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ASSESSMENT OF BIOCHEMICAL ALTERATIONS AND ENDOTHELIAL GLYCOCALYX BIOMARKERS FOR THE EARLY DETECTION OF RENAL IMPAIRMENT IN CHRONIC HEART FAILURE

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Abstract: Renal dysfunction frequently accompanies chronic heart failure (CHF) and is closely linked to the progression of cardiorenal syndrome, persistent systemic inflammation, and vascular endothelial injury. Consequently, identifying early indicators of renal impairment in this patient population remains a significant clinical challenge.

Objective: To investigate the associations between renal function, assessed by glomerular filtration rate (GFR), and selected biochemical, inflammatory, and endothelial dysfunction biomarkers in patients with class II–III CHF.

Materials and Methods: A total of 100 patients with CHF caused by ischemic heart disease and arterial hypertension were enrolled in the study. Based on cystatin C-derived estimated GFR (eGFR), participants were categorized into two groups: those with eGFR values of 60–90 mL/min/1.73 m² (n=50) and those with eGFR exceeding 90 mL/min/1.73 m² (n=50). Serum concentrations of cystatin C, N-terminal pro–B-type natriuretic peptide (NT-proBNP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), heparan sulfate, and syndecan-1 were measured and analyzed.

Results: Individuals with mildly reduced renal function (eGFR 60–90 mL/min/1.73 m²) exhibited significantly elevated concentrations of cystatin C, NT-proBNP, IL-6, heparan sulfate, and syndecan-1 compared with those whose eGFR was above 90 mL/min/1.73 m² ($p<0.001$). Mean cystatin C-based eGFR values were 72.9±1.3 and 101.8±1.3 mL/min/1.73 m² in the respective groups. These findings suggest that deterioration of renal function in CHF is accompanied by intensified inflammatory activity and endothelial injury, particularly involving disruption of the endothelial glycocalyx.

Keywords: chronic heart failure, renal dysfunction, estimated glomerular filtration rate, cystatin C, NT-proBNP.

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Introduction

Chronic heart failure (CHF) remains one of the most prevalent cardiovascular diseases worldwide and continues to pose a significant medical, social, and economic burden. According to reports from the World Health Organization and the European Society of Cardiology, more than 64 million people globally are living with CHF, and this number is projected to increase substantially over the next decade [15].

Research has demonstrated that the progression of CHF is not solely determined by impaired myocardial pumping function but also by pathological changes occurring in various organs and tissues. Among these, renal dysfunction plays a particularly important role. A reduction in cardiac output leads to decreased renal blood flow, which subsequently promotes sodium and water retention. These alterations further increase the workload on the heart, creating a vicious cycle that accelerates disease progression. The development of renal dysfunction in patients with CHF is associated with poorer clinical outcomes, including increased mortality, higher rates of rehospitalization, and greater healthcare costs. During the last decade, considerable attention has been devoted to investigating the mechanisms responsible for renal impairment in CHF. Current concepts suggest that cardiorenal interactions represent a complex network involving hemodynamic, neurohormonal, and molecular pathways rather than a simple one-way process [14].

Traditionally, assessment of renal function in CHF has relied on serum creatinine levels and estimated glomerular filtration rate (eGFR). However, recent studies have identified several limitations of these conventional markers. Serum creatinine typically increases only after a substantial loss of nephron function has occurred, making it relatively insensitive for detecting early stages of renal impairment [9].

Furthermore, creatinine concentrations are influenced by factors such as age, sex, muscle mass, nutritional status, and certain medications, thereby limiting its diagnostic accuracy [4]. Similarly, commonly used equations for estimating GFR, including CKD-EPI and MDRD, were primarily developed for stable clinical conditions and may not adequately account for the hemodynamic and fluid balance alterations frequently observed in CHF patients [12].

As a result, growing attention has been directed toward novel biomarkers of renal function, particularly cystatin C. Cystatin C is a low-molecular-weight protein that is continuously synthesized by all nucleated cells and freely filtered through the glomeruli [7]. Its major advantage is that its concentration is largely independent of muscle mass, sex, and nutritional status, allowing a more accurate estimation of GFR compared with creatinine-based measurements [18,19]. Recent investigations have demonstrated that cystatin C-based eGFR possesses strong prognostic value for predicting cardiovascular risk and overall mortality [7,8].

Elevated cystatin C levels in CHF have been linked not only to hemodynamic disturbances but also to inflammatory activity and neurohormonal activation. Consequently,

cystatin C is increasingly regarded as an integrated marker reflecting both renal function and systemic pathophysiological processes [2,3].

In addition, several studies have reported significant associations between cystatin C and inflammatory mediators. Correlations with tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) suggest a close relationship between inflammation and renal dysfunction in CHF patients [17].

Recent evidence has also identified endothelial dysfunction as a central component of CHF pathogenesis. The vascular endothelium and its surface glycocalyx layer function not merely as passive barriers but as biologically active structures involved in the regulation of vascular tone, inflammatory responses, and coagulation processes [6,7].

The endothelial glycocalyx is a highly organized and dynamic structure located on the luminal surface of endothelial cells. It consists of glycoproteins, proteoglycans, and glycosaminoglycans, including syndecans, glypicans, heparan sulfate, chondroitin sulfate, and hyaluronic acid. Contemporary studies characterize the glycocalyx as an active biological interface that participates in metabolic regulation and signal transduction in addition to its barrier function [13].

The glycocalyx performs several essential physiological functions. It protects the vascular wall from mechanical injury, converts shear stress into endothelial signaling, stimulates nitric oxide (NO) production, and reduces thrombogenicity [18,19]. Moreover, it acts as a selective filtration barrier for albumin and other plasma proteins, thereby regulating capillary permeability.

Recent investigations have demonstrated that glycocalyx degradation represents one of the earliest manifestations of endothelial dysfunction. Its disruption may occur in response to oxidative stress, inflammation, hyperglycemia, and ischemia-reperfusion injury [1,2].

In CHF, one of the principal mechanisms responsible for glycocalyx damage is the shedding of proteoglycans induced by inflammatory mediators and proteolytic enzymes. Matrix metalloproteinases, heparanase, and neutrophil elastase contribute to the breakdown of glycocalyx components and their subsequent release into the circulation [15,16].

The degradation of the glycocalyx results in increased capillary permeability, development of interstitial edema, microcirculatory disturbances, reduced endothelial NO production, and enhanced leukocyte and platelet adhesion. These alterations contribute to impaired organ perfusion, particularly within the kidneys, leading to nephron hypoxia and progressive renal injury in CHF patients [2].

Among the biomarkers of glycocalyx injury, syndecan-1 has attracted considerable interest. Syndecan-1 is a major transmembrane proteoglycan of the endothelial glycocalyx responsible for anchoring heparan sulfate chains to the cell surface. Damage to the glycocalyx results in the shedding of syndecan-1 into the bloodstream, causing a measurable increase in its circulating concentration [11].

Moreover, elevated syndecan-1 levels have been associated with declining renal function, reduced eGFR, and the progression of interstitial fibrosis [5].

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Considering the evidence presented above, the present study aimed to perform a comparative evaluation of biochemical parameters in patients with chronic heart failure of functional classes II–III according to glomerular filtration rate.

Materials and Methods

This study was conducted in 2024–2025 and included 100 patients with chronic heart failure (CHF) secondary to ischemic heart disease (IHD) and arterial hypertension (AH) who were treated at the National Medical Center. Participants were stratified into two groups according to their cystatin C-based estimated glomerular filtration rate (eGFR).

The first group consisted of 50 patients with an eGFR of 60–90 mL/min/1.73 m². The mean age of these patients was 67.98 ± 1.3 years; 20 (40%) were male and 30 (60%) were female.

The second group, which served as the comparison group, included 50 patients with an eGFR greater than 90 mL/min/1.73 m². Their mean age was 65.0 ± 1.5 years, with 20 (40%) males and 30 (60%) females.

The distribution of CHF functional classes II and III was comparable between the two groups. Baseline demographic and clinical characteristics of the study participants are presented in Table 1.

Table 1.
Baseline demographic and clinical characteristics of the patients.

Indications		**Group I (eGFR 60–90 mL/min/1.73 m²) (n = 50)**	**Group II (eGFR >90 mL/min/1.73 m²) (n = 50)**	**p and χ^2**
Age		67,98 ± 1,3	65 ± 1,5	>0,05
Sex	Male	20 (40%)	20 (40%)	χ^2=0 p>0,05
	Female	30 (60%)	30 (60%)	
Body mass index, kg/m^2		28,8 ± 0,7	28,3 ± 0,8	>0,05
Arterial Blood Pressure, mmHg	Systolic	135,2 ± 2,8	139,1 ± 2,8	>0,05
	Diastolic	83,8 ± 1,2	83,5 ± 1,4	>0,05
Obesity		14 (28%)	17 (34%)	χ^2=0.842 p>0,05
Family History		27 (54%)	19 (38%)	χ^2=5.153 p<0,05

In Group I, the mean serum cystatin C level was 1.05 ± 0.02 ng/mL, while the cystatin

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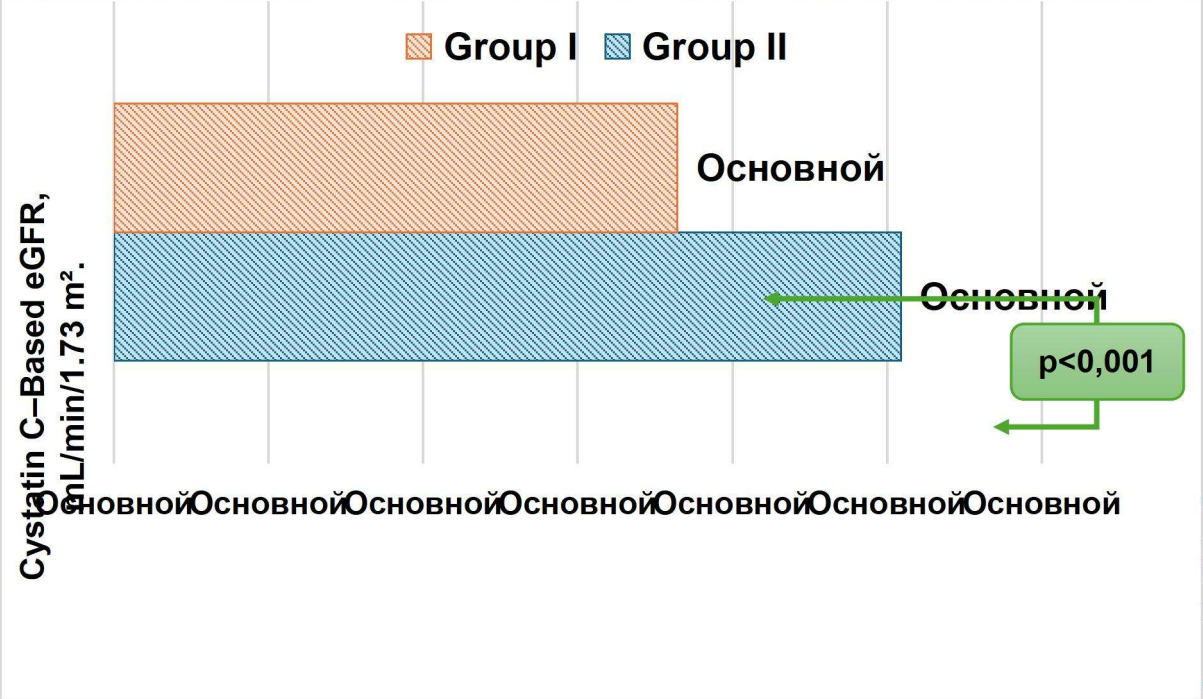
C-based estimated glomerular filtration rate (eGFR) was 72.9 ± 1.3 mL/min/1.73 m². In Group II, the corresponding values were 0.76 ± 0.01 ng/mL and 101.8 ± 1.3 mL/min/1.73 m²,



natriuretic peptide (NT-proBNP), is one of the most widely recognized biomarkers of chronic heart failure and has been incorporated into contemporary diagnostic guidelines. Therefore, we performed a comparative assessment of NT-proBNP levels in patients from both study groups. The obtained results are presented in Figure 2.

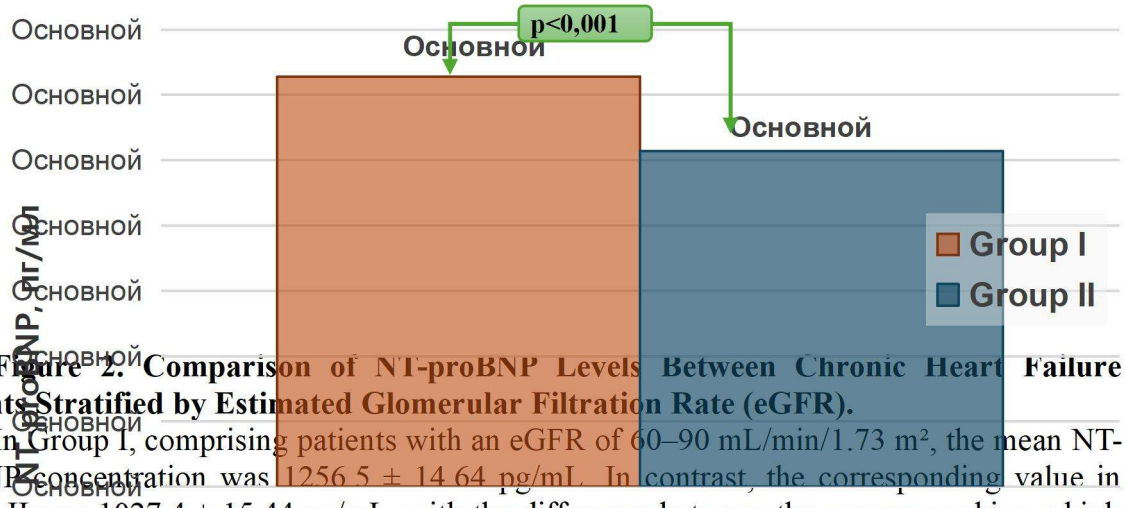


Figure 2. Comparison of NT-proBNP Levels Between Chronic Heart Failure Patients Stratified by Estimated Glomerular Filtration Rate (eGFR).

In Group I, comprising patients with an eGFR of 60–90 mL/min/1.73 m², the mean NT-proBNP concentration was 1256.5 ± 14.64 pg/mL. In contrast, the corresponding value in Group II was 1027.4 ± 15.44 pg/mL, with the difference between the groups reaching a high

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level of statistical significance ($p<0.001$).

The elevated NT-proBNP levels observed in Group I, where renal function was relatively impaired, may be regarded as one of the manifestations of cardiorenal interaction. This finding can be explained, on the one hand, by increased intracardiac pressure and myocardial wall stress and, on the other hand, by reduced renal clearance of NT-proBNP. Furthermore, renal dysfunction contributes to the accumulation of NT-proBNP in the circulation, resulting in further elevation of its plasma concentration.

Conversely, the lower NT-proBNP levels detected in Group II suggest relatively preserved cardiac hemodynamics and a lesser degree of neurohormonal activation in the presence of maintained renal function.

At the next stage of the study, we performed a comparative analysis of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are recognized markers of systemic inflammation in chronic heart failure, in both patient groups. The obtained results are presented in Figure 3.

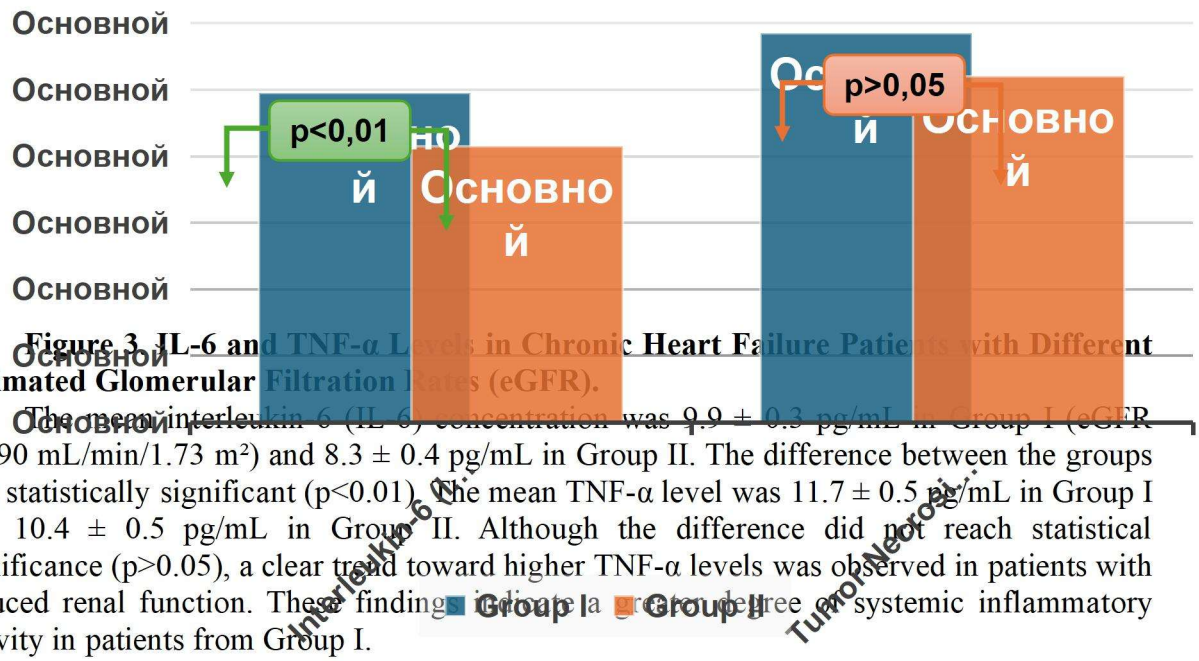
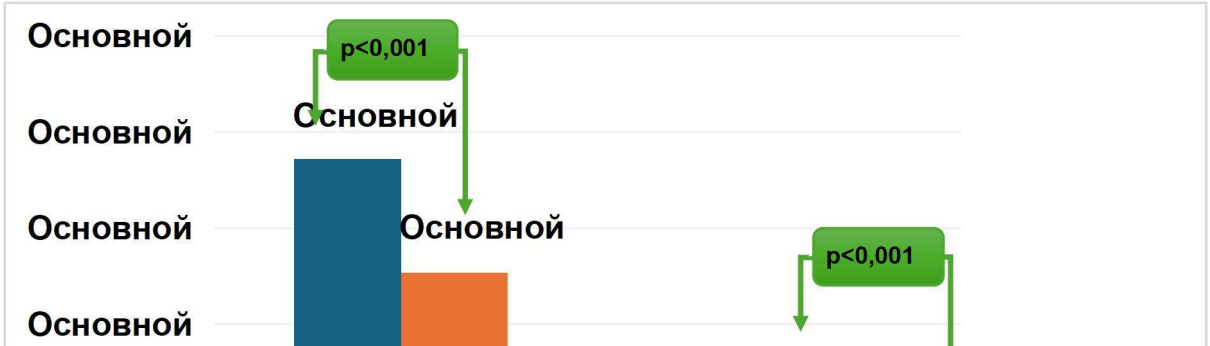


Figure 3. IL-6 and TNF-α Levels in Chronic Heart Failure Patients with Different Estimated Glomerular Filtration Rates (eGFR).

The mean interleukin-6 (IL-6) concentration was 9.9 ± 0.3 pg/mL in Group I (eGFR 60–90 mL/min/1.73 m²) and 8.3 ± 0.4 pg/mL in Group II. The difference between the groups was statistically significant ($p<0.01$). The mean TNF-α level was 11.7 ± 0.5 pg/mL in Group I and 10.4 ± 0.5 pg/mL in Group II. Although the difference did not reach statistical significance ($p>0.05$), a clear trend toward higher TNF-α levels was observed in patients with reduced renal function. These findings indicate a greater degree of systemic inflammatory activity in patients from Group I.

As discussed above, the endothelial glycocalyx is a gel-like biological layer lining the luminal surface of blood vessels. It is composed primarily of glycosaminoglycans, including heparan sulfate and hyaluronan, proteoglycans such as syndecans and glypicans, as well as plasma proteins. In recent years, the glycocalyx has been increasingly recognized as an important indicator of endothelial integrity, and its condition can be assessed using circulating biomarkers, particularly heparan sulfate and syndecan-1.

Taking this into consideration, we performed a comparative evaluation of these two



markers of glycocalyx dysfunction in the study groups. The results are presented in Figure 4.

Figure 4. Comparison of Heparan Sulfate and Syndecan-1 Levels in Patients with Chronic Heart Failure Stratified by Estimated Glomerular Filtration Rate (eGFR).

In the patients of Group I, the mean heparan sulfate concentration was 236.2 ± 5.5 ng/mL, whereas in Group II it was 176.7 ± 1.5 ng/mL. A highly significant difference was observed between the groups ($p<0.001$). These findings indicate that alterations in the endothelial glycocalyx are more pronounced in patients with an eGFR of 60–90 mL/min/1.73 m².

A comparative analysis of syndecan-1, another well-established marker of glycocalyx injury, revealed mean values of 103.3 ± 2.02 ng/mL and 71.1 ± 0.55 ng/mL in Groups I and II, respectively. Similar to heparan sulfate, the difference between the groups was highly significant ($p<0.001$). These results further support the close association between declining renal function and endothelial dysfunction, as well as glycocalyx shedding, a process characterized by the release of membrane-bound molecules, particularly proteoglycans and receptors, into the circulation.

The findings of the present study demonstrate that elevated levels of cystatin C, interleukin-6, heparan sulfate, and syndecan-1 in patients with an eGFR of 60–90 mL/min/1.73 m² reflect the important contribution of systemic inflammation and endothelial dysfunction, particularly glycocalyx injury, to the early development of cardiorenal syndrome.

Conclusion

The results of this study showed that patients with chronic heart failure (CHF) of NYHA functional classes II–III and reduced renal function exhibited significantly higher cystatin C concentrations (1.05 ± 0.02 mg/L vs. 0.76 ± 0.01 mg/L; $p<0.001$) and NT-proBNP levels (1256.5 ± 14.64 pg/mL vs. 1027.4 ± 15.44 pg/mL; $p<0.001$) compared with patients with preserved renal function. These findings suggest a progressive worsening of cardiorenal interactions as renal function declines.

Furthermore, reduced eGFR was associated with a significant increase in interleukin-6 levels (9.9 ± 0.3 pg/mL vs. 8.3 ± 0.4 pg/mL; $p<0.01$) and a tendency toward higher TNF-α concentrations, indicating enhanced systemic inflammatory activity.

In addition, significantly elevated levels of heparan sulfate (236.2 ± 5.5 ng/mL vs.

176.7 ± 1.5 ng/mL; p<0.001) and syndecan-1 (103.3 ± 2.02 ng/mL vs. 71.1 ± 0.55 ng/mL; p<0.001) confirmed the presence of endothelial glycocalyx injury and aggravated endothelial dysfunction in patients with impaired renal function. These biomarkers may therefore serve as valuable tools for the early detection and assessment of cardiorenal alterations in patients with chronic heart failure.

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