.

On October 1, 2025, the patient underwent an ultrasonic Doppler examination of the lower extremity veins, which did not reveal any intravascular elements in the superficial and deep veins of the legs.Abdomen ultrasound performed on October 1, 2025 showed hepatomegaly and diffuse changes in the liver.On October 8, 2025, spirometry was conducted, which showed impaired pulmonary function (obstruction). A mild obstruction was reported. Reduced airflow was observed at the level of the distal bronchi. The bronchodilator test with salbutamol was negative, with a 1 % increase in FEV1. Echocardiographic findings obtained on 30 September 2025, are presented in Table 3.

Given the presumptive diagnosis at admission and as part of the differential diagnostic work-up, contrast-enhanced MSCT of the lungs was performed to exclude malignancy and rare conditions, including interstitial lung diseases. The findings are shown in Figures 2, 3, and 4.

Given the complaints of dry mouth, the patient was examined for diabetes mellitus, which was ruled out. A salivary gland ultrasound examination was performed on October 14, 2025, which showed diffuse changes in the salivary glands and mildly enlarged parotid glands; no hypoechogenic areas were observed. Later, right heart catheterisation (RHC) was performed, and the haemodynamic data are presented in Table 4.

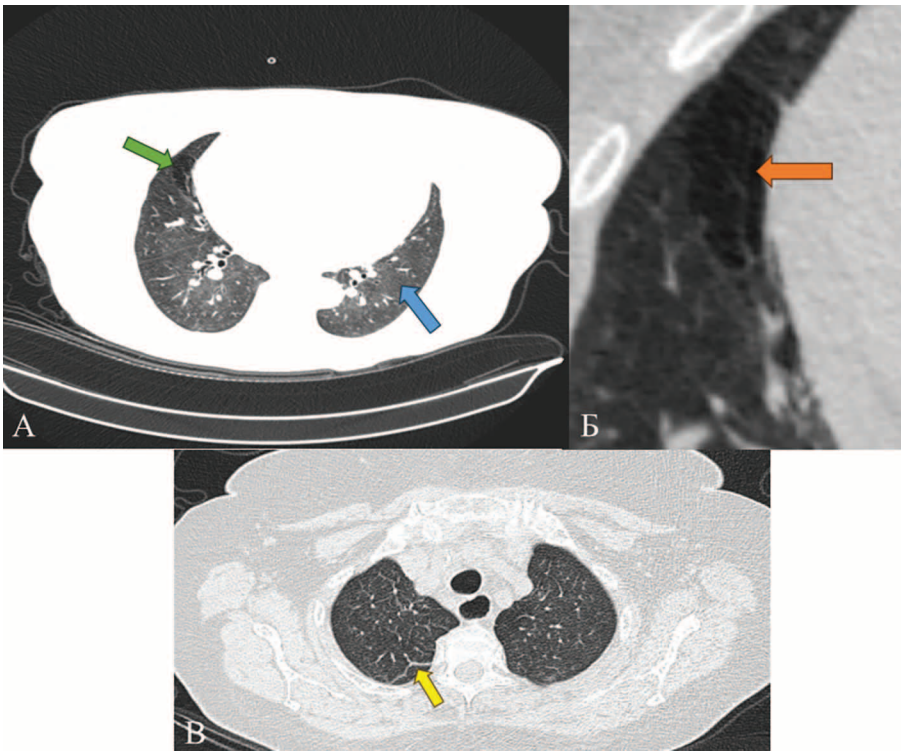


Figure 2. *MSCT pulmonary angiography, native phase scanning, pulmonary electron window, axial projection: A — mosaic density of lung tissue is determined, caused by the presence of areas of normal (blue arrow) and increased (green arrow) airiness associated with uneven blood flow. B — in the area of increased airiness, narrowing of the vessel lumen is visible (orange arrow), associated with obstruction or hypoxic vasostriction. C — at the level of the apical segments on both sides, uniform thickening of the interlobular septa is visible (yellow arrow), associated with venous congestion in the pulmonary circulation.*

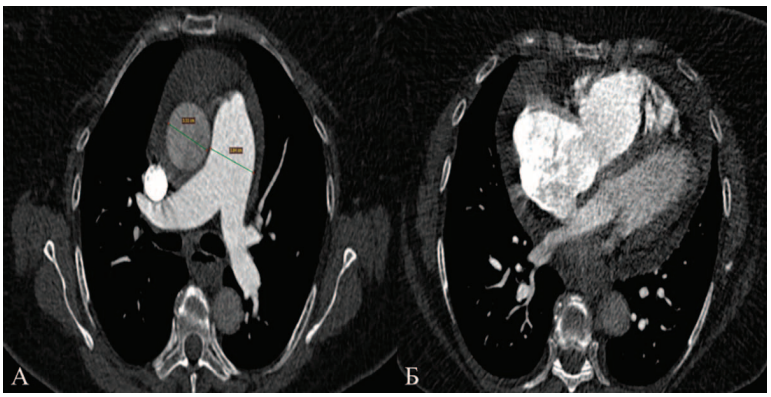


Figure 3. *MSCT pulmonary angiography, pulmonary artery contrast phase, soft tissue electron window, axial projection: A — a dilated main pulmonary artery is visible, as well as an increase in the ratio of the pulmonary artery diameter to the diameter of the ascending aorta to 1.1. B — The right ventricle and right atrium are significantly enlarged compared to the left chambers of the heart. In addition, a moderate amount of pericardial effusion is observed.*

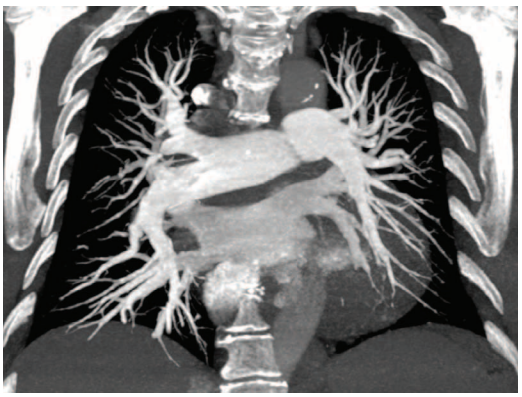


Figure 4. *MSCT pulmonary angiography, pulmonary artery contrast phase, soft tissue electron window, coronary projection with MIP reconstruction (maximum intensity projection): no signs of acute or chronic pulmonary embolism.*

Inpatient treatment consisted of Dapagliflozin 10 mg, Spironolactone 25 mg, Carvedilol 6.25 mg twice daily, Prednisolone 5 mg 2 tablets @ 07:00 am; no other cardiotropic drugs were prescribed due to predisposition to hypotonia. Given the diagnostic complexity of the case, the patient's medical data were referred for a telemedicine consultation to the E.I. Chazov National Medical Research Centre in order to determine the optimal further management strategy. The patient stayed in the hospital for one and a half months with no significant improvement in her condition; she was discharged on her own request. Later, an expert opinion was received stating absence of any solid evidence of chronic thromboembolic pulmonary hypertension. Immunological abnormalities are noteworthy, and a salivary gland biopsy together with ophthalmologic testing is required to rule out SS. According to right heart catheterisation findings, severe precapillary pulmonary hypertension was confirmed (pulmonary artery wedge pressure: 10 mm Hg); however, there was no indication that diuretic therapy had been discontinued. Taking into account test results, mixed origin pulmonary hypertension cannot be ruled out, including pulmonary veno-occlusive disease, (post/precapillary type, since there are risk factors of diastolic dysfunction). Currently, supportive therapy is recommended, while PAH-specific therapy is associated with a risk of life-threatening complications.

The patient was notified of the expert opinion and was referred for an additional examination by an eye specialist and dentist (in outpatient settings). Ophthalmologic examination revealed a positive Schirmer test result (3 mm after 5 minutes). A biopsy of the submandibular gland was performed (see Figure 5).

Salivary gland scintigraphy was also performed and demonstrated no reduction in radioactive tracer uptake in either the parotid or the submandibular glands (see ***Figure 6***).

Radiopharmaceutical retention was observed in the right lobe of thyroid gland, which is in line with the history of adenoma. The patient was referred to a MRI of her neck soft tissue for anatomical details and confirmation of the gland biopsy results, which can be false negative (see ***Figure 7***).

On December 30, 2025, the patient lost consciousness in the stairwell; loss of consciousness was not accompanied by unprompted defecation and urination. The patient gained consciousness within minutes and called for an ambulance, which transported her to the outpatient therapeutic ward. According to the patient, she had eight similar episodes of syncope last month. The patient was examined by a neurologist, who ruled out the neurogenic nature of syncope. Given the past medical history, the patient was admitted to the rheumatology ward. She underwent another immunological testing, which revealed antinuclear antibodies; immunoblot testing showed positive anti-SS-A/Ro, SS-B (La) antibodies and anticentromere antibodies CENT-B. The patient was diagnosed with systemic scleroderma, specifically the limited form (CREST syndrome), associated with secondary Sjögren's syndrome, Raynaud's phenomenon, sclerodactyly (non-pitting swelling of the fingers), and oesophageal dysmotility manifested by dysphagia. Prednisolone dose titration therapy was initiated.

Table 4. *Right heart catheter probing (Swan-Ganz catheter) from October 5, 2025.*

Parameters	Value
Systolic BP:	125/80/90 mmHg (cuff)
RA Pressure:	8/4 (mean 8) mmHg
RV Pressure:	59/10 (mean 12) mmHg
PA Pressure:	62/31 (mean 33) mmHg
PAWP:	mean 10 mmHg
Cardiac Output:	0.511 ml/min
Cardiac Index:	2.88 l/min*m^2
PA SO2:	69.0 %
Pulmonary vascular resistance:	361 dynes/s*cm^2 or 5 Wood Units
Total pulmonary resistance:	518 dynes/s*cm^2 or 6 Wood Units
After iloprost inhalation, 10 minutes Hemodynamic parameters were measured and calculated:	
Systolic BP:	125/85/91 mmHg (cuff)
AP Pressure:	3/0 (mean 2) mmHg
RV Pressure:	47/5 (mean 8) mmHg
PA Pressure:	49/24 (mean 25) mmHg
PAWP:	mean 6 mmHg
Cardiac Output:	0.65 ml/min
Cardiac Index:	3.67 l/min*m^2
PA SO2:	76.0 %
Pulmonary vascular resistance:	234 dynes/s*cm^2 or 3 Wood Units
Total pulmonary resistance:	308 dynes/s*cm^2 or 4 Wood Units

Note: BP — blood pressure; PA — pulmonary artery; PAWP — pulmonary artery wedge pressure; RA — right atrium; RV — right ventricle; SO2 — saturation.

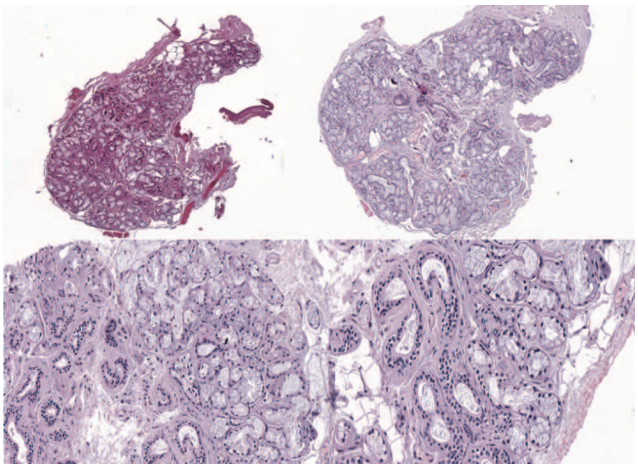
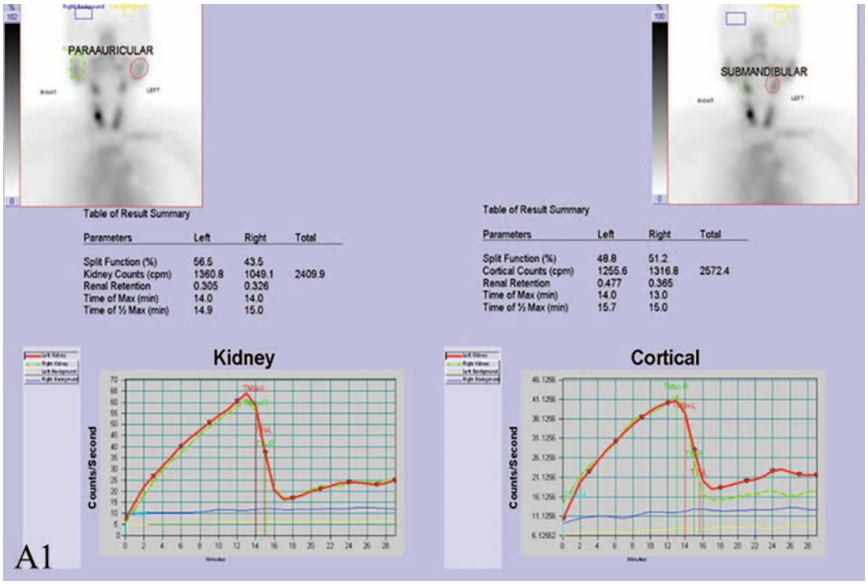
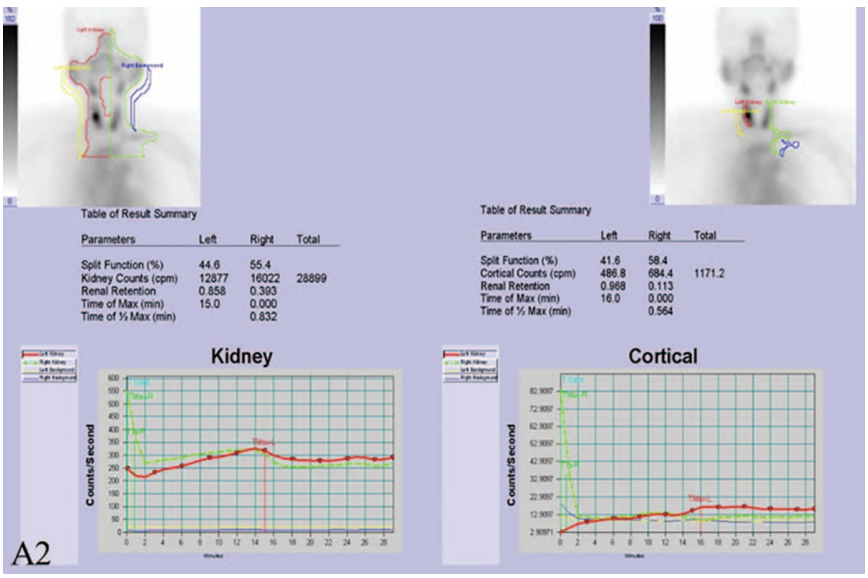


Figure 5. *Microscopy of salivary gland biopsy material. No signs of acinar atrophy or inflammatory infiltration in the gland parenchyma are demonstrated. Morphological activity index 0.*





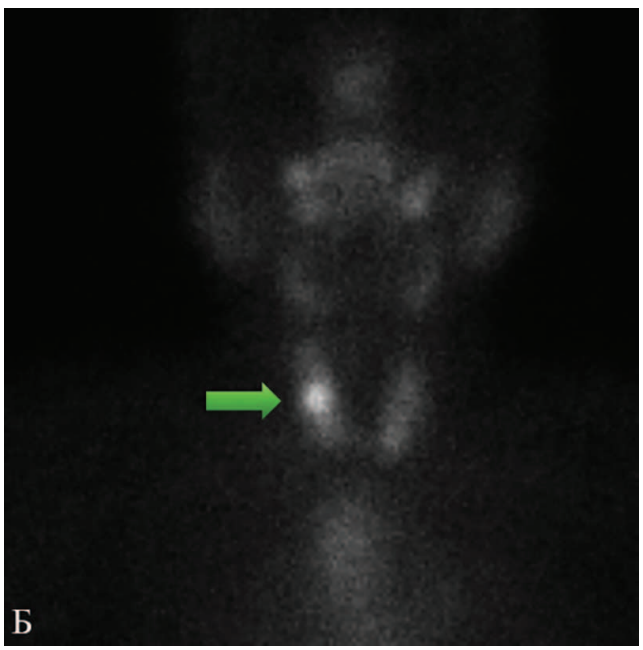


Figure 6. *Scintigraphy of salivary glands with lemon juice loading. A1,2 — no signs of dysfunction of the parotid and submandibular salivary glands. B — a focus of radiopharmaceutical hyperfixation is visualized in the projection of the middle third of the right lobe of the thyroid gland (green arrow).*

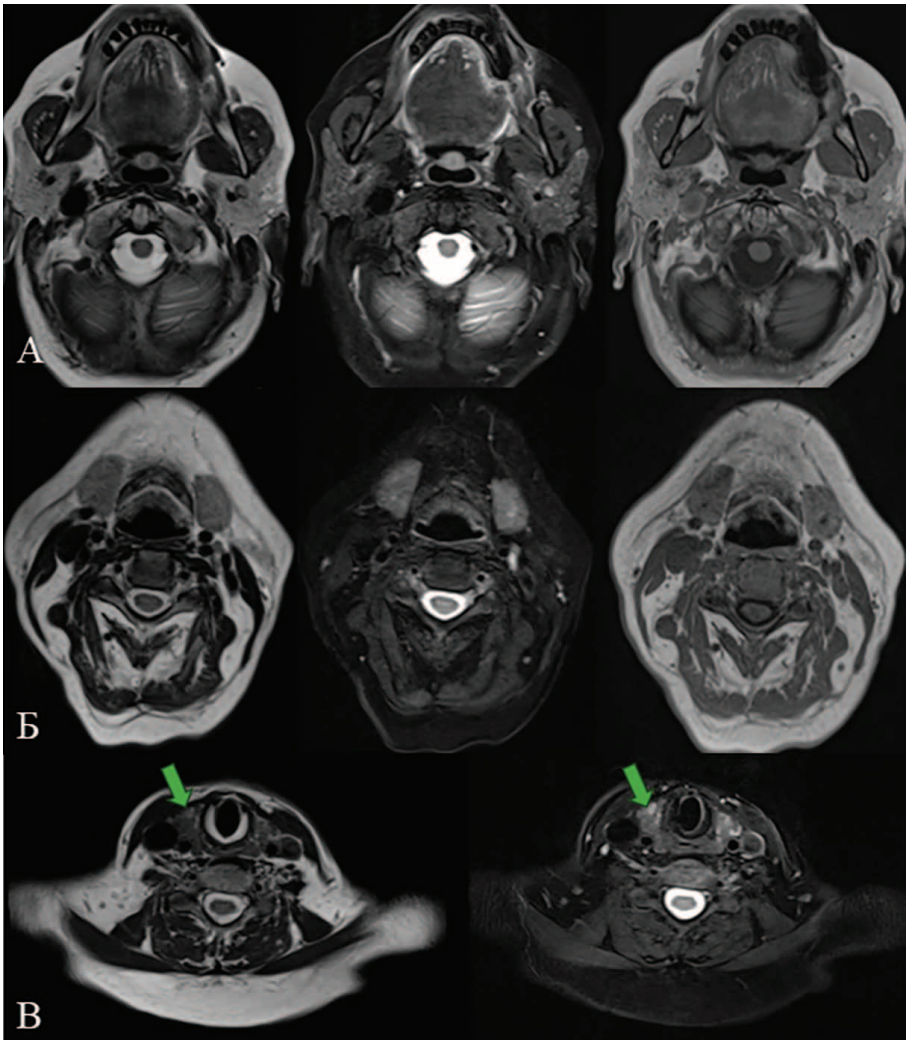


Figure 7. *MRI of the soft tissues of the neck at the level of the parotid salivary glands (A), at the level of the submandibular salivary glands (B), at the level of the thyroid gland (C), T2-weighted image pulse sequences, T2-weighted image with signal suppression from fat tissue and T1-weighted image, axial projection: the salivary glands appear symmetrical, not enlarged, have clear contours and a uniform structure; a hyperintense nodule is visible in the right lobe of the thyroid gland (green arrow).*

Discussion

Overlap syndrome is a concept describing an overlap between symptoms of several diseases in one patient. The patient indeed meets the criteria for several pathologies, hence a clear diagnosis is challenging. According to the 2016 ACR/EULAR classification criteria, a diagnosis of Sjögren's syndrome is established when the total score is 4 or higher. These criteria are applicable to patients who have at least one symptom of ocular or oral dryness, as assessed by the AECG questionnaire, or who have positive findings in at least one domain of the ESSDAI suggestive of Sjögren's syndrome, provided that no exclusion criteria are present (e.g., previous head and neck radiotherapy, hepatitis C, HIV, sarcoidosis, or amyloidosis) [7]. ESSDAI is the Sjögren's Syndrome Disease Activity Index developed by EULAR, and the score of <5 indicates low disease activity [8].

In this case, the suspicion of SS was justified, as in addition to mucosal dryness, the patient had positive findings in several ESSDAI domains, namely pulmonary involvement (3 points) and haematological involvement (2 points), indicating that the disease activity was not low. According to the 2016 EULAR/ACR classification criteria, the patient scored 4 points, even without corneal and conjunctival staining, which was not performed; therefore, the diagnosis of Sjögren's syndrome was considered justified. However, given the presence of anticentromere antibodies CENT-B, Raynaud's phenomenon, scleredema and oesophageal dysfunction, the secondary nature of SS, caused by limited CTD, cannot be ruled out.

A study based on the French National Health Insurance Database demonstrated that among connective tissue disorders (CTDs) associated with SS, systemic lupus erythematosus (SLE) accounted for 28 % of cases, rheumatoid arthritis for 53 %, and SSD for 13 % [9]. Groups with various CTDs demonstrate some differences. Patients with SLE and SS have the following characteristics: relatively late onset of the disease; high incidence of Raynaud's phenomenon and joint symptoms; as well as a high positive response to autoantibodies (especially anti-SS-A/SS-B antibodies). The most common symptom is oral sores [10].

SSD is also a multisystem autoimmune connective tissue disorder characterised by microvascular injury, dysregulation of both adaptive and innate immunity, and progressive fibrosis of the skin and internal organs.

Common clinical manifestations of SSD include Raynaud's phenomenon, skin thickening, calcinosis, telangiectasias, gastroesophageal reflux disease, gastrointestinal dysmotility, arthritis, interstitial lung disease, and pulmonary hypertension. Among these manifestations, Raynaud's phenomenon, characterised by vasospasm of the fingers, is an early clinical sign that typically precedes the development of fibrotic changes, suggesting that vascular involvement is an early manifestation of the disease and plays a key role in its initial pathogenesis. Pulmonary hypertension is usually a later sign of SSD, which manifests 10–15 years after diagnosis [11]. However, in the present case, upon hospital admission the patient did not present with Raynaud's phenomenon and did not have any typical complaints. Similar to SS, SSD is more common in women than in men, with the women-to-men ratio being 3–4:1; however, in men SSD results in poorer outcomes [12].

According to the WHO classification, CTD-associated PAH is included in group 1 of pulmonary hypertensions. Among the group 1 subtypes associated with connective tissue diseases, SSD accounts for approximately 75% of all cases of CTD-associated PAH [13]. PAH has been reported to occur in 8–12% of patients with SSD and represents one of the leading causes of mortality in this population. Together with pulmonary fibrosis, it accounts for up to 60% of all SSD-related deaths [14]. The median survival is approximately 4 years. Studies have demonstrated that the combination of early disease detection through improved screening recommendations and the use of PAH-specific therapies improves survival in patients with SSD-associated PAH, a condition that is otherwise associated with a poor prognosis [15].

It appears that SS and SSD in the present case are the elements of one pathological autoimmune process. A combination of these pathologies has been described in literature sources. Of particular interest is the study by Drosos et al., which described a cohort of 23 patients with CREST syndrome who underwent clinical, histopathological, and serological evaluation for the presence of Sjögren's syndrome. Fourteen patients were found to have positive findings consistent with Sjögren's syndrome. No significant differences were observed between these patients and the remaining nine individuals. In addition, the characteristics of patients with CREST syndrome were compared with those of 29 randomly selected patients with primary SS. Parotid gland enlargement was observed significantly more frequently in patients with primary SS than in those with CREST syndrome ($p < 0.01$). Virtually none of the patients with concomitant CREST syndrome and SS had detectable anti-Ro(SSA) or anti-La(SSB) antibodies [16]. However, in the study by Oddis et al., anti-SSA(Ro) antibodies were identified in the serum of five out of six patients with the CREST variant of systemic scleroderma and features of SS [17]. If the presence of SS in our patient is excluded and the condition is considered a "pure" form of SSD with an initial presentation dominated by visceral manifestations, particularly PAH, such a presentation would be uncommon and would also be of considerable practical interest to clinicians.

Conclusion

The treatment outcomes of SSD-associated PAH remain unsatisfactory compared with those observed in patients with SSD overall. Therefore, new diagnostic and treatment approaches are required. Given the substantial role of specific components of the immune system in disease pathogenesis, a promising therapeutic approach in the future will likely involve the combination of targeted immunomodulation with combination vasodilator therapy. Prospective studies involving patients with SS, SSD and PAH have not yet been conducted. Therefore, studies focusing on the early initiation of therapy would be important to determine whether vasodilators may exert disease-modifying effects and whether their use should be started earlier, before overt signs of organ damage develop. Clinicians should maintain a high index of suspicion and carefully evaluate patients with PAH for the possible presence of both SSD and SS, as these conditions may remain undiagnosed during routine assessment. An erroneous diagnosis of idiopathic PAH may deprive patients with an underlying connective tissue disease of the opportunity to receive immunosuppressive therapy and to benefit from the most appropriate combination of vasodilator agents.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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Pushnikova M.A.: writing the case report, analyzing and interpreting the literature, providing organizational support for the publication

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Nedzelskaya V.S.: editing, writing, and interpreting the examination results
Balina V.A.: literature review, collaboration of the author team

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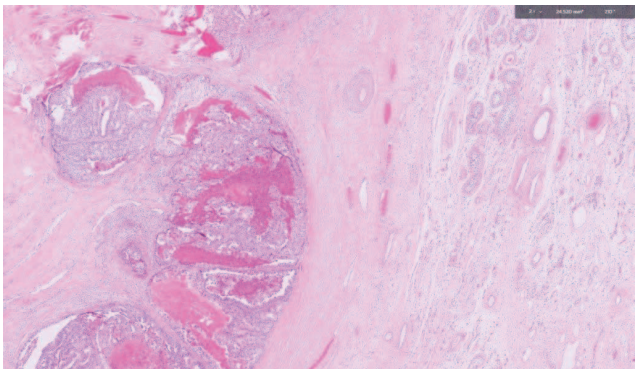
Najla Saleh Ben Ghashir, Babitha Alingal Mohamed, Aref Chehal et al Pure Adenocarcinoma with Intestinal Differentiation of The Testis as The First Presentation of a Testicular Teratoma: A Case Report with Literature Review of Management. The Russian Archives of Internal Medicine. 2026; 16(2): 137-144. DOI: 10.20514/2226-6704-2026-16-2-137-144. EDN: RXLWMO

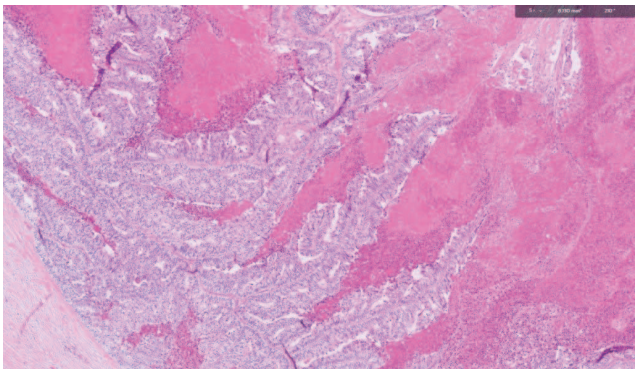
Исправление от редакции

При публикации этой статьи в № 2 журнала за 2026 год по технической причине (при вёрстке номера) были пропущены все панели к рисункам (Панель 1, подпанели 1.A–1.H; Панель 2, подпанели 2.A-2.D.), иллюстрирующие гистоморфологию и иммунопрофиль первичной опухоли яичка и метастатическую аденокарциному в забрюшинном лимфатическом узле. Ниже публикуются недостающие панели с подписями на русском и английском языке. Редакция приносит извинения авторам и читателям.

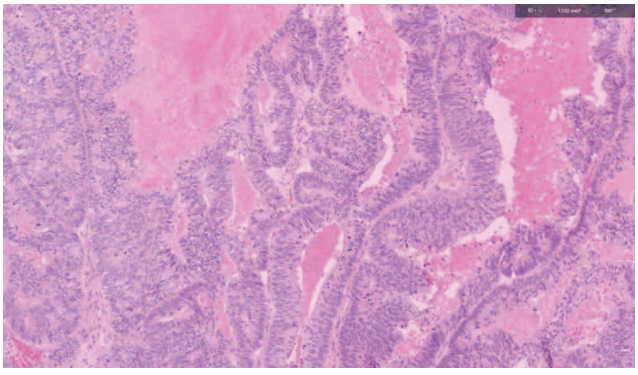
Панель 1. Гистоморфология и иммунологический профиль первичной опухоли яичка
Panel 1. Histomorphology and immunoprofile of primary testicular tumor



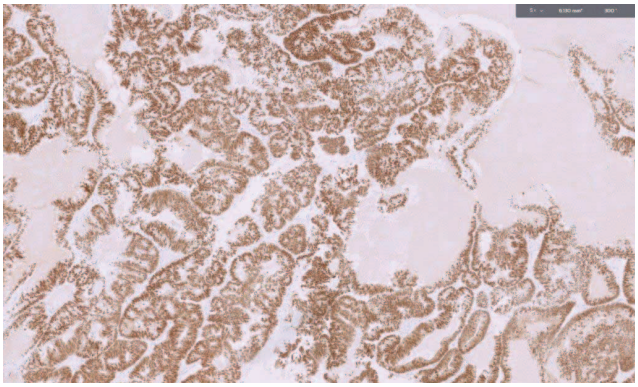
1.A. *Окраска гематоксилином и эозином (HandE), увеличение ×2. Паренхима яичка (справа) и опухоль (слева)*
1.A. *HandE-stained section (X2 magnification) showing testicular parenchyma (right side) and tumor (left side)*



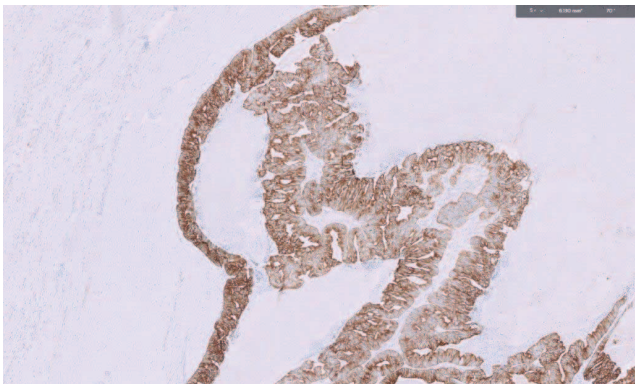
1.B. *Окраска гематоксилином и эозином (HandE), увеличение ×5. Аденокарцинома с обширными участками некроза*
1.B. *HandE-stained section (X5 magnification) showing an adenocarcinoma with extensive necrosis*



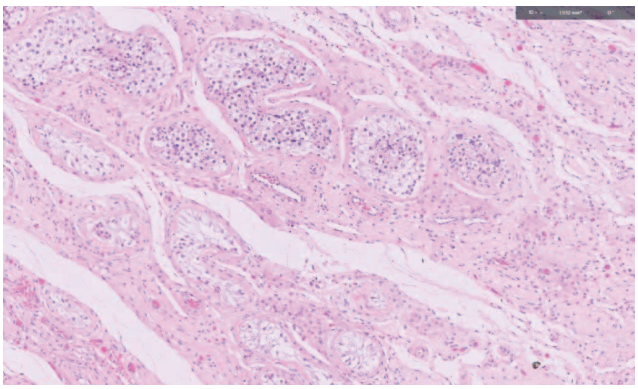
1.C. *Окраска гематоксилином и эозином (HandE), увеличение ×10. Аденокарцинома с кишечной дифференцировкой, представленная цилиндрическими клетками со стратифицированными ядрами, расположенными в тубулоацинарном паттерне*
1.C. *HandE-stained section (X10 magnification) showing an adenocarcinoma with enteric differentiation comprising columnar cells with stratified nuclei, arranged in a tubuloacinar pattern*



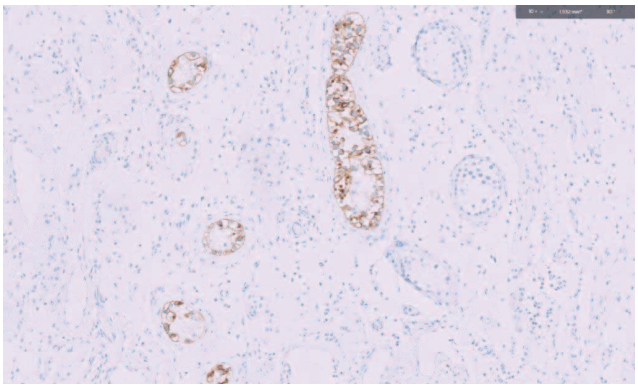
1.D. *Клетки опухоли демонстрируют сильное и диффузное положительное окрашивание на CDX2, что подтверждает кишечную дифференцировку*
1.D. *Tumor cells are strongly and diffusely positive for CDX2 supporting enteric differentiation*



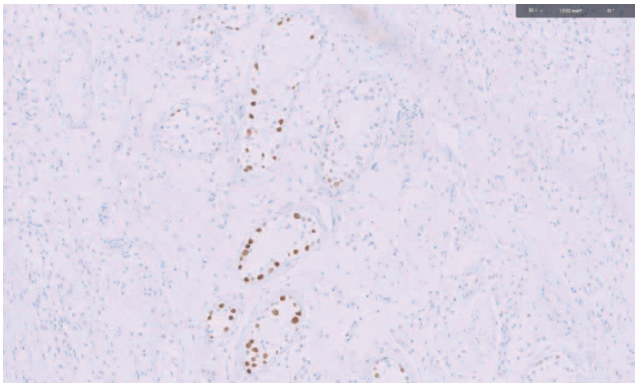
1.E. *Клетки опухоли демонстрируют положительное окрашивание на CK20, что подтверждает кишечную дифференцировку*
1.E. *Tumor cells are positive for CK20 supporting enteric differentiation*



1.F. *Окраска гематоксилином и эозином (HandE), увеличение ×10. Семенные канальцы с герминогенной неоплазией in situ (GCNIS)*
1.F. *HandE stained section (X10 magnification) showing seminiferous tubules with GCNIS*

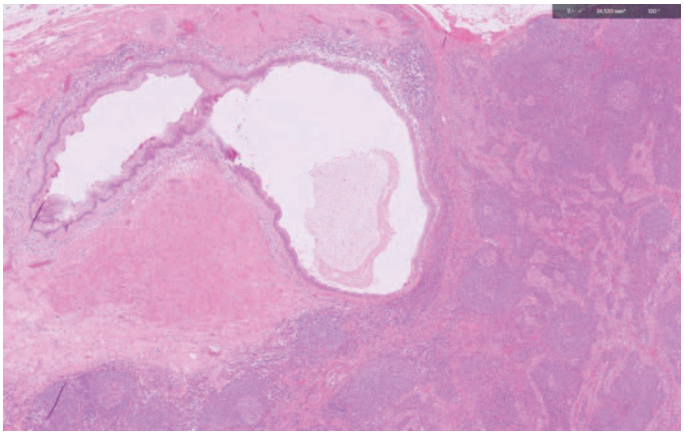


1.G. *GCNIS иммунореактивна к PLAP (положительное окрашивание)*
1.G. *GCNIS is immunoreactive for PLAP*

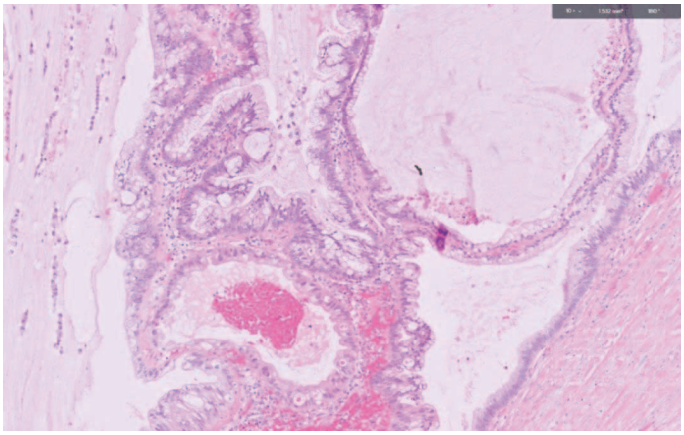


1.H. *GCNIS иммунопозитивна к OCT4 (положительное окрашивание)*
1.H. *GCNIS is immunopositive for OCT4*

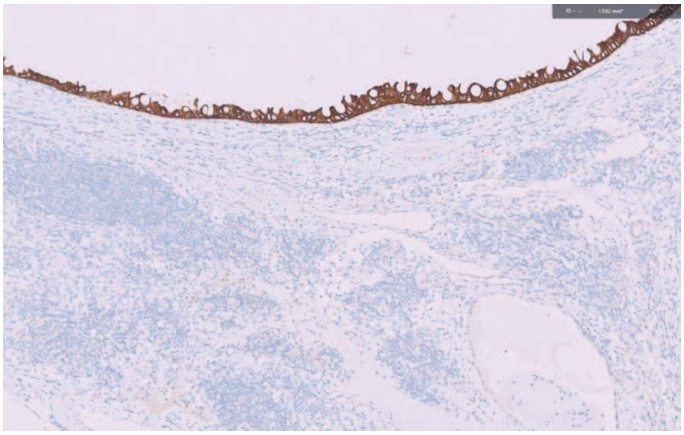
Панель 2. Метастатическая аденокарцинома в забрюшинном лимфатическом узле
Panel 2. Metastatic adenocarcinoma in retroperitoneal lymph node



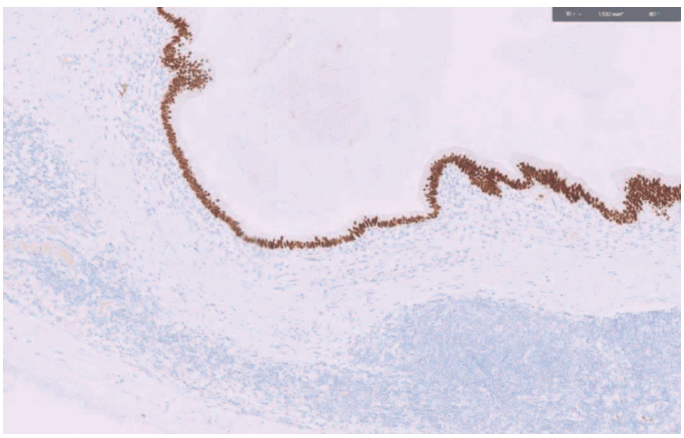
2.A. *Окраска гематоксилином и эозином (HandE), увеличение ×2. Метастатическая аденокарцинома с поражением лимфатического узла*
2.A. *HandE-stained section (X2 magnification) showing metastatic adenocarcinoma involving lymph node*



2.B. *Окраска гематоксилином и эозином (HandE), увеличение ×10. Метастатическая аденокарцинома с муцинозными (слизистыми) характеристиками*
2.B. *HandE-stained section (X10 magnification) showing metastatic adenocarcinoma with mucinous features*



2.C. *Метастатическая аденокарцинома иммунореактивна к CK20 (положительное окрашивание)*
2.C. *Metastatic adenocarcinoma immunoreactive for CK20*



2.D. *Метастатическая аденокарцинома иммунопозитивна к CDX2 (положительное окрашивание)*
2.D. *Metastatic adenocarcinoma immunopositive for CDX2*