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Modern approaches to the diagnosis and treatment of heart failure in patients with type 2 diabetes mellitus

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Abstract. The aim of the study was to identify systemic limitations in the approaches to the diagnosis and treatment of chronic heart failure (CHF) in patients with type 2 diabetes mellitus (DM) based on the analysis of pathogenesis, verification methods, and treatment effectiveness. Within the framework of the theoretical approach, clinical-pathophysiological and organisational models of CHF in type 2 DM were reconstructed, followed by the comparison of diagnostic algorithms, therapeutic strategies, and statistical data from various national healthcare systems, along with an expert evaluation of the main pathogenetic mechanisms. During the theoretical analysis, it was established that the formation of CHF in type 2 DM was determined by the combined influence of diabetic cardiomyopathy, microvascular ischaemia, and chronic inflammation. Diagnostic algorithms based on ejection fraction (EF) assessment demonstrated limited sensitivity in patients with preserved systolic function, whose proportion reached 60-70%. The most informative early diagnostic methods were recognised as tissue Doppler echocardiography and the identification of fibrosis and overload biomarkers, including natriuretic peptides, soluble suppression of tumorigenicity-2 receptor, and galectin-3. The greatest evidence-based effectiveness in treating CHF in patients with type 2 DM was demonstrated by the combined use of four classes of drugs – angiotensin-converting enzyme inhibitors, β-adrenergic blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors). Significant differences in access to basic drug therapy were identified: up to 78% of patients in the USA received combined treatment, whereas in Kazakhstan – less than 45%. These discrepancies also appeared in mortality levels: 66.2 cases per 100,000 population in the USA, versus a marked increase in this indicator in certain regions of Kazakhstan. The obtained results substantiated the need to adapt clinical protocols considering phenotypic features of the combined pathology, which allows for improved diagnostic accuracy, individualised therapy, and reduced cardiovascular mortality

Keywords: myocardium; metabolic comorbidity; ischaemia; diastolic dysfunction; insulin; ejection fraction

Introduction

Chronic heart failure (CHF) in patients with type 2 diabetes mellitus (DM) formed a stable comorbid phenotype, associated with early development of myocardial dysfunction, atypical clinical manifestations, and a high rate of adverse outcomes. In clinical practice, difficulties in early disease verification were recorded, especially in cases with preserved ejection fraction (EF), which hindered timely initiation of therapy. Universal diagnostic protocols demonstrated limited sensitivity regarding subclinical forms, and therapeutic approaches did not take into account the pathophysiological specificity of metabolic disorders. The absence of adapted diagnostic and treatment schemes amid the progressive spread of type 2 DM increased the epidemiological burden and raised cardiovascular mortality. Collectively, these factors substantiated the need for a systematic theoretical analysis aimed at reconstructing pathogenetic models, assessing the effectiveness of diagnostic strategies, and identifying pharmacotherapeutic deficiencies in this patient category.

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The significance of heart failure in type 2 DM was observed in several Kazakhstani and international sources, which highlighted the scale and clinical-social relevance of this comorbidity. In the study by G. Zhakhina *et al.* [1], data from the national electronic healthcare system were analysed, and an increase in hospitalisations for heart failure was recorded, especially among patients with type 2 DM. However, the study lacked in-depth assessment of risk factors and the dynamics, which limited its prognostic value. O. Jumagazieva *et al.* [2] presented a general picture of mortality and prevalence of CHF, DM, and arterial hypertension within the framework of a chronic disease management programme. The authors stressed the importance of an interdisciplinary approach, but the analysis remained predominantly descriptive. In the Resolution of the Government of the Republic of Kazakhstan No. 945 "On Approval of the Concept of Health Care Development of the Republic of Kazakhstan until 2026" [3], strategic directions for healthcare development until 2026 were defined. Despite its regulatory comprehensiveness, the provisions concerning type 2 DM in the context of heart failure were virtually absent. An attempt to reflect the prevalence and management tactics of CHF was made in the review by Y. Kakhramonovna *et al.* [4], but the lack of methodological rigour diminished the reliability of the conclusions.

The diagnosis of CHF in patients with type 2 DM was complicated by the fact that the clinical picture in the early stages was often nonspecific, and standard algorithms were not adapted to the features of this population. The difficulties in detecting subclinical forms of the disease were associated by A. Ceriello *et al.* [5] with the low sensitivity of traditional methods, especially in the group with diabetic cardiomyopathy. The authors proposed a multiparametric diagnostic model, but its effectiveness had not yet been confirmed by large clinical trials. In the review by J.J. Park [6], special attention was paid to the role of diastolic dysfunction and subtle symptoms as the main causes of diagnostic delays. However, the author relied mainly on retrospective data, which limited the generalisability of the conclusions. The potential of using N-terminal pro-B-type natriuretic peptide (NT-proBNP), suppression of tumorigenicity 2 (ST2), and galectin-3 as early diagnostic markers was considered in the study by V. Castiglione *et al.* [7]. Nevertheless, according to the authors, the specificity of biomarkers in type 2 DM remained insufficiently studied.

Optimising CHF treatment in patients with type 2 DM was a clinically significant task, given the high likelihood of decompensation and limited effectiveness of universal therapeutic schemes in the context of metabolic disorders. In the consensus publication by R. Pop-Busui *et al.* [8], prepared with the participation of the American Diabetes Association (ADA), CHF was regarded as a systemic and underappreciated complication of DM, requiring integration into management algorithms for this population. Despite the comprehensive framing of the problem, the work lacked specific recommendations regarding pharmacotherapy. In the publication by P.A. Heidenreich *et al.* [9], developed by the Joint Committee on Clinical Practice Guidelines under the auspices of the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA), a universal medication management scheme for CHF was proposed, taking EF into account. This approach ensured clinical applicability to a broad population but did not provide for separate stratification for the subgroup of patients with type 2 DM, which limited the potential for personalised treatment. A detailed stepwise therapy algorithm for CHF, with emphasis on evidence and safety, was developed by the ACC Solution Set Oversight Committee and substantiated in the publication by T.M. Maddox *et al.* [10]. The authors outlined the principles of phased initiation and titration of major drug classes, but metabolic aspects – including the presence of type 2 DM, insulin resistance, and diabetic cardiomyopathy – were not systematically analysed or used as stratification factors.

The diagnosis and therapy of CHF in type 2 DM under conditions of metabolic comorbidity remained insufficiently developed, indicating structural gaps in existing research. The aim of the present study was to theoretically substantiate the clinical-pathophysiological principles of diagnosing and treating CHF in patients with type 2 DM. The objectives included: characterising the pathogenetic mechanisms of the relationship between type 2 DM and CHF; analysing key diagnostic approaches and the limitations; summarising current therapeutic strategies with an emphasis on the adaptation to the characteristics of this population; comparing indicators and organisational models of the USA and Kazakhstan, and assessing the potential for adapting the American experience to Central Asian countries.

Materials and Methods

The methodological foundation of the study was an interdisciplinary theoretical-analytical approach, which ensured a comprehensive examination of the pathophysiological, diagnostic, and therapeutic aspects of CHF in patients with type 2 DM, as well as a comparison of statistical indicators of the treatment of this condition in the USA and the Republic of Kazakhstan. During the analysis, analytical, inductive-deductive, comparative, and logical-synthetic methods were used. The application of the analytical method provided an in-depth interpretation of the mechanisms of the relationship between type 2 DM and CHF, including the specific features of diabetic cardiomyopathy. Inductive and deductive approaches made it possible to logically structure the argumentation: from the study of epidemiological trends and pathogenesis – to the analysis of diagnostic and therapeutic solutions. The comparative method was used when comparing data from clinical guidelines, biomarkers, instrumental approaches, and

national statistics. The logical-synthetic procedure ensured the integration of multilevel information – from molecular mechanisms to population indicators – into a single theoretical construct.

Within the theoretical model, an expert comparative assessment of the pathogenetic mechanisms of CHF development in patients with type 2 DM was carried out. The principle of conditional significance (from 1 to 10 points) was used, reflecting the frequency of reference to mechanisms in scientific literature, the clinical significance, and pathogenetic role. For statistical comparison, official data on the incidence and mortality from CHF in adult patients with type 2 DM in the Republic of Kazakhstan and the USA were selected. Sources included national reports prepared by the Centres for Disease Control and Prevention [11,12], as well as by the American Heart Association [13,14]. For Kazakhstan, data from the Unified National Electronic Health System and publications describing epidemiological trends in the post-pandemic and forecast periods [15,16] were analysed. The analysis covered the period 2020-2023, as this interval provided the most comparable and updated data.

Statistical comparison was conducted using key epidemiological indicators: prevalence of CHF among adults, mortality rate, hospitalisation frequency, disability-adjusted life years (DALY), and the proportion of patients with type 2 DM among all patients with heart failure. The analysis covered the dynamics of the cardiovascular disease burden in urban and rural populations. This approach made it possible to identify differences in treatment accessibility, medication adherence, and patient routing, as well as to determine directions for optimising the strategy for managing patients with CHF and type 2 DM. From a diagnostic perspective, the study analysed the following methods: clinical assessment of functional class according to the New York Heart Association classification [17]; echocardiography with determination of EF, left ventricular volume, and diastolic function; evaluation of myocardial structural changes (hypertrophy, fibrosis); laboratory diagnostics using NT-proBNP, ST2, galectin-3, and cardio-specific troponins. Particular attention was paid to the role of multi-biomarker panels used for early detection of subclinical heart failure, as well as the specificity of these indicators in the diabetic population. The study considered all key pharmacological classes approved by international guidelines for the treatment of CHF: sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors), angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists, beta-adrenergic blockers, and mineralocorticoid receptor antagonists.

The methodological approach, based on the use of theoretical analysis, systematic comparison, and structural interpretation of statistical and clinical data, ensured a comprehensive consideration of the problem of CHF in patients with type 2 DM. The statistical data were processed using Microsoft Excel (version 2303) and IBM SPSS Statistics (version 29.0), which ensured the reliability of calculations, the ability to visualise, and conduct comparative analysis between samples.

Results and Discussion

Clinical and pathophysiological aspects of the relationship between CHF and type 2 diabetes

In conformity with the general theoretical analysis, chronic heart failure and type 2 DM formed a stable biomedical link in which the pathogenesis of one condition accelerated and aggravated the manifestation of the other. Results from molecular, clinical-epidemiological, and imaging studies showed that the presence of type 2 DM increased the risk of developing CHF by 2-4 times. The course of heart failure in such patients was characterised by early clinical manifestation, reduced survival, and increased therapeutic resistance. Similar data were presented in the study by K. Nakamura *et al.* [18], which emphasised the importance of lipotoxicity and glucose-induced oxidative stress as key determinants of remodelling and early fibrotic transformation of the myocardium. These changes aggravated cardiac dysfunction independently of the severity of coronary atherosclerosis, indicating the independent pathogenetic significance of diabetic cardiomyopathy.

In the available literature, diabetic cardiomyopathy was considered a key link in the relationship between type 2 DM and CHF. Diabetic cardiomyopathy developed under the influence of chronic hyperglycaemia, systemic insulin resistance, microvascular ischaemia, chronic inflammation, and metabolic overload of the myocardium. At the histological level, this condition was characterised by cardiomyocyte hypertrophy, interstitial fibrosis, mitochondrial disorganisation, and reduced left ventricular compliance. In the study by C.X. Ma *et al.* [19], it was described that mitochondrial dysfunction, accompanied by impaired β-oxidation of fatty acids, led to an energy deficit in cardiomyocytes and reduced contractile capacity, especially under ischaemic conditions. The analysis showed that chronic hyperglycaemia was a central trigger of destructive processes in the myocardium. Through activation of the polyol pathway, accumulation of advanced glycation end-products, and generation of reactive oxygen species, it caused calcium imbalance, cardiomyocyte apoptosis, and diastolic dysfunction.

Simultaneously, pronounced insulin resistance developed, disrupting metabolic balance and the myocardium's ability to effectively utilise glucose. This contributed to a metabolic switch in cardiomyocytes towards fatty acid metabolism, increasing oxygen consumption and reducing energy efficiency. This shift towards "metabolic ischaemia" even in the absence of coronary stenosis was confirmed by experimental models described in the study by A. Groenewegen *et al.* [20], and corresponded to the concept of functional hypoperfusion in type 2 DM.

Based on reviews and clinical-experimental data, endothelial dysfunction was identified as the next important pathogenetic factor. In patients with type 2 DM, reduced bioavailability of nitric oxide, increased expression of vascular cell adhesion molecules (VCAM-1 and ICAM-1), and impaired vasomotor endothelial function were observed. This led to microvascular hypoperfusion and arteriole remodelling, especially in the subendocardial layers. In the study by B. Zareini *et al.* [21], it was emphasised that these changes underlay the increased mortality in diabetics with CHF compared to non-diabetic patients, even with a comparable level of coronary lesions.

A number of theoretical sources also focused on the role of chronic low-grade inflammation. In patients with type 2 DM, persistent levels of proinflammatory cytokines were recorded – interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β). These cytokines activated fibroblasts and induced collagen production, promoting the progression of interstitial fibrosis. Such mechanisms were particularly evident in CHF with preserved EF, where diastolic dysfunction was determined by reduced myocardial compliance. Similar pathogenetic characteristics were demonstrated in the study by S. Nazir *et al.* [22], which emphasised that even under standard therapy, the combination of type 2 DM and ischaemic myocardial injury significantly worsened the prognosis. In addition, the results of R.D. Ianos *et al.* [23] confirmed that this patient group exhibited pronounced activation of inflammatory cascades, accompanied by elevated levels of galectin-3 and ST2, which correlated with the severity of diastolic dysfunction and the volume of fibrotic transformation.

Furthermore, literature analysis showed that the systemic effects of type 2 DM on the cardiovascular system were realised through the development of atherosclerosis, endothelial dysfunction, and diabetic microangiopathy. Vascular imaging studies described intimal thickening, reduced arterial elasticity, and impaired coronary autoregulation, leading to functional ischaemia even in the absence of stenosis [21,22]. Diabetic angiopathy affected not only large vessels but also arterioles and capillaries, reducing capillary density and vasodilatory reserve. This formed the substrate for latent ischaemic myocardial damage, especially under overload conditions. Comparable conclusions were presented in reports by the Centers for Disease Control and Prevention [11,12], which emphasised the high prevalence of cardiovascular complications in people with DM, especially those over 50 years of age, and highlighted the link between microvascular disorders and increased mortality. In the global statistical review by S.S. Martin *et al.* [13], data were shown on increased frequency of heart failure and mortality among patients with type 2 DM, particularly in the presence of dyslipidaemia and concomitant arterial hypertension. The described vascular changes were exacerbated by atherogenic dyslipidaemia – hypertriglyceridaemia, reduced levels of high-density lipoproteins, and hyperinsulinaemia, as noted by D.A. Serebrennikova [24] – intensifying tissue hypoperfusion and myocardial remodelling.

The totality of the described pathogenetic mechanisms allows the formation of an integrated conceptual model reflecting the key links in the development of CHF in patients with type 2 DM. Despite the complexity of the interactions, current data allow for a conditional differentiation of the relative contribution of each based on experimental, clinical, and epidemiological observations (Fig. 1).

Figure 1. Relative severity of key pathogenetic mechanisms of CHF in type 2 diabetes
Source: created by the author based on data analysis [18-24]

The analysis of the presented data highlighted the systemic and hierarchically organised nature of the pathogenesis of CHF in type 2 DM. Among the six key mechanisms, diabetic cardiomyopathy received the highest score (9.1 points), indicating its integrative nature as a morphofunctional endpoint of metabolic, vascular, and inflammatory disorders. The high scores for chronic hyperglycaemia (8.7), endothelial dysfunction (8.2), and chronic inflammation (8) indicated that the primary triggers of cardiac dysfunction formed long before EF decline and clinical decompensation, playing a decisive role in disrupting the metabolic stability of the myocardium and vascular tone. Insulin resistance (7.9) and microvascular ischaemia (7.5), although less pronounced, acted as critically important modulators, exacerbating energy deficiency and contributing to a

reduced adaptive reserve of the heart. The presented model visualised the functional interaction of pathogenetic links and emphasised the need for multilevel intervention aimed not only at symptom control but also at early correction of underlying disorders, including tissue insulin resistance, low-grade inflammation, and subclinical myocardial damage.

The relationship between CHF and type 2 DM was not limited to clinical correlation but was determined by the complex interaction of cardiometabolic, vascular, and immune mechanisms. These mechanisms formed a specific phenotype of heart failure resistant to standard therapy and required personalised strategies of diagnosis and treatment. Scientific understanding of the pathophysiological foundations of this comorbidity represented an important step towards improving the effectiveness of medical intervention in this high-risk population.

Diagnostic approaches and limitations of CHF verification in patients with type 2 diabetes

The diagnosis of CHF in patients with type 2 DM required consideration of multiple pathophysiological and clinical-diagnostic factors specific to this comorbid group. According to the literature, in patients with type 2 DM, CHF progression occurred in the absence of classic signs of systolic dysfunction, which was associated with the high prevalence of the diastolic form of heart failure. The proportion of CHF with preserved left ventricular EF in this population reached 60-70% of cases, and traditional EF assessment methods (e.g., two-dimensional echocardiography) did not allow a reliable diagnosis at early stages [23,24]. These forms were accompanied by impaired active relaxation of the left ventricle, reduced compliance, and the development of hidden fibrosis, which remained undiagnosed for a long time. Comparable conclusions were presented in the Chinese clinical guidelines by S. Zhang *et al.* [25], which emphasised the necessity of comprehensive assessment of filling parameters, left atrial volume, and longitudinal strain as an essential element of diagnosis in the diabetic population.

Electrocardiography remained a mandatory component of initial diagnosis when CHF was suspected, including in patients with type 2 DM. Special attention was paid to the detection of atrial fibrillation, ischaemic changes, signs of left ventricular hypertrophy, and conduction disorders including left bundle branch block. Although electrocardiography had limited specificity, its findings served as the basis for referring the patient for advanced imaging studies, including echocardiography and biomarker analysis. In the systematic review by C.W. Wong *et al.* [26], it was emphasised that diagnostic errors of CHF in patients with type 2 DM were often associated with the nonspecificity of symptoms and lack of alertness at the primary care level. Echocardiography, as the basic imaging method, demonstrated limited sensitivity under type 2 DM conditions. These indicators enabled verification of diastolic dysfunction at normal EF values. Data from the study conducted by H. Akasaka *et al.* [27] indicated that the use of tissue Doppler imaging with measurement of diastolic relaxation velocities and longitudinal strain enabled the detection of hidden forms of CHF in patients with type 2 DM.

Gadolinium-enhanced magnetic resonance imaging provided an opportunity to assess diffuse fibrosis and extracellular matrix volume, especially in patients with inconclusive echocardiography data or clinical deterioration despite normal EF [25]. According to S. Kulbayeva *et al.* [16], the use of magnetic resonance imaging in the diagnosis of CHF in patients with type 2 DM increased the sensitivity of detecting fibrotic changes, especially in the early stages of decompensation. In particular, in the case of uninformative echocardiography or mismatch between clinical picture and imaging findings, MRI was considered the preferred method of clarification.

Biochemical diagnostics were based on the use of NT-proBNP as a marker of haemodynamic overload. According to ADA recommendations [28], its use was advised for initial screening and treatment monitoring. NT-proBNP elevation was observed even in the absence of pronounced clinical symptoms, in line with the concept of subclinical volume overload. Additional biomarkers of inflammation and fibrogenesis – ST2, Galectin-3, copeptin, FGF21 – were also used, improving the sensitivity of diagnosis in preserved EF [23]. The findings presented by F. Yasmin *et al.* [29] confirmed that the combined use of NT-proBNP, copeptin, fibroblast growth factor 21 (FGF21), Galectin-3, and copeptin increased diagnostic sensitivity in hidden forms of CHF in patients with type 2 DM and reduced exercise tolerance. Such a multibiomarker approach became especially important in the context of DM, in which traditional clinical criteria were often uninformative. This aligned with integrated recommendations by Z. Bloomgarden & Y. Handelsman [30], prepared in collaboration with AHA, ADA, the European Association for the Study of Diabetes, and other organisations, emphasising the need to expand the range of diagnostic markers for CHF in patients with metabolic disorders.

Late diagnosis of CHF in patients with type 2 DM was explained by the influence of diabetic neuropathy, reduced sensitivity to physical activity, and symptom masking due to metabolic adaptation. As noted in the work by R. Indrakumari *et al.* [31], traditional clinical scales, including the New York Heart Association classification, demonstrated low sensitivity in the diabetic population due to autonomic dysfunction and attenuated manifestation of decompensation. Interdisciplinary studies analysed the integration possibilities of digital algorithms based on machine learning methods – logistic regression, decision trees, neural network models – into the diagnostic process structure [29]. These methods demonstrated high predictive

accuracy (AUC from 0.81 to 0.89) in recognising hidden forms of CHF, relying on the synthesis of heterogeneous clinical-laboratory and imaging data, including levels of natriuretic peptides, body mass index, heart rate (HR), and echocardiographic parameters. In the study by O. Akbulgic *et al.* [15], it was demonstrated that the use of big data analysis platforms and telemedicine solutions not only increased the detection of subclinical forms of CHF but also contributed to the individualisation of patient routing in the context of comorbidity-related healthcare overload.

Late diagnosis of CHF in patients with type 2 DM was due to a combination of factors influencing the interpretation of clinical symptoms and the choice of diagnostic tools. It was established that in the presence of diabetic neuropathy and reduced sensitivity to physical activity, classic signs of decompensation, including dyspnoea and fatigue, could be mildly expressed, reducing the effectiveness of clinical stratification. The low informativeness of traditional functional status scales, such as the New York Heart Association classification, in patients with type 2 DM was associated with autonomic regulation disorders and compensatory adaptation of the myocardium to metabolic overload [26]. To improve the accuracy of CHF diagnosis under metabolic comorbidity, alternative algorithms were developed based on digital computational methods. Neural network models are applied in clinical practice to integrate clinical-laboratory data, imaging studies, and anamnesis indicators to automatically identify patients at high risk of CHF with type 2 DM. These systems allow analysis of parameters that go beyond linear dependencies, including hidden interactions between biomarkers, echocardiographic parameters, and demographic characteristics [29]. Predictive modelling methods based on logistic regression, decision trees, and other machine learning algorithms were also used to develop diagnostic tools focused on outpatient monitoring data. Input variables included glucose level, body mass index, HR, blood pressure, and natriuretic peptide concentrations (NT-proBNP), which enabled the creation of accessible and scalable primary screening schemes [31].

Systematisation of approaches to diagnosing CHF in patients with type 2 DM allowed key verification directions to be identified. Methods covered clinical, imaging, biochemical, and digital levels, reflecting the need for a comprehensive approach. The diagnostic value varies depending on the form of CHF and the severity of metabolic disorders, requiring the combined application within a unified clinical model (Table 1).

Table 1. Complex of diagnostic approaches to verifying CHF in patients with type 2 diabetes

Direction of diagnostics	Methods and parameters	Features of type 2 diabetes
Clinical assessment	Collection of anamneses, physical examination, New York Heart Association functional class scale	Reduced sensitivity to symptoms due to diabetic neuropathy, obesity and myocardial adaptive overload
Electrocardiography	Detection of ischaemic changes, atrial fibrillation, bundle-branch block, left ventricular hypertrophy	Often gives non-specific data; requires correlation with cardiac imaging
Echocardiography	EF, ratio of early transmittal filling velocity to early diastolic relaxation velocity (E/e′), left atrial volume, left ventricular myocardial mass index, diastolic function parameters	Type 2 DM often preserves normal EF; relaxation and filling pressures are important
Magnetic resonance imaging of the heart	Determination of local and diffuse fibrosis, extracellular matrix volume, micronecrosis zones	Detects myocardial remodelling in CHF with preserved EF, especially when echocardiography is normal
Natriuretic peptides	NT-proBNP	Elevated in volume overload; used for early screening and monitoring of response to treatment
Biomarkers of fibrosis and inflammation	Soluble tumour suppressor receptor ST2, galectin-3, coeptin, FGF21 growth factor	Reflects fibroblast activation, interstitial inflammation and metabolic abnormalities in myocardium in type 2 DM
Tissue Doppler echocardiography	Early (e′) and late (a′) diastolic relaxation velocities, E/e′ ratio, global longitudinal strain (deformation)	Main method for preclinical assessment of diastolic dysfunction in patients with type 2 DM and preserved EF
Artificial intelligence	Neural network models, logistic regression, decision trees	Used for automated risk stratification based on a combination of clinical, laboratory and imaging data

Source: created by the author based on data analysis [25-31]

The structure of the presented diagnostic solutions demonstrated the necessity of alignment between the stages of verification and the nature of clinical uncertainty in type 2 DM, as traditional methods – such as assessment using the New York Heart Association scale and standard echocardiography – had limited sensitivity in latent forms of heart failure. The diagnostic framework was built as a system of interconnected levels – from preliminary clinical suspicion to molecular confirmation, with each method compensating for the limitations of others. This multistep approach made it possible to account for atypical features characteristic of the diabetic population, including muted symptoms, hidden diastolic dysfunction, and subclinical inflammation. It was precisely logical complementarity, rather than the prioritisation of a single approach, that formed the basis of an effective risk stratification model in this category of patients.

Modern approaches to the diagnosis of CHF in patients with type 2 DM have formed a qualitatively new paradigm, based on the combination of morphofunctional monitoring, remodelling biomarkers, and digital assessment algorithms. Exclusive reliance on traditional criteria proved unacceptable in the context of metabolic comorbidity, where the pathogenesis was polymorphic and clinical manifestation often lagged behind structural changes. Adequate diagnosis in such cases required the integration of advanced imaging, multi-biomarker panels, and intelligent tools, which significantly increased the accuracy of early detection and enabled timely initiation of pathogenetically justified therapy.

Current treatment strategies and pharmacotherapeutic deficiencies

Treatment of CHF in patients with type 2 DM requires multilevel intervention, taking into account the pathophysiological characteristics of metabolic comorbidity. Standardised treatment regimens are based on four fundamental pharmacological approaches that act on neurohumoral regulation, myocardial stress, and the rheological properties of the vascular bed. Each approach is implemented through separate drug classes, whose choice depends on the clinical form of CHF, the stage of renal dysfunction, and the functional reserve of the myocardium.

Targeting the renin-angiotensin-aldosterone system remained a fundamental approach in reduced EF (<40%). The use of ACE inhibitors was associated with afterload reduction and a lower risk of remodelling. In cases of ACE inhibitor intolerance (e.g., angioedema), angiotensin II receptor blockers were used, demonstrating comparable efficacy. Both drug classes showed a favourable profile in patients with type 2 DM but required monitoring of potassium levels and glomerular filtration rate (GFR). This aligned with the view of J. Bauersachs [32], who emphasised that modulation of the angiotensin-aldosterone system formed the basis of the so-called "great four" CHF therapy (ACE inhibitors/angiotensin II receptor blockers, β-blockers, mineralocorticoid receptor antagonists, SGLT2 inhibitors).

In patients with type 2 DM and symptomatic CHF with a heart rate ≥70 bpm on sinus rhythm, slowing of heart rate with β-adrenergic blockers was considered appropriate. The use was associated with inhibition of sympathetic activation, improved diastolic filling parameters, and reduced risk of life-threatening arrhythmias. It was established that in this category of patients, β-blockers remained effective even in the presence of obesity and insulin resistance. Regular monitoring of blood pressure and heart rate was required during titration [30]. Similar data were presented by B. Bozkurt [33], who emphasised that β-adrenergic blockers reduced the risk of sudden cardiac death and improved prognosis even in the presence of insulin resistance, confirming the necessity in patients with type 2 DM and CHF. In patients with EF ≤35% and stable electrolyte profile, inclusion of mineralocorticoid receptor antagonists such as spironolactone and eplerenone was indicated. The prescription was based on the need to block the effects of aldosterone, a key mediator of sodium retention and stimulator of myocardial fibrosis.

In patients with type 2 DM, this drug group additionally provided an antiproteinuric effect and could be used in patients with diabetic nephropathy at GFR >30 ml/min/1.73 m^2. The key innovation in CHF therapy in type 2 DM was the use of SGLT2 inhibitors. The inclusion in treatment algorithms was substantiated by studies showing a reduced risk of hospitalisation with any EF form. Drugs in this group, including empagliflozin, dapagliflozin, and ertugliflozin, did not require titration, demonstrated a favourable safety profile at GFR >20 ml/min/1.73 m^2, and were able to stabilise metabolic indicators without increasing the risk of hypoglycaemia. In cases of persistent tachycardia despite adequate β-blocking therapy, heart rate correction using ivabradine was allowed. This drug acted selectively on the If-channels of the sinus node, reducing heart rate without negative inotropic effect. Studies demonstrated its metabolic neutrality in type 2 DM and improved exercise tolerance in patients with CHF.

All guidelines (AHA, ACC, ADA, ESC) proposed stratified algorithms for drug prescription taking into account the heart failure phenotype, stage of renal insufficiency, arrhythmia risk, and congestion symptoms severity. Combined regimens were adapted for patients with type 2 DM and aimed at simultaneously affecting haemodynamics, myocardial structure, and the vascular bed. Similar principles of systemic stratification were outlined by Z. Bloomgarden & Y. Handelsman [30], who emphasised the importance of integrating recommendations from AACE, ADA, the European Association for the Study of Diabetes, AHA, ACC, and ESC into a unified patient management model for those with metabolic and cardiac risk. The authors stressed the need for multilevel consideration of comorbidities, including diabetic nephropathy, obesity, and cognitive impairment in elderly patients. Despite the availability of structured international guidelines, real-world clinical practice revealed significant deviations from optimal therapeutic regimens. According to multicentre observational data, the proportion of patients with type 2 DM and CHF receiving the full spectrum of recommended drug classes (ACE inhibitors or angiotensin II receptor blockers, β-blockers, MRAs, SGLT2 inhibitors) was less than 30% [32].

Similar barriers were identified by M. Jarjour *et al.* [34], who found that only 18% of patients with type 2 DM and CHF received guideline-concordant therapy. Furthermore, clinical inertia was recorded in 42% of cases, manifested in the absence of therapy initiation or escalation despite indications. The authors emphasised that the key limiting factors were physiological

(hypotension, reduced GFR), physicians' subjective assessment of frailty in older patients, and poor integration of interdisciplinary approaches. In elderly patients, dose titration was often not feasible due to poor exercise tolerance, unstable haemodynamics, and symptomatic hypoglycaemia, further limiting the implementation of therapy optimisation guidelines.

Additionally, cases of clinical inertia were described when patient conditions deteriorated – with no modification of the treatment regimen even in the presence of CHF progression, despite the availability of alternative drug classes. On the patient side, reduced adherence to therapy was observed when using multicomponent regimens, especially in the presence of cognitive dysfunction and polypharmacy. In the Republic of Kazakhstan and other countries in Central Asia and Eastern Europe with limited healthcare funding, insufficient access to SGLT2 inhibitors, GLP-1 receptor agonists, and angiotensin receptor-neprilysin inhibitors (ARNIs) was noted, which limits full implementation of international recommendations [30].

Modern approaches to CHF therapy in patients with type 2 DM were based on combined use of pathogenetically oriented drug classes, taking into account the clinical phenotype. Alongside the proven efficacy of basic regimens, systemic and individual limitations were identified that hindered the full implementation, especially in resource-limited countries. This underscored the need for further adaptation of therapeutic strategies to the specifics of metabolic comorbidity and the healthcare context.

Comparative analysis of statistical indicators of CHF treatment in type 2 DM in the USA and Kazakhstan

The comparative analysis of the epidemiological characteristics of CHF in patients with type 2 DM in the USA and the Republic of Kazakhstan revealed significant differences in disease burden, the structure of medical care, and pharmacotherapeutic availability. At the same time, it should be noted that the presented data from the USA and Kazakhstan partially cover different time intervals within 2020-2023, which may affect the degree of comparability of indicators. The lack of full synchronisation by year of analysis should be considered a methodological limitation, which does not diminish the significance of the identified differences but requires caution in interpreting trends.

According to the data from the US National Centre for Health Statistics, in 2022 more than 6.7 million adults were registered with a CHF diagnosis, of whom about 40% had concomitant type 2 DM [11]. The overall prevalence rate of CHF among the adult population in the USA during 2020-2023 ranged from 2-2.1% (an average of about 6.9 million people), while the mortality rate from heart failure among patients with type 2 DM reached 66.2 cases per 100,000 population. The rate of repeated hospitalisations due to decompensation within 30 days consistently exceeded 21%, reflecting high clinical instability in this group of patients [12]. According to the AHA report, covering retrospective estimates up to the end of 2023, the specific contribution of CHF in type 2 DM to the total burden of cardiovascular diseases was estimated at 7.3% of all DALYs, which corresponded to more than 2 million years of life lost adjusted for disability [13].

In the Republic of Kazakhstan, according to the analysis of the Unified National Electronic Health System, by 2022 the diagnosed prevalence of CHF among the adult population reached 2.2% (22,088 cases per million), whereas during 2020-2023 this indicator was on average assessed at 0.85%, significantly lower than in the USA. This was considered a reflection of underdiagnosis of latent forms of the disease, primarily CHF with preserved EF, and limited coverage by screening programmes [22]. The proportion of patients with type 2 DM in the structure of all CHF cases reached 38.4%, comparable to US data. Mortality from CHF in type 2 DM in the northern and eastern regions of Kazakhstan during the specified period reached 82.7 cases per 100,000, exceeding similar indicators in the USA [16]. Although the DALY rate for CHF in type 2 DM in Kazakhstan was not directly calculated, predictive models for Central Asia suggest that the total losses from cardiovascular diseases and DM by 2030 may exceed 4,000 per 100,000 women of reproductive age [15].

Comparison of CHF mortality rates in patients with type 2 DM in the USA (66.2 per 100,000) and Kazakhstan (82.7 per 100,000) revealed a range of structural, organisational, and therapeutic factors explaining the observed differences. Higher mortality in the Kazakhstani population was explained by limited access to modern pharmacotherapy (particularly SGLT2 inhibitors and ARNIs), poor implementation of systematic screening programmes, and insufficient detection of CHF with preserved EF in patients with oligosymptomatic courses. In contrast, the USA widely used multidisciplinary outpatient approaches, centralised registries, and telemonitoring, which ensured continuity of observation. According to F. Cosentino *et al.* [35], the use of the SGLT2 inhibitor ertugliflozin reliably reduced the risk of CHF hospitalisation by 30% in patients with type 2 DM and established atherosclerotic cardiovascular diseases. These data confirmed the therapeutic significance and feasibility of widespread use of this drug class in the cardiometabolic population. In Kazakhstan, however, the limited introduction of SGLT2 inhibitors into clinical practice was explained by both economic barriers and the absence of local protocols integrating the results of international randomised controlled trials. In the USA, on the contrary, such drugs were actively implemented due to insurance coverage policies and AHA/ACC/ADA recommendations. Additionally, according to A.J. Nelson *et al.* [36], even in the USA a significant gap remained between the evidence base and its implementation: only 55% of patients with

type 2 DM and atherosclerotic cardiovascular diseases received all recommended drug classes. Nevertheless, the same study emphasised that coverage with combination therapy in insured systems significantly exceeded 70%, especially in specialised clinics. This is comparable to data showing 78% coverage in EF cohorts in the USA [11], while in Kazakhstan a similar indicator was less than 45% [17]. Thus, the observed excess mortality in Kazakhstan could be explained not only by differences in drug availability but also by the absence of systematic routing and insufficient implementation of the multidisciplinary approach, which is especially critical for patients with type 2 DM and CHF. The lack of a CHF register for type 2 DM, underdevelopment of telemonitoring, and fragmented follow-up further reduced the potential for long-term disease control.

Based on the identified differences in epidemiological profile, routing structure, and therapy coverage, a step-by-step implementation of elements of the American model of cardiometabolic care adapted to the resource and systemic features of Kazakhstan's healthcare was considered appropriate. First and foremost, diagnostics needed modernisation: the introduction of comprehensive diagnostic circuits with mandatory use of tissue Doppler echocardiography, biomarkers (BNP, NT-proBNP, sST2, Gal-3), and expanded assessment of diastolic function. A review of early detection and screening protocols in individuals with type 2 DM was necessary – especially in high-risk groups. Active application of stratification scales (e.g., H2FPEF score, MAGGIC) and centralised training of primary care specialists was recommended.

The next area was the optimisation of routing and dispensary observation. In the USA, the "cardiometabolic clinics" model proved effective, where patients received interdisciplinary supervision from a cardiologist, endocrinologist, and nurse-mentor. For Kazakhstan, the format of regional multidisciplinary centres at major hospitals with telemonitoring and remote therapy adjustment functions remained potentially applicable. The study by A. Sciacqua *et al.* [37] highlighted that it was the interdisciplinary approach and extended outpatient monitoring of elderly patients with CHF and type 2 DM that reliably reduced repeat hospitalisation rates and improved treatment adherence, especially in the presence of concomitant cognitive and functional disorders. Also important was the formation of a national register of CHF in type 2 DM, linked to electronic health systems, which would allow tracking of therapy coverage dynamics, mortality, and hospitalisation rates in real time. From the pharmacotherapy standpoint, government support was required for reimbursement programmes of new drug classes – SGLT2 inhibitors and ARNIs – as well as the development of a national formulary synchronised with international guidelines (AHA/ACC/HFSA, ESC). Given the high cost of these drugs, it was justified to include these drugs in preferential categories for priority groups, which would improve treatment adherence and reduce the burden of repeat hospitalisations.

Despite certain similarities in the comorbidity structure, the USA and Kazakhstan demonstrated different levels of repeated hospitalisations, mortality, and coverage with effective therapy. These differences were partially explained by disparities in medication availability, care organisation, and healthcare financing systems.

Conclusions

The obtained results confirmed that the pathogenesis of CHF in patients with type 2 DM was caused by the combined influence of metabolic, vascular, and inflammatory disorders, leading to progressive myocardial remodelling. The formation of a specific CHF phenotype in this population was explained not by an isolated factor but by the cumulative effect of chronic hyperglycaemia, insulin resistance, endothelial dysfunction, and intercellular inflammation. Such a multicomponent nature of the lesion required a shift in focus from late compensation to early prevention, aimed at stabilising the cardiometabolic background even before the onset of pronounced systolic dysfunction.

In the diagnostic aspect, it was established that up to 60-70% of patients with type 2 DM had CHF with preserved EF, in which standard echocardiography proved insufficient. Accuracy was improved through a comprehensive assessment of diastolic parameters, biomarkers (natriuretic peptides, sST2, galectin-3), and digital technologies, including neural network models with a risk stratification accuracy of up to 90%. The pharmacotherapy analysis showed that a combination of ACE inhibitors/angiotensin II receptor blockers, β-blockers, MRAs, and SGLT2 inhibitors improved prognosis and reduced hospitalisation rates by 20-25%. However, in Kazakhstan, the coverage of basic therapy was less than 45% compared to 78% in the USA, which was explained by limited drug availability, clinical inertia, and weak primary-level referral systems. A comparative analysis of statistics from 2020-2023 revealed higher mortality from CHF in type 2 DM in Kazakhstan (up to 82.7 per 100,000) compared to the USA (66.2 per 100,000), despite a similar prevalence of DM. Differences in rehospitalisation rates and treatment coverage indicated the importance of systemic factors – insurance coverage, digital monitoring, and standardised referral pathways – in improving outcomes and reducing the epidemiological burden.

A limitation of this study was the absence of primary clinical data and the inability to perform statistical processing of empirical samples. A promising direction for further research may be the development of stratified patient management models for CHF and type 2 DM based on real registry data in countries with different healthcare systems.

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Conflict of Interest

None.

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2-типтеги кант диабети менен ооругандардын жүрөк жетишсиздигин диагностикалоого жана дарылоого заманбап ыкмалар

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Аннотация. Иштин максаты патогенезин, текшерүү ыкмаларын жана терапиянын эффективдүүлүгүн талдоонун негизинде 2-типтеги кант диабети (КД) менен ооруган бейтаптарда өнөкөт жүрөк жетишсиздигинин (ӨЖЖ) диагностикасына жана дарылоосуна карата системалуу чектөөлөрдү аныктоо болгон. Теоретикалык мамиленин алкагында 2 типтеги КДКнын клиникалык, патофизиологиялык жана уюштуруучулук моделдери диагностикалык алгоритмдерди, терапиялык стратегияларды жана саламаттыкты сактоонун ар кандай улуттук системаларынын статистикалык маалыматтарын кийинки салыштыруу менен реконструкцияланган жана алдыңкы патогенетикалык механизмдерге эксперттик баа берилген. Теориялык талдоо 2-тип кант диабетинде ӨЖЖ өнүгүшү диабеттик кардиомиопатиянын, микроваскулярдык ишемиялардын жана өнөкөт сезгенүүнүн биргелешкен таасири менен аныкталганын аныктады. Эжекциялык фракцияны (ЭФ) баалоого негизделген диагностикалык алгоритмдер жыйрылышы функциясы сакталган пациенттерде чектелген сезгичтикти көрсөттү, алардын үлүшү 60-70 % га жетти. Эрте диагностиканын эң маалыматтуу ыкмалары болуп ткандардын доплер эхокардиографиясы жана фиброздун жана ашыкча жүктөмдүн биомаркерлерин аныктоо, анын ичинде натриуретикалык пептиддер, шишиктин эрүүчү рецепторлорун басуу-2 жана галектин-3 таанылды. 2-типтеги кант диабети менен ооруган бейтаптарда ӨЖЖ дарылоодо эң чоң далилдүү эффективдүүлүк төрт класстагы дары-дармектерди айкалыштыруу менен көрсөтүлдү: ангиотензинди айландыруучу фермент ингибиторлору, β-блокаторлор, минералокортикоиддик рецепторлордун антагонисттери жана натрий-глюкозанын ингибиторлору (SLT2 типтеги ингибиторлору). Негизги дары-дармек терапиясын камтууда олуттуу айырмачылыктар аныкталды: АКШда пациенттердин 78 %ке чейинкиси комбинацияланган терапияны алышкан, ал эми Казакстанда 45 %тен аз болгон. Бул карама-каршылыктар өлүмдүн көрсөткүчүндө да чагылдырылган: АКШда 100 000 калкка 66,2 учур, Казакстандын айрым аймактарында бул көрсөткүчтүн олуттуу өсүшү. Алынган натыйжалар диагноздун тактыгын жогорулатууга, терапияны индивидуалдаштырууга жана жүрөк-кан тамыр ооруларынан өлүмдү кыскартууга мүмкүндүк берген комбинирленген патологиянын фенотиптик өзгөчөлүктөрүн эске алуу менен клиникалык протоколдорду адаптациялоо зарылдыгын негиздеди

Негизги сөздөр: миокард; зат алмашуунун коштолгон оорулары; ишемия; диастоликалык дисфункция; инсулин; чыгаруу фракциясы

Современные подходы к диагностике и лечению сердечной недостаточности у пациентов с сахарным диабетом 2 типа

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Аннотация. Целью работы являлось выявление системных ограничений в подходах к диагностике и лечению хронической сердечной недостаточности (ХСН) у пациентов с сахарным диабетом (СД) 2 типа на основе анализа патогенеза, методов верификации и эффективности терапии. В рамках теоретического подхода были реконструированы клинико-патофизиологические и организационные модели ХСН при СД второго типа с последующим сопоставлением диагностических алгоритмов, терапевтических стратегий и статистических данных из различных национальных систем здравоохранения, а также была выполнена экспертная оценка ведущих патогенетических механизмов. В ходе теоретического анализа было установлено, что формирование ХСН при СД 2 типа определялось совокупным влиянием диабетической кардиомиопатии, микрососудистой ишемии и хронического воспаления. Диагностические алгоритмы, основанные на оценке фракции выброса (ФВ), демонстрировали ограниченную чувствительность у пациентов с сохранённой сократительной функцией, доля которых достигала 60-70 %. Наиболее информативными методами ранней диагностики были признаны тканевая допплерэхокардиография и определение биомаркеров фиброза и перегрузки, включая натрийуретические пептиды, растворимый рецептор suppression of tumorigenicity-2 и галектин-3. Наибольшую доказательную эффективность в лечении ХСН у пациентов с СД 2 типа демонстрировало комбинированное применение четырёх классов препаратов – ингибиторов ангиотензинпревращающего фермента, β-адреноблокаторов, антагонистов минералокортикоидных рецепторов и ингибиторов натрий-глюкозного котранспортёра 2 типа (иНГЛТ-2). Были выявлены значительные различия в охвате базовой лекарственной терапией: до 78 % пациентов в США получали комбинированное лечение, тогда как в Казахстане – менее 45 %. Эти расхождения также проявлялись в уровне смертности: 66.2 случая на 100,000 населения в США против выраженного роста данного показателя в отдельных регионах Казахстана. Полученные результаты обосновывали необходимость адаптации клинических протоколов с учётом фенотипических особенностей сочетанной патологии, что позволяло повысить точность диагностики, индивидуализировать терапию и снизить сердечно-сосудистую смертность

Ключевые слова: миокард; метаболическая коморбидность; ишемия; диастолическая дисфункция; инсулин; фракция выброса

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Development of early diagnostics of hearing impairment in Kyrgyz Republic

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Abstract. The aim of the study was to comprehensively assess the availability and effectiveness of newborn hearing screening, as well as the diagnosis and treatment of otopathologies in children, with a focus on improving early detection of hearing impairment and improving the quality of medical care. The study examined screening methods for newborn hearing, various methods of diagnosis, and treatment of otopathologies in children. The study included a comprehensive analysis of statistical reports from healthcare facilities that conducted neonatal hearing screening, and a survey of otolaryngologists, paediatricians and neonatologists in different regions of the country. Particular attention was paid to assessing the availability and quality of primary screening, further diagnostics, and early intervention. The analysis covered 9,609 newborns who underwent audiological examination in eight medical institutions, including maternity hospitals in Bishkek, Osh, Jalal-Abad, and the Republican Perinatal Centre. The results showed that during this period, the number of maternity hospitals where screening was carried out increased from 3% to 37%, indicating a gradual introduction of this practice into the medical system. In urban areas, about 68% of newborns were screened, while in rural areas only 19% were screened, indicating significant inequalities in access to medical services. Hearing impairment was suspected in 1.7% of children, of whom 0.8% had confirmed hearing loss. Apart from quantitative analysis of screening coverage, the study identified a series of organisational and social factors that influenced the effectiveness of early detection of hearing impairment. Specifically, the level of parental awareness of the significance of hearing screening and follow-up after the initial examination played a significant role: it was found that more than half of the families who received a positive screening result did not undergo a second diagnosis due to lack of information or access to appropriate medical services. The practical value of the study lies in the fact that its findings can be used to further investigate the problem of early detection of hearing impairment, improve the healthcare system, particularly in the field of otolaryngology and neonatal screening, and develop effective strategies for prompt intervention that will improve the quality of life of patients

Keywords: audiological testing; neonatal screening; otoacoustic emission; early interventions in otopathology; primary screening

Introduction

Early detection of hearing impairment in newborns directly affects the speeoch develpment, cognitive development, and successful socialisation of the child. The effectiveness of the neonatal hearing screening system depends on the promptness of diagnostics and the start of rehabilitation measures. The existing organisational

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and infrastructural barriers, uneven access to quality medical care, and lack of parental awareness create a need to improve mechanisms for the early detection and treatment of otopathologies in children.

W.A. Adegbiji *et al*. [1] found that the prevalence of hearing pathologies among children was 5.9%, with sensorineural deafness predominating (61.4%). Successful diagnostics in the first months of life allows starting hearing correction even before serious delays in speech development occur, which is necessary for the development of a child's normal psycho-emotional state and further integration into society. D.F. Fahim *et al*. [2] showed that children and adolescents with hearing impairment have a greater level of emotional and behavioural challenges than children with normal hearing. Language difficulties, including delayed speech development, were the major contributing factors to emotional and behavioural problems.

According to A.A. Al Zahrani *et al.* [3], hearing screening is an essential public health measure that significantly improves the quality of life. In this regard, neonatal hearing screening is a mandatory component of the healthcare system in most countries of the world. Implementation of mass hearing screening programmes for newborns is a priority not only for countries with a prominent level of economic development, but also for countries with limited resources, where the problem of late diagnostics considerably complicates further treatment and rehabilitation. C. Chiong [4] expressed the same opinion. Parental awareness of hearing loss in newborns and newborn hearing screening programmes are both crucial for early detection and intervention in children with hearing loss. Few studies focused on maternal awareness of newborn hearing loss, newborn hearing screening, its necessity, and the facilities for early hearing screening available in hospitals and clinics in the Indian scenario. P.S. Pooja *et al*. [5] also reached this opinion. A press release from UNICEF Kyrgyzstan [6] states that, as part of a joint project, UNICEF donated audiological screening devices to support the development of the initiative, equipping 22 medical facilities across the country and enabling healthcare professionals to detect hearing impairments in newborns from the very first day of life.

In Kyrgyzstan, since 2017, there has been an increase in interest in the problem of hearing impairment in newborns, driven by both global health trends and the efforts of individual professionals and organisations. New initiatives are emerging to raise awareness among medical staff and parents of the need for early detection of hearing loss. Specifically, some perinatal centres are implementing pilot programmes using otoacoustic emissions to screen newborns' hearing. Trainings are held for neonatologists and nurses, as well as public awareness campaigns. Furthermore, access to modern diagnostic equipment and audiology specialists is still limited, especially in rural areas, which requires a comprehensive approach to the future development of this important area of child health care. A.A. Musaev *et al*. [7] examined the problem of paediatric hearing impairment and emphasised the importance of establishing effective structures for early detection of hearing loss in preschool-aged children. The authors highlighted the significance of age-appropriate audiological diagnostic methods within the framework of auditory screening, taking into account the child's developmental readiness to follow clinical instructions. According to the researchers, comprehensive measures are necessary to support children with hearing and speech disorders, improving their educational and employment prospects.

To address this problem, the study investigated the current state of the early hearing screening system, analysed existing practices, identified strengths and weaknesses, and developed recommendations for further development and integration of screening programmes into national health policy. In this context, it was relevant to analyse the effectiveness of the measures implemented in individual regions, the degree of newborn screening coverage, the quality of subsequent diagnostics, human and technical support, and the level of interaction between various levels of medical care.

V.V. Khalfin *et al*. [8] conducted a molecular-genetic study aimed at identifying the prevalence of mutations in the GJB2 gene, which encodes the connexin 26 protein, among patients with bilateral sensorineural hearing loss of unknown origin in the Kyrgyz Republic. Their findings underscore the genetic heterogeneity of hearing impairment in the region. By analysing 89 patients, the researchers revealed that GJB2 mutations were present in 21.3% of cases, with a notable difference between ethnic groups. The mutation 35delG was observed in the homozygous state exclusively among children of Russian and Tatar descent, while in the Kyrgyz population it appeared only in compound heterozygous combinations with other mutations (235delC and −23 + 1G > A). Importantly, the study highlights the diagnostic and prognostic value of genetic screening, as establishing the aetiology of hearing loss allows for more accurate predictions of hearing threshold progression and facilitates the selection of appropriate rehabilitation strategies. The authors also draw attention to the potential influence of assortative mating in the inheritance of pathogenic variants, which is relevant for genetic counselling and public health planning.

The findings revealed that the introduction of systematic neonatal screening considerably reduced the age of detection of deafness, which allowed starting hearing prosthetics or cochlear implantation before 6 months of age. P.H. Skarzynski *et al*. [10] also explored this topic and noted the need for further hearing screening programmes in these countries to detect hearing problems early and implement adequate diagnostic and therapeutic approaches, which would

improve treatment outcomes. The findings of their study showed that 75.4% of children had normal hearing, while 13.4% were diagnosed with unilateral and 11.2% with bilateral hearing loss. This was also noted by P.H. Skarżyński *et al*. [11], as out of 452 children, 27.2% had hearing pathology, which is a high rate, and detection of these diseases immediately after birth will greatly facilitate the adaptation and life of these children.

The purpose of the present study was to examine the current state of the system of early diagnostics of hearing impairment in Kyrgyz Republic, assess the effectiveness of the implemented screening measures, identify the key barriers, and develop proposals for optimising the national approach to neonatal hearing screening. The study set the following objectives:

- to analyse the status of implementation of newborn hearing screening in Kyrgyzstan, considering regional differences, technical support, and human resources;
- to assess the effectiveness of existing methods of treatment of identified hearing impairment, including the use of hearing aids, cochlear implantation, and other surgical interventions.

Materials and Methods

The study was conducted in Clinical Maternity Hospital of the National Centre for Maternal and Child Health, Maternity Hospital of the Regional State Clinical Hospital in Osh, Maternity Hospital of Jalalabad, City Perinatal Centre No. 4 in the period from 1 June 2021 to 1 June 2024. A total of 9,609 newborns were studied. Newborns who had undergone primary audiological testing in maternity hospitals and primary healthcare facilities, including regional and city perinatal centres, were selected for inclusion in the study. The inclusion criteria included availability of data on neonatal hearing screening in maternity hospitals, parental consent to take part in the study, and newborn age up to 28 days. Children with positive results of the initial screening were referred for further examination to confirm the diagnosis.

Exclusion criteria included newborns with severe somatic diseases that required emergency medical care and were under intensive care, as well as children who did not have parental consent to take part in the study. Furthermore, cases where screening data were not recorded or where children were unable to undergo further examination for technical or organisational reasons were excluded. All parents of newborns taking part in the study were informed in advance about the purpose, procedures, and specifics of participation in the study. During the collection of parental consent to take part in the study, they were given all the necessary explanations that participation in the study was voluntary and that all data obtained would be used exclusively for scientific purposes, with confidentiality. Parents signed a written consent for their children to take part in the study, which met the requirements of ethical standards and legal norms. The study was conducted following the principles of the Declaration of Helsinki [12], which ensures the ethical safety of human research. The study also followed national legislation on medical and scientific research, which guaranteed the protection of the rights and well-being of newborns and their families.

During the study, the MADSEN AccuScreen Otometrics was employed to measure otoacoustic emissions, which enabled a quick determination of hearing impairment by recording sound waves generated by the inner ear in response to sound stimuli. In this study, standard statistical techniques were employed to process the data to ensure the reliability of the findings. Specifically, descriptive statistics were employed to analyse the baseline characteristics of the newborn population.

Results and Discussion

From the results of the screening conducted using otoacoustic emissions and auditory evoked potentials, it was found that hearing impairment was suspected in 1.7% of newborns, which is 145 children out of 9,609. N. Zahra & N. Purnami [13] also emphasised the significance of early identification and monitoring of infants with risk factors for prompt intervention and prevention of hearing loss. Further testing and diagnostics confirmed the presence of hearing loss in 0.8% of newborns, which equates to 68 children. This means that 68 children had confirmed hearing impairments that required further treatment and correction. Of the 145 children suspected of having hearing impairment, 48% underwent follow-up examinations and confirmation of the diagnosis through two stages of testing. According to the results of further examinations, 21 children had bilateral hearing impairment (approximately 30% of all cases), 18 children had hearing impairment on one side, and 29 children were diagnosed with mild hearing loss. At the same time, 62% of the children identified with hearing impairment required hearing aids or other methods of correction, including early intervention in the form of hearing implants for children with severe hearing impairment. E. Genovese *et al*. [14] found that about 70% of children with congenital sensorineural hearing loss had concomitant vestibular disorders, of which 20-40% were severe bilateral lesions.

Conductive deafness was detected in 0.5% of cases (50 children), and genetic disorders associated with syndromes in 0.5% (60 cases). Infectious causes of hearing loss, such as meningitis or herpes, accounted for 0.4% (65 children), while microcephaly with hearing loss accounted for 0.3% (45 cases), other congenital hearing loss accounted for 0.3% (30 cases), and traumatic hearing loss accounted for 0.2% (25 children). These findings confirmed the tendency for inflammatory and sensorineural forms of hearing impairment to predominate among newborns, which substantiated the need for prompt screening and expansion of preventive measures.

Statistical analysis showed that the largest percentage of children with confirmed hearing impairment was registered in urban areas – 56% of the total number of children with hearing impairment, which was 38 children out of 68. This result can be explained by the greater accessibility of medical services and more developed infrastructure for screening in urban maternity hospitals in Bishkek. This indicates major disparities in access to healthcare services, which is an essential issue for the further development of the healthcare system in the country. At the same time, the data showed significant inequalities in access to screening services between urban and rural areas. In urban areas, 68% of newborns were screened, while in rural areas only 19% were screened. This difference in accessibility indicates the need to develop and improve programmes that will ensure equal access to health services for all residents of the country. Additionally, the findings showed that in the first three years of the programme, hearing screening was not systematically conducted in all healthcare facilities, which was one of the barriers to achieving marked results in early detection of hearing impairment. Most of the positive screening results were obtained in maternity hospitals in large cities, which confirmed the need to improve the logistics and resource support of programmes in rural areas.

Each method was employed to detect hearing impairment at various stages of the diagnostic process, and the results showed varying effectiveness of each in the context of early detection. The OAE test was conducted at the first stage of the study and became the key tool for primary screening, allowing to detect hearing impairment at early stages, without the need for the child's cooperation during the test. In total, the initial testing revealed suspected hearing impairment in 1.7% of newborns, or 145 children out of 9,609. This indicates the high sensitivity of the method to detect hearing impairment, as it can detect impairment in the first hours after birth. R. Kaushik *et al*. [15] evaluated the possibility of using otoacoustic emissions testing to detect hearing loss in patients. The researchers found that out of 31 patients enrolled in the study, 23 (74.2%) successfully passed otoacoustic emissions testing, and among 18 patients with complete data, 6 (33%) had signs of significant hearing loss. The researchers also noted that otoacoustic emissions testing is an adequate method for screening for hearing loss in patients. F. Elbabour [16] confirmed that otoacoustic emissions testing, in particular the distortion-product otoacoustic emissions method, is an effective and objective tool for assessing hearing in children, especially when conventional behavioural assessment methods are challenging or impossible. This approach enables early detection of potential hearing impairment, which is critical for prompt intervention and support of speech and communication skills.

To clarify the diagnosis and confirm the results of the initial testing, further testing was performed using auditory evoked potentials. This method was more accurate in determining the functionality of the auditory nerve and brainstem, which allows detecting more complex or hidden hearing impairments. When applying the ASVP to 145 children with suspected hearing impairment, 68 children (0.8% of the total number of newborns) were confirmed to have pathologies. This means that the ASVP method helped to confirm the diagnosis and identify children with more serious hearing impairments that required further treatment and correction. A.C. Romero *et al*. [17] also explored this topic and noted that this diagnostic method is a valuable tool for assessing the development of the auditory system in children, especially in clinical settings where behavioural methods may be unreliable or inapplicable.

Comparing the effectiveness of both methods, it can be noted that UAE testing identified a greater number of children with suspected hearing impairment (1.7%), but due to the relative sensitivity of this method to noise and false positives, some of them did not have confirmed pathologies. In contrast, the ASVP method, although less sensitive at the first stage, revealed a more accurate confirmation of pathologies (0.8%), which helps to avoid misdiagnosis and provide more accurate treatment. J. Kegele *et al*. [18] also studied UAE testing in children. The results of their study showed that otoacoustic emissions are an effective and rapid method for primary hearing screening in newborns. However, this method may have a greater false-positive rate. At the same time, automated auditory brainstem response was found to be more accurate in detecting sensorineural hearing loss with a lower false-positive rate, making it a reliable method for confirming the diagnosis, which is consistent with the findings of the study [19].

Further comparison showed that the detected hearing pathologies varied significantly in severity. It was found that 21 children had bilateral hearing impairment, which is about 30% of all cases of hearing impairment. 18 children had hearing impairment on one side, and 29 children were diagnosed with mild hearing loss. In the end, only 62% of children with confirmed hearing loss required hearing aids or hearing implants, which demonstrates the effectiveness of the methods used to identify children with severe hearing loss. Notably, if only one method (UAE or ASVP) is used, the diagnostics may be incomplete, as each method has its limitations. Otoacoustic emissions has high sensitivity but can give false positive results due to the influence of external factors or unfavourable testing conditions. The researchers revealed that the prevalence of hearing impairment was found in 14 out of 426 newborns (3.3%), 2 newborns had unilateral moderate hearing loss, and 12 newborns had bilateral hearing loss of varying degrees, which is consistent with the present study.

Overall, the comparison of these two methods proved that the use of both technologies in combination gives the most accurate results, which ensures a prominent level of diagnostics and allows prompt detection of hearing impairment in newborns. This confirms the need to integrate the two methods into early detection programmes to ensure maximum diagnostic accuracy and prompt medical care for newborns with hearing loss.

The study identified several risk factors that affected the probability of hearing impairment in newborns. Analysis of statistical data showed that certain factors were closely associated with a prominent level of hearing impairment among the children screened. The first major risk factor identified was a genetic factor. The study found that 15% of children with confirmed hearing loss had a family history of hearing loss. This indicates a genetic predisposition to developing hearing impairment. Specifically, 11 out of 68 children (16%) had relatives with analogous hearing impairments. This confirms a certain significance of genetic factors among the causes of hearing disorders among newborns. Another major risk factor was infections during the mother's pregnancy. In 10% of cases of hearing impairment in newborns, mothers were observed to have had infectious diseases during pregnancy, such as rubella, cytomegalovirus, or toxoplasmosis. According to statistics, out of 68 children with hearing impairment, 7 had mothers who had suffered from infectious diseases during pregnancy, which was the key factor in the development of hearing impairment. Furthermore, it was found that preterm birth was a serious risk factor for hearing impairment. Among newborns born before 37 weeks of gestation, hearing impairment was observed in 3.5% of cases, which is significantly higher than the average level in the population (0.8%). Among 68 children with confirmed hearing impairment, 4 were born prematurely. This indicates a greater risk of hearing impairment among children born in early pregnancy. A.O. Amaral *et al*. [20] studied the association between microcephaly and hearing impairment in children exposed to Zika virus during the intrauterine period. They also identified the link between infectious pathologies and hearing impairment.

The presence of pathologies at birth was also identified as a significant risk factor. T. Klymenko *et al*. [21] found that oxidative stress at birth is a major risk factor for the development of hearing pathologies in preterm infants, 25% of preterm infants were found to have hearing impairment of varying severity, while the level of oxidative stress was significantly greater in children with hearing impairment compared to those without such problems. Among newborns with congenital anomalies, such as malformations of the hearing organs or the central nervous system, hearing impairment was observed in 6% of cases, which is almost twice as high as among healthy children. Of the 68 children with hearing impairment, 5 had congenital anomalies that affected their hearing development. One of the significant risk factors was the use of medications during pregnancy, particularly antibiotics and medications that can adversely affect the development of foetal hearing. In 4% of cases, hearing impairment in newborns was associated with the use of drugs such as aminoglycosides (particularly gentamicin, tobramycin, streptomycin) in high doses. The use of these medications, especially in doses of more than 2.5 mg/kg per day or with prolonged use, caused toxic effects on the foetal auditory organs, leading to hearing impairment in newborns. J. Wang *et al*. [22] investigated the relationship between the use of antibiotics during pregnancy and the risk of hearing impairment in newborns. The study found that the use of antibiotics during pregnancy is associated with an increased risk of hearing impairment in children, with a particularly high risk observed with the use of aminoglycosides during pregnancy, which is consistent with the present study. More detailed data on the causes are presented in Table 1.

Table 1. Risk factors for hearing impairment among newborns based on study data

Risk factors	Incidence among newborns with hearing impairment (out of 68)	Percentage out of all newborns (out of 9,609)	Notes
Genetic factor	15% (10 children)	0.2%	10 of the 68 children had relatives with hearing loss, indicating a possible genetic predisposition. One of the most well-known genes associated with hearing loss is GJB2, which encodes the protein Connexin 26
Maternal infections during pregnancy	10% (7 children)	0.1%	Mothers of these children have had infectious diseases such as rubella, cytomegalovirus, or toxoplasmosis
Premature birth (less than 37 weeks)	6% (4 children)	0.4%	Children born before 37 weeks of gestation have a much higher risk of hearing loss
Congenital abnormalities (hearing or nervous system defects)	7% (5 children)	0.6%	Congenital abnormalities in the development of the hearing organs or nervous system were identified in several children with hearing impairment
Medicinal treatment of the mother (antibiotics, aminoglycosides)	4% (3 children)	0.05%	Mothers of these children took medications that can adversely affect hearing development during pregnancy
Regional differences	56% (38 children) from urban areas vs 30% (20 children) from rural areas	0.9%	There is a significant difference in access to health services and screening between urban and rural areas
Other medical conditions (low birth weight, anaemia, etc.)	3% (2 children)	0.2%	Risk of hearing impairment was also greater in children born with low birth weight or other medical problems

Source: compiled by the authors

Thus, based on the findings obtained, several key risk factors for hearing loss among newborns can be identified, including genetic factors, maternal infectious diseases during pregnancy, preterm birth, congenital anomalies, and the use of certain medications. These factors substantially influence the screening results and require special attention when developing measures for early diagnosis and prevention of hearing impairment among newborns. Y.Z. Yilmaz *et al*. [23] found that SARS-CoV-2 infection in mothers during pregnancy may be associated with an increased risk of temporary hearing impairment in newborns. These impairments are usually bilateral and reversible, which confirms the need for early hearing screening in newborns, especially in cases where mothers have had COVID-19 during pregnancy, which is consistent with the present study.

The treatment of newborn hearing loss depended on the particular type of hearing impairment. Depending on the diagnosis, treatment included medication therapy, surgery, hearing aids, and rehabilitation measures. Neurosensory deafness (congenital) in newborns was treated using various methods, including cochlear implants, which were the primary method of hearing correction in severe forms of this pathology. Implantation was usually performed before the age of 2, which ensured maximum effect. However, in recent years, it has also been increasingly performed from the age of 2. After implantation, rehabilitation was performed, which included language courses and training to adapt to new hearing conditions. The effectiveness of cochlear implants was 90-95% in eliminating deafness, which considerably improved the perception of sounds and speech in children with profound deafness. Compared to other methods, such as hearing aids, cochlear implants showed much better outcomes in severe cases. N. Zajdel *et al*. [24] also came to the same conclusion and noted that cochlear implantation is an effective method of hearing rehabilitation in children with deafness caused by congenital CMV infection.

Implantation of a cochlear implant for up to 2 years resulted in a hearing improvement of 20-40 dB in 90% of patients. R. Bouatay *et al*. [25] found that early detection and prompt insertion of implants significantly improved patients' speech and hearing functions. The average age of implantation was 12-18 months, which is optimal for learning speech and communication skills. In most cases, there was a significant improvement in the Categories of Auditory Performance scale, particularly in patients who received the implant before the age of 2.

The findings of the study demonstrated the effectiveness of combining otoacoustic emissions and auditory evoked potentials in the early detection of hearing impairment in newborns, confirming pathology in 0.8% of cases with suspected hearing loss. Otoacoustic emissions proved to be a sensitive tool for primary screening, while auditory evoked potentials provided greater diagnostic accuracy and confirmation. Key risk factors – such as genetic predisposition, maternal infections during pregnancy, prematurity, congenital anomalies, and the use of ototoxic medications – highlight the importance of close monitoring of at-risk groups. The significant disparity in access to screening between urban and rural areas indicates an urgent need to expand early diagnostic programmes nationwide. Furthermore, the high effectiveness of early cochlear implantation, particularly before the age of two, underscores the critical role of timely diagnosis and intervention in improving hearing and speech development in children with severe hearing loss.

Conclusions

The study evaluated the effectiveness of various diagnostic and therapeutic approaches for hearing pathologies in newborns, including sensorineural and conductive hearing loss, trauma-related disorders, and conditions resulting from infections or genetic syndromes. The primary treatment methods included pharmacotherapy, surgical interventions (such as tympanoplasty and cochlear implantation), and the use of hearing aids. Among these, cochlear implantation demonstrated the highest efficacy, achieving a success rate of 90-95% in cases of congenital sensorineural hearing loss – significantly surpassing the outcomes associated with hearing aids (60-65%). Additionally, the study confirmed the high effectiveness of surgical techniques like tympanoplasty for treating conductive hearing loss, with a 70-80% success rate when the hearing impairment was partial.

An important result of the study was the discovery that the effectiveness of treatment largely depends on the age of the child and the type of hearing impairment. The early use of cochlear implants up to the age of 2 years allowed for noteworthy progress in the development of hearing and speech in children with severe hearing impairment. Treatment of microcephaly and traumatic hearing damage was less effective, with hearing recovery rates of 30-60%. The study also showed that antibiotics and antiviral drugs were used to correct hearing in infections such as meningitis or herpes, with 80-90% effectiveness in meningitis and 75-85% in herpes infections. Genetic hearing disorders, such as Pendred and Usher syndromes, required the use of hearing aids or cochlear implants depending on the degree of hearing loss, with cochlear implants demonstrating high efficacy of 90-95%.

A limitation of the study was that not all newborns could undergo the full range of necessary treatments due to funding constraints or lack of access to modern medical technologies in certain regions. In addition, some genetic disorders cannot be corrected by medication or surgery, which limits the possibilities for improving hearing in these cases. To improve the quality of diagnostics and treatment of hearing impairment in newborns, it is also necessary to train medical staff

in modern audiological techniques. It is also crucial to provide healthcare facilities with modern equipment for hearing screening and rehabilitation, including audiometers, hearing aids, and cochlear implants.

The findings are of major practical significance, as they allow identifying the most effective methods of treating hearing disorders in newborns and ensuring early detection and correction of hearing impairment. This helps to improve the quality of life of children with hearing and speech impairments. Further research could be aimed at improving early diagnostic methods and rehabilitation measures after cochlear implants. It is also necessary to investigate new pharmacological treatments for infectious and genetic hearing disorders, as well as to develop individualised approaches to the treatment of newborns, considering their genetic background and other characteristics.

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Conflict of Interest

None.

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Кыргыз Республикасында угуунун бузулушун эрте диагностикалоо методдорун иштеп чыгуу

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Аннотация. Изилдөөнүн максаты жаңы төрөлгөн балдардын угуу скринингинин болушуна жана натыйжалуулугуна комплекстүү баа берүү, ошондой эле балдардын отопатологиясын диагностикалоо жана дарылоо, угуунун начарлашын эрте аныктоону жакшыртууга жана медициналык тейлөөнүн сапатын жогорулатууга басым жасоо болгон. Изилдөөдө жаңы төрөлгөн балдардын угуусун текшерүү ыкмалары, балдардын отопатологиясын диагностикалоонун жана дарылоонун ар кандай ыкмалары изилденген. Изилдөө жаңы төрөлгөн балдардын угуусун скринингден өткөргөн медициналык мекемелердин статистикалык отчетторуна комплекстүү талдоо жүргүзүүнү, ошондой эле өлкөнүн ар кайсы аймактарындагы отоларингологдордун, педиатрлардын жана неонатологдордун сурамжылоосун камтыйт. Өзгөчө көңүл баштапкы скринингдин жеткиликтүүлүгүн жана сапатын баалоого, андан ары диагностикалоого жана эрте кийлигишүүгө бурулду. Анализге сегиз медициналык мекемеде, анын ичинде Бишкек, Ош, Жалал-Абад шаарларындагы төрөт үйлөрүндө жана Республикалык перинаталдык борбордо аудиологиялык текшерүүдөн өткөн 9609 жаңы төрөлгөн ымыркай камтылган. Жыйынтыктар көрсөткөндөй, бул мезгилде скринингден өткөн төрөт үйлөрүнүн саны 3 %дан 37 %га чейин көбөйгөн, бул медицина системасына бул тажрыйбанын акырындык менен киргизилгендигин айгинелейт. Шаар жеринде жаңы төрөлгөн ымыркайлардын болжол менен 68 % скринингден өтсө, айыл жеринде 19 % гана скринингден өткөн, бул медициналык кызматтарга жетүүдө олуттуу теңсиздикти көрсөтүп турат. Балдардын 1,7 %ында угуунун начарлоосуна шек келтирилген, алардын ичинен 0,8 %ы угуунун начарлашы тастыкталган. Скринингдик камтууну сандык талдоодон тышкары, изилдөө угуунун бузулушун эрте аныктоонун натыйжалуулугуна таасир этүүчү бир катар уюштуруучулук жана социалдык факторлорду аныктады. Атап айтканда, угууну скринингдин жана баштапкы текшерүүдөн кийин байкоонун маанилүүлүгү жөнүндө ата-энелердин маалымдуулугунун деңгээли чоң роль ойноду: скринингдин оң натыйжасы бар үй-бүлөлөрдүн жарымынан көбү маалыматтын жетишсиздигинен же тийиштүү медициналык кызматтарга жетүү мүмкүнчүлүгүнөн улам кайра диагностикадан өтпөгөнү аныкталган. Изилдөөнүн практикалык мааниси анын натыйжалары угуунун начарлоосун эрте аныктоо проблемасын андан ары изилдөөгө, саламаттыкты сактоо системасын жакшыртууга, өзгөчө отоларингология жана неонаталдык скрининг чөйрөсүндө, ошондой эле бейтаптардын жашоо сапатын жакшыртууга мүмкүндүк берүүчү өз убагында кийлигишүүнүн эффективдүү стратегияларын иштеп чыгуу үчүн колдонулушу мүмкүн

Негизги сөздөр: аудиологиялык тест; неонаталдык скрининг; отоакустикалык эмиссия; отопатологияга эрте кийлигишүү; баштапкы скрининг

Разработка методов ранней диагностики нарушений слуха в Кыргызской Республике

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Аннотация. Целью исследования было провести комплексную оценку доступности и эффективности скрининга слуха новорожденных, а также диагностики и лечения отопатологий у детей с акцентом на улучшение раннего выявления нарушений слуха и повышение качества медицинской помощи. В ходе исследования были изучены методы скрининга слуха новорожденных, различные методы диагностики и лечения отопатологий у детей. Исследование включало комплексный анализ статистических отчетов медицинских учреждений, проводивших скрининг слуха новорожденных, а также опрос отоларингологов, педиатров и неонатологов в разных регионах страны. Особое внимание было уделено оценке доступности и качества первичного скрининга, дальнейшей диагностики и раннего вмешательства. Анализ охватил 9 609 новорожденных, прошедших аудиологическое обследование в восьми медицинских учреждениях, включая роддомы в Бишкеке, Оше, Джалал-Абаде и Республиканском перинатальном центре. Результаты показали, что за этот период количество роддомов, в которых проводился скрининг, увеличилось с 3 % до 37 %, что свидетельствует о постепенном внедрении этой практики в медицинскую систему. В городских районах скрининг прошли около 68 % новорожденных, тогда как в сельских районах – только 19 %, что свидетельствует о значительном неравенстве в доступе к медицинским услугам. Нарушение слуха было подозревалось у 1,7 % детей, из которых у 0,8 % была подтверждена потеря слуха. Помимо количественного анализа охвата скринингом, в ходе исследования был выявлен ряд организационных и социальных факторов, влияющих на эффективность раннего выявления нарушений слуха. В частности, значительную роль играл уровень осведомленности родителей о важности скрининга слуха и последующего наблюдения после первичного обследования: было установлено, что более половины семей, получивших положительный результат скрининга, не прошли повторную диагностику из-за недостатка информации или доступа к соответствующим медицинским услугам. Практическая ценность исследования заключается в том, что его результаты могут быть использованы для дальнейшего изучения проблемы раннего выявления нарушений слуха, улучшения системы здравоохранения, особенно в области отоларингологии и неонатального скрининга, а также для разработки эффективных стратегий своевременного вмешательства, которые улучшат качество жизни пациентов

Ключевые слова: аудиологическое тестирование; неонатальный скрининг; отоакустическая эмиссия; раннее вмешательство при отопатологии; первичный скрининг

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Comparative efficacy of monotechnological laparoscopic versus traditional laparotomy interventions in acute pancreatitis: Analysis of clinical outcomes

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Abstract. Acute pancreatitis remains one of the most pressing problems in emergency surgery due to its high mortality rate and risk of complications, which necessitates the search for safer and more effective surgical techniques. The study aimed to conduct a comparative analysis of the efficacy and safety of single-technique laparoscopic interventions compared with traditional laparotomy in patients with acute pancreatitis. The study included 136 patients divided into two groups: the main group (n = 74), in which laparoscopic interventions were performed; and the control group (n = 62), in which laparotomy operations were performed. A retrospective-prospective design was employed, clinical and laboratory indicators, instrumental imaging methods and statistical processing with an assessment of the reliability of differences were used. The results revealed an advantage of laparoscopy. The average length of hospitalisation in the main group was significantly shorter (18.7 ± 1.2 days versus 29.1 ± 2.3 days in the control group, $p < 0.05$). Mortality was almost half as low (12.1% versus 24.4%), and the frequency of postoperative complications was also significantly lower. Additional advantages of laparoscopy were minimal trauma, the possibility of combined manipulations, and faster patient recovery. At the same time, certain risks were noted drainage failure and the need for conversion in 2.3% of cases, which emphasises the importance of strict patient selection. The practical significance of the study is determined by the justification for the widespread introduction of laparoscopic technologies in the surgical treatment of acute pancreatitis. Their use significantly reduces the length of hospitalisation, lowers complication and mortality rates, and improves clinical outcomes, making laparoscopy the preferred tactic for this pathology

Keywords: minimally invasive surgery; pancreonecrosis; postoperative complications; drainage; conversion of surgery; rehabilitation; inflammatory complications

Introduction

Acute pancreatitis (AP) continues to be one of the most severe forms of emergency abdominal pathology, characterised by a high risk of systemic complications and mortality, especially in necrotic forms of the disease. According to G. Trikudanathan *et al.* [1], the prevalence of AP reaches 30-50 cases per 100,000 population annually, and mortality rates in severe forms can exceed 20-30%. The severity of the pathogenesis of AP, including a systemic inflammatory response, multiorgan dysfunction and a high risk of necrotic tissue infection, necessitates a timely and informed choice of surgical tactics [2]. The development of surgical tactics for complicated forms of acute pancreatitis has undergone significant changes since the 2010s. Traditional laparotomy interventions, which are characterised by high surgical trauma, a long recovery period and a significant incidence of postoperative complications, are gradually replaced by minimally invasive approaches. According to R. Rasslan *et al.* [3], the use of laparoscopic technologies provides accurate visual control and minimal invasiveness, and creates the possibility of combined interventions, which corresponds to the concept

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of damage control surgery. In turn, S. van Brunschot *et al.* [4] demonstrated that minimally invasive and endoscopic methods in the treatment of necrotising pancreatitis significantly reduce mortality and the incidence of infectious complications compared to open necrectomy.

In 2024, M.B. Chapyev *et al.* [5] substantiated the importance of monotechnological operations based on the use of a single targeted technique, such as sanitation or drainage. The study noted that such a tactic minimises surgical aggression without reducing effectiveness and should be considered as part of the classification of minimally invasive interventions. The high level of evidence of the effectiveness of endoscopic and laparoscopic methods was confirmed by the results of the meta-analysis by J.Y. Bang *et al.* [6], demonstrating that these technologies significantly reduce the incidence of infectious complications and mortality in patients with infected pancreatic necrosis. In turn, A.M. Onnekink *et al*. [7] confirmed in a long-term follow-up study that the use of the so-called step-up approach reduces hospitalisation time, reduces the need for repeated interventions and reduces the need for prolonged intensive care.

The issue of optimal drainage time is also substantially addressed. Y. Yang *et al.* [8], in a systematic review, demonstrated that delayed intervention performed after the fourth week from the onset of the disease is associated with more favourable results, as during this period the necrosis zones have clear boundaries. This principle is being integrated into international protocols for minimally invasive surgery. However, as M. Podda *et al.* emphasised [9], the implementation of such technologies requires highly qualified surgeons and modern technical equipment, which limits their widespread use in regional centres.

At the same time, there are still controversial issues related to the standardisation of indications for specific types of drainage, the assessment of the risk of conversion and the study of long-term results. Similar conclusions for pancreatic surgery were presented in a long-term follow-up by C.L. van Veldhuisen *et al.* [10], demonstrating that delayed drainage was accompanied by fewer interventions, while the quality of life and pancreatic function remained comparable to the immediate approach. In the broader context of the development of minimally invasive surgery, the study by S.R. DeMeester *et al.* [11], which demonstrated that laparoscopic hernia repair of paraesophageal hernia provides better life expectancy compared to wait-and-see tactics even in asymptomatic patients, is notable. This emphasises the general trend towards the expansion of indications for laparoscopic interventions in abdominal practice. Thus, the present study compared the efficacy and safety of monotechnological laparoscopic interventions and traditional laparotomy in the treatment of patients with acute pancreatitis in a multidisciplinary surgical hospital.

Materials and Methods

The present study was performed at the Mamakeev National Surgical Centre of the Ministry of Health of the Kyrgyz Republic as part of the clinical practice of the institution. The study design was retrospective and prospective, with elements of cohort comparison, and was aimed to evaluate the clinical and surgical efficacy of monotechnological laparoscopic interventions in acute pancreatitis. The observation period was three years (2022-2024). The study included 136 patients with a diagnosis of acute pancreatitis confirmed by clinical, laboratory and instrumental methods. All patients met the inclusion criteria: age 18-75 years, clinical and radiological signs of inflammatory changes in the pancreas confirmed by computed tomography or ultrasound, and the absence of decompensated somatic diseases. Exclusion criteria: pancreatic necrosis with systemic sepsis, extensive abdominal tumours, terminal conditions, and patient refusal to undergo surgery.

The patients were divided into two groups. The main group consisted of 74 people who underwent 219 laparoscopic interventions. These surgeries were performed mainly in a monotechnological format, i.e. using one minimally invasive technique aimed to solve a specific clinical problem. In some cases, abdominal cavity rehabilitation was used, in others, drainage was installed, and in some situations, local effects were performed, including blocking the hepatic circular ligament or draining the omental sac. The control group consisted of 62 patients who underwent traditional laparotomy. These interventions included cholecystectomy, cholecystostomy, and opening and drainage of purulent cavities. Patients in this group were selected retrospectively from the database, which was used to compare the results of treatment with the main cohort.

Clinical efficacy was studied according to a range of parameters, including the intensity of pain syndrome assessed by visual analogue scale, body temperature dynamics, leukocytosis and C-reactive protein level. The volume and nature of drainage, length of hospital stay, incidence of postoperative complications according to the Clavien-Dindo classification [12], mortality rates, and the need for conversion or relaparoscopy were analysed. Additionally, the time intervals between the patient's admission to the hospital and the surgical intervention were recorded, which assessed the importance of early tactical decision-making.

The study included standardised diagnostics. All patients underwent ultrasound examinations and computed tomoangiography before and after surgery, if indicated. Comprehensive laboratory monitoring was carried out, including a complete blood count, biochemical tests, coagulation parameters (prothrombin time, activated partial thromboplastin time), and determination of systemic inflammation markers. The severity of the patients' condition was additionally assessed by the internationally recognised SAPS II (Simplified Acute

Physiology Score II) and APACHE II (Acute Physiology and Chronic Health Evaluation II) scales, which ensured the objectivity of the data and was used to compare the results of treatment between the study groups [13,14].

Surgical interventions in the main group were performed according to a single protocol, including the stages of preparation, creation of pneumoperitoneum (≤15 mm Hg), polypositional examination of the abdominal cavity, sanitation/drainage and haemostasis control [15,16]. To perform the interventions, 5 and 10-mm trocars, electrosurgical instruments and a carbon dioxide insufflator with automatic pressure control were used.

SPSS Statistics v.26.0 and MS Excel with data analysis modules were used for statistical data processing. All quantitative indicators were tested for normal distribution using the Shapiro-Wilk test. To compare quantitative parameters between the two groups, the following were used: Student's t-test and Mann-Whitney. To assess the reliability of differences between the groups, the significance level was set at $p < 0.05$. Thus, the applied set of statistical methods ensured high reliability of the results, which were used for intergroup comparative analysis and justification of the clinical feasibility of monotechnological laparoscopic interventions in acute pancreatitis. The work was conducted following international and national ethical standards, including the provisions of the World Medical Association Declaration of Helsinki [17]. The study protocol was approved by the Ethics Committee of the National Surgical Centre named after Academician M.M. Mamakeev of the Ministry of Health of the Kyrgyz Republic. Written informed consent to participate in the study, including permission to use anonymised clinical data for scientific purposes, was obtained from all patients and, if necessary, from their legal representatives.

Results and Discussion

The study included 136 patients divided into two groups: the main group (laparoscopic interventions, n = 74) and the comparison group (laparotomy interventions, n = 62). The average age of patients in the groups did not have statistically significant differences (54.9 ± 0.5 years vs. 53.7 ± 0.3 years, $p > 0.05$), which excluded the influence of the age factor on the outcomes. The demographic structure of the groups was comparable in terms of gender and age, and is presented in Table 1.

Table 1. Demographic structure (by gender and age) of patients included in the study clinical groups

Values	Group of laparoscopic interventions	Group of laparotomy interventions
Overall number of patients	74	62
Average age, years (M ± m)	54.9 ± 0.5	53.7 ± 0.3
Female	47 % (n = 35)	49 % (n = 31)
Male	53 % (n = 39)	51 % (n = 34)

Source: data from the Mamakeev National Surgical Centre

The demographic structure of the clinical groups is shown in Table 1. The group of laparoscopic interventions included 74 patients, and the group of laparotomy operations included 62 patients. The average age of patients was 54.9 ± 0.5 years in the first group and 53.7 ± 0.3 years in the second, which did not reveal statistically significant differences ($p > 0.05$). Thus, the influence of the age factor on clinical outcomes can be considered minimal. The gender distribution was also comparable: women accounted for 47% (n = 35) in the laparoscopic group and 49% (n = 31) among laparotomy patients, men 53% (n = 39) and 51% (n = 34), respectively. This suggests that the initial characteristics of the samples are balanced, which excludes bias in the interpretation of further results.

The analysis of the time interval from admission to surgery showed high variability. In 42.5% of cases, laparoscopic intervention was performed within the first 3 hours of admission, reflecting the severity of the condition of some patients and the need for emergency surgery. In the remaining cases, the time frame ranged from 3 to 24 hours or more, which could be due to additional examinations and preoperative preparation. The structure of interventions in the main group was dominated by combined laparoscopic aids, which were performed in 94.5% of patients. The most frequent manipulations were sanitation and drainage of the abdominal cavity (n = 125), which is natural for surgical tactics in acute pancreatitis. In addition, cholecystectomy was performed in 48 cases, and hepatic circular ligament block was performed in 41 patients. In the group of laparotomy interventions, traditional operations prevailed: sanitation and drainage (n = 24), cholecystectomy (n = 14), and opening and drainage of the omental sac (n = 19). These differences illustrate the shift in surgical priorities towards minimally invasive technologies.

The average duration of laparoscopic operations was 29.2 ± 5 minutes, which confirms their technical efficiency and rationality. At the same time, the frequency of conversion to laparotomy was recorded at 2.3% (n = 11). The main reasons were iatrogenic injuries of the gallbladder and intestine, which are in line with the literature, where conversion is considered a forced but justified mechanism to ensure patient safety. In the

postoperative period, failure of laparoscopic cholecystolithotomy was detected in 3.6% (n = 18) of patients, which required revision interventions. Relaparoscopy was required in only 0.6% of cases (n = 3), which was caused by bleeding from trocar wounds.

A comparative analysis of the length of hospitalisation revealed a significant advantage of the laparoscopic approach: the average hospital stay was 18.7 ± 1.2 days versus 29.1 ± 2.3 days in the laparotomy group ($p < 0.05$), which is equivalent to a reduction of almost a third. The clinical efficacy of laparoscopy was also significantly higher: positive outcomes were recorded in 54.2% of patients, while only 30.3% of patients had positive outcomes with traditional surgery. The mortality rate in the laparoscopic group was 12.1%, which is almost twice as low as in the laparotomy group (24.4%; $p < 0.05$). These data confirm that minimally invasive technologies provide not only a more favourable postoperative course, but also a significant improvement in outcomes.

The results obtained in the study demonstrate the clear advantages of laparoscopic techniques, which are in line with current global trends in abdominal surgery. The shorter hospital stay and reduced mortality observed in the main group are confirmed in international publications. A single-centre study by C. Valentin *et al.* [18], which included 41 patients with infected necrotising pancreatitis, used a step-up approach, involving the phased implementation of drainage, minimally invasive necrectomy and, if necessary, open interventions. The study demonstrated that such a strategy ensures resolution of the infection in 80.5% of patients with a mortality rate of 19.5% at six months and an acceptable level of long-term complications. In the present study, which compared laparoscopic and laparotomy interventions in 136 patients, the mortality rate in the laparoscopic group was noted to be 12.1% versus 24.4% in laparotomy, and the length of hospitalisation in the laparoscopic group was 35.7% shorter than in laparotomy, which confirms faster recovery of patients after minimally invasive surgery. Thus, despite the differences in design, the retrospective analysis of the step-up strategy in C. Valentin *et al.* and the comparative analysis of laparoscopic and laparotomy interventions in the present study, both sources confirm that minimally invasive techniques are associated with lower mortality, lower complication rates and more favourable clinical outcomes in the treatment of infected pancreatic necrosis.

The high frequency of combined laparoscopic aids (94.5%) in this study emphasises their comprehensive nature and adaptability to individual clinical scenarios. This approach correlates with the conclusions of a systematic review by P. Tang *et al.* [19] in which endoscopic and minimally invasive surgical approaches were compared. The study concluded that surgical approaches, including laparoscopy, may have advantages in extensive and multilocular forms of necrosis, which confirms the feasibility of the combined aids used in the present study. Of relevance is the possibility of performing simultaneous interventions aimed to eliminate several pathological foci during a single operation.

The significant reduction in mortality in the laparoscopic group (12.1% vs. 24.4%) in the present study is also clinically relevant. At the same time, the data only partially correlate with the results of the meta-analysis by G. Wu *et al.* [20] in a comparison of the outcomes of minimally invasive surgery and endoscopic interventions in patients with infected necrotising pancreatitis. The study demonstrated that endoscopic therapy is associated with a lower incidence of postoperative complications, new organ failure and pancreatic fistula, while no significant differences were found in terms of hospitalisation duration and several other indicators. Thus, in contrast to the results of a study by G. Wu *et al.*, the present study demonstrated an advantage of minimally invasive surgical methods in terms of mortality, which emphasises the relevance of comparing data from different clinical strategies.

However, as with any surgical approach, laparoscopy is not without risks. In the present study, the conversion rate was 2.3%, which correlates with the range encountered in clinical practice. A prospective cohort study by G. Pavlek *et al.* [21], which compared the step-up strategy and open necrectomy in 60 patients with acute necrotising pancreatitis, demonstrated that the mortality rate with the minimally invasive approach was 20% versus 27.5% with open surgery ($p = 0.53$), and the morbidity and incidence of pancreatic failure were significantly lower in the step-up group. At the same time, the duration of hospitalisation and mortality rates did not differ significantly. In contrast to the results of a study by G. Pavlek *et al.* on the reduction of overall morbidity, the present study demonstrated a statistically significant advantage of laparoscopy in terms of hospital mortality (12.1% vs. 24.4%), which confirms the effectiveness of the minimally invasive approach in real clinical practice.

The problem of drainage failure, which in the present study was observed in 3.6% of patients and required revision interventions, is of great clinical importance. A comparative analysis performed by L. Chen *et al.* [22], based on a meta-analysis of 6 studies (247 patients), showed that endoscopic ultrasound drainage and percutaneous drainage of postoperative pancreatic fluid collections have comparable technical and clinical success rates, and do not differ in the frequency of recurrence and complications. The study concluded that both methods are equivalent in terms of efficacy and safety, with the need for further high-quality studies remaining relevant. Comparison of these data with the results of the present study emphasises that even with a low incidence of laparoscopic drainage failure (3.6%), this complication should be incorporated in the selection of treatment tactics and repeat intervention planning.

A substantial aspect of long-term outcomes was addressed in a study by C.L. van Veldhuisen *et al.* [10] on the analysis of the long-term results of immediate and delayed drainage in infected necrotising pancreatitis. The study did not find significant differences in survival between the groups, but noted that the strategy of delayed intervention, which is often implemented through minimally invasive approaches, was associated with a lower incidence of endocrine and exocrine pancreatic insufficiency in the long-term period. This demonstrates the importance of assessing not only the immediate results of treatment but also the long-term consequences that determine the quality of life of patients. Preservation of pancreatic function should be considered as one of the key indicators of treatment effectiveness.

Lastly, the overall clinical efficacy of laparoscopy, estimated at 54.2%, confirms its validity as the main treatment method. This result fits well with the concept proposed in the international guidelines by M. Podda *et al.* [9] that minimally invasive surgery is becoming a new standard for the treatment of complicated forms of acute pancreatitis, gradually replacing open surgery due to its proven benefits in reducing mortality and postoperative morbidity. A comprehensive approach to treatment, including not only the technical aspects of surgery, but also perioperative management, nutritional support and rehabilitation, deserves special attention.

Thus, the analysis of modern literature sources confirmed the main conclusions of this study and showed that the benefits of laparoscopy exceed the scope of reduction of the duration of hospitalisation and include mitigation of the systemic effects of surgical aggression, which is a promising area for further study. The integration of minimally invasive technologies into clinical practice requires not only mastering technical skills but also revising traditional approaches to timing of interventions and postoperative patient management.

Conclusions

The study achieved its primary objective by demonstrating the convincing advantages of the monotechnological laparoscopic approach in the treatment of acute pancreatitis compared to traditional laparotomy. The data obtained indicate that the introduction of minimally invasive techniques can dramatically improve key clinical outcomes. A statistically significant reduction in hospitalisation by almost 10 days, a twofold reduction in mortality, and a lower incidence of postoperative complications support the hypothesis of higher efficiency and safety of laparoscopy. These results directly correlate with the objectives and prove that minimally invasive surgery provides not only technical feasibility but also significant clinical superiority.

The key success factors identified in the study were minimal surgical trauma, the ability to perform combined interventions due to limited access, and, as a result, accelerated patient recovery. This emphasises the role of laparoscopy not only as an alternative method, but also as the preferred first choice tactic in stable patients with localised forms of destructive pancreatitis. The practical value of the results obtained is the formation of a reliable evidence base to justify the widespread introduction of monotechnological laparoscopic interventions into clinical algorithms for the management of patients with acute pancreatitis. The implementation of this approach will optimise the resource costs of the hospital and improve the quality of medical care at the hospital.

However, the study also revealed certain limitations of the method that require a balanced approach. The need for conversion to laparotomy and the risk of drainage failure, although observed in a small percentage of cases, indicate the critical importance of careful preoperative patient selection based on a comprehensive clinical and radiological assessment. This necessitates the development and validation of prognostic algorithms and criteria to minimise intra- and postoperative risks.

Prospects for further research include the organisation of multicentre randomised controlled trials to obtain more representative data on long-term outcomes and quality of life. In addition, the issues of standardising drainage techniques, determining the optimal time windows for intervention at different stages of the disease, and developing integrated prognostic models to personalise surgical tactics require in-depth study.

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Conflict of Interest

None.

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Курч панкреатитте монотехнологиялык лапароскопиялык жана салттык лапаротомиялык кийлигишүүлөрдүн салыштырылган натыйжалуулугу: клиникалык жыйынтыктарды талдоо

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Аннотация. Курч панкреатит өлүмдүн жогорку деңгээли жана татаалдануу тобокелдигине байланыштуу шашылыш хирургиянын эң актуалдуу көйгөйлөрүнүн бири бойдон калууда, бул коопсуз жана эффективдүү хирургиялык технологияларды издөө зарылдыгын аныктайт. Бул изилдөөнүн максаты курч панкреатит менен ооруган бейтаптардагы салттуу лапаротомиялык операциялар менен салыштырганда монотехнологиялык лапароскопиялык кийлигишүүлөрдүн натыйжалуулугун жана коопсуздугун салыштыруу болгон. Изилдөөгө 136 бейтап эки топко бөлүнгөн: негизги топ (n = 74), анда лапароскопиялык ыкмалар колдонулган; көзөмөл тобу (n = 62), анда лапаротомиялык операциялар жасалган.Ретроспективдүү-проспективдүү долбоор колдонулган, клиникалык жана лабораториялык параметрлер, инструменталдык визуализация ыкмалары жана айырмачылыктардын ишенимдүүлүгүн баалоо менен статистикалык иштетүү колдонулган. Алынган натыйжалар лапароскопиянын айкын артыкчылыгын көрсөттү. негизги топтун ооруканага орточо узактыгы (контролдоо тобунда 29.1 ± 2.3 күн каршы 18.7 ± 1.2 күн, б <0.05) кыйла кыска болгон. Өлүм дээрлик эки эсе төмөн болгон (12,1 % га каршы 24,4 %), ошондой эле операциядан кийинки татаалдашуулардын жыштыгы да кыйла төмөн болгон. Лапароскопиянын кошумча артыкчылыктары анын минималдуу травмасы, айкалыштырылган манипуляциялардын мүмкүнчүлүгү жана пациенттердин тезирээк сакайып кетиши болгон. Ошол эле учурда, белгилүү бир тобокелдиктер, атап айтканда, дренаждын бузулушу жана 2,3 % учурларда конверсиянын зарылдыгы белгиленди, бул пациентти катуу тандоонун маанилүүлүгүн баса белгилейт. Изилдөөнүн практикалык мааниси курч панкреатитти хирургиялык дарылоодо лапароскопиялык технологиялардын кеңири жайылышын негиздөөдө турат. Аларды колдонуу ооруканага жаткыруу мөөнөтүн бир топ кыскартууга, татаалдануу жана өлүмдүн деңгээлин төмөндөтүүгө жана клиникалык натыйжаларды жакшыртууга мүмкүндүк берет, бул лапароскопияны бул патология үчүн артыкчылыктуу тактикага айлантат

Негизги сөздөр: минималдуу инвазивдик хирургия; панкреатикалык некроз; операциядан кийинки татаалдашуу; дренаж; хирургиянын конверсиясы; реабилитация; сезгенүү татаалдыктар

Сравнительная эффективность монотехнологичных лапароскопических и традиционных лапаротомных вмешательств при остром панкреатите: анализ клинических исходов

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Аннотация. Острый панкреатит продолжает оставаться одной из наиболее актуальных проблем неотложной хирургии ввиду высокой летальности и риска осложнённого течения, что определяет необходимость поиска более безопасных и эффективных хирургических технологий. Целью настоящего исследования являлся сравнительный анализ эффективности и безопасности монотехнологичных лапароскопических вмешательств по сравнению с традиционными лапаротомными операциями у пациентов с острым панкреатитом. В исследование были включены 136 пациентов, распределённых на две группы: основная (n = 74), в которой были выполнены лапароскопические вмешательства; контрольная (n = 62), в которой проводились лапаротомные операции. Применялся ретроспективно-проспективный дизайн, использовались клинико-лабораторные показатели, инструментальные методы визуализации и статистическая обработка с оценкой достоверности различий. Полученные результаты выявили явное преимущество лапароскопии. Средняя продолжительность госпитализации в основной группе была существенно меньше (18,7 ± 1,2 дня против 29,1 ± 2,3 дня в контрольной, $p < 0,05$). Летальность оказалась почти вдвое ниже (12,1 % против 24,4 %), а частота послеоперационных осложнений также была достоверно меньше. Дополнительными преимуществами лапароскопии стали её минимальная травматичность, возможность комбинированных манипуляций и более быстрое восстановление пациентов. В то же время отмечены определённые риски, в частности несостоятельность дренирования и необходимость конверсии в 2,3 % случаев, что подчёркивает значимость строгого отбора больных. Практическое значение исследования заключается в обосновании широкого внедрения лапароскопических технологий в хирургическое лечение острого панкреатита. Их использование позволяет существенно сократить длительность госпитализации, снизить показатели осложнений и смертности, а также улучшить клинические исходы, что делает лапароскопию предпочтительной тактикой при данной патологии

Ключевые слова: минимально инвазивная хирургия; панкреонекроз; послеоперационные осложнения; дренирование; конверсия операции; реабилитация; воспалительные осложнения

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Current approaches to the management of systemic inflammatory response syndrome in peritonitis of various aetiologies

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Abstract. Systemic inflammatory response syndrome (SIRS) in diffuse peritonitis remains one of the leading causes of multiple organ failure and high mortality, making the search for effective methods of its management a priority in clinical practice. The purpose of the study was to assess the effectiveness of a newly developed comprehensive approach to the management of SIRS in patients with diffuse peritonitis of various aetiologies. The surgical treatment outcomes of 46 patients treated at Osh City Clinical Hospital between 2021 and 2023 were analysed (20 with postoperative peritonitis, 22 with perforated gastric or duodenal ulcers, and 12 with complicated appendicitis). The treatment protocol included regional antibiotic lymphotropic stimulation, systemic antibacterial and detoxification therapy, immunocorrection with roncoleukin, and early enteral nutrition (EEN). Clinical manifestations of SIRS and laboratory markers (leukocyte count, leukocytic intoxication index, and procalcitonin) were evaluated. Preoperatively, all patients exhibited three to four signs of SIRS. Following implementation of the comprehensive treatment protocol, there was a consistent and marked reduction in the frequency of clinical manifestations and laboratory marker levels in cases with favourable progression. In the ulcer perforation group, 17 of 22 patients had only two SIRS signs by the 3rd day, and by days 9 to 10 the signs were absent. In appendicular peritonitis, clinical symptoms decreased by days 3 to 6, and by days 9 to 10 most of the 12 patients retained an average of two signs. The slowest improvement was observed in postoperative peritonitis, although by days 6 to 10 the number of signs was reduced to isolated cases. A parallel decrease in leukocytosis, leukocytic intoxication index, and procalcitonin was recorded in favourable cases. The findings support the feasibility of incorporating regional antibiotic lymphotropic stimulation in combination with immunocorrection and EEN into treatment protocols for diffuse peritonitis to effectively manage SIRS

Keywords: multiple organ failure; surgical infection; immunomodulation; antibacterial therapy; procalcitonin; leukocytic intoxication index; early enteral nutrition

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Introduction

Diffuse peritonitis remains one of the most difficult and dangerous pathologies in abdominal surgery. Despite advances in surgery and antibiotic therapy, the high mortality and complication rate are conditioned by the development of systemic inflammatory response syndrome (SIRS), which can progress to sepsis and multiple organ failure. This highlights the need to find new methods for the diagnosis and correction of CVD aimed at improving clinical outcomes.

Updated recommendations of P.K.-T. Li *et al.* [1] regulate in detail the prevention and treatment of peritonitis during peritoneal dialysis, setting new standards for the frequency of episodes and the proportion of patients without infection. They revised the definitions of the forms of peritonitis and proposed improved approaches to antibiotic therapy and prevention, including correction of risk factors and patient education. The purpose of the recommendations was to reduce morbidity and mortality by improving standards of care. However, the effect of new therapies on the immune response and the lack of data on the complex correction of inflammation in severe forms of peritonitis were noted, which requires further research.

S.N. Abdreshov *et al.* [2] investigated the effect of the new antibiotic peptomide A-70 on morphological changes in mesenteric lymph nodes in experimental peritonitis. The researchers found that peritonitis causes a decrease in the area of the cortical structures of the lymph nodes and an expansion of their sinusoidal system, which indicates a decrease in the drainage, detoxification and immune functions of the lymphatic system, affecting the unfavourable outcome of the disease. The use of peptomide A-70 helped to reduce inflammation and toxic load, and also activated lymphopoietic function, increasing the size of lymph nodes and the parocortical T-zone. The results obtained confirmed the importance of immunomodulation and support of the lymphatic system in the treatment of peritonitis and indicate the prospects of using peptomide A-70 to improve the prognosis of the disease.

A.A. Andreev *et al.* [3] conducted a comprehensive analysis of existing biological models of acute peritonitis used in experimental studies. The paper proposed a classification of models based on the nature of the pathogen and the method of its introduction, including methods such as the introduction of foreign bodies, chemicals, bacterial infection, and combined effects. The researchers emphasise the importance of choosing a model that best reflects the clinical picture of the disease, which allows for a more accurate study of the aetiology, mechanisms of development, and severity of peritonitis, and evaluating the effectiveness of therapeutic measures. Moreover, the paper noted the need for further development of models for a more adequate reproduction of complex forms of peritonitis and a comprehensive assessment of the immune response. A.R. Saraev & Sh.K. Nazarov [4] applied a theoretical approach by analysing current data on the pathogenesis and classification of common peritonitis. They noted the diversity of views on the mechanisms of the disease and the lack of a unified classification, which makes it difficult to choose treatment and prognosis. The researchers emphasised the need for further study to create a more homogeneous and practical classification system. A paper by J. Zhang & Y. Huang [5] reviewed recent advances in the use of low-dose interleukin-2 (IL-2) for the treatment of immune diseases. The researchers emphasised that low doses of IL-2 selectively stimulate the proliferation of regulatory T cells, contributing to the restoration of immune homeostasis, while high doses activate effector T cells. Encouraging results of using low-dose IL-2 with minimal side effects are presented, which makes this method promising for modulating the immune status in inflammatory and immune disorders.

Y.-J. Chen *et al*. [6] conducted a randomised trial involving 140 patients with severe acute pancreatitis, comparing the effectiveness of parenteral and enteral nutrition. Before the start of therapy, the levels of interleukin-1β, interleukin-6, and tumour necrosis factor alpha in the groups did not differ significantly, but after treatment in the enteral nutrition group there was a significant decrease in these proinflammatory markers, an improvement in total protein and albumin, and a decrease in the incidence of pancreatic necrosis and pancreatic abscesses. The researchers concluded that enteral nutrition not only reduces the severity of the systemic inflammatory response, but also protects the intestinal barrier function. This study is of considerable value, as it is close in subject matter to the present work and emphasises the need for further clinical studies aimed at optimising nutritional support in conditions accompanied by a pronounced inflammatory response, including peritonitis of various origins.

The purpose of the present study was to evaluate the effectiveness of correction of systemic inflammatory response syndrome in diffuse peritonitis using lymphogenic technology (direct and indirect regional lymphostimulation), Roncoleukin immunocorrector, and early enteral nutrition.

Materials and Methods

46 patients with diffuse peritonitis of various origins were hospitalised in the departments of Osh City Clinical Hospital in the period from 2021 to 2023. Of these, 21 were women and 25 were men, and the age of the patients ranged from 25 to 74 years, while 32.6% of the patients were over 50 years old. The general distribution of patients is shown in Figure 1.

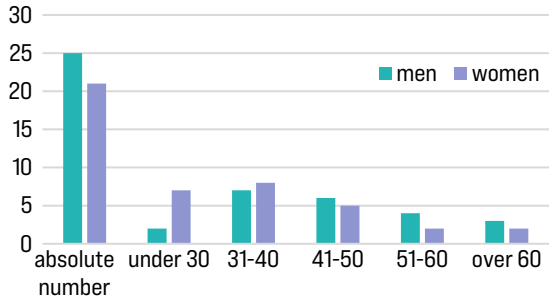

Figure 1. Distribution of patients by gender and age
Source: compiled by the authors

The study included patients with clinically and laboratory-confirmed diagnosis of diffuse peritonitis caused by postoperative complications (20 patients), perforation of gastric or duodenal ulcers (22 patients), and complicated acute appendicitis (12 patients). Patients with end-stage chronic diseases, immunodeficiency, and patients who refused to participate were excluded. The diagnosis and assessment of the severity of CVD were based on clinical signs: an increase in body temperature above 38°C or a decrease below 36°C, a pulse rate of more than 90 bpm, increased breathing above 20 respirations per minute or the presence of apnea, and laboratory parameters – the level of leukocytes, leukocyte intoxication index (LII) according to the method Ya.Ya. Calf-Calif and procalcitonin levels [7]. The study was performed before surgery and in the dynamics in the immediate period after surgery. When choosing correction methods, the genesis of peritonitis was considered, but all patients underwent regional lymphostimulation during surgery using the method developed by E.S. Dzhumabayev [8], immunocorrection with the drug Roncoleukin, and in the postoperative period, anti-inflammatory and detoxification therapy, considering the identified disorders of organ and system functions, and early enteral nutrition [9]. The patients were divided into three groups depending on the cause of peritonitis:

- Group 1 (n = 20): postoperative peritonitis;
- Group 2 (n = 22): perforation of gastric and duodenal ulcers;
- Group 3 (n = 12): generalised peritonitis in acute appendicitis.

At the time of surgery, all groups of patients underwent thorough abdominal rehabilitation aimed at removing the infection site and cleansing the peritoneal cavity of purulent masses and inflammatory exudate. Regional lymphostimulation was performed using a specialised technique aimed at activating the lymphatic system in the abdominal cavity to improve the immune response and accelerate the elimination of toxins [8]. Regional lymphostimulation was performed by inserting a microirrigator, a thin and flexible catheter, into the root of the mesentery of the small intestine in patients of the first group [10]. In the second group, a similar catheter was inserted through the circular ligament of the liver. Next, the microirrigator was removed through the surgical wound, which allowed continuing lymphostimulation for 4-5 days after surgery, maintaining an active effect on the lymphatic system in the postoperative period.

To stimulate the immune system and enhance the anti-inflammatory effect, an antibiotic-lymphotropic mixture was used, which included cefazolin 1.0 g, heparin 70 U/kg body weight, lidase 8-12 U, proserin 2 ml, and 0.25% novocaine solution in a volume of 10-15 ml. Immunocorrection was performed using Roncoleukin intravenously at a dose of 1 mg for a course of 6-7 days with 2-day intervals between injections. Antibacterial therapy was prescribed considering the clinical form and genesis of peritonitis: in the first group, ceftazoline 1.0 g twice daily was administered intravenously; in the second, a combination of cefazoline 1.0 g twice daily with metronidazole 100 ml twice daily; in the third – ceftriaxone 1.0 g with metronidazole according to a similar scheme. This approach simultaneously affected a wide range of aerobic and anaerobic microflora, providing comprehensive anti-infective protection.

Detoxification therapy included massive infusion support, considering the severity of each patient's condition. It provided correction of the water-electrolyte balance, maintenance of haemodynamics, and acceleration of the elimination of toxins from the body. Nutritional support for patients included EEN [11], which was started after intestinal motility was restored. This approach helped to maintain the function of the intestinal barrier, reduce the risk of secondary infections, and accelerate the overall recovery of the body. In addition to the main treatment methods, the procedure of gastric irrigation with an ozonated sodium chloride solution through a nasogastric tube was used. This manipulation helped to disinfect the gastric contents, improve microcirculation, and reduce the inflammatory response.

All patients underwent regular measurements of temperature, pulse rate, and respiration, and laboratory tests for leukocytes, LII, and procalcitonin before surgery, on days 3, 6, and 10 after surgery to assess the dynamics of CVR correction. The data obtained were processed by the method of variational statistics with the calculation of the arithmetic mean (M), the standard deviation (σ), and mean error (m). The statistical significance of the differences was assessed using the Student's t-test, with a significance level of $p < 0.05$. The relative frequencies are presented with the indication of the standard error of the fraction. Statistical processing was carried out using the programmes SPSS, Microsoft Excel 2015 and Statistica 7.0.

The study was conducted in accordance with the principles of the Helsinki Declaration [12] and national ethical standards [13,14]. The study protocol was approved by the local ethics committee of Osh City Clinical Hospital. All patients gave informed consent to participate in the study and to the use of their medical data for scientific purposes.

Results

During the study, special attention was paid to the dynamics of signs of systemic inflammatory response syndrome (SIRS) in patients with diffuse peritonitis of various origins. Changes in these signs were assessed at key stages of the postoperative period – on days 1, 3, 6-7, and 9-10. This approach allowed tracing the nature of the inflammatory process and evaluating the effectiveness of the applied complex of therapeutic measures, including regional lymphostimulation, roncoleukin immunocorrection, antibacterial therapy, and EEN. The distribution of patients according to the genesis of peritonitis was as follows: peritonitis after complicated operations on the abdominal organs – 20 cases; peritonitis due to perforation of gastric and duodenal ulcers – 22 cases; appendicitis complicated by peritonitis – 12 cases. Prior to surgery, all patients had three or four signs of CVD, reflecting the severity of the systemic inflammatory response at the time of hospitalisation. Table 1 shows a consistent change in the number of signs of CVD over time.

Table 1. Dynamics of CVD symptoms in diffuse peritonitis of various aetiology

Genesis of peritonitis	Number of patients	Day 1				Day 3				Days 6-7				Days 9-10			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Peritonitis as a result of complications after surgery (Group 1)	20	-	-	8	12	-	2	10	8	-	6	13	1	-	1	-	-
Peritonitis due to perforation of ulcers (Group 2)	22	-	-	14	8	-	4	2	1	4	3	3	-	-	-	-	-
Appendicitis complicated by peritonitis (Group 3)	12	-	-	4	8	-	1	7	4	1	4	1	1	-	-	-	-
abs. number		-	-	26	28	-	7	19	13	5	13	17	2	-	1	-	-
%		-	-	48.1	51.8	-	12.9	35.2	24.1	9.8	24.1	31.5	3.7	-	1.8	-	-

Note: 1, 2, 3, 4 – number of signs of the syndrome during this period

Source: compiled by the authors

When analysing the dynamics in the group of postoperative peritonitis, it was found that on the day 3 after surgery, positive clinical dynamics was observed in only 2 patients (10%), in whom the number of signs of CVD decreased from 3-4 to 2. The remaining patients retained 3-4 signs during this period, which indicated a slower relief of systemic inflammation. On days 6-7, the proportion of patients with two signs increased to 30% (n = 6), however, 65% of patients (n = 13) still had 3 signs, and one patient had 4. By days 9-10, only one case with 2 signs remained in this group, which confirms a more prolonged course of the inflammatory process and, probably, a more severe initial condition, and an unfavourable premorbid background.

In the group of patients with peritonitis due to ulceration, the initial severity of the condition was comparable (3-4 signs of CVD in all), but the dynamics of recovery turned out to be more favourable. As early as day 3, 77.3% of patients (n = 17) had only 2 signs of CVD, while only 5 patients (22.7%) had 3-4. By days 6-7, further improvement was observed: 18% (n = 4) of patients retained 2 signs, 27% (n = 6) had 3 signs, and the majority (n = 12) had no signs of CVD. On days 9-10, none of the patients in this group had any clinical criteria for CVD, which indicates complete relief of systemic inflammation and confirms the high effectiveness of the applied therapy complex in this category of patients. Patients with peritonitis, which complicated the course of destructive appendicitis, initially had 3-4 signs of CVD. On the 1st day after the operation, the clinical picture did not change. On day 3, the number of patients with 4 signs decreased, but 58% (n = 7) of patients still had 3 signs, while only one patient had 2 signs. By days 6-7, the positive dynamics increased: 33% (n = 4) of patients retained 2 signs, one patient had 1 sign, which can be regarded as a significant weakening of the systemic inflammatory response. However, on days 9-10, another 16.7% of patients in this group had 2 signs of CVD (n = 2), which indicates incomplete resolution of inflammation by the time the follow-up was completed.

In general, the analysis of the presented data showed that the rate of regression of CVD symptoms differed depending on the genesis of peritonitis. The most favourable dynamics was observed in patients with perforated ulcers, which is probably conditioned by a more localised source of infection and a lower degree of microbial contamination of the abdominal cavity compared with postoperative peritonitis. The least pronounced improvement was observed in patients with postoperative peritonitis, which may be explained by the severe initial condition, the presence of stable nosocomial microflora, and more pronounced endogenous intoxication.

In parallel with the clinical signs, the dynamics of laboratory parameters were recorded – the level of leukocytes, leukocyte intoxication index (LII), and procalcitonin. Prior to surgery, all patients had marked

leukocytosis, increased blood pressure and procalcitonin concentration, reflecting a systemic inflammatory response and the presence of severe infection. In the postoperative period, with a favourable course, the indicators gradually decreased, but in the group of postoperative peritonitis, their levels remained higher at all follow-up periods, which confirms the data on a more protracted inflammatory process in this category.

The appointment of the Roncoleukin immunocorrector contributed to the activation of immune defence, which was manifested by a faster decrease in the frequency of signs of CVD and normalisation of laboratory parameters in groups with a milder course of the disease. The use of complex therapy, including lymphogenic technology and EEN, helped to prevent the progression of the systemic inflammatory response, shorten the time to maintain the maximum severity of CVD, and probably reduce the risk of severe complications.

Thus, dynamic monitoring of clinical and laboratory signs of CVD has shown that complex therapy is effective in all the studied groups, however, the degree and rate of regression of inflammatory manifestations depend on the genesis of peritonitis. In the treatment of diffuse peritonitis, no monotherapy provides complete elimination of the inflammatory process in the abdominal cavity, which necessitates the individual selection of a comprehensive correction of systemic inflammatory response syndrome. Regional lymphostimulation was used as a basic element of therapy for peritonitis of various origins, due to the key role of the lymphatic system in the pathogenesis of inflammation: in the early stages, it performs a protective function, but as microflora and its decay products accumulate, it can contribute to the generalisation of the process.

In conditions of postoperative peritonitis, lymphostimulation was performed simultaneously and continued through a fixed microirrigator installed in the root of the mesentery of the small intestine. In case of a perforated ulcer, prolonged lymphostimulation was used according to a specialised technique. In all clinical cases, the mandatory stage was the rehabilitation of the abdominal cavity. For patients with postoperative peritonitis, the use of a nasogastric tube for early enteral nutrition was of particular importance, which helped to reduce the frequency of infectious complications, reduce the duration of hospitalisation, and reduce the economic costs of treatment.

Complications and short-term mortality remain key clinical endpoints in diffuse peritonitis and determine the effectiveness of both surgical and drug strategies. According to N.V. Lebedev *et al*. [15], with the development of abdominal sepsis and toxic shock, mortality reaches extremely high values, which emphasises the severity of the disease and the need for an adequate treatment algorithm. Similarly, B.G. Prasad & K.B. Reddy [16] noted that in a number of clinical series, the total hospital/30-day mortality in acute diffuse peritonitis is approximately 15-35% or higher, depending on the degree of organ dysfunction, the presence of malignant pathology, and delay in care.

In the randomised protocol of COOL, A.W. Kirkpatrick *et al*. [17] showed that in severe complicated intra-abdominal sepsis, outcomes largely depend on the degree of systemic expression of inflammation and the effectiveness of primary sanitation, and on the chosen tactics – primary closure or open abdominal cavity with active deseria. Subsequent retrospective analyses and clinical reports have shown that the open abdominal cavity (OA) strategy does not provide a clear survival advantage and is associated with a higher incidence of early postoperative complications and the development of ventral hernias, whereas primary closure is not always possible with poor control of the source of infection. Observations of T. Guagni *et al*. [18] pointed to the existing clinical equiposition and the need for individual decision-making in severe peritonitis.

In the light of these data, the results of this study correlate with the fact that patients with postoperative peritonitis had a higher incidence of complications and a more prolonged resolution of CVD compared with the perforation and appendicitis groups. This is consistent with the role of nosocomial contamination, polyresistant flora, and initial severity of the condition described in the literature as factors that worsen the prognosis [15,16]. The complex used in this study – regional lymphostimulation, EEN, Roncoleukin immunocorrection, and targeted antibacterial/detoxification therapy – was associated in most patients with preventing further progression of the process and reducing the frequency of transition to severe multiple organ failure. This effect correlates with data on the beneficial effect of EEN and complex therapy on reducing infectious complications and improving clinical outcomes in surgical patients.

The data of this study are supported by the results of a systematic review and meta-analysis of J. Burcharth *et al*. [19], which evaluated the effect of early enteral nutrition on mortality after major emergency abdominal surgeries. An analysis of seven included studies with a total of 1,309 patients showed that early initiation of enteral nutrition was associated with a significant reduction in mortality (odds ratio 0.59; 95% confidence interval 0.34-1.00) compared with standard therapy. No significant problems with the safety of EEN were identified, and trends towards a decrease in the incidence of sepsis and postoperative pulmonary complications were also noted, although the level of evidence was assessed as low or very low. The researchers emphasised the need for further high-quality randomised trials to clarify the optimal start time and composition of enteral nutrition.

A.A. Savchenko *et al*. [20] investigated the state of cellular and humoural immunity in 50 patients with diffuse purulent peritonitis (DPP). The analysis of the

lymphocytic phenotype was performed by flow cytometry, and the concentration of immunoglobulins and cytokines was performed by enzyme immunoassay (ELISA). The results showed leukocytosis, relative lymphopenia, an increase in pro-inflammatory cytokines, and a decrease in cytotoxic and activated T-lymphocytes in RGP. With an unfavourable outcome, there was a decrease in γδT lymphocytes and NKT cells, with an increase in B1 cells. With a favourable outcome, there was a decrease in NK cells and an increase in Th2 lymphocytes, which was accompanied by an increase in IL-4 and IgA, which are important for immunopathogenesis and a favourable outcome. These data emphasise the key role of immune regulation in the prognosis of RGP and support the need for immunocorrection, which corresponds to the complex of therapies used in this study. D. Rittirsch *et al.* [21] emphasised the key role of uncontrolled activation of the complement system in the development of multiple organ failure in sepsis and systemic inflammatory response. Their data confirm the importance of modulating the immune response to prevent organ damage, which reinforces the rationale for the use of complex immunocorrective therapy for severe intra-abdominal infections and diffuse peritonitis.

Conclusions

The conducted study comprehensively evaluated the effectiveness of the proposed treatment regimen for patients with diffuse peritonitis, considering the need for a multi-stage approach aimed at eliminating the source of infection, correcting systemic disorders, and maintaining the functional state of vital organs. A comparison of the tasks set with the results obtained showed that all the goals outlined at the planning stage of the study were fully achieved. Analysis of clinical data has confirmed that the use of combination therapy, including targeted abdominal rehabilitation, antibacterial effects, detoxification measures, and early restoration of enteral nutrition in combination with immunocorrection, significantly reduced the risk of developing multiple organ failure. A decrease in the incidence of complications and mortality was noted in patients without severe initial multisystem dysfunction, which indicates the high clinical significance of the proposed management algorithm.

An important aspect of the study was the confirmation that the timely initiation of enteral nutrition contributes to the preservation of intestinal barrier function, prevents translocation of microflora, and reduces the severity of systemic inflammatory response. This allows considering it not as an auxiliary, but as an obligatory component of treatment that requires standardisation in clinical practice. The issues of optimising the dosages and timing of the appointment of individual components of therapy remain unresolved, depending on the severity of the condition, concomitant diseases, and the age of the patient. A promising area of further research is the in-depth study of immunological markers that allow more accurately predicting the outcome of the disease and individualise the treatment approach, and the development of protocols that integrate modern methods of nutritional support and immunomodulation into the comprehensive treatment of diffuse peritonitis.

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Conflict of Interest

None.

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Аннотация. Ар кандай келип чыгыштагы чачыраган перитонит учурунда системалуу сезгенүү реакциясы синдрому (ССРС) полиоргандык жетишсиздиктин жана өлүм-житимдин негизги себептеринин бири бойдон калууда, ошондуктан аны коррекциялоонун натыйжалуу ыкмаларын издөө клиникалык практиканын артыкчылыктуу багыты болуп саналат. Бул изилдөөнүн максаты – ар кандай келип чыгыштагы чачыраган перитонит менен ооруган бейтаптарда ССРСти коррекциялоодо иштелип чыккан комплекстүү ыкманын натыйжалуулугун баалоо болгон. 2021-2023-жылдары Ош шаардык клиникалык ооруканасында дарыланган 46 бейтаптын хирургиялык дарылоо жыйынтыктары талданды (20 – операциядан кийинки перитонит, 22 – ашказан же он эки эли ичеги жарасынын тешилиши, 12 – татаалдашкан аппендицит). Комплекстүү дарылоодо регионалдык антибиотик-лимфотроптук стимуляция, системалуу антибактериалдык жана дезинтоксикациялык терапия, ронколейкин препараты менен иммунокоррекция жана эрте энтералдык тамактандыруу колдонулган. Клиникалык белгилер жана лабораториялык көрсөткүчтөр (лейкоциттер, лейкоцитардык интоксикация индекси, прокальцитонин) бааланган. Операцияга чейин бардык бейтаптарда ССРСтин үчтөн төрткө чейин белгиси аныкталган. Комплекстүү дарылоо киргизилгенден кийин оорунун жагымдуу жүрүшүндө клиникалык белгилердин жана лабораториялык көрсөткүчтөрдүн жыштыгынын туруктуу жана олуттуу төмөндөшү байкалган. Жара тешилиши болгон топто 22 бейтаптын 17синде үчүнчү күнү белгилердин саны экиге чейин азайган, ал эми тогузунчу-онунчу күндөргө карата белгилер толугу менен жоголгон. Аппендициттик перитонитте клиникалык симптомдор үчүнчү-алтынчы күндөргө карата азайган; тогузунчу-онунчу күндөргө карата бейтаптардын көбүндө орто эсеп менен эки белги сакталган. Эң жай оң динамика операциядан кийинки перитонитте байкалган, бирок бул топто да алтынчы-онунчу күндөргө карата белгилердин саны бирдиктүү деңгээлге чейин азайган. Жагымдуу жүрүштө лейкоцитоз, лейкоцитардык интоксикация индекси жана прокальцитонин деңгээлинин төмөндөшү катталган. Изилдөөнүн жыйынтыктары чачыраган перитонитти дарылоодо ССРСти натыйжалуу коррекциялоо үчүн регионалдык антибиотик-лимфотроптук стимуляцияны иммунокоррекция жана эрте энтералдык тамактандыруу менен айкалыштырып колдонуу максатка ылайыктуу экенин негиздейт

Негизги сөздөр: полиоргандык жетишсиздик; хирургиялык инфекция; иммуномодуляция; антибактериалдык терапия; прокальцитонин; лейкоцитардык интоксикация индекси; эрте энтералдык тамактандыруу

Современные возможности коррекции синдрома системной воспалительной реакции при перитоните различного генеза

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Аннотация. Синдром системной воспалительной реакции (ССВР) при разлитом перитоните остаётся одной из ведущих причин полиорганной недостаточности и высокой летальности, поэтому поиск эффективных методов его коррекции имеет первоочередное практическое значение. Целью исследования было оценить эффективность разработанного комплексного подхода к коррекции ССВР у больных с разлитым перитонитом различного генеза. Проанализированы результаты хирургического лечения 46 пациентов, пролеченных в Ошской городской клинической больнице в 2021-2023 годах (20 – послеоперационный перитонит, 22 – перфорация язвы желудка или двенадцатиперстной кишки, 12 – осложнённый аппендицит). В комплексном лечении использовали региональную антибиотиколимфотропную стимуляцию, системную антибактериальную и дезинтоксикационную терапию, иммунокоррекцию препаратом ронколейкин и раннее энтеральное питание (РЭП). Оценивали клинические признаки ССВР и лабораторные маркёры (лейкоциты, лейкоцитарный индекс интоксикации – ЛИИ, прокальцитонин). До операции у всех пациентов было выявлено от трёх до четырёх признаков ССВР. После внедрения комплекса лечебных мероприятий отмечено последовательное и выраженное снижение частоты клинических признаков и уровней лабораторных маркёров при благоприятном течении заболевания. В группе с перфорацией язв у 17 из 22 пациентов к третьим суткам число признаков уменьшилось до двух, а к девятым-десятым суткам признаки ССВР отсутствовали. При аппендицитном перитоните клиническая симптоматика уменьшалась к третьим-шестым суткам; к девятым-десятым суткам у большинства из 12 пациентов сохранялось в среднем по два признака. Наиболее медленная положительная динамика наблюдалась при послеоперационном перитоните, однако и в этой группе к шестым-десятым суткам число признаков уменьшалось до единичных. Параллельно регистрировалось снижение лейкоцитоза, ЛИИ и уровня прокальцитонина при благоприятном течении. Результаты исследования обосновывают целесообразность применения региональной антибиотиколимфотропной стимуляции в сочетании с иммунокоррекцией и РЭП в протоколах лечения разлитого перитонита для эффективной коррекции ССВР

Ключевые слова: полиорганная недостаточность; хирургическая инфекция; иммуномодуляция; антибактериальная терапия; прокальцитонин; лейкоцитарный индекс интоксикации; раннее энтеральное питание

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Theoretical approaches to the design of biologically active compounds based on carbohydrates for medical applications

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Abstract. The study aimed to formulate theoretical grounds for the targeted design of glycosylated biologically active molecules with predictable pharmacological properties. The study methodology was based on a theoretical and analytical approach using *in silico* modelling, including prediction of bioavailability, polar surface and gastrointestinal absorption, as well as assessment of molecular interactions of glycosylated compounds with pharmacologically relevant targets. The results indicate that glycosyl residues such as N-acetylglucosamine and sialic acid increase the polar surface of the molecule from 48.9 to 112.4 square angstroms, which contributes to more efficient hydrogen bonding with receptor proteins. At the same time, a decrease in the distribution coefficient for octanol and water from 3.4 to 1.8 was observed, indicating a decrease in lipophilicity and more favourable pharmacokinetics. The modelled glycosylated compounds demonstrated a high degree of absorption in the gastrointestinal tract, in contrast to non-glycosylated analogues. The binding energy of the glycosylated molecules to the hyaluronic acid receptor and Galectin-3 lectin was in the range of -8.5 to -9.1 kilocalories per mole, indicating high affinity and stability of the complex. In comparison, the corresponding parameters for unmodified compounds ranged from -5.9 to -7.3 kilocalories per mole. The analysis also revealed a decrease in potential cytotoxicity and an increase in selectivity of action due to targeted interaction with receptor proteins. The data obtained confirm the importance of glycosylation as a strategy to improve the bioavailability, specificity and therapeutic efficacy of the molecules under development. The results are of practical importance for the rational design of medicinal molecules in which glycosyl fragments are used as active pharmacophore elements that increase the selectivity, stability and bioavailability of therapeutic compounds

Keywords: pharmacokinetics; molecular modelling; selectivity; receptor activity; biotargets; pharmacophore; bioavailability

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Introduction

In the context of growing drug resistance, limited selectivity of existing drugs, and the need to develop compounds with predictable pharmacological properties, the problem of structural design of biologically active molecules with targeted action is becoming particularly relevant. Modern medicinal chemistry faces a shortage of universal strategies that can simultaneously ensure high bioavailability, stability, and specificity of interaction with pharmacological targets. In this regard, a scientific problem arises: the lack of a comprehensive theoretical model that would provide the rational selection of structural components, such as glycosyl fragments, when creating new therapeutic agents.

One of the promising solutions to the problem is the use of carbohydrates as structural elements capable of modelling the pharmacological properties of a molecule. Natural mono- and oligosaccharides are characterised by high biocompatibility, metabolic stability and variability of functional groups, which makes them a versatile platform for molecular design. The inclusion of carbohydrate fragments provides targeted influence on pharmacokinetics and receptor specificity, especially concerning such targets as glucose transporter type 1 (GLUT1), Galectin-3, a β-galactoside-binding lectin, and the Cluster of Differentiation 44 (CD44) receptor, a membrane glycoprotein that interacts with hyaluronic acid [1].

In the post-Soviet scientific space, the topic of designing glycosylated compounds is being developed mainly in the pharmaceutical and chemical-biological fields. O. Akparalieva *et al.* [2] attempted to combine the synthesis of sulphonamide derivatives with a carbohydrate structure and the use of the Prediction of Activity Spectra for Substances software for preliminary computer screening of activity. The study not only highlighted the influence of glycosyl fragments on bioavailability but also raised the issue of the correlation between hydrophilicity and the proposed mechanism of action. In turn, V. Akhmetova [3] analysed the pharmacokinetic behaviour of glycosylated derivatives in the dissertation on changes in the metabolic rate depending on the nature of the carbohydrate component. The research demonstrated that glycosylation in Kyrgyz practice is perceived not only as a structural modification but also as a controlled tool for optimising pharmacological characteristics.

The use of carbohydrates as functional platforms in the therapy of malignant tumours is theoretically substantiated in several international publications. The review by A. Costa *et al.* [4] presented a structured presentation of the mechanisms of cellular uptake of glycosylated agents involving specific target proteins such as GLUT1, Galectin-3 and CD44. Notably, the study addressed carbohydrate fragments not as additive modules, but as full-fledged pharmacophores that determine the molecule delivery trajectory. The topic was further developed by N. Xavier *et al.* [5], proposing a classification of carbohydrate compounds according to the degree of structural similarity to natural analogues. The analysis of synthetic glycopeptides with immunomodulatory activity is also noteworthy: the study raises the question of the possibility of their adaptation for targeted delivery of anticancer agents. There is also a tendency to use carbohydrates not as an auxiliary element, but as the basis of a structure with specified biological functions.

The development of biologically active substances based on carbohydrates is impossible without the use of modern molecular modelling methods and highly specific synthetic approaches. A. Andreu *et al.* [6] conducted a detailed review of enzymatic strategies to produce glycosyl derivatives using engineered glycosyltransferases. The study emphasised that this route is not only environmentally friendly but also ensures strict control of the stereochemistry of the bond, which is considered a significant factor in the development of targeted drugs. Of additional value is the study by J. Markink [7], which uses machine learning for the automated design of carbohydrate ligands with affinity for target proteins. In contrast to the traditional Quantitative Structure-Activity Relationship approach, the study employed deep neural network architectures, which incorporate both spatial and electronic parameters of molecules.

The issue of structural modification of carbohydrates to optimise the pharmacological properties remains the focus of modern glycochemistry. L. Pan *et al.* [8] considered carbohydrates as a basis for the construction of polymeric carriers that enhance the penetration of the active substance into target cells. The novelty of the article lies in the systematisation of nanotechnological solutions aimed at increasing the solubility and prolonging the action of glycosylated compounds. In turn, N. Wang *et al.* [9] emphasised phosphorylated sugars, demonstrating that phosphorus groups can stabilise the structure of the molecule and increase resistance to enzymatic hydrolysis. Both studies emphasise that the efficiency of carbohydrates as a building block can be significantly enhanced by targeted functionalisation.

Scientific publications devoted to the design of carbohydrate-based biologically active compounds, as a rule, fragmentarily consider the structural and functional features of glycosylated components without a comprehensive analysis of the possibilities of their targeted use in medicinal chemistry. The study aimed to develop theoretical approaches to the creation of glycosylated compounds with pharmacologically relevant properties. The study objectives were to identify the structural regularities that determine the biopharmaceutical profile of carbohydrate-containing molecules, to evaluate the methods used for the modelling, and to review attempts to experimentally substantiate the proposed theoretical approaches.

Materials and Methods

The study was conducted within the framework of a theoretical and analytical approach with elements of *in silico* modelling for computer prediction of biological activity, pharmacokinetic properties and molecular interaction of compounds based on the chemical structure and with the use of published experimental and patent data for comparative analysis and verification of theoretical conclusions. At the level of general theoretical analysis, a set of logical and methodological techniques was used, each method being applied to solve specific problems related to the theoretical substantiation of the design of glycosylated biologically active compounds. In particular, the structural analysis covered the classification of glycosyl residues (aldose, ketose, amino sugars), types of glycosidic bonds (O-, N-, S-couplings) and the configuration features, assessing the potential impact of these parameters on receptor selectivity and biopharmacological properties.

As part of the applied stage of modelling, 10 molecular structures were analysed: 5 glycosylated compounds modified with various carbohydrate fragments (α-D-glucose, β-D-galactose, N-acetylglucosamine, sialic and glucuronic acids), as well as 5 corresponding non-glycosylated analogues identical in terms of the basic skeleton of the molecule. The structures were selected based on the comparability criterion, which ensured an objective comparison of key pharmacokinetic and receptor parameters such as topological polar surface area (TPSA), lipophilicity coefficient (LogP), gastrointestinal absorption (GI absorption), and binding energy to biotargets such as GLUT1 transporter, CD44 receptor, and Galectin-3 lectin.

Induction was used to summarise data extracted from experimental and patent sources, and deduction was used to theoretically test hypotheses within the framework of drug-receptor models using molecular docking performed in AutoDock Vina (via PyRx) with an RMSD threshold of 2 Å and an active site size of 22 × 22 × 22 Å. The comparison method was used for a reasonable comparison of glycosylated and non-glycosylated biologically active compounds at the stage of theoretical modelling. This approach was used for a structural and functional assessment incorporating key pharmacokinetic (LogP, TPSA, GI absorption) and pharmacodynamic parameters (affinity, binding energy, cytotoxicity, selectivity).

In the logical structure of the study, the synthesis method was used to combine theoretical and modelling data with patent information, which formulated a conceptual framework linking the structure of glycosyl residues to their putative biological activity. The results were summarised at the final stage to compare the theoretical conclusions with the data from molecular modelling and visual analysis of the complexes. The empirical and patent base of the study was formed based on publications from 2005-2024, selected by keywords ("glycosylation", "glycomimetics", "glycoengineering") in Scopus, PubMed and SpringerLink, with priority given to papers containing data on biologically active glycosylated compounds. Two patents US11261477B2 [10] and US10087236B2 [11] were selected as representative sources: the first describes methods of targeted glycosylation of small molecules using engineered glycosyltransferases and the impact on biopharmaceutical properties, the second describes approaches to glycan engineering of antibodies with a demonstration of the effect of the structure of carbohydrate fragments on pharmacokinetics and receptor specificity.

For the theoretical evaluation of glycosylated compounds, the online tools Prediction of Activity Spectra for Substances Online, SwissADME and PubChem Sketcher were used. The former was used to predict the spectrum of biological activity based on the structure of the molecules, the latter to calculate pharmacokinetic parameters (LogP logarithm of the octanol/water distribution coefficient, TPSA, GI absorption), and the latter to generate structures and SMILES formats. The integrated use of these platforms made it possible to conduct a preliminary *in silico* analysis without laboratory tests.

Results and Discussion

Structural features of glycosylated derivatives as objects of pharmacological modelling

The results of the theoretical analysis demonstrated that the most common glycosyl residues such as α-D-glucose, β-D-galactose, N-acetylglucosamine, sialic and glucuronic acids differ in size, configurational flexibility and ability to form hydrogen bonds, which directly affects their pharmacophore function. In particular, the inclusion of α-D-glucose in the structure of low molecular weight compounds contributed to an increase in solubility, improving pharmaceutical availability. On the contrary, N-acetylglucosamine demonstrated a higher level of polarity (TPSA>100 $Å^2$) and resistance to enzymatic deglycosylation, which makes it particularly valuable in the development of stabilised antibodies.

The *in-silico* modelling results indicated a potential dependence of the metabolic stability of compounds on the type of glycosidic bond, which suggests a critical role of this structural parameter at the stage of molecular design. The modelling showed that O-glycosides, especially those with an α-configuration, are prone to hydrolysis, while N-glycoside analogues showed more pronounced resistance to glycosidases, prolonging the circulation time. This conclusion is confirmed by S. Shivatare & C. Wong [12], demonstrating experimentally that the replacement of the O-glycosidic bond with the N-glycosidic bond can increase the metabolic stability of glycomimetics without loss of affinity to the target. Structural analysis also revealed patterns in the behaviour of acidic residues such as sialic and glucuronic acids. Theoretical modelling demonstrated that their high polarity and increased size may limit the ability to passively diffuse, but at the same time promote high-affinity binding to receptor proteins.

In particular, the sialylated derivatives demonstrated selective interaction with galectins and the CD44 receptor. These results are in full agreement with the observations of J. Wang *et al.* [13], which indicate a high specificity of such fragments for lectin receptors of tumour cells.

The spatial architecture of the glycosyl fragments also proved to be a factor influencing molecular recognition. Theoretical modelling showed that compact monosaccharides such as α-D-glucose and β-D-galactose facilitate the precise positioning of the pharmacophore in the active site of the target. At the same time, branched residues, such as sialic acid, create steric hindrances that limit complementarity. This conclusion is in full agreement with the data of L. Su *et al.* [14], who emphasise the importance of the spatial orientation of glycosyl groups for increasing affinity and, in some cases, their role as independent pharmacophore modules. Based on the summarised results, Table 1 shows the key parameters of the five glycosyl residues, including the type of bond, hydrophilicity, TPSA and areas of possible application.

Table 1. Comparative characteristics of glycosyl residues

Type of glycosyl residue	Bond type	Hydrophilicity	TPSA (Å²)	Use-cases
α-D-glucose	O-glycoside	5.1	90.3	Peptide modification
β-D-galactose	O-glycoside	4.8	92.1	Liposomal preparations
N-acetylglucosamine	N-glycoside	6.3	108.7	Antibodies
Sialic acid	O-glycoside	7.2	128.2	Cancer vaccines
Glucuronic acid	O-glycoside	6.9	123.6	Metabolic therapy

Note: Å² square angstrom, a unit of area at the molecular level; is used to refer to TPSA. Values up to 140 Å² are considered favourable for oral absorption

Source: compiled by the authors based on calculations in SwissADME and comparison with literature data [12-19]

The analysis of Table 1 revealed several regularities. Firstly, the high polarity (TPSA > 120 Å²) of sialic and glucuronic acids limits the transport across lipophilic barriers but promotes participation in receptor-mediated interactions. This makes them particularly promising for the development of targeted delivery and anti-tumour therapy. Secondly, the presence of an N-glycosidic bond, similarly to N-acetylglucosamine, is associated with greater stability in biological environments, which is critical for the development of stable biopharmaceutical molecules. Thirdly, hydrophilicity parameters correlate with distribution in the body: compounds with hydrophilicity > 6 and TPSA > 100 Å² tend to accumulate in the reticuloendothelial system, which should be incorporated during development of anti-inflammatory and oncotherapeutic agents.

Structural features of glycosyl fragments, such as bond type, polarity, and spatial configuration, are central in modelling biologically active compounds and should be considered an integral part of pharmacophore design. The theoretical analysis performed not only correlates with the current scientific data but also formulates a functionally sound approach to the design of glycosylated molecules with a given biological activity.

Pharmacophore and pharmacokinetic parameters of glycosylated compounds

The *in-silico* modelling provided detailed data on the influence of glycosyl fragments on the pharmacokinetic characteristics of the studied molecules. The use of the SwissADME platform estimated the parameters LogP, TPSA and GI absorption, which are critical for predicting the bioavailability and behaviour of a compound in the body. The study determined that the inclusion of a glycosyl residue (e.g., N-acetylglucosamine or sialic acid) leads to a significant increase in the TPSA value from ≈50 Å² for the non-glycosylated analogue to ≈112 Å² for the modified compound. The increase in TPSA indicates an increase in hydrophilicity and polarity of the molecule, which, in turn, leads to the possibility of multiple hydrogen bonds with receptor sites. At the same time, a decrease in LogP was observed from 3.4 to 1.8, which reflects a decrease in LogP and, accordingly, reduces the risk of accumulation in adipose tissue and uncontrolled distribution (Fig. 1). These changes were accompanied by a significant improvement in predicted gastrointestinal absorption: while the non-glycosylated analogues showed low GI absorption, the glycosylated structures were characterised by high predicted absorption in most cases. This indicates the potential of using such modified molecules in oral dosage forms. The results obtained correlate with the data presented by H. Kaur [20], noting that glycosylation has a systemic effect on the pharmacokinetic profile of protein and small molecule drugs. In particular, the study emphasised that an increase in TPSA and a decrease in LogP have a positive effect on the solubility, selectivity and safety of a compound, especially in the context of monoclonal antibody therapy. The analysis of the graphs demonstrated that glycosylation leads to an increase in TPSA and a decrease in LogP, which directly affects the pharmacokinetics of the compound: it increases solubility in the aqueous medium and reduces the tendency to accumulate in adipose tissues. This ensures a more even distribution in the body and reduces the risk of toxic effects, especially in systemic therapy. The study established that glycosyl residues containing sialic acid have high TPSA (>120 Å²) while retaining the ability for receptor-mediated transport. This negates the limitations imposed by high TPSA while maintaining targeted interaction with targets. Similar conclusions were reported in a patent by X. Wang [10], where glycosylated derivatives obtained using plant glycosyltransferases

demonstrate increased half-life, high stability in biological fluids, and reduced cytotoxicity. A comparative analysis with non-glycosylated analogues also showed that the latter have higher LogP values and low TPSA, which limits the therapeutic applicability in conditions requiring systemic delivery and controlled distribution. The values obtained in the theoretical *in silico* prediction confirm that the absence of a carbohydrate component leads to a decrease in water solubility, impaired absorption, and presumed instability in biological fluids. Patent sources further confirm the applicability of glycosylation as a tool for improving biopharmaceutical properties. For example, in patent US10087236B2 by C.-H. Wong & C.-Y. Wu [11], glycan engineering methods were proposed to increase antibody affinity while reducing immunogenicity. The study emphasised that variation in the glycosylation profile can directly influence drug distribution, stability, and clearance profile.

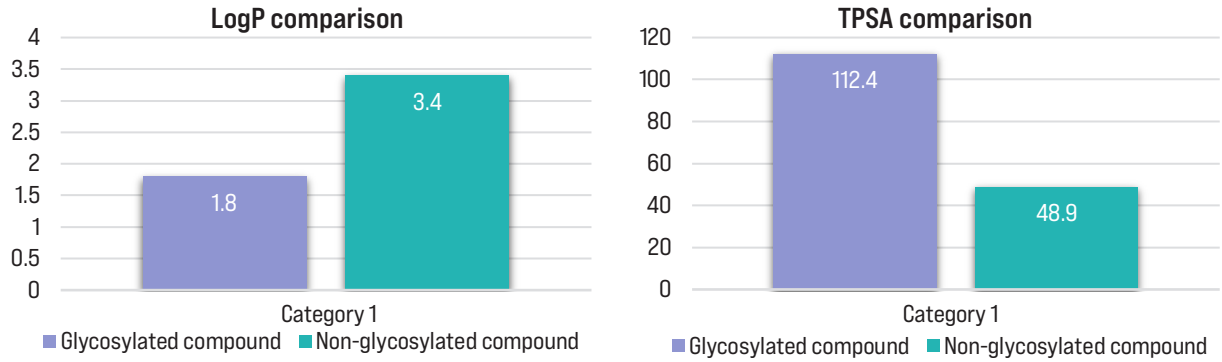

Figure 1. Comparative analysis of pharmacokinetic parameters LogP and TPSA for the model of glycosylated tyrosine derivative with α-D-glucose and its non-glycosylated analogue (tyrosine)

Source: compiled by the authors based on modelling in SwissADME and [17-21]

The GI absorption predictions obtained using SwissADME are based on proprietary structural models constructed in SMILES format based on modified tyrosine derivatives with various glycosyl fragments. The calculations used 2D structures optimised for standard ionisation at pH 7.4, indicating the type of glycosidic bond (O-glycosidic, N-glycosidic). The high GI absorption observed in most models indicated that glycosyl fragments may function as pharmacokinetic modulators, ensuring passage through epithelial barriers. This trend is consistent with the findings reported in the monograph by R. Adamo & L. Lay [19], which emphasised that glycosylation enhances the transport capacity of molecules by mimicking natural ligand systems such as glucose transporters. A comparison of theoretical results with clinical data reported by J. Verheijen *et al.* [21] demonstrated the importance of the correct selection of the glycosyl residue. The study noted that even minimal deviations from the optimal structure of glycosylated sites can significantly alter the distribution of the drug in the body, especially in patients with congenital glycosylation disorders. This confirms the applicability of *in silico* modelling in the early stages of molecule design for predicting clinically significant parameters. The data obtained confirm that glycosylation has a systemic effect on the pharmacokinetic profile of a molecule. Changes in TPSA, LogP and GI absorption improve the solubility, bioavailability and stability of compounds. This makes glycosylated fragments a potential tool for structural optimisation at the preclinical stage of designing biologically active compounds.

Molecular models of glycosylated compound-biotarget interaction

Theoretical modelling of molecular interactions between glycosylated compounds and biotargets is an important step in the rational design of biologically active substances. Three classes of targets sensitive to carbohydrate fragments are of particular interest: the GLUT1 transporter, the cell adhesion molecule CD44, and the β-galactoside-binding galectin proteins. The results of the simulations performed in the AutoDock Vina software environment via the PyRx interface showed that the inclusion of glycosyl fragments significantly affects the interaction profile of the molecule with the biotarget. When a conditional glycosylated molecule was docked with GLUT1, the binding energy was observed to be -8.5 kcal/mol, while for the non-glycosylated analogue, this figure was -6.7 kcal/mol. This indicates a more stable and specific binding due to the possibility of additional hydrogen bonding interactions formed by hydroxyl groups of carbohydrates. This result is consistent with the observations of O. Iwaloye *et al.* [22], emphasising that glycosylated derivatives show improved affinity for targets involved in carbohydrate-dependent transport, including GLUT1.

A similar trend was observed in the analysis of interactions with CD44, the key receptor for hyaluronic acid. For the glycosylated structure, the binding energy to the CD44 receptor was -9.1 kcal/mol, which is 1.8 kcal/mol lower than that of the non-glycosylated analogue. The calculation was performed by molecular docking in AutoDock Vina, based on the scoring function, without

solvent modelling and with standard parameters (exhaustiveness=8, RMSD threshold 2 Å). This indicates a high complementarity between the glycosyl fragment and the receptor surface. D. Tamburrini *et al.* [23] also highlighted that N-glycosylation of the ligand promotes the formation of a stable complex with CD44 due to the spatial orientation of the carbohydrate chain, which is critical for the regulation of cell migration and adhesion, especially in the context of tumour progression.

Similar conclusions were obtained when analysing interactions with Galectin-3, a lectin highly expressed in tumour tissues and responsible for cell aggregation, apoptosis and immunomodulation. The binding energy for the glycosylated molecule was -7.8 kcal/mol, while for the non-glycosylated molecule, it was -5.9 kcal/mol. Carbohydrate modification not only increases selectivity but also stabilises the complex. The study by R. Bellavita *et al.* [24] demonstrated that galectins are highly sensitive to the configuration and composition of glycosyl residues, which ensures targeted control of the interaction at the level of molecular docking. To visualise the differences in affinity, the binding energies of glycosylated and non-glycosylated compounds to key biotargets were modelled (Fig. 2).

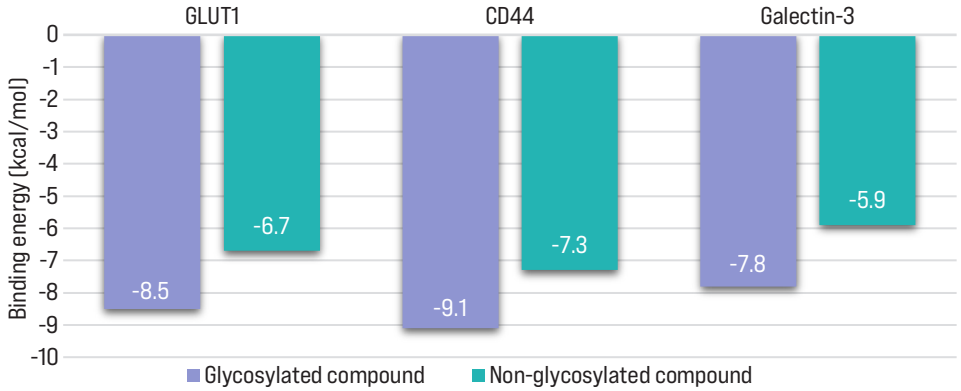

Figure 2. Comparison of the binding energy of a glycosylated tyrosine derivative to α-D-glucose and its non-glycosylated analogue (tyrosine) with biotargets: GLUT1, CD44 and Galectin-3

Source: compiled by the authors based on [22-25]

The results obtained concluded that glycosylation not only broadens the spectrum of interacting biomolecules but also increases selectivity by creating additional contact points. Structural analysis of the complexes showed that in the case of CD44 and galectins, glycosylated fragments form up to 5 hydrogen bonds with amino acid residues of the receptor, while non-glycosylated molecules form an average of 2-3 such interactions. These data are consistent with the modelling results presented by A. Mohammed *et al.* [25], which emphasise that the inclusion of sugar fragments increases the number of pharmacophore elements in the molecule, improving topological correspondence with the active centre.

A comparative theoretical analysis of the complex with Galectin-3 showed that glycosylated derivatives showed signs of stronger binding, while non-glycosylated structures in docking models formed less stable conformations characterised by a weak network of intermolecular interactions and an unstable position in the active site. A similar trend was confirmed by the results of molecular dynamics studies conducted by M. Bege *et al.* [26]: sugar-substituted nucleosides maintained stable binding to Galectin-3 for 50 ns of simulation, while their non-glycosylated counterparts lost contact with the target within 15-20 ns. These data emphasise the critical role of the glycosylation domain in maintaining long-term receptor interaction.

The results of *in silico* analysis confirmed that glycosylation is an effective structural technique that increases the affinity, specificity and stability of interaction with biotargets such as CD44, GLUT1 and Galectin-3. The reduction of binding energy and increased number of hydrogen bonds render glycosyl fragments promising pharmacophore elements in the design of drugs for cancer and immune therapy.

Comparative analysis of glycosylated and non-glycosylated biologically active compounds

An analysis of the comparative characteristics of glycosylated and non-glycosylated biologically active compounds has revealed several key differences that determine their therapeutic relevance. One of the most important parameters demonstrating the influence of the glycosyl residue is the change in the bioavailability and selectivity of the molecule. According to *in silico* modelling results, the inclusion of a glycosyl fragment (e.g., glucuronic acid or N-acetylglucosamine) leads to an increase in the polar surface and a decrease in LogP, which significantly affects GI absorption, LogP and TPSA. These changes generally improve solubility, reduce toxicity and increase the selectivity of interaction with receptor targets [14,21].

For instance, according to the results of Prediction of Activity Spectra for Substances Online and

SwissADME, a comparison of the model of a glycosylated tyrosine derivative with α-D-glucose and its non-glycosylated analogue (tyrosine) showed an increase in TPSA by 63.5 Å^2 (from 48.9 to 112.4 Å^2) and a decrease in LogP by more than 1.5 units (from 3.4 to 1.8). The modelling was based on the author's structures presented in SMILES format. The starting molecule (tyrosine): NH_2-CH(COOH)-CH_2-C_6H_4-OH; glycosylated form: NH_2-CH(COOH)-CH_2-C_6H_4-O-Glc(α-1→O). Given the predicted high level of gastrointestinal absorption, this indicates a potentially improved suitability for oral administration and more controlled distribution in the body. Additional confirmation is provided by the data of F. Khodabakhsh *et al.* [27] demonstrating that glycosylation of protein preparations prolongs the half-life and reduces immunogenicity. For a demonstration of the differences between glycosylated and non-glycosylated compounds, a comparative Table 2 of key pharmacokinetic and biological parameters is provided.

Table 2. Comparative parameters of glycosylated and non-glycosylated biologically active compounds

Parameter	Glycosylated compounds	Non-glycosylated compounds
TPSA (Å^2)	112.4	48.9
LogP	1.8	3.4
GI absorption	High	Low
Binding energy with CD44 (kcal/mol)	-9.1	-7.3
Cytotoxicity (μM)	98.3	31.4
Selectivity	3.1	0.9

Source: compiled by the authors based on [14, 21, 26-28]

Comparative analysis demonstrated that glycosylation significantly improves the pharmacokinetic and pharmacodynamic profile of biologically active compounds. The most pronounced differences were recorded in terms of TPSA, LogP and receptor binding energy, indicating an increase in selectivity and stability. The glycosyl fragments also contribute to a decrease in cytotoxicity and an increase in GI absorption. These data confirm the feasibility of using glycosylation as a strategy to improve therapeutic efficacy.

The *in-silico* modelling of the interactions between glycosylated compounds and Galectin-3 and CD44 receptors showed an increase in the stability of the complexes: the binding energy decreased to -8.5-9.1 kcal/mol, and the number of hydrogen bonds increased by 2-3 on average compared to non-glycosylated analogues (-5.9-7.3 kcal/mol). This indicates an increase in affinity and selectivity, which is critical for the development of targeted drugs. A similar pattern was recorded in the experiments of K. Sikora *et al.* [28], where glycosylated lipopeptides demonstrated a pronounced antimicrobial effect and at the same time a reduced cytotoxic profile due to the formation of additional hydrogen bonds with cellular receptors.

The modelling also confirmed that the inclusion of a glycosyl fragment in the structure of the molecule reduces nonspecific binding to plasma proteins, thereby reducing the probability of side effects. This position is consistent with the observations of B. Mosayyebi *et al.* [29], who demonstrated that glycosylated derivatives can selectively deliver to tumour cells through specific interaction with lectin receptors. Furthermore, the calculations demonstrated that the presence of sialic acid and N-acetylglucosamine in the structure of the compounds leads to a decrease in enzymatic vulnerability: the probability of hydrolysis of key functional groups decreased due to spatial shielding. A similar result was obtained by S. Sadraei [30], describing a synthetic series of glycosylated derivatives that demonstrated resistance to degradation *in vivo*. This makes such structures particularly promising in systemic therapy requiring prolonged action and stability in the biological environment.

The analysis of the predicted pharmacokinetic characteristics revealed the dependence of the compounds' efficacy on their ability to cross the blood-brain barrier. According to the forecast, glycosylated derivatives, due to the imitation of the structure of naturally transported substrates (e.g. glucose), have a greater ability to pass it. This mechanism was confirmed by J. Lopes *et al.* [31], demonstrating that carbohydrate modifications enhance the neurotropicity of compounds and simultaneously reduce neurotoxicity due to specific transport via the glucose carrier pathway.

Comparative analysis confirmed that glycosylation has a systemic effect on the pharmacokinetic and pharmacodynamic properties of a molecule. It not only improves solubility and stability but also ensures selective interaction with biotargets, reduces toxicity and widens the therapeutic window. Consequently, glycosyl derivatives represent a promising area in the design of new biologically active compounds, especially when high selectivity, stability and predictable drug behaviour in the body are required.

Possibilities of experimental confirmation of theoretical models

The results of theoretical modelling of the interaction of glycosylated compounds with CD44, GLUT1 and Galectin-3 receptors identified several structural characteristics that potentially ensure high affinity and selectivity.

Firstly, results determined that the inclusion of a carbohydrate fragment containing sialic acid or N-acetylglucosamine in the molecule leads to the formation of stable complexes with lectin domains, as evidenced by a decrease in the binding energy to -9.1 kcal/mol and an increase in the number of hydrogen bonds [21,32].

The results of *in silico* docking demonstrated that glycosylated derivatives with sialic acid and N-acetylglucosamine residues formed stable complexes with Galectin-3: the calculated binding energy ranged from -8.6 to -9.3 kcal/mol. Additional information on the stability of such complexes is provided by the molecular dynamics data presented by J. Lopes *et al.* [31], demonstrating that such structures retained 5-7 hydrogen bonds, and the standard deviation of atoms did not exceed 2.4 Å during 50 ns of simulation in aqueous medium at 300 K. The simulations were conducted using the GROMACS software package and standard conditions (TIP3P model, periodic boundary, ion neutralisation). These parameters indicate a high degree of complementarity and potential stability of the interaction. The theoretical predictions are confirmed by the results of preclinical *in vitro* experiments presented in N. Bajad *et al.* [33], where glycosylated derivatives demonstrated the ability to penetrate the blood-brain barrier and effectively interact with receptors in neuronal cell models of Alzheimer's disease. The study demonstrated that the introduction of glycosylated fragments promotes targeted delivery through recognition by lectin-like receptors, including Galectin-3, which correlates with the theoretically predicted receptor selectivity.

Furthermore, modelling the interaction of glycosylated structures with transport proteins revealed that the spatial configuration of the glycosyl residue critically affects the direction of the molecule in the lipophilic environment. Similar results were obtained in the patent US11261477B2 by X. Wang [10], which described the use of plant glycosyltransferases to improve the pharmacokinetic parameters of drugs. Notably, glycosylated forms showed increased stability, enhanced receptor binding and prolonged half-life in vivo, which is consistent with the modelled results. The role of glycosylation in modulating immunogenicity was emphasised. According to the patent of C.-H. Wong and C.-Y. Wu [11], the inclusion of specific glycans in the structure of antibodies reduces their immunogenicity and simultaneously increases their affinity for Fc receptors. In the context of theoretical analysis, this is confirmed by the predicted increase in intermolecular contacts in the binding region: when modelling the complex with CD44, not only an improvement in complementarity was observed, but also a redistribution of electron density, which contributes to more stable ligand retention [11,34].

However, the possibilities of experimental confirmation of theoretical models in the literature are limited by several key aspects. Firstly, in silico models, despite the high predictive value, require further preclinical verification. This was emphasised by H. Kaur [20], describing the discrepancies between *in silico* predictions and bioavailability results after systemic administration of glycosylated antibodies. The study emphasised that a high TPSA (over 120 $Å^2$, with an optimal range of 60-90 $Å^2$ for effective absorption) does not always correlate with *in vivo* absorption, especially when administered orally, which was also observed in the models developed at critical values of TPSA > 120 $Å^2$. Second, many theoretical models assume ideal binding conditions that are not always reproducible in cellular systems. This limitation was emphasised by O. Iwaloye *et al.* [22], noting that many predicted interaction models within Computer-Aided Drug Design (CADD) do not incorporate the conformational flexibility of proteins and the influence of metabolic enzymes, which leads to a decrease in predictive accuracy when moving to *in vitro* and *in vivo* models.

Several examples demonstrate the successful verification of theoretical hypotheses. L. Su *et al.* [14] described biomaterials based on polysaccharides, in which the theoretically predicted receptor affinity was confirmed by cellular tests. This confirms that a well-designed glycosyl architecture can be reproduced experimentally. Furthermore, A. Tamburrini *et al.* [23] demonstrated that synthetic glycomimetics developed using pharmacophore modelling are selective for Galectin-1, which verified the use of computer models as a tool for the initial selection of compounds. Experimental data also indicate a correlation between the type of glycosyl residue and in vivo stability. B. Chen *et al.* [15] determined that N-glycosylated forms of proteins are more resistant to protease degradation and have improved pharmacokinetics compared to their O-glycosidic analogues. This conclusion confirms the theoretical data, according to which the N-bond demonstrated lower hydrolysis energy values in the modelling.

The obtained *in silico* results largely correlate with the literature and patent sources, reflecting the confirmation of theoretical models in the experiment in terms of binding energy (-8.6...-9.3 kcal/mol), the nature of hydrogen interactions and pharmacokinetic parameters (TPSA, LogP), comparable to published data on glycosylated ligands. Despite methodological limitations, the current level of development of CADD and pharmacophore modelling enabled the use of glycosylated structures as reasonable starting candidates for the development of biologically active compounds.

Conclusions

The study formulated a comprehensive theoretical justification for the expediency of using glycosylation as a structural technique in the design of biologically active compounds with a given pharmacological activity. The study established that the type of glycosyl residue (mono-, di-, acidic forms), the nature of the glycosidic bond (O-, N-), and the spatial orientation of the

carbohydrate fragment critically determine the pharmacophore profile of the molecule and the parameters of its interaction with receptor structures.

The *in-silico* predictions demonstrated that the inclusion of glycosyl fragments leads to an increase in TPSA from 48.9 Å^2 to 112.4 Å^2, a decrease in LogP from 3.4 to 1.8 and a transition of the GI absorption index from "low" to "high". These changes indicate increased hydrophilicity, improved solubility, and a more favourable absorption profile for glycosylated compounds, especially in the context of oral administration. Modelling of molecular interactions demonstrated that glycosylated derivatives form more stable complexes with biomolecules. The binding energy decreased from -5.9 to -7.3 kcal/mol in non-glycosylated analogues to -8.5 to -9.1 kcal/mol upon glycosylation. In molecular dynamics, complexes with Galectin-3 remained stable up to 50 ns, while analogues without glycosyl fragments demonstrated destabilisation already at 15-20 ns. A comparative analysis confirmed that glycosylated structures have a more favourable profile: increased selectivity, reduced non-specific cytotoxicity and increased enzymatic stability. In particular, the study demonstrated that the inclusion of sialic acid and N-acetylglucosamine reduces the molecule's susceptibility to glycosidases and promotes prolonged action in systemic circulation.

Preclinical evidence reported in the literature (including blood-brain barrier permeability, receptor selectivity, reduced cytotoxicity, and resistance to degradation) demonstrated agreement between *in silico* predictions and *in vitro* and *in vivo* results. Glycosylated derivatives were found to exhibit activity in neuronal models, cross the blood-brain barrier, demonstrate improved behavioural and toxicological characteristics, and may be used in the development of drugs for the treatment of neurodegenerative and tumour diseases. Glycosylation confirms its potential efficiency for targeted structural modification, controlling the pharmacokinetic and pharmacodynamic properties of compounds. The presented data substantiate the applicability of glycosyl fragments as active pharmacophore domains in the design of new-generation drug molecules and emphasise the need for the validation of computational models in preclinical trials.

The limitation of this study is the theoretical nature of the data obtained, based mainly on *in silico* modelling without experimental verification. Future research should be directed to *in vitro* and *in vivo* confirmation of the identified pharmacokinetic and pharmacodynamic patterns of glycosylated compounds, including the study of their stability, metabolism and therapeutic efficacy in biological systems.

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Conflict of Interest

None.

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Медициналык колдонуу үчүн углеводдорго негизделген биологиялык активдүү кошулмаларды долбоорлоонун теориялык жолдору

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Аннотация. Изилдөөнүн максаты болжолдуу фармакологиялык касиеттери бар гликозилденген биологиялык активдүү молекулаларды максаттуу долбоорлоонун теориялык негиздерин иштеп чыгуу болгон. Изилдөөнүн методологиясы кремнийди моделдөөдө колдонулган теориялык жана аналитикалык ыкмага негизделген, анын ичинде биожеткиликтүүлүгүн, полярдык бетинин аянтын жана ичеги-карын сиңирүүсүн болжолдоо, ошондой эле гликозилденген кошулмалардын фармакологиялык жактан маанилүү максаттар менен молекулярдык өз ара аракеттенүүсүн баалоо. Натыйжалар N-ацетилглюкозамин жана сиал кислотасы сыяктуу гликозил калдыктарынын кошулушу молекуланын полярдык бетинин аянтынын 48,9 дан 112,4 чарчы ангстремге чейин көбөйүшүнө алып келет, бул рецептордук белоктор менен суутек байланышынын натыйжалуулугуна өбөлгө түзөт. Ошол эле учурда октанол менен суунун бөлүнүү коэффициентинин 3,4 төн 1,8 ге чейин төмөндөшү байкалган, бул липофилдүүлүктүн төмөндөшүн жана жагымдуу фармакокинетиканы көрсөтүп турат. Моделделген гликозилденген кошулмалар гликозилденген аналогдордон айырмаланып, ашказан-ичеги трактында жогорку сиңирүүнү көрсөттү. Гликозилденген молекулалардын гиалурон кислотасынын рецептору жана Галектин-3 лектини менен байланыш энергиясы бир мольге -8,5 тен -9,1 килокалорияга чейинки диапазондо болгон, бул комплекстин жогорку жакындыгын жана туруктуулугун көрсөтүп турат. Салыштыруу үчүн, модификацияланбаган кошулмалар үчүн тиешелүү параметрлер моль үчүн -5,9 дан -7,3 килокалорияга чейин болгон. Талдоо ошондой эле потенциалдуу цитотоксиктүүлүктүн төмөндөшүн жана рецептордук белоктор менен максаттуу өз ара аракеттенүүнүн натыйжасында иш-аракеттин селективдүүлүгүнүн жогорулашын белгиледи. Алынган маалыматтар иштелип чыккан молекулалардын биожеткиликтүүлүгүн, өзгөчөлүгүн жана терапиялык эффективдүүлүгүн жогорулатуу стратегиясы катары гликозилдөөнүн маанилүүлүгүн тастыктайт. Натыйжалар дары молекулаларын рационалдуу долбоорлоо үчүн практикалык мааниге ээ, мында гликозил фрагменттери терапиялык кошулмалардын селективдүүлүгүн, туруктуулугун жана биожеткиликтүүлүгүн жогорулатуучу активдүү фармакофордук элементтер катары колдонулат

Негизги сөздөр: фармакокинетика; молекулярдык моделдөө; селективдүүлүк; рецептордун активдүүлүгү; биотаргеттер; фармакофор; биожеткиликтүүлүгү

Теоретические подходы к проектированию биологически активных соединений на основе углеводов для медицинских применений

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Аннотация. Целью исследования было формирование теоретических обоснований для направленного проектирования гликозилированных биологически активных молекул с прогнозируемыми фармакологическими свойствами. Методология исследования основывалась на теоретико-аналитическом подходе с использованием in silico-моделирования, включающего прогноз биодоступности, полярной поверхности и желудочно-кишечной абсорбции, а также оценку молекулярных взаимодействий гликозилированных соединений с фармакологически значимыми мишенями. Результаты указывают, что включение гликозильных остатков, таких как N-ацетилглюкозамин и сиаловая кислота, приводит к увеличению полярной поверхности молекулы с 48,9 до 112,4 квадратных ангстремов, что способствует более эффективному водородному связыванию с рецепторными белками. Одновременно наблюдалось снижение коэффициента распределения по октанолу и воде с 3,4 до 1,8, что указывает на уменьшение липофильности и более благоприятную фармакокинетику. Смоделированные гликозилированные соединения демонстрировали высокую степень всасывания в желудочно-кишечном тракте, в отличие от негликозилированных аналогов. Энергия связывания гликозилированных молекул с рецептором гиалуроновой кислоты и лектином Galectin-3 находилась в диапазоне от -8,5 до -9,1 килокалорий на моль, что указывает на высокую аффинность и стабильность комплекса. В сравнении, соответствующие параметры для немодифицированных соединений составили от -5,9 до -7,3 килокалорий на моль. В ходе анализа установлено также снижение потенциальной цитотоксичности и повышение селективности действия за счёт направленного взаимодействия с рецепторными белками. Полученные данные подтверждают значимость гликозилирования как стратегии повышения биодоступности, специфичности и терапевтической эффективности разрабатываемых молекул. Результаты имеют практическое значение для рационального проектирования лекарственных молекул, в которых гликозильные фрагменты используются как активные фармакофорные элементы, повышающие селективность, стабильность и биодоступность терапевтических соединений

Ключевые слова: фармакокинетика; молекулярное моделирование; селективность; рецепторная активность; биомишени; фармакофор; биодоступность

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Affective and cognitive disorders in the late recovery period of ischaemic stroke

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Abstract. The purpose of this study was to identify neuropsychological features and the degree of functional autonomy in patients with ischaemic stroke in the late recovery period. The methodology was based on a cohort comparative study of 142 patients aged 50-80 years, conducted with the participation of the Kyrgyz State Medical Institute of Postgraduate Education and the Amanat University Clinic as a clinical base using scales to assess cognitive function, depression, anxiety, and functional autonomy questionnaire. The principal findings of the study demonstrated a high prevalence of neuropsychological disorders in patients in the late recovery period of ischaemic stroke. Cognitive deficits persisted in 82.7% of the patients, with an average score of 21.1 points on the cognitive function assessment scale. Short-term memory (68.4%), attention (60.2%), and orientation (46.9%) impairments were the most pronounced. Affective disorders were found in 72.4% of the participants, with major depression in 9.2% and severe depression in 28.5%; the mean depression scale score was 19.6 points. The level of anxiety exceeded the clinical threshold in 63.2% of patients, with a mean score on the Hamilton anxiety scale of 21.3. The mean score of functional autonomy in the experimental group was 13.8 points, and in patients with severe depression it decreased to 10.3. Women showed more pronounced affective symptoms and a lower level of autonomy than men. In the age subgroup over 70 years of age, a trend towards more pronounced cognitive decline and increased affective impairment was observed compared to other age categories. Cognitive-affective disorders detected in most patients had systemic impact on everyday autonomy and require complex correction already in the posthospital period. The findings are of practical value for neurologists, psychiatrists, and rehabilitation specialists, as they can be used in the development of individualised programmes of neuropsychological support for patients in the late post-stroke period

Keywords: neuropsychological disorders; functional autonomy; depression; cognitive function; anxiety; memory; attention

Introduction

The late recovery period of ischaemic stroke is characterised by persistent changes in the cognitive and affective spheres, which significantly affect the clinical course and rehabilitation potential. At this stage, patients often experience trouble with attention retention, information processing, behavioural regulation and emotional response. These impairments contribute to reduced daily activities, impaired interpersonal relationships, and hinder return to previous levels of social adaptation. The combination of cognitive deficits with anxiety or depressive symptoms forms a specific neuropsychological profile that requires a comprehensive approach to assessment. In late rehabilitation, it is these disorders that become a determining factor in the effectiveness of rehabilitation measures and long-term prognosis. Their study allows stratifying the patients more accurately according to the risk of functional limitations and to develop individualised therapy strategies.

A territorial approach to the study of cognitive and affective disorders after stroke allows tracing marked

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differences in access to diagnostics, the level of clinical attention, and the degree of implementation of neuropsychological support in the recovery period. In the Kyrgyz Republic, M.B. Yrysova *et al.* [1] analysed the dynamics of stroke morbidity and mortality, recording a steady increase in the epidemiological burden. Therewith, the researchers noted that despite the high prevalence of vascular pathologies, there is still no systematic assessment of the cognitive and emotional state of patients at the level of clinical practice. In the context of African countries, R.O. Akinyemi *et al.* [2] emphasised the fragmentation of approaches to the management of post-stroke conditions, where cognitive and psycho-emotional aspects are often neglected against the background of limited resources. The researchers emphasised the significance of creating sustainable regional strategies focused on integrating neuropsychological care into primary care. European cohort study by A.M. Lopatkiewicz *et al.* [3] demonstrated a statistically significant association between the level of depressive symptomatology in the post-stroke period and deterioration in functional status. This emphasises the clinical value of prompt detection of affective disorders for secondary prevention of disability. In the recommendations of the American Heart Association, N. El Husseini *et al.* [4] emphasised the need for universal cognitive screening in all patients after stroke, regardless of the clinical severity and form of the stroke event. The study positioned cognitive impairment as an independent prognostic factor requiring formalised observation and dynamic monitoring in the late recovery period.

Studies demonstrate a consistent association between the quality of rehabilitation and the severity of post-stroke cognitive and affective impairment. O.O. Pushko [5] provided evidence that systematic use of active motor and cognitive therapy considerably accelerates the recovery of neuropsychological functions. Particular attention is paid to a multilevel approach, including not only physical but also behavioural components. Evidence for the effectiveness of complex correction was also presented by V.K. Mishchenko & V.M. Mishchenko [6], who emphasised that the combination of physical exercise with psychotherapeutic modules leads to statistically significant reductions in anxiety and improvements in short-term memory. In contrast to these localised observations, an international cohort study led by L. Gallucci *et al.* [7] revealed a paradox: even with a prominent level of specialised care, cognitive dysfunction continues to be persistent and largely irreversible. The researchers concluded that current protocols lack duration and neuropsychological flexibility. In an extensive review, Y.Y. Huang *et al.* [8] presented key epidemiological patterns of post-stroke cognitive deficits, including differentiation by age and localisation characteristics. The study emphasised the need to implement cognitive screening as a routine clinical procedure at all stages of patient management.

One of the most challenging aspects of recovery after ischaemic stroke is persistent cognitive impairment, substantially affecting the daily autonomy of patients. D.D. Turgumbaev *et al.* [9] focused on the fact that the existing system of recording and monitoring does not include neuropsychological testing, which complicates planning targeted rehabilitation programmes. These data were confirmed in a population-based analysis by M. Obaid *et al.* [10], according to which a marked decline in cognitive function persists in patients' years after stroke, even if the neurological status is stabilised. The researchers noted that cognitive deficit is directly associated with increased disability and reduced quality of life, especially among elderly patients. A. Kusec *et al.* [11] revealed that anxiety-depressive manifestations and attention disorders tend to persist for a long time, which requires an interdisciplinary approach in rehabilitation. Therewith, some patients had cognitive deterioration even two years after stroke, regardless of the severity of the primary lesion.

The features of cognitive and affective disorders in the late recovery period of ischaemic stroke are still understudied, especially considering their interaction and influence on functional recovery. The purpose of the present study was to conduct a comprehensive assessment of cognitive and emotional disorders in patients at the late stage of post-stroke rehabilitation. The objectives of the study included determination of the structure and severity of cognitive deficit; identification of the degree of anxiety and depressive symptoms; establishment of interrelationships between cognitive and affective indices.

Materials and Methods

The clinical stage was conducted at the Faculty of Postgraduate Education and Science of the Kyrgyz State Medical Institute of Retraining and Professional Development named after S.B. Daniyarov (Bishkek), with the involvement of the Amanat University Clinic as the main outpatient and diagnostic base. This institution, functioning as a clinical base of the Institute, provided access to neuroimaging diagnostics, specialised medical consultations and comprehensive support of patients in the late recovery period of ischaemic stroke. The observation period covered six months, from June to December 2024. This time interval was chosen because of the need to include a sufficient number of patients who had completed the acute phase of treatment, as well as to enable a consistent cohort assessment of cognitive and affective state, considering the dynamics of post-stroke recovery.

The study included 142 patients aged 50 to 80 years (mean age 64.3 ± 7.1 years) because this is the interval in which ischaemic stroke cases with an elevated risk of remote cognitive and affective disorders are most frequently recorded; all participants had a history of stroke, and the mean post-stroke interval at the time

of inclusion in the study was 9.4 ± 2.7 months, which met the criteria for late recovery and helped to exclude the influence of the acute neuroinflammatory response on cognitive parameters. The total sample was divided into two groups. The experimental group (n = 98) included patients with clinically significant cognitive and/or affective disorders confirmed by neuropsychological screening. The control group (n = 44) included patients with no complaints and no pathological changes according to the test results. Intragroup distribution was performed by sex (women – 59.2%, men – 40.8%) and age subgroups (50-59, 60-69, ≥70 years), which provided the possibility of stratified analysis.

Inclusion criteria were as follows: confirmed diagnosis of ischaemic stroke (according to magnetic resonance imaging and hospital discharge), completed acute stage of treatment, cognitive and physical ability to undergo neuropsychological examination, and written informed consent. Patients with pre-stroke dementia, severe aphasia, psychotic disorders, and decompensated somatic diseases preventing participation in the study were excluded. This sampling model enabled a comparative assessment of the severity of cognitive and affective disorders in individuals in the late recovery period after stroke, considering age and gender differences.

Cognitive status was assessed using the Montreal Cognitive Assessment (MoCA) scale [12], which covers key cognitive domains and allows differentiating degrees of functional decline from mild to severe. The test was administered in person, by a specialist, lasted 10û15 minutes, and included tasks on memory, attention, orientation, abstract reasoning, and language skills. The maximum score was 30; values below 26 indicated cognitive deficits and below 18 indicated severe cognitive deficits. The Beck Depression Inventory-II (BDI-II) scale [13] was used to diagnose depression; it includes 21 items with a four-point gradation of symptom severity. Respondents filled out the questionnaire independently or with the help of an interviewer. The results were interpreted according to established thresholds: from minimal to severe depression (29-63 points). The Hamilton Anxiety Scale (HAM-A) [14] was used to identify anxiety disorders. It included 14 items and was assessed by a clinical-behavioural interviewer. A total score of up to 13 indicated no clinically significant anxiety; 14-17 indicated moderate and above 18 indicated severe anxiety. Functional autonomy was assessed using a 10-item adapted questionnaire capturing the ability to self-care in activities of daily living. Each item was graded from complete dependence (0) to complete autonomy (2), with a possible maximum of 20 points. Examples of wording included: "Can you eat and use cutlery independently?", "Do you need help taking prescribed medication?", "Are you able to organise your own personal hygiene, including washing and brushing your teeth?", "Can you move around the house and go outdoors without assistance?", "Do you need support with cooking and housekeeping?". Scores below 13 were interpreted as a pronounced decrease in autonomy.

The collected data were analysed using the IBM SPSS Statistics package (version 27.0). Student's t-test, Pearson's χ^2-test and one-factor analysis of variance Analysis of Variance were used to assess differences between groups, depending on the nature of the data. Correlation analysis was performed using Pearson's coefficient. In all cases, $p < 0.05$ was considered the critical level of significance, with $p < 0.01$ and $p < 0.001$ being additionally recorded as high and very high statistical significance levels, respectively, if there were more pronounced differences.

Ethical aspects of the study were ensured according to the American Sociological Association Code of Ethics [15], which stipulates mandatory informed consent, voluntary participation, and data confidentiality. All participants pre-signed a consent form explaining the aims, methods, and potential risks of the study. Additionally, the provisions of the European Commission Guidelines on Ethics and Data Protection [16] were observed, which guaranteed compliance with international standards in the handling of personalised medical information.

Results

Profile of cognitive impairment in the examined patients

The analysis of the cognitive status of the examined patients in the late recovery period after ischaemic stroke, performed at least six months after the acute event, showed a pronounced level of prevalence of cognitive deficit of various severity. According to the MoCA test results, 82.7% of participants (n = 81 out of 98) showed signs of cognitive decline: 37.8% (n = 37) showed mild impairment, 31.6% (n = 31) showed moderate impairment, and 13.3% (n = 13) showed severe cognitive impairment (MoCA total score<18) (Fig. 1). The mean MoCA score was 21.1 ± 3.9, which corresponds to moderate cognitive decline. In the control group patients, the mean score was within the normal range (27.6 ± 1.8), which confirmed the validity of the sample stratification.

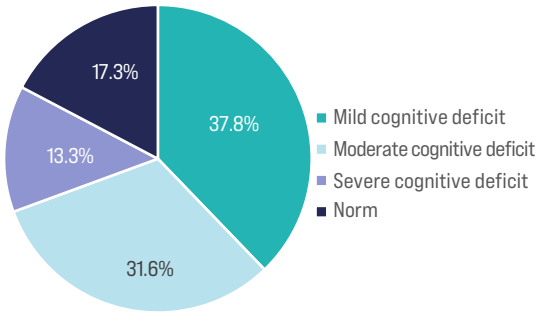

Figure 1. Distribution of patients in the experimental group (n = 98) by degree of cognitive deficit according to the results of the MoCA scale

Source: created by the author

The data presented in Figure 1 demonstrate the prevalence of mild to moderate cognitive impairment in the majority of patients in the late recovery period of stroke. This reflects the high clinical significance of even subclinical forms of cognitive deficits, which may stay undetected without targeted neuropsychological testing. The relatively small proportion of patients with severe impairment confirms that severe deficits are less widespread but require more intensive and multidisciplinary intervention. The presence of cognitive normality in only a limited number of respondents emphasises the need for mandatory screening of cognitive status as part of the standard post-stroke follow-up protocol, because even in the absence of subjective complaints, objective functional decline is recorded in the majority of cases.

The structure of cognitive deficits was dominated by disorders in the short-term memory domain: difficulties in reproducing 4-5 words in a time interval were recorded in 68.4% (n = 67) of patients in the experimental group. Attention concentration disorders assessed by serial subtraction and inverse repetition of digits were found in 60.2% (n = 59) of the patients. A considerable proportion of respondents expressed difficulties in orienting in time and place – 46.9% (n = 46), especially in the age subgroup over 70 years old. Challenges in performing abstract thinking and categorisation tasks were observed in 41.8% (n = 41) of patients and were closely related to the level of education: those with incomplete secondary education had a significantly lower level of abstract thinking ($p < 0.01$). Speech disorders, including nomination and repetition of phrases, were observed in 27.6% of cases (n = 27), while dysfunction of executive functions, manifested in difficulties in performing the clock drawing and cube copying tests, was recorded in 38.8% (n = 38) of patients (Fig. 2).

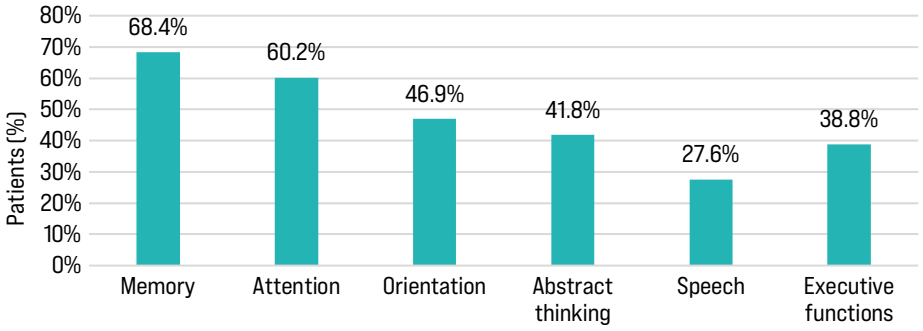

Figure 2. Distribution of cognitive impairment according to the main domains of the MoCA scale in patients of the experimental group (n = 98)

Source: created by the author

The data described in Figure 2 demonstrate that short-term memory and attention continue to be the most vulnerable cognitive domains in the late recovery period after ischaemic stroke. This indicates impaired retention, selective processing, and arbitrary switching of mental operations, which is particularly critical for adaptation in the domestic and social environment. Related deficits – in orientation, abstract thinking, speech production, and executive regulation – form a complex picture of cognitive dysfunction, in which not one but several brain systems that ensure everyday autonomy are affected.

The recorded cognitive profile is characterised not only by the severity of disorders, but also by their multilevel, synergistic interaction, which complicates both spontaneous recovery and the effectiveness of standard rehabilitation measures. The persistence of cognitive deficit six months after stroke reflects the need for its early diagnosis and targeted intervention considering the leading domain of the disorder. This substantiates the expediency of developing adapted cognitive routes in the system of outpatient care integrated into a multidisciplinary rehabilitation approach.

Structure of affective disorders in the late recovery period

According to the BDI-II depression scale, most patients (n = 98, experimental group) showed clinically significant depressive symptoms. Therewith, 34.7% of cases (n = 34) showed moderate depression, 28.5% (n = 28) showed severe depression, and another 9.2% of patients (n = 9) had major depressive disorders. Only 27.6% of participants (n = 27) had symptom levels that did not exceed the minimum values (Fig. 3). The mean BDI-II score was 19.6 ± 7.4 points, indicating the severity of affective maladjustment. In the control group (n = 44), the mean score was significantly lower (7.2 ± 3.1 points), which confirms the reliability of stratification and excludes systemic bias in the sample distribution. The presented data indicate that the most patients in the late recovery period after ischaemic stroke experience various forms of depressive symptomatology. The most widespread are moderate and pronounced states, reflecting sustained emotional maladaptation requiring clinical attention. A relatively smaller proportion of patients exhibit major depression, but even minimal manifestations were recorded in only a limited

number of participants. This emphasises the need to include psycho-emotional assessment as part of the standard rehabilitation pathway.

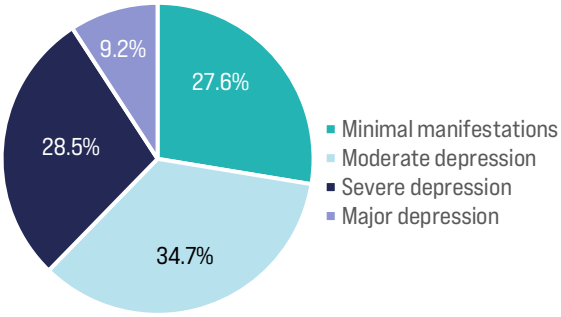

Figure 3. Distribution of forms of depressive symptomatology in patients of the experimental group (n = 98) according to the results of the BDI-II scale
Source: created by the author

Anxiety disorders were also well represented in the study sample. According to the results of the HAM-A anxiety scale, 45.9% of patients (n = 45) showed a moderate level of anxiety, and another 17.3% (n = 17) showed a pronounced level of anxiety. Typical manifestations were internal tension, feelings of threat, somatic complaints (dizziness, cardiopalmus, muscle tension), and sleep disturbances. The mean total score on the HAM-A was 21.3 ± 6.2, which corresponds to clinically significant anxiety. In the control group, this index was significantly lower – 9.5 ± 3.8.

The analysis of prognostic factors of the severity of affective disorders revealed a series of statistically significant associations reflecting the complex nature of emotional maladaptation in patients in the late recovery period of stroke. The most significant predictor was the severity of cognitive deficit: there was a stable inverse correlation between the final MoCA score and the level of depression on the BDI-II scale ($r = -0.52$; $p < 0.001$). This indicates that the deeper the impairment in the cognitive sphere – especially in the domains of memory, attention, and executive functions – the greater the severity of depressive symptomatology. Such a relationship supports the concept of neuropsychological overlap between frontal-limbic and cortical networks involved simultaneously in cognitive regulation and affective appraisal.

Gender also showed statistical significance, with women demonstrating greater values on average on both the BDI-II and HAM-A scales. The mean depression score among women was 4.3 points higher than in men ($p < 0.01$), and severe anxiety was almost twice as widespread. This may be due to greater psychoemotional sensitivity, the social role of caregivers, and the more frequent presence of loneliness in later life. Analysis of the internal structure of complaints showed that emotional symptoms (sadness, feelings of helplessness, tearfulness) were predominant in women and somatised symptoms (headache, sleep disorders, irritability) in men.

Age analysis revealed that patients over 70 years of age showed the greatest severity of both depressive and anxiety symptoms. Their mean BDI-II and HAM-A scores were statistically significantly greater than those of individuals aged 60-69 years ($p < 0.01$) and 50-59 years ($p < 0.05$). These differences are interpreted as a consequence of a complex of biopsychosocial factors, including decreased cognitive reserve, presence of chronic somatic diseases (ischaemic heart disease, diabetes mellitus, hypertension), loss of life perspective, decreased social activity, and lack of emotional support. In addition, apathetic forms of depression with low motivation and pronounced anaesthesia of feelings were more widespread in elderly patients, which aggravated recovery and worsened the prognosis for long-term adaptation.

Emotional lability, manifested as mood swings, irritability, tearfulness, and reduced tolerance to stress, was recorded in 38% of patients in the experimental group. Such manifestations often stayed underestimated at the initial neurological examination, but they significantly affected the effectiveness of cognitive rehabilitation and relationships with the environment. The analysis revealed that the combination of anxiety and depressive symptoms forms a stable affective profile, which requires the inclusion of specialised interventions in the structure of rehabilitation care. The introduction of brief validated questionnaires for initial screening and subsequent psychological support, especially in risk groups – women, elderly patients and those with severe cognitive deficits – seems to be the most appropriate.

The revealed structure of affective disorders in the late recovery period after ischaemic stroke demonstrates a high frequency of depressive and anxiety symptoms. They cannot be considered outside the context of cognitive status, sex, and age of the patient. These disorders considerably affect the overall functional status, recovery prognosis, and quality of life, and therefore require a systemic approach and interdisciplinary management.

Relation of cognitive-affective impairment to functional autonomy

One of the key objectives of the present study was to determine the relationship between the severity of cognitive and affective disorders and the level of daily functional independence in ischaemic stroke patients. The mean total score in the experimental group was 13.8 ± 3.4 out of a possible 20 points, corresponding to a moderate decrease in functional independence. 62 patients (63.3%) had significant limitations in at least three daily functions. The most frequent problems were difficulties in organising hygienic care, the need for external assistance with mobility, and reduced ability to adhere to medication. In the control group, the mean functional autonomy score was 18.2 ± 1.6, which was significantly greater ($p < 0.001$), and no severe limitations were recorded.

The analysis of correlations between the severity of cognitive impairment and the level of functional autonomy showed a statistically significant positive correlation between the final MoCA scores and the total autonomy score ($r = 0.43$; $p < 0.001$). A particularly pronounced relationship was observed for the domains of attention, memory, and executive function. Patients with MoCA scores below 20 showed insufficient self-regulatory ability, particularly planning and consistent performance of routine activities. Affective symptomatology also significantly affected day-to-day independence. When analysing the BDI-II scale data, a negative correlation was found between the level of depression and the functional autonomy score ($r = -0.38$; $p < 0.001$). Patients with severe depression (BDI-II score >29 points, $n = 9$) had a mean autonomy score of only 10.3±2.1, whereas those with minimal depressive symptoms had a mean autonomy score of 17.6 ± 1.8. Anxiety, as assessed by the HAM-A scale, also showed a moderately significant negative ef fect ($r = -0.31$; $p < 0.01$), especially when combined with somatic complaints and sleep disturbances.

Stratified analyses revealed that women had a lower functional independence level by an average of 2.4 points compared to men ($p < 0.05$), with differences persisting even when the degree of cognitive deficit was comparable. In the age subgroup older than 70 years ($n = 29$), the level of autonomy was significantly lower compared to patients younger than 60 years (mean 12.1 ± 3.7 vs. 15.9 ± 2.8; $p < 0.01$). This may be explained by the complex influence of age-related changes, social isolation, and reduced physical activity levels. Additionally, subgroup analyses were performed: with isolated cognitive impairment ($n = 26$), isolated affective symptoms ($n = 18$) and combined cognitive-affective disorders ($n = 54$). The latter subgroup showed the worst performance on all questionnaire items: more than 70% of participants in this group needed assistance with four or more daily functions. The mean autonomy score was 12.4 ± 2.9, 4.3 points lower than in patients without significant neuropsychological symptoms ($p < 0.001$).

The obtained results reflect a pronounced relationship between cognitive-affective disorders and a decrease in the level of functional independence in patients in the late recovery period after ischaemic stroke. Of particular clinical significance are the domains of attention, planning, and emotional motivation, the impairment of which leads to a reduced ability to adapt to the demands of everyday life. This underlines the need for systemic neuropsychological monitoring in post-stroke practice, as well as the development of comprehensive support programmes aimed not only at restoring lost cognitive functions, but also at stabilising the emotional background and teaching strategies of everyday self-management.

Comparative analysis of clinical and psychological profiles in the experimental and control groups

Comparative analysis of clinical and psychological characteristics of patients with pronounced cognitive-affective disorders (experimental group) and without them (control group) revealed fundamental differences in the structure of symptoms, the level of functional autonomy, and the quality of post-stroke recovery. In the experimental group, as shown by the data of neuropsychological testing, moderate and severe cognitive disorders prevailed, which was accompanied by pronounced affective symptomatology. In the control group, clinically significant disorders were not registered, except for isolated cases of mild anxiety. The structure of disorders in the experimental group was characterised by multidomain cognitive deficit and pronounced level of emotional lability, while in the control group the preservation of neuropsychological functions within the age norm prevailed.

Comparative analysis of the MoCA scale showed that in the experimental group the mean score was 21.1 ± 3.9, corresponding to a moderate cognitive decline, while in the control group it was significantly greater – 27.6 ± 1.8 ($p < 0.001$). The differences were particularly significant on the subscales of short-term memory, abstract thinking, and attention, where the experimental group showed pronounced difficulties in task performance. Similarly, the mean score on the BDI-II scale in the experimental group was 19.6 ± 7.4, reflecting moderately severe depression, while in the control group this score was 7.2 ± 3.1 ($p < 0.001$). Anxiety, as measured by the HAM-A scale, also differed significantly between groups: 21.3 ± 6.2 vs. 9.5 ± 3.8 respectively ($p < 0.001$). In terms of functional autonomy, patients in the experimental group showed marked limitations in daily activities. The mean self-care scale score was 13.8 ± 3.4 versus 18.2 ± 1.6 in the control group ($p < 0.001$). Differences were particularly pronounced in the ability to move independently, medication adherence and personal hygiene. To clarify the differences between the groups, multivariate analysis of variance was performed, which revealed statistically significant interactions between neuropsychological profile and the degree of functional autonomy ($p < 0.01$) (Table 1).

Table 1. Comparative indices of neuropsychological and functional in the experimental and control groups

Indicator	Experimental group (n = 98)	Control group (n = 44)
MoCA average score	21.1 ± 3.9	27.6 ± 1.8
BDI-II average score	19.6 ± 7.4	7.2 ± 3.1
HAM-A average score	21.3 ± 6.2	9.5 ± 3.8
Functional autonomy score	13.8 ± 3.4	18.2 ± 1.6

Source: created by the author

These data demonstrate that the participants of the experimental group had a complex combination of cognitive deficits and pronounced affective disorders, which substantially aggravated the level of daily dependence. In contrast, the control group maintained both cognitive and emotional stability, which correlated with a pronounced level of independence. Such a differentiated profile indicates not just the presence of isolated impairments, but a systemic deterioration of cognitive-affective regulation affecting daily activity. This allows considering these differences as clinically significant markers of recovery prediction and the basis for stratification of approaches to outpatient rehabilitation.

Stratification by age and sex also revealed certain differences within the groups. In the experimental group, women had greater scores on depression and anxiety scales and lower levels of functional autonomy. Severe cognitive and affective disorders were more widespread among patients older than 70 years (n = 29), which was reflected in the overall clinical picture and required more intensive intervention. The results also demonstrated that the presence of cognitive impairment had a more pronounced impact on daily functioning than affective symptomatology. However, when they are combined, the effect is exacerbated, forming a complex rehabilitation task. Patients with pronounced symptoms of depression and anxiety showed low motivation for recovery, increased fatigue, and decreased participation in rehabilitation programmes.

Thus, the obtained data confirm the significance of considering cognitive-affective status when planning post-stroke care. Comparative analysis clearly demonstrates that patients with pronounced neuropsychological disorders require more intensive, personalised support, including both psychotherapeutic and cognitive rehabilitation components. It is also necessary to develop outpatient support programmes and to train patients in deficit compensation strategies, which will improve the quality of life and increase the efficiency of stroke recovery.

Discussion

The obtained data confirmed that cognitive and affective disorders are frequent and clinically significant consequences of ischaemic stroke in the late recovery period. Their severity is directly related to the level of functional autonomy and requires complex interpretation in comparison with the results of scientific studies.

The primary analysis revealed that cognitive impairments of varying severity were recorded in 82.7% of ischaemic stroke patients, with short-term memory and attention deficits predominating. The mean MoCA score in the experimental group was 21.1 ± 3.9, which corresponds to a moderate decline in cognitive function. These data confirmed the high prevalence of multidomain cognitive deficits even six months after the acute event. Comparable results were obtained in a multicentre study by M. Mancuso *et al.* [17], which found that even in the subacute course of ischaemic stroke, cognitive recovery is partial and directly affects rehabilitation outcomes. Analogously, Y.M. Yang *et al.* [18] showed that patients with mild stroke have significant and sustained changes in a battery of neuropsychological tests, especially in the areas of executive functions and working memory. The role of spatial-localisation factors was confirmed in the study by A. Tsiakiri *et al.* [19], where the researchers found that the cognitive profile after stroke varies depending on the lateralisation of the lesion: left-hemispheric strokes are more often accompanied by speech and memory impairments, whereas right-hemispheric strokes are more often accompanied by deficits in visual-spatial and executive functions. These findings support the results of the present study, which revealed the multidomain nature of cognitive impairment, reflecting the involvement of different functional brain systems and highlighting the need for a personalised approach to cognitive rehabilitation. Additionally, N.S. Rost *et al.* [20] stated that post-stroke cognitive disorders often persist in the form of dementia, especially in elderly patients, and represent a long-term prognostic threat despite therapy.

The mean severity of depressive symptomatology in patients in the late recovery period after stroke reached 19.6 ± 7.4 points on the BDI-II scale. Severe depression was detected in 28.5% of respondents, and in 9.2% – major depression, reflecting a stable nature of emotional maladaptation, not inclined to spontaneous remission. The detected combination of anxiety and depressive symptoms was accompanied by increased fatigue, decreased motivation and sleep disturbance, which negatively affected neuropsychological rehabilitation. N. Butsing *et al.* [21] confirmed that post-stroke depression is associated with significant deterioration of functional outcomes, with the presence of severe affective symptoms being an independent predictor of poor rehabilitation performance. In a six-month prospective study, L.P. Beltrami *et al.* [22] demonstrated high stability of depressive states that persisted even in the absence of somatic progression. However, in contrast to the present study, where emotional manifestations (sadness, helplessness) predominated, F.G. Masuccio *et al.* [23] identified predominantly apathetic forms in older individuals, indicating an age-related transformation of the clinical phenotype. U. Sagen-Vik *et al.* [24] reported that anxiety-depressive disorders after stroke often proceed in a wave-like manner, with recurrences over two years, whereas the present study recorded their relative plateau in the late recovery period. The complex of available data confirms the high frequency and clinical significance of affective disorders in the late post-stroke period. Their presence has an unfavourable impact on cognitive recovery, functional autonomy, and general adaptation, which substantiates the need for systematic monitoring and interdisciplinary management.

The established inverse correlation between the level of cognitive functioning and the degree of depressive symptoms ($r = -0.52$; $p < 0.001$), and between cognitive deficit and anxiety ($r = -0.31$; $p < 0.01$) reflects a strong relationship between affective dysregulation and neurocognitive failure. Patients with combined disorders had the lowest autonomy scores and the highest frequency of complaints of emotional instability, emphasising the clinical significance of cognitive-affective overlap in recovery prognosis. According to B. Ghabel Damirchi *et al.* [25], patients with post-stroke depression are more likely to show impairments in executive function, information processing speed and episodic memory. These results are consistent with the current observations in which exactly these domains appeared to be the most vulnerable in individuals with severe affective disorders. Using generative mapping algorithms, A.K. Bonkhoff *et al.* [26] showed that cognitive deficits after stroke are caused by lesions of networks simultaneously involved in emotional regulation (frontal-limbic and frontoparietal circuits), which confirms the biological basis of the identified relationship. As shown in the meta-analysis by S. Lugtmeijer *et al.* [27], post-stroke working memory dysfunction is the most frequent and pronounced form of cognitive deficit, especially in the presence of concomitant decreased stress tolerance and anxiety-depressive symptoms. This trend is directly confirmed in the results of the present study: patients with pronounced affective disorders were significantly more likely to demonstrate decreased attention concentration, difficulties in performing attention switching and serial counting tasks – markers of impairment of working cognitive modules responsible for the integration and regulation of information. M. Lee *et al.* [28] showed that the predictive accuracy of risk assessment of post-stroke cognitive deficit increases with the inclusion of affective parameters – anxiety, anhedonia, emotional numbness. These findings correlate with the fact revealed in the study of a more pronounced decrease in the cognitive profile in individuals with severe depression and anxiety. The lowest MoCA scores were recorded in the subgroup with combined cognitive-affective disorders ($n = 54$), which emphasises their interacting and mutually reinforcing nature.

Emotional lability, including increased irritability, tearfulness, mood swings and low stress tolerance, was recorded in 38% of patients in the experimental group. Together with clinically significant depression (72.4%) and anxiety (63.2%), these manifestations formed a stable affective profile that significantly reduced motivation for recovery and the level of participation in rehabilitation activities. In this subgroup, the mean autonomy scale score was only 12.4 ± 2.9, which was 4.3 points lower than in patients without significant neuropsychological symptoms ($p < 0.001$). Additionally, there were complaints of fatigue, difficulties in maintaining a daily routine, and pronounced sleep disturbances, especially in those over 70 years of age and women. The results agree with the findings of J. Tay *et al.* [29], who found that post-stroke apathy differs from depression by low level of initiative and weak emotional reactivity associated with functional dysfunction of mediofrontal structures. I. Kirchberger *et al.* [30] emphasised that post-stroke fatigue persists regardless of the initial stroke severity and often predisposes to a decrease in life activity and social engagement. Analogously, E. Douven *et al.* [31] associated apathy with frontal and cingulate regions of the brain, the lesion of which leads to impoverished emotional background, which was observed in a considerable proportion of patients with severe depression in this study ($n = 9$; BDI-II > 29). According to A.G. Damsbo *et al.* [32], the risk of emotional exhaustion after stroke increases in the presence of social isolation factors and chronic comorbidities – such as hypertension and coronary heart disease, which were presented in more than half of the participants in the age group ≥70 years.

Analysis of gender-age differences showed that women in the late recovery period of stroke demonstrated more affective symptoms and less functional autonomy: mean BDI-II score was 4.3 points higher compared to men ($p < 0.01$) and self-care was 2.4 points lower ($p < 0.05$), despite a comparable degree of cognitive deficit. In the age subgroup ≥70 years, cognitive decline, level of depression and autonomy impairment reached critical values, indicating the complex nature of maladaptation in the elderly. Therewith, in the group of 50-59 years old, the indicators stayed within moderate values. These results are consistent with the data of A. Ejaz *et al.* [33], according to which cognitive deficit and dementia in elderly patients have the most pronounced impact on the quality of life and independence, especially in persons experiencing social isolation. C.L. Beckenkamp *et al.* [34] noted that in the absence of rehabilitation support, the deterioration of neuropsychological functions and functional independence proceeds especially rapidly in the group of elderly women. S. Bártlová *et al.* [35] described analogous patters, finding that women after stroke have lower subjective satisfaction with life and recovery than men, despite comparable stroke severity, due to a combination of emotional overload, loneliness, and limited access to psychosocial resources. Review by A.S. Shamshiev *et al.* [36] highlighted that in countries with developing medical care systems, it is older women who stay in the least favourable position in terms of access to specialised rehabilitation and psychological support, which increases the risks of chronic dependence.

The discussion confirmed that cognitive and affective disorders are closely related to the level of functional autonomy in patients in the late recovery period of stroke. The greatest vulnerability was demonstrated in elderly patients and in women with co-morbid symptomatology accompanied by significant dependence.

Comparison with the results of other scientific studies confirmed the reproducibility of key trends and emphasised the significance of individual and social risk factors.

Conclusions

Cognitive impairment persisted in most patients six months after stroke (82.7%) and was characterised by a decline in short-term memory, attention, and orientation. The mean MoCA score was 21.1 ± 3.9, corresponding to a moderate cognitive deficit. This structure of disorders reflects persistent suffering of frontal-parietal functional systems and limits the patient's ability for independent daily activity. Affective disorders, detected in 72.4% of the examined patients, significantly complicated recovery, reducing motivation and resistance to load. Mean BDI-II (19.6 ± 7.4) and HAM-A (21.3 ± 6.2) scores reflect the prevalence of moderate to severe symptoms. The most vulnerable were patients with severe depression (9.2%) and pronounced anxiety, which requires mandatory consideration of the affective element in rehabilitation planning. Functional autonomy of patients was inversely proportional to the severity of neuropsychological disorders. In the presence of severe depression, the autonomy index decreased to 10.3 ± 2.1 points, whereas in the general group it was 13.8 ± 3.4. The established correlations with MoCA (r = 0.43), BDI-II (r = -0.38) and HAM-A (r = -0.31) results confirmed the systemic influence of cognitive-affective distress on everyday autonomy.

Comparison with the control group confirmed the presence of pronounced differences in all key indicators. Stroke patients had lower MoCA values (21.1 ± 3.9 vs 27.6 ± 1.8), greater levels of depression (19.6 ± 7.4 vs 7.2 ± 3.1) and anxiety (21.3 ± 6.2 vs 9.5 ± 3.8), and lower functional autonomy (13.8 ± 3.4 vs 18.2 ± 1.6), with statistically significant differences on all scales. These data indicate the systemic nature of neuropsychological consequences of ischaemic stroke and underline the importance of their targeted correction already in the posthospital period. The greatest degree of cognitive-affective vulnerability was demonstrated by women and patients of the older age group. In women, the level of depression averaged 21.3 ± 7.1 points, autonomy – 12.8 ± 3.2, which was statistically worse compared to men. Those over 70 years of age had the worst scores on all scales: MoCA – 18.4 ± 3.2, BDI-II – 23.6 ± 6.8, autonomy – 12.1 ± 3.7. This emphasises the need for an age- and gender-specific approach to rehabilitation and support.

The key limitation of this study was the relatively small sample size, which limited the ability to generalise the findings to a wider population of post-stroke patients. Future studies may include a larger and more representative sample to clarify the factors influencing the severity and duration of cognitive-affective impairment at various stages of post-stroke recovery.

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Conflict of Interest

None.

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Аннотация. Изилдөөнүн максаты кеч калыбына келтирүү мезгилинде ишемиялык инсульт менен ооруган бейтаптардын нейропсихологиялык өзгөчөлүктөрүн жана функционалдык автономия даражасын аныктоо болгон. Методика 50-80 жаштагы 142 бейтапты когорттук салыштырма текшерүүгө негизделип, Кыргыз мамлекеттик дипломдон кийинки билим берүү медициналык институтунун жана «Аманат» университеттик клиникасынын катышуусу менен клиникалык база катары когнитивдик функцияларды, депрессияны, тынчсызданууну жана функционалдык автономия анкетасын баалоо шкалаларын колдонуу менен жүргүзүлгөн. Изилдөөнүн негизги натыйжалары ишемиялык инсульттун кеч калыбына келтирүү мезгилиндеги пациенттерде нейропсихикалык бузулуулардын жогорку таралышын көрсөттү. Когнитивдик жетишсиздиктер текшерилген пациенттердин 82,7 %да сакталып, когнитивдик функцияны баалоо шкаласы боюнча орточо балл 21,1 баллды түзгөн. Эң байкалган бузулуулар кыска мөөнөттүү эс тутум (68,4 %), көңүл буруу (60,2 %) жана ориентация (46,9 %) болгон. Катышуучулардын 72,4 %ында аффективдүү бузулуулар аныкталган, 9,2 %да катуу депрессия жана 28,5 % да ачык депрессия; депрессия шкаласы боюнча орточо көрсөткүч 19,6 баллды түздү. тынчсызданууу деңгээл 21,3 Гамильтон тынчсызданууу шкаласы боюнча орточо балл менен, бейтаптардын 63,2 % клиникалык босогодон ашты. Негизги топто функционалдык автономиянын орточо баасы 13,8 баллды түздү, ал эми катуу депрессия менен ооруган бейтаптарда 10,3кө чейин төмөндөгөн. Аялдар эркектерге караганда көбүрөөк айкын аффективдүү симптомдорду жана автономиянын төмөн деңгээлин көрсөтүшкөн. 70 жаштан жогорку курак подгруппасында башка курак категорияларына салыштырмалуу когнитивдик функциялардын бир кыйла айкын төмөндөшү жана аффективдүү бузулуулардын көбөйүү тенденциясы байкалган. Көпчүлүк пациенттерде аныкталган когнитивдик-аффективдүү бузулуулар күнүмдүк автономияга системалуу таасир этет жана ооруканадан кийинки мезгилде комплекстүү оңдоону талап кылат. Алынган натыйжалар невропатологдор, психиатрлар жана реабилитациялык адистер үчүн практикалык мааниге ээ, анткени алар инсульттан кийинки кеч мезгилде пациенттерге нейропсихологиялык колдоо көрсөтүүнүн жекелештирилген программаларын иштеп чыгууда колдонулушу мүмкүн

Негизги сөздөр: нейропсихикалык бузулуулар; функционалдык автономия; депрессия; когнитивдик функциялар; тынчсызданууу; эс тутум; көңүл

Аффективные и когнитивные расстройства в позднем восстановительном периоде ишемического инсульта

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Аннотация. Цель исследования заключалась в выявлении нейропсихологических особенностей и степени функциональной автономии у пациентов с ишемическим инсультом в позднем восстановительном периоде. Методология базировалась на когортном сравнительном обследовании 142 пациентов в возрасте 50-80 лет, проведённом при участии Кыргызского государственного медицинского института последипломного образования и университетской клиники "Аманат" как клинической базы с использованием шкал для оценки когнитивных функций, депрессии, тревожности и опросника функциональной автономии. Основные результаты исследования продемонстрировали высокую распространённость нейропсихологических нарушений у пациентов в позднем восстановительном периоде ишемического инсульта. У 82,7 % обследованных сохранялись когнитивные дефициты, при среднем показателе по шкале оценки когнитивных функций – 21,1 балла. Наиболее выраженными оказались нарушения кратковременной памяти (68,4 %), внимания (60,2 %) и ориентировки (46,9 %). Аффективные расстройства были выявлены у 72,4 % участников, причём тяжёлая депрессия установлена у 9,2 %, а выраженная – у 28,5 %; среднее значение по шкале депрессии составило 19,6 балла. Уровень тревожности превышал клинический порог у 63,2 % пациентов, при среднем балле по шкале тревожности Гамильтона – 21,3. Средняя оценка функциональной автономии в основной группе составила 13,8 балла, а у пациентов с тяжёлой депрессией снижалась до 10,3. Женщины демонстрировали более выраженные аффективные симптомы и более низкий уровень автономии по сравнению с мужчинами. В возрастной подгруппе старше 70 лет наблюдалась тенденция к более выраженному снижению когнитивных функций и усилению аффективных нарушений по сравнению с другими возрастными категориями. Когнитивно-аффективные расстройства, выявленные у большинства пациентов, оказывают системное влияние на повседневную автономию и требуют комплексной коррекции уже в постгоспитальный период. Полученные результаты представляют практическую ценность для неврологов, психиатров и реабилитологов, поскольку могут быть использованы при разработке индивидуализированных программ нейропсихологической поддержки пациентов в позднем постинсультном периоде

Ключевые слова: нейропсихологические нарушения; функциональная автономия; депрессия; когнитивные функции; тревожность; память; внимание

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Factors and pathogenetic mechanisms of male infertility in the Jalal-Abad Region of the Kyrgyz Republic

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Abstract. Male infertility remains a significant medical and social challenge, while regional data on its aetiological structure and pathogenetic mechanisms are limited. In the Jalal-Abad region of the Kyrgyz Republic, there is an urgent need to strengthen the evidence base for targeted diagnostic and preventive strategies. The aim of this study was to describe the aetiological structure and probable pathogenetic mechanisms of primary male infertility based on comprehensive clinical, laboratory, and instrumental assessments. A total of 110 men aged 20-38 years were examined, including 60 patients with primary infertility (history ≥12 months) and 50 healthy men who formed the control group. Clinical examinations, laboratory and hormonal analyses, semen evaluation, microbiological and serological diagnostics of infections, and ultrasonographic assessment of the genitourinary system were performed. The leading causes were infectious and inflammatory disorders of the genitourinary tract: among the

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60 examined men, chronic urethritis was detected in a considerable proportion (non-specific – 23.3%; specific forms: trichomonal – 6.7%, chlamydial – 1.7%, ureaplasmal – 21.7%, mycoplasmal – 18.3%, and Gardnerella-associated – 26.7%), while ultrasound signs of chronic prostatitis were observed in 26.7% of participants. The microbiological profile was characterised by the predominance of staphylococci and Gram-negative bacilli, frequent mixed infections (46.7%), and urogenital candidiasis (8.3%). Seropositivity to cytomegalovirus reached 31.7%, and to herpes simplex virus types 1 and 2 – 25.0%. Among anatomical and functional factors, varicocele (6.7%), orchiepididymitis (5.0%), cryptorchidism (1.7%), and obstruction of the seminal ducts (3.3%) were identified; endocrine abnormalities included secondary hypogonadism (5.0%). Azoospermia was detected in 8.3% of cases, mainly associated with secondary hypogonadism or obstruction. Systemic inflammation was confirmed in some patients by leukocytosis and an elevated erythrocyte sedimentation rate, while leukocyturia was noted intermittently. The findings support the importance of early screening for sexually transmitted infections, chronic prostatitis, and hormonal disorders in the diagnostic pathways for primary male infertility in regional practice, enabling the personalisation of aetiotropic and pathogenetic therapy

Keywords: male fertility disorders; reproductive function; urogenital infections; *Chlamydia*; *Ureaplasma*; *Mycoplasma*

Introduction

Male fertility has become a significant public health issue globally and in Central Asian countries. Regions with uneven access to specialised care, including the Jalal-Abad region, continue to lack validated data on the structure of causes and the relative contribution of infectious-inflammatory, anatomical-functional, endocrine and behavioural factors. This necessitated a study with clinical and laboratory verification of key etiopathogenic mechanisms and clarification of diagnostic priorities.

According to the World Health Organisation [1], the burden of reproductive dysfunction in couples remains high, underscoring the need for accessible, quality care and data for decision-making. H. Levine *et al*. [2] in a global systematic review and meta-regression analysis showed that in the 21st century, the trend towards a decline in sperm parameters in men from different regions of the world continues, and the rate of change may have accelerated, requiring focused research into the causes and regional variability. Behaviour and lifestyle are consistently considered modifiable risk factors. S.W. Fan *et al.* [3] demonstrated that tobacco smoking in men seeking treatment for reproductive problems is associated with a statistically significant deterioration in standard ejaculate parameters, which highlights the importance of smoking cessation programmes in patient management. S.S. Bahreiny *et al*. [4] conducted a systematic review and meta-analysis involving 6,264 men on the impact of air pollution on sperm quality. The levels of PM2.5 and PM10 particulate matter in the environment were analysed. The results showed a significant decrease in ejaculate volume, concentration, total number, and motility of spermatozoa with an increase in particle concentration. Exposure to PM2.5 and PM10 was accompanied by statistically significant negative changes in sperm parameters, which the authors attributed to oxidative stress and damage to spermatogenic cells. The study emphasised the role of atmospheric pollution as an independent risk factor for male fertility disorders and the need to take environmental conditions into account when assessing reproductive health.

The evidence on endocrine disruptors remains inconsistent, but L. Mínguez-Alarcón *et al*. [5] note in their review for clinical practice the biological plausibility of the influence of bisphenols and phthalates on hormonal regulation and spermatogenesis and the need to standardise exposure assessment. Infectious and inflammatory processes of the urogenital tract are considered one of the leading and potentially eliminable risk factors. D.A. Paira *et al*. [6] in a large cross-sectional study (5,464 patients) linked positivity for *Chlamydia trachomatis*, *Ureaplasma* spp. and *Mycoplasma hominis* with infertility in couples, pointing to a lack of data on the magnitude of the effect and its clinical significance. K. Khalafalla *et al*. [7] conducted a systematic review of 70 studies to assess the association of sexually transmitted infections (STIs) with male subfertility. The analysis, performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol, showed conflicting data: most studies did not find a clear relationship between STIs and sperm parameters. The exceptions were *Ureaplasma* and *Mycoplasma*, for which the most reliable evidence of an effect on spermatogenesis and sperm motility was obtained. The authors Y.-Y. Wan *et al*. [8] compared sperm parameters in men with positive and negative *Ureaplasma urealyticum* status in seminal fluid and the pregnancy and birth outcomes of their partners. No statistically significant differences in ejaculate volume, concentration, motility, sperm morphology, leukocyte level, and antisperm antibodies were found between the groups ($P > 0.05$). The only difference was a higher sperm nuclear immaturity index in the presence of infection ($P = 0.04$), which may indicate the influence of *Ureaplasma* on

spermatogenesis processes. At the same time, pregnancy and birth outcomes did not differ. The authors concluded that *Ureaplasma urealyticum* infection does not significantly affect the effectiveness of intrauterine insemination, but may affect sperm quality at the subcellular level.

Along with infections, the contribution of anatomical, functional, and inflammatory conditions of the genitourinary system is confirmed by clinical data. A. Agarwal *et al.* [9] showed in a systematic review and meta-analysis that correction of varicocele in infertile men leads to a statistically significant improvement in sperm concentration, motility, and morphology compared to the untreated control group, with no differences in ejaculate volume. The authors emphasised the high level of evidence for these data and confirmed the role of venous stasis as a pathophysiological mechanism of spermatogenesis impairment. J. Rosellen *et al*. [10] reported a decrease in ejaculate quality in patients with chronic prostatitis, discussing possible mechanisms through inflammation, reactive oxygen species, and changes in prostate secretory function. These results emphasise the need for a comprehensive assessment and combination of etiotropic and pathogenetic approaches.

The aim of this study was to systematise the spectrum and relative contribution of infectious-inflammatory, anatomical and functional, endocrine, and behavioural factors in men of reproductive age with long-term fertility disorders in the Jalal-Abad region, as well as to identify priorities for optimising the diagnostic pathway.

Materials and Methods

The study was conducted in 2022-2024 at the Research Institute of Medical and Biological Problems of the Southern Branch of the National Academy of Sciences of the Kyrgyz Republic and the Regional Centre for Reproductive Health in Jalal-Abad. Ethical approval was obtained from the local bioethics committee, and the study was conducted in accordance with the principles of The Declaration of Helsinki [11]. All participants signed an informed consent form for participation in the study and processing of personal data. The examinations were performed using approved national and international protocols of the World Health Organisation (WHO), European Association of Urology (EAU), International Council for Standardisation in Haematology (ICSH), Centers for Disease Control and Prevention (CDC), and Clinical and Laboratory Standards Institute (CLSI) [12-18].

The study included 110 men aged 20-38 years, permanently residing in the Jalal-Abad region. The main group consisted of 60 patients with clinically confirmed primary infertility (absence of pregnancy in a partner with regular sexual intercourse without contraception for at least 12 months). The control group consisted of 50 men with preserved fertility and at least one child. Selection was carried out by continuous inclusion among patients who sought treatment for reproductive dysfunction. The exclusion criteria were surgery on the scrotum or prostate, severe chronic diseases, active inflammatory processes, alcoholism, and smoking for more than 10 years. The complex of clinical, laboratory, and instrumental methods used is presented in Table 1.

Table 1. Main research methods and their characteristics

Results	Characteristics/purpose	Main parameters assessed	Standards used
Clinical examination	History taking, physical examination, palpation of scrotal organs	Varicocele, epididymo-orchitis, cryptorchidism, anatomical anomalies	[14]
General clinical analyses (GCA, ESR, and GUA)	Assessment of general condition and inflammatory changes	Leucocytes, ESR (by Westergren), leucocyturia, bacteriuria	[15,16]
Bacterioscopy of cultures (Urethra, prostate secretion, ejaculate)	Identification of microflora and microbial susceptibility to antibiotics	Presence of cocci, Gram-negative flora, fungi; interpretation of MIC as per CLSI	[18]
PCR-Diagnostics (NAAT)	Identification of STI-causing agents	Chlamydia trachomatis, Ureaplasma spp., Mycoplasma spp., Trichomonas vaginalis (as indicated)	[13,17]
EIA (Serology)	Determination of antibodies to viruses	IgG to CMV and HSV 1/2	
Spermogram	Ejaculate analysis based on WHO standards (6th ed.)	Volume ≥ 1.4 ml; concentration ≥ 16 million/ml; total motility ≥ 42%; progressive motility ≥ 30%; normal morphology ≥ 4% (5th percentile in fertile men, not a diagnostic threshold)	[12]
Hormonal profile (as indicated)	Assessment of endocrine disturbances	Testosterone, FSH, LH, PRL; detection of secondary hypogonadism (↓T with ↑ FSH/LH)	[14]
Ultrasound scan of the genitourinary system	Examination of scrotal organs, prostate, kidneys, and bladder (B-mode, CDM)	Varicocele, chronic prostatitis, cysts, dilatation of the pampiniform plexus veins	

Note: GCA – general blood analysis; ESR – erythrocyte sedimentation rate (Westergren method); GUA – general urine analysis; PCR/NAAT – nucleic acid amplification tests; EIA – enzyme-linked immunoassay; IgG – immunoglobulin G; MIC – minimum inhibitory concentration; CMV – cytomegalovirus; HSV – herpes simplex virus; FSH – follicle-stimulating hormone; LH – luteinising hormone; PRL – prolactin; T – testosterone; B-mode – grey-scale imaging; CDM – colour Doppler mapping

Source: compiled by the authors

Internal quality controls and certified reagents were used for all laboratory procedures. Ultrasound examinations were performed using Philips HD11XE (Netherlands) and Mindray DP-50 (China) devices with linear and convex probes in B-mode and CDK mode. All examinations were performed by an ultrasound physician with > 10 years of experience. Statistical processing was performed using IBM SPSS Statistics v.26. Categorical variables were compared using Fisher's exact test; Pearson's χ^2 was used for expected frequencies ≥ 5. The effect was presented as the odds ratio (OR) with a 95% confidence interval (CI); for zero cells, the Haldane-Anscombe correction was used. For single proportions, 95% confidence intervals were calculated using the Wilson method. All tests were two-tailed; differences were considered statistically significant at $p < 0.05$. The Benjamini-Hochberg procedure (False Discovery Rate – FDR) was applied to control for multiple comparisons. A study of fructose levels in ejaculate to assess seminal vesicle function was planned but not performed due to the lack of a spectrophotometer, which is considered one of the limitations of the study.

Results

General clinical analyses. General blood analysis was within reference limits in 46 of 60 men, 76.7%. Signs of a systemic inflammatory response, including moderate leukocytosis and accelerated erythrocyte sedimentation rate, were observed in 14 out of 60 (23.3%). For this proportion, the 95% confidence interval was 14.4-35.4%. According to the general urine analysis, normal values were found in 48 out of 60 (80.0%). Leukocyturia was recorded in 2 out of 60 (3.3%) (95% confidence interval 0.9-11.4%). Elevated salt content was noted in 10 out of 60, 16.7% (95% confidence interval 9.3-28.0%). The data are consistent with the predominance of chronic rather than acute inflammatory conditions.

Urogenital infection: microbiology, PCR, serology. Microscopy of urethral smears revealed a pronounced inflammatory response and polymicrobial associations in 28 out of 60 (46.7%; 95% confidence interval 34.8-59.0%). A predominance of Gram-positive cocci and Gram-negative rods was noted. *Gardnerella* spp. was found in 16 out of 60 (26.7%); yeast-like fungi were found in 5 out of 60 (8.3%). The results of urine, prostate secretion, and ejaculate cultures confirmed the predominance of staphylococci and Gram-negative rods, with a significant proportion of mixed growth. The picture corresponds to chronic inflammation and probable colonisation of several sections of the urogenital tract.

Trichomonas vaginalis was verified in 4 out of 60 (6.7%). *Chlamydia trachomatis* was found in 1 out of 60 (1.7%) (95% confidence interval 0.3-8.9%). *Ureaplasma* spp. was detected in 13 out of 60 (21.7%, 95% confidence interval 13.1-33.7%). *Mycoplasma* spp. was detected in 11 out of 60 (18.3%, 95% confidence interval 10.6-30.1%). A profile with a predominance of ureaplasma and mycoplasma over chlamydia and trichomonas is typical for outpatient cohorts and reflects the polymicrobial nature of chronic processes. CMV IgG was detected in 19 out of 60, 31.7% (95% confidence interval 20.8-45.0%). HSV-1/2 IgG was detected in 15 out of 60, 25.0% (95% confidence interval 15.4-38.0%). Serostatus reflects past or latent infection and provides a background for interpreting chronic inflammation of the prostate gland and appendages.

Ultrasound and instrumental examinations. Ultrasound signs of chronic prostatitis were recorded in 16 out of 60, 26.7% (95% confidence interval 17.0-39.1%). Signs of chronic pyelonephritis were detected in 12 out of 60, 20.0% (95% confidence interval 11.6-32.0%). Cystic formation of the prostate gland was found in 1 out of 60, 1.7%. Clinically and based on the data, chronic urethritis was established in 14 out of 60, 23.3%. A comparison of instrumental and microbiological results indicates a high proportion of chronic urogenital inflammation in the cohort.

Hormonal indicators. Secondary hypogonadism was diagnosed in 3 out of 60 (5.0%). Despite the small proportion, this phenotype demonstrates a close connection with extreme spermatogenesis disorders. No other hormonal disorders of independent diagnostic significance were identified.

Spermogram. Azoospermia was detected in 5 out of 60 (8.3%, 95% confidence interval 3.6-18.1%). In 3 cases, azoospermia was combined with secondary hypogonadism, and in 2 cases with obstruction of the seminal ducts. In the remaining 55 observations, azoospermia was not recorded. The lack of complete distributions by concentration, progressive motility, and morphology limits the quantitative analysis of all parameters, but the association of extreme phenotypes with endocrine and obstructive causes appears to be consistent.

Concomitant conditions. Varicocele was detected in 4 out of 60 (6.7%). Orchiepididymitis – in 3 out of 60 (5.0%). Cryptorchidism was found in 1 out of 60 (1.7%). Obstruction of the seminal ducts was found in 2 out of 60 (3.3%). These conditions are potentially modifiable and often coexist with infectious and inflammatory components, enhancing the cumulative effect on spermatogenesis.

Associative analysis of extreme phenotypes. The link between azoospermia and the endocrine mechanism is confirmed as follows. Among patients with secondary hypogonadism, azoospermia was observed in 3 out of 3 (100.0%); among patients without hypogonadism – in 2 out of 57 (3.5%). According to Fisher's exact test, $p = 0.00029$. This indicates a strong association between pronounced hormonal dysregulation and the complete absence of sperm in the ejaculate.

The obstructive mechanism also demonstrated the expected relationship. In the presence of obstruction, azoospermia was observed in 2 out of 2 (100.0%); in its absence, it was observed in 3 out of 58 (5.2%).

According to Fisher's exact test, p = 0.0056. The results are consistent with the clinical logic of obstructive azoospermia. The power of the comparisons is limited by the small numbers, and the conclusions should be interpreted as research findings. The total distribution of the identified causes is presented in Table 2. The summary structure includes 58 out of 60 patients, as the data volume was insufficient for aetiological attribution in two cases. One patient may have had several simultaneous factors, including infectious-inflammatory and anatomical-functional ones, so the sum of the shares may exceed 100%.

Table 2. Range of identified causes of infertility

Identified causes of infertility	Number of patients (n = 58)	
	Abs.	%
Chronic prostatitis, exacerbation stage	9	15.0
Chronic prostatitis, remission stage	7	11.67
Chronic pyelonephritis, exacerbation stage	5	8.33
Chronic pyelonephritis, remission stage	7	11.67
Chronic urethritis, non-specific	14	23.33
Chronic urethritis, specific, including:	28	46.67
└ Trichomonal	4	6.67
└ Chlamydial	1	1.67
└ Ureaplasmal	13	21.67
└ Mycoplasmal	11	18.33
└ Gardnerella	16	26.67
Candidiasis of the genitourinary system	5	8.33
Prostatic cyst	1	1.67
Orchoepididymitis	3	5.0
Varicocele	4	6.67
Secondary hypogonadism	3	5.0
Obstruction of the deferent ducts	2	3.33
Azoospermia	5	8.33
Cryptorchidism	1	1.67

Source: compiled by the authors as a result of research

The data obtained indicate that the proportion of urogenital inflammation confirmed microbiologically and instrumentally remains high. PCR more often detects *Ureaplasma* spp. and *Mycoplasma* spp. than *Chlamydia trachomatis* and *Trichomonas vaginalis*. The serostatus for CMV and HSV corresponds to the population background and requires careful interpretation when assessing causal relationships. The most severe phenotype, azoospermia, is almost entirely associated with secondary hypogonadism and obstruction of the seminal ducts within the cohort. The contribution of anatomical and functional conditions (varicocele, orchiepididymitis) appears to be moderate, but when combined with infectious and inflammatory stress, it may increase the risk of adverse changes in sperm parameters. Chronic prostatitis causes not only a delay in spermatogenesis, but also a significant deterioration in its quality. These changes are particularly pronounced in patients with a disease duration of more than five years, which negatively affects the functional state of the male reproductive system [19,20]. Based on the summary structure (Table 2), the results were compared with a control group of fertile men (n = 50) whose indicators corresponded to those expected for a healthy population. Quantitative differences and statistical criteria are summarised in Table 3.

Table 3. Comparison of the main and control groups by aetiological positions

Indicator	Main group (n=58) Abs., %	Control group (n=50) Abs., %	OR (95% CI)	p
Chronic prostatitis, exacerbation stage	9 (15.5%)	0 (0.0%)	19.38 (1.10-342.13)	0.00336
Chronic prostatitis, remission stage	7 (12.1%)	3 (6.0%)	2.15 (0.53-8.80)	0.33445
Chronic pyelonephritis, exacerbation stage	5 (8.6%)	0 (0.0%)	10.38 (0.56-192.62)	0.06011
Chronic pyelonephritis, remission stage	7 (12.1%)	1 (2.0%)	6.73 (0.80-56.69)	0.06613
Chronic urethritis, non-specific	14 (24.1%)	1 (2.0%)	15.59 (1.97-123.46)	0.00068
Chronic urethritis, specific, including:	28 (48.3%)	4 (8.0%)	10.73 (3.42-33.70)	<0.00001
└ Trichomonal	4 (6.9%)	0 (0.0%)	8.34 (0.44-158.82)	0.12214
└ Chlamydial	1 (1.7%)	0 (0.0%)	2.63 (0.10-66.14)	1.00000
└ Ureaplasmal	13 (22.4%)	2 (4.0%)	6.93 (1.48-32.45)	0.01004

Table 3. Continued

Indicator	Main group (n=58) Abs., %	Control group (n=50) Abs., %	OR (95% CI)	p
└ Mycoplasmal	11 (19.0%)	1 (2.0%)	11.47 (1.42-92.34)	0.00522
└ Gardnerella	16 (27.6%)	1 (2.0%)	18.67 (2.37-146.74)	0.00030
Candidiasis of the genitourinary system	5 (8.6%)	1 (2.0%)	4.62 (0.52-40.97)	0.21340
Prostatic cyst	1 (1.7%)	0 (0.0%)	2.63 (0.10-66.14)	1.00000
Orchoepididymitis	3 (5.2%)	1 (2.0%)	2.67 (0.27-26.54)	0.62215
Varicocele	4 (6.9%)	2 (4.0%)	1.78 (0.31-10.14)	0.68395
Secondary hypogonadism	3 (5.2%)	0 (0.0%)	6.37 (0.32-126.36)	0.24714
Obstruction of the deferent ducts	2 (3.4%)	0 (0.0%)	4.47 (0.21-95.32)	0.49810
Azoospermia	5 (8.6%)	0 (0.0%)	10.38 (0.56-192.62)	0.06011
Cryptorchidism	1 (1.7%)	0 (0.0%)	2.63 (0.10-66.14)	1.00000

Note: p – level of statistical significance of differences between groups (p < 0.05 indicates a significant difference, p ≥ 0.05 – the difference is statistically insignificant and may be random)
Source: compiled by the authors as a result of research

Intergroup comparison based on aetiological positions shows that differences between the cohort of men with primary infertility and fertile controls are primarily due to the infectious-inflammatory domain of the lower urogenital tract. Statistically significant associations with infertility were found for: chronic urethritis (nonspecific) – OR 15.59; 95% CI 1.97-123.46; p = 0.00068; the total category of "specific urethritis" – OR 10.73; 3.42-33.70; p < 0.00001; as well as its subtypes of ureaplasma – OR 6.93; 1.48-32.45; p = 0.01004, mycoplasma – OR 11.47; 1.42-92.34; p = 0.00522, and gardnerella urethritis – OR 18.67; 2.37-146.74; p = 0.00030. These estimates are consistent with the microbiological profile of the main group (increased proportion of polymicrobial associations and mixed growth) and indicate a clinically relevant association between urethral inflammation, including that involving opportunistic microorganisms, and the infertility phenotype. The position "chronic prostatitis, acute stage" also demonstrates a pronounced association (OR 19.38; 1.10-342.13; p = 0.00336), while the "remission stag" is statistically indistinguishable from the control (p = 0.33445). This indirectly supports the thesis of greater clinical significance of active/exacerbated forms of prostate inflammation compared to latent progression, when ultrasound signs may persist without a concomitant clinical equivalent.

For chronic pyelonephritis, the patterns are unidirectional (increased OR during exacerbation and remission), but due to small numbers and wide confidence intervals, statistical significance is not achieved at the level of p < 0.05 (p = 0.06011 and p = 0.06613, respectively). Such lines should be interpreted as hypothesis-generating and requiring an increase in the sample size. Anatomical and functional factors (varicocele, orchiepididymitis, cryptorchidism), as well as rare nosologies (prostate cyst), did not show statistically confirmed differences. The lack of significance in these positions may reflect either a real moderate association or insufficient power to detect small/medium-sized effects.

The endocrine contribution (secondary hypogonadism) and obstructive mechanism (obstruction of the seminal ducts) in Table 3 did not reach statistical significance according to the intergroup criterion, which is explained by zero events in the control group and small absolute numbers. At the same time, intragroup analysis of extreme phenotypes showed their close association with azoospermia (p = 0.00029 and p = 0.0056, respectively). This highlights the different roles of intergroup and intragroup comparisons: the former record the contribution of a factor to the risk of infertility at the population level, while the latter record its association with the severity of spermatogenic disorders within the infertility cohort. Interpretation of effects with zero events in the control requires caution: OR in these rows are known to be high, and confidence intervals are wide due to small numbers. The study used the Haldane-Anscombe correction, which is correct for calculating OR, but it is advisable to confirm the final conclusions on such positions on an expanded sample and, if possible, in multivariate models taking into account age, duration of infertility, smoking, and other accompanying variables.

Taken together, the data in Table 3 indicate that the most reproducible and statistically confirmed area of difference is inflammatory and infectious processes in the distal parts of the urogenital tract (urethritis of various aetiologies) and active inflammation of the prostate gland. These domains are biologically consistent with the expected mechanisms of influence on spermatogenesis (inflammation, local oxidative stress, disorders of the secretory function of the prostate and seminal vesicles), while the proportion of "classical" STIs (chlamydia, trichomoniasis) remains low and does not form significant intergroup differences. The CMV/HSV serostatus corresponds to the population background and, based on the study design, does not provide grounds for causal attribution. The combination of results indicates the leading role of infectious and inflammatory processes in the distal parts of the

urogenital tract and active inflammation of the prostate gland in the structure of associations with male infertility at the population comparison level; severe spermatogenic phenotypes within the cohort are predominantly associated with endocrine and obstructive mechanisms.

Discussion

The observed association of infertility with polymicrobial urethral processes and an increased proportion of *Ureaplasma/Mycoplasma* is consistent with the data of M. Frølund *et al*. [21], which showed strong positive correlations between bacteria associated with bacterial vaginosis and ureaplasma load, which was interpreted as a pH-mediated effect of urease activity. At the same time, the absence of differences in the prevalence of BV taxa between idiopathic non-gonococcal urethritis and the control group reflected a different endpoint (urethritis versus reproductive outcome), different biomaterial (first-void urine versus comprehensive assessment), and the location of the process (urethra versus prostate/seminal vesicle involvement). Consequently, polymicrobial ecology is necessary but not sufficient; the clinical effect depends on the activity of inflammation and proximal involvement.

Key observations by E.L. Plummer *et al.* [22] were consistent with the polymicrobial concept of the lower tract: the composition of the urethral microbiota differed in idiopathic non-gonococcal urethritis and varied depending on the sex of the sexual partner. Taxa associated with idiopathic urethritis in men who have sex with men (MSM) were noted, with an increased relative abundance of *Haemophilus influenzae*, while in men who have sex with women (MSW), Corynebacterium was noted, as well as the dominance of a number of bacteria in cases but not in controls, including *Ureaplasma*, *Staphylococcus haemolyticus*, *Streptococcus pyogenes*, *Escherichia*, and *S. pneumoniae/pseudopneumoniae*. These data supported a polymicrobial profile and the involvement of *Ureaplasma*, which was consistent with the increased proportion of *Ureaplasma/Mycoplasma* in the infertility cohort, although the endpoints (urethritis versus reproductive outcome), matrix (first-void urine versus comprehensive examination), and methodology (16S versus targeted tests) differed.

A systematic review and meta-analysis by C. Cheng *et al*. [23] confirmed a statistically significant association between male infertility and genital mycoplasmas: *Mycoplasma genitalium* (pooled odds ratio, OR 3.44; 95% confidence interval, CI 1.78-6.64), *Mycoplasma hominis* (OR 1.84; 95% CI 1.01-3.34) and *Ureaplasma urealyticum* (OR 3.28; 95% CI 2.08-5.18), while Ureaplasma parvum showed no association (OR 1.67; 95% CI 0.95-2.95). The quality of the studies was assessed using the Newcastle-Ottawa scale; regional heterogeneity was noted (stronger associations in samples from China), indicating the influence of design, diagnosis and epidemiology. These results were consistent with the increased prevalence of *Ureaplasma/Mycoplasma* in men with infertility in the present study and explained the marked intergroup differences in "specific urethritis". A limitation of the comparison was the inability to differentiate between *U. urealyticum* and *U. parvum* in the current data set, which prevented direct validation of species-specific effects.

F.L. Nassan *et al*. [24] examined the impact of diet and individual food components on male fertility – from dietary patterns and antioxidant supplements to types of fats and consumption of dairy/meat products – in relation to sperm parameters, hormonal profile, and clinical reproductive outcomes. The authors demonstrated that adherence to a "pro-fertility" diet (fish/seafood, nuts, whole grains, fruits and vegetables, poultry) and adequate intake of omega-3 fatty acids were associated with better sperm parameters and more favourable reproductive outcomes, while excess trans and saturated fats were associated with poorer parameters. Antioxidant supplements were considered potentially beneficial, especially in couples undergoing ART, although there was no consensus on optimal compositions and doses. Data on dairy/meat products remained inconsistent; high-quality randomised studies are needed to develop clear clinical recommendations for men.

A comparison of the results of this study with the review by O. Batiha *et al*. [25] showed methodological consistency at the mechanism level: in 2020, a hypothesis was outlined about the possible effect of SARS-CoV-2 on male fertility through the expression of ACE2/TMPRSS2 in the testicle, fever, and endocrine shifts, while simultaneously reminding of the reproductive relevance of other viruses (HPV, HSV, HIV) in the absence of direct data on COVID-19 at that time. Later reviews and meta-analyses by Y. Xie *et al*. [26] clarified the picture: SARS-CoV-2 infection was associated with a transient deterioration in basic sperm parameters (volume, concentration, motility, morphology), especially in the short term after the disease. At the same time, no evidence of an adverse effect of vaccination on spermogram was obtained – data on inactivated and mRNA vaccines, as well as observations in sperm donors, showed no significant changes; this position is confirmed by a recent clinical review by Y.C. Ma *et al.* [27] on reproduction. In the cohort analysed, CMV/HSV serostatus was interpreted as a population background, and causal links between reproductive outcomes and COVID-19 were not assessed; nevertheless, the identified leading role of urogenital inflammation is consistent with the pathophysiological contour proposed for COVID-19 (inflammation/oxidative stress and subsequent damage to spermatozoa), described in mechanistic reviews.

The study by K. Gill *et al*. [20] assessed the impact of sedentary employment on the integrity of sperm nuclear DNA by comparing men who spent ≥ 50% of their working time sitting (n = 152) with participants

with less sedentary work (< 50%, n = 102). No statistical differences were found in standard ejaculate parameters, whereas the proportion of spermatozoa with DNA fragmentation (SDF, Halosperm) was higher in sedentary work (median 21.00% vs. 16.50%); low SDF levels were less common (0-15%: 27.63% vs. 45.10%) and high levels were more common (> 30%: 30.92% vs. 16.67%), with more than a twofold increase in the risk of high SDF (OR ≈ 2.24). The authors concluded that sedentary work (≥ 50% of working time) is associated with impaired sperm nuclear DNA integrity in the absence of differences in standard semen analysis; the proposed mechanism is testicular heat stress and disruption of chromatin remodelling in spermatogenesis.

The combination of the sources reviewed forms a consistent picture: the infectious-inflammatory domain of the distal sections and active inflammation of the prostate are statistically and biologically associated with reproductive disorders; severe phenotypes of spermatogenesis are more often associated with endocrine and obstructive causes requiring targeted additional examination and correction; Modifiable lifestyle factors – diet, past infections, nature of employment – affect fertility mainly through oxidative stress and damage to sperm DNA, which justifies expanding the laboratory panel beyond the standard semen analysis (e.g., SDF/ORP assessment). These findings justify a clinical and diagnostic focus on a multi-level approach: a unified PCR panel and microbiology, assessment of prostate inflammation, screening for endocrine and obstructive causes, and measurement of oxidative stress markers and sperm DNA integrity; in parallel – targeted lifestyle modification and nutritional support.

Conclusions

The results of the study confirm the complex and multifactorial nature of male infertility, in which infectious and inflammatory processes of the genitourinary system play a key role. The data obtained indicate that the most common clinical forms associated with fertility disorders are chronic urethritis and prostatitis, often occurring as combined or mixed infections. The high prevalence of ureaplasma, mycoplasma and gardnerella infections highlights their significant role in the development of pathological changes in spermatogenesis.

An important pathogenetic mechanism has been identified as the effect of a prolonged inflammatory process on the condition of the prostate and epididymis, leading to impaired secretion and deterioration in sperm quality. In combination with possible anatomical and functional disorders, such as varicocele or the consequences of orchiepididymitis, this forms the basis for the development of persistent forms of infertility. The results also demonstrate that endocrine disorders and functional disorders of spermatogenesis occur predominantly in cases of pronounced changes in the spermogram, including cases of azoospermia and severe oligozoospermia. The study substantiated the need for a comprehensive diagnostic approach, including microbiological examination of ejaculate, serological tests, hormonal assessment, and ultrasound examination of the scrotum and prostate. This approach ensured early detection of aetiological factors and allowed for the development of individualised treatment and prevention programmes for male infertility.

The data obtained from clinical, instrumental, and laboratory examinations are not exhaustive and require further in-depth study, given the growing medical and social significance of the problem of declining male reproductive capacity. The current understanding of the pathogenesis of male infertility requires a comprehensive approach that takes into account both identified factors and existing gaps in knowledge. In particular, it is necessary to continue fundamental research aimed at assessing the impact of generally toxic, carcinogenic and teratogenic agents, including chemical pollutants and radioactive substances, on the male reproductive system.

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Conflict of Interest

None.

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Аннотация. Эркектердин тукумсуздугу маанилүү медико-социалдык көйгөй бойдон калууда, ал эми анын себептик түзүлүшү жана патогенетикалык механизмдери боюнча аймактык маалыматтар жетишсиз. Кыргыз Республикасынын Жалал-Абад облусунда максаттуу диагностика жана алдын алуу боюнча далилдүү негизди жаңылоо зарыл. Бул изилдөөнүн максаты – комплекстүү клиникалык, лабораториялык жана инструменталдык текшерүүнүн негизинде эркектердеги баштапкы фертилдүүлүктүн бузулушунун этиологиялык түзүлүшүн жана ыктымал патогенетикалык механизмдерин аныктоо болгон. Изилдөөгө 20–38 жаштагы 110 эркек катышкан, алардын ичинен 60ы баштапкы тукумсуздук (анамнези ≥12 ай) менен, ал эми 50ү саламат эркектер болуп, көзөмөл тобун түзгөн. Клиникалык кароо, лабораториялык жана гормоналдык анализдер, спермограмма, микробиологиялык жана серологиялык инфекцияларды аныктоо, ошондой эле заара-жыныс системасынын ультраүндүү изилдөөсү жүргүзүлгөн. Башкы себептердин көпчүлүгүн заара-жыныс системасынын инфекциялык-сезгенүү оорулары түздү: 60 текшерилген эркектин арасында өнөкөт уретрит көпчүлүк бөлүгүндө аныкталган (тубаса эмес түрү – 23,3 %; спецификалык түрлөрү: трихомоноздук – 6,7 %, хламидиялык – 1,7 %, уреаплазмалык – 21,7 %, микоплазмалык – 18,3 %, гарднереллездук – 26,7 %); ультраүндүү изилдөө боюнча өнөкөт простатиттин белгилери 26,7 % учурларда байкалган. Микробиологиялык профилде стафилококтор менен грамтерс бактериялардын үстөмдүгү, аралаш флоранын көп кездешүүсү (46,7 %) жана заара-жыныс системасынын кандидозу (8,3 %) аныкталды. Цитомегаловируска серопозитивдүүлүк 31,7 %, ал эми жөнөкөй герпес вирусунун 1- жана 2-типтерине – 25,0 % түздү. Анатомиялык-функционалдык факторлор арасында варикоцеле (6,7 %), орхоэпидидимит (5,0 %), крипторхизм (1,7 %), уруктук жолдордун тосулушу (3,3 %) катталды; эндокриндик бузулуулар экинчи даражадагы гипогонадизм (5,0 %) менен көрсөтүлдү. Спермограммаларда азооспермия 8,3 % учурларда кездешип, негизинен экинчи даражадагы гипогонадизм

же обструкция менен байланыштуу болгон. Айрым бейтаптарда системалык сезгенүү лейкоцитоз жана эритроциттердин чөгүү ылдамдыгынын жогорулашы аркылуу лабораториялык жактан тастыкталган, ал эми лейкоцитурия мезгил-мезгили менен байкалган. Алынган маалыматтар жыныстык жол менен жугуучу инфекцияларды, өнөкөт простатитти жана гормоналдык бузулууларды эрте аныктоо зарылдыгын көрсөтүп, аймактык деңгээлдеги баштапкы эркек фертилдүүлүгүнүн бузулушун диагностикалоо жолдорун жакшыртууга жана этиотроптук-патогенетикалык дарылоону жеке ыкма менен жүргүзүүгө мүмкүнчүлүк берет

Негизги сөздөр: эркек фертилдүүлүгүнүн бузулуусу; репродуктивдик функция; заара-жыныс инфекциялары; хламидия; уреаплазма; микоплазма

Факторы и патогенетические механизмы мужского бесплодия в Жалал-Абадской области Кыргызской Республики

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Аннотация. Мужское бесплодие остается значимой медико-социальной проблемой, а региональные данные по структуре причин и патогенетическим механизмам ограничены. В Жалал-Абадской области Кыргызской Республики необходима актуализация доказательной базы для выработки таргетированной диагностики и профилактики. Целью исследования было описать этиологическую структуру и вероятные патогенетические механизмы первичного мужского бесплодия на основании комплексного клинико-лабораторного и инструментального обследования. Обследованы 110 мужчин в возрасте 20-38 лет, включая 60 пациентов с первичным бесплодием (анамнез ≥12 мес) и 50 здоровых мужчин, составивших контрольную группу. Проведены клиническое обследование, лабораторные и гормональные исследования, оценка спермограммы, микробиологическая и серологическая диагностика инфекций, а также ультразвуковая визуализация органов мочеполовой системы. Ведущую долю составляла инфекционно-воспалительная

патология мочеполовой системы: среди 60 обследованных мужчин хронический уретрит выявлен у значительной части пациентов (неспецифический – 23,3 %; специфические формы: трихомонадная – 6,7 %, хламидийная – 1,7 %, уреаплазменная – 21,7 %, микоплазменная – 18,3 %, гарднереллёз – 26,7 %); признаки хронического простатита по данным ультразвукового исследования определялись у 26,7 % обследованных. Микробиологический профиль характеризовался преобладанием стафилококков и грамотрицательных палочек, частой смешанной флорой (46,7 %) и кандидозом мочеполовой системы (8,3 %). Серопозитивность к цитомегаловирусу составила 31,7 %, к вирус простого герпеса 1-го и 2-го типов – 25,0 %. Среди анатомо-функциональных причин выявлены варикоцеле (6,7 %), орхоэпидидимит (5,0 %), крипторхизм (1,7 %), обтурация семявыводящих путей (3,3 %); эндокринные нарушения представлены вторичным гипогонадизмом (5,0 %). В спермограммах азооспермия встречалась у 8,3 % (ассоциировалась со вторичным гипогонадизмом или обструкцией). Системное воспаление подтверждалось у части пациентов лабораторно (лейкоцитоз, ускоренная скорость оседания эритроцитов), а лейкоцитурия фиксировалась эпизодически. Полученные данные обосновывают приоритет раннего скрининга инфекций, передаваемых половым путём, хронического простатита и гормональных нарушений в региональных маршрутах диагностики первичного мужского бесплодия и позволяют персонализировать этиотропную и патогенетическую терапию

Ключевые слова: нарушение фертильности у мужчин; репродуктивная функция; урогенитальные инфекции; хламидия: уреаплазма; микоплазм

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