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Heparan Sulfate and Its Associations with Biochemical and Echocardiographic Parameters in Patients with Chronic Heart Failure Stratified by Cystatin C-Based Estimated Glomerular Filtration Rate.

Abdigaffar Gadaev
Tashkent State Medical University, Tashkent, Uzbekistan

Matluba Rakhimova
Tashkent State Medical University, Tashkent, Uzbekistan

Yulduz Bakhronova
Tashkent State Medical University, Tashkent, Uzbekistan

Corresponding Author:

Yulduz Bakhronova
Tashkent State Medical University
Tashkent, Uzbekistan
Email: yulduzbaxronova98@gmail.com

Abstract

Background: Endothelial glycocalyx degradation may contribute to vascular dysfunction, systemic inflammation, and renal impairment in chronic heart failure (CHF). Heparan sulfate, a major component of the endothelial glycocalyx, is released into the circulation following glycocalyx injury.

Objective: To evaluate circulating heparan sulfate concentrations in patients with clinically stable CHF stratified by cystatin C-based estimated glomerular filtration rate (eGFR) and to examine their associations with renal, inflammatory, neurohormonal, and echocardiographic parameters.

Methods: This cross-sectional observational study included 100 patients with New York Heart Association functional class II–III CHF and 32 age- and sex-matched controls. Patients with CHF were stratified into Group I (eGFR 60–89 mL/min/1.73 m²; n = 50) and Group II (eGFR ≥90 mL/min/1.73 m²; n = 50). Serum heparan sulfate, cystatin C, N-terminal pro-B-type natriuretic peptide (NT-proBNP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) concentrations were measured. Echocardiographic parameters were assessed using standard

methods. Associations were evaluated using Spearman's rank correlation analysis, and the discriminatory performance of heparan sulfate was assessed using receiver operating characteristic curve analysis.

Results: Serum heparan sulfate concentrations were significantly higher in Group I than in Group II (236.2 ± 5.5 vs. 176.7 ± 1.5 ng/mL; P < 0.001) and the control group (63.1 ± 2.8 ng/mL; P < 0.001). Compared with Group II, Group I had higher cystatin C concentrations (1.05 ± 0.02 vs. 0.76 ± 0.01 mg/L; P < 0.001), lower cystatin C-based eGFR (72.9 ± 1.3 vs. 101.8 ± 1.3 mL/min/1.73 m²; P < 0.001), higher NT-proBNP concentrations (1256.5 ± 14.64 vs. 1027.4 ± 15.44 pg/mL; P < 0.001), higher IL-6 concentrations (9.9 ± 0.3 vs. 8.3 ± 0.4 pg/mL; P < 0.01), and a higher E/e′ ratio (15.2 ± 0.25 vs. 10.5 ± 0.21; P < 0.001). In Group I, heparan sulfate correlated positively with cystatin C (r_s = 0.68), IL-6 (r_s = 0.53), TNF-α (r_s = 0.49), NT-proBNP (r_s = 0.62), and E/e′ (r_s = 0.52), and inversely with eGFR (r_s = −0.64) and left ventricular ejection fraction (r_s = −0.48; all P < 0.001). Similar but weaker associations were observed in Group II. Receiver operating characteristic analysis yielded an area under the curve of 0.968 (95% confidence interval, 0.934–1.000; P < 0.001). A heparan sulfate cutoff of ≥191.0 ng/mL distinguished mildly reduced from preserved eGFR with 88.0% sensitivity and 94.0% specificity.

Conclusion: Circulating heparan sulfate concentrations were elevated in patients with clinically stable CHF and were highest among those with mildly reduced cystatin C-based eGFR. Higher heparan sulfate concentrations were associated with poorer renal filtration, greater systemic inflammatory and neurohormonal activity, lower left ventricular systolic function, and higher estimated left ventricular filling pressure. These findings support the potential value of heparan sulfate as an integrative research biomarker of endothelial glycocalyx injury within the cardiorenal continuum; however, its clinical utility requires validation in larger multicenter studies.

Keywords: chronic heart failure; heparan sulfate; endothelial glycocalyx; estimated glomerular filtration rate; renal dysfunction; cardiorenal syndrome

Introduction

Background

CHF is a complex clinical syndrome associated with substantial morbidity, mortality, recurrent hospitalization, and a high burden of comorbidities. Renal dysfunction is particularly important in CHF because the heart and kidneys are closely interconnected through hemodynamic, neurohormonal, inflammatory, and vascular mechanisms. Consequently, dysfunction of either organ may contribute to progressive impairment of the other, forming the pathophysiological basis of the cardiorenal continuum. Reduced renal function is also associated with heart failure progression and adverse cardiovascular outcomes [1-3].

Accordingly, contemporary heart failure and chronic kidney disease guidelines emphasize systematic assessment of renal function as an integral component of risk stratification and clinical management in patients with CHF [2-5].

The mechanisms underlying cardiorenal interactions extend beyond reduced renal perfusion and venous congestion and include endothelial dysfunction, systemic inflammation, oxidative stress, and disruption of the vascular barrier [1,6].

The endothelial glycocalyx is a carbohydrate-rich layer covering the luminal surface of vascular endothelial cells. It consists predominantly of proteoglycans, glycosaminoglycans, glycoproteins, and associated plasma proteins and contributes to the regulation of vascular permeability, mechanotransduction, leukocyte adhesion, coagulation, and endothelial barrier function. Heparan sulfate is one of the principal glycosaminoglycan components of the endothelial glycocalyx and plays an important role in maintaining endothelial integrity and regulating interactions with growth factors, enzymes, and inflammatory mediators [7,8].

Chronic inflammation, oxidative stress, abnormal shear stress, and increased vascular pressure may promote enzymatic degradation and shedding of the endothelial glycocalyx. These changes impair endothelial barrier function, increase vascular permeability, enhance leukocyte–endothelial interactions, and contribute to a proinflammatory and prothrombotic endothelial phenotype [7,8].

Heparanase-mediated cleavage of heparan sulfate chains contributes to glycocalyx remodeling and the release of heparan sulfate fragments into the circulation [8]. Circulating heparan sulfate may therefore serve as an indicator of endothelial glycocalyx injury. However, because it is not specific to a single vascular bed, increased circulating heparan sulfate may reflect systemic glycocalyx shedding rather than isolated cardiac or renal endothelial injury.

Clinical evidence supports the potential relevance of circulating glycocalyx components in heart failure. Kim et al. reported that serum markers of endothelial glycocalyx degradation, including heparan sulfate, were increased in patients with acute decompensated heart failure with reduced ejection fraction. Higher circulating heparan sulfate was also independently associated with increased all-cause mortality [9]. However, most available evidence has been obtained from patients with acute or decompensated heart failure, whereas the clinical significance of

circulating heparan sulfate in clinically stable CHF remains insufficiently characterized.

In particular, limited information is available regarding the relationship between circulating heparan sulfate and mildly reduced renal filtration in patients with CHF whose estimated glomerular filtration rate (eGFR) remains ≥60 mL/min/1.73 m². Moreover, the associations of heparan sulfate with cystatin C-based eGFR, systemic inflammatory activity, neurohormonal activation, and echocardiographic indices of cardiac function have not been comprehensively evaluated within a single clinical study. Characterizing these relationships may improve understanding of the biological mechanisms linking endothelial glycocalyx injury to early alterations within the cardiorenal continuum [6].

Therefore, this study aimed to evaluate circulating heparan sulfate concentrations in patients with clinically stable CHF stratified according to cystatin C-based eGFR (60–89 vs. ≥90 mL/min/1.73 m²) and to determine their associations with renal function, inflammatory biomarkers, N-terminal pro-B-type natriuretic peptide, and echocardiographic parameters.

Materials and Methods

Study Design and Participants

This cross-sectional observational study was conducted between 2024 and 2025 at the Department of Internal Diseases in Family Medicine No. 2, Tashkent State Medical University, and the National Medical Center, Tashkent, Uzbekistan.

The study included 100 patients with clinically stable New York Heart Association (NYHA) functional class II–III chronic heart failure (CHF) secondary to ischemic heart disease and/or arterial hypertension. The control group comprised 32 age- and sex-matched apparently healthy individuals without clinical evidence of heart failure or renal dysfunction.

The diagnosis of CHF was established in accordance with the 2021 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2023 Focused Update [2,4]. Renal function was assessed using cystatin C-based estimated glomerular filtration rate (eGFR). Patients with CHF were stratified into two groups according to their eGFR: Group I included patients with an eGFR of 60–89 mL/min/1.73 m² (n = 50), whereas Group II included patients with an eGFR ≥90 mL/min/1.73 m² (n = 50).

Eligibility Criteria

Eligible participants were adults aged ≥18 years with clinically stable NYHA functional class II–III CHF, cystatin C-based eGFR ≥60 mL/min/1.73 m², and complete clinical, laboratory, and echocardiographic data.

The exclusion criteria were acute coronary syndrome, acute decompensated heart failure, acute kidney injury, eGFR <60 mL/min/1.73 m², active infectious or inflammatory disease, autoimmune disease, malignant neoplasm, severe hepatic impairment, pregnancy, or breastfeeding.

Clinical Assessment

Demographic and clinical characteristics, including age, sex, anthropometric measurements, body mass index, medical history, cardiovascular risk factors, comorbidities, NYHA functional class, blood pressure, heart rate, and guideline-directed medical therapy, were recorded for all participants.

Echocardiographic Assessment

Transthoracic echocardiography was performed using a MyLab ultrasound system (Esaote, Genoa, Italy) equipped with a 2.2-MHz transducer. Examinations were performed using M-mode, two-dimensional imaging, pulsed-wave Doppler, and tissue Doppler imaging in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [10,11].

The evaluated parameters included left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular end-diastolic and end-systolic volumes, left atrial volume, left ventricular ejection fraction (LVEF), transmitral early (E) and late (A) diastolic flow velocities, tissue Doppler-derived early diastolic mitral annular velocity (e′), the E/A ratio, and the E/e′ ratio. Left ventricular diastolic function was assessed according to current international recommendations.

Blood Sampling and Routine Biochemical Measurements

Venous blood samples were collected from all participants in the morning after an overnight fast of 8–12 h. Serum was separated by centrifugation, divided into aliquots, and stored at −80 °C until biomarker analysis.

Routine biochemical parameters, including alanine aminotransferase, aspartate aminotransferase, total bilirubin, glucose, urea, creatinine, total protein, potassium, sodium, and lipid profile components, were measured using reagents supplied by Human GmbH (Wiesbaden, Germany) on a Mindray BA-88A semi-automated biochemical analyzer (Mindray, Shenzhen, China).

Cystatin C Measurement and Estimation of Glomerular Filtration Rate

Serum cystatin C concentrations were measured using a commercially available Human CST3 (Cystatin C) ELISA Kit (FineTest®, Wuhan Fine Biotech Co., Ltd., Wuhan, China; catalog No. EH0110), according to the manufacturer's instructions. The assay was based on a double-antibody sandwich enzyme-linked immunosorbent assay. Optical density was measured at 450 nm using a Mindray MR-96A semi-automated microplate reader (Mindray, Shenzhen, China). The analytical measurement range was 0.313–20 ng/mL, and the analytical sensitivity was 0.188 ng/mL.

Serum samples were diluted 50- to 100-fold, as appropriate, using the sample dilution buffer supplied with the kit. Cystatin C concentrations obtained from the standard curve were multiplied by the corresponding dilution factor. The resulting concentrations, initially expressed in ng/mL, were converted to mg/L by dividing by 1000.

Cystatin C-based eGFR was calculated using the 2012 Chronic Kidney Disease Epidemiology Collaboration Cystatin C equation [12]:

eGFR = 133 × min(Scys/0.8, 1)^−0.499 × max(Scys/0.8, 1)^−1.328 × 0.996^Age × 0.932 [if female],

where Scys denotes serum cystatin C expressed in mg/L, and eGFR is expressed in mL/min/1.73 m².

To minimize potential preanalytical variability, participants were instructed to avoid excessive fluid intake, high-protein meals, strenuous physical activity, and substantial emotional stress before blood collection.

Measurement of N-Terminal Pro-B-Type Natriuretic Peptide

Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were measured by enzyme-linked immunosorbent assay using commercially available reagents supplied by Vector-Best (Novosibirsk, Russia), according to the manufacturer's instructions. The analytical measurement range was 0–2500 pg/mL, and the analytical sensitivity was 20.0 pg/mL.

Measurement of Inflammatory Biomarkers

Serum interleukin-6 (IL-6) concentrations were measured by enzyme-linked immunosorbent assay using the Interleukin-6-IFA-BEST reagent kit (Vector-Best, Novosibirsk, Russia; catalog No. A-8768), according to the manufacturer's instructions. The reference interval applied in the study was 0–7 pg/mL.

Serum tumor necrosis factor-α (TNF-α) concentrations were measured by enzyme-linked immunosorbent assay according to the manufacturer's instructions. Optical density was measured using a Mindray MR-96A semi-automated microplate reader (Mindray, Shenzhen, China). The reference interval applied in the study was 0–8.1 pg/mL.

Measurement of Heparan Sulfate

Serum heparan sulfate concentrations were measured using a commercially available Heparan Sulfate ELISA Kit (DRG International, Springfield, NJ, USA; catalog No. EIA-5225), according to the manufacturer's instructions. The assay was based on a quantitative double-antibody sandwich enzyme-linked immunosorbent assay. Serum heparan sulfate concentrations were calculated from the standard calibration curve and expressed in ng/mL.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) and R Statistical Software version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

The distribution of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed continuous variables are presented as mean ± standard error of the mean, whereas non-normally distributed variables are presented as median and interquartile range. Categorical variables are presented as frequencies and percentages.

Comparisons among the three study groups were performed using one-way analysis of variance for normally distributed continuous variables and the Kruskal–Wallis test for non-normally distributed continuous variables. When the overall comparison was statistically significant, appropriate post hoc pairwise comparisons were performed. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate.

Associations between serum heparan sulfate concentrations and renal, biochemical, inflammatory, neurohormonal, and echocardiographic parameters were evaluated using Spearman's rank correlation analysis. Correlation coefficients are reported as Spearman's r_s.

The discriminatory performance of serum heparan sulfate for differentiating patients with CHF and mildly reduced eGFR (60–89 mL/min/1.73 m²) from those with preserved eGFR (≥90 mL/min/1.73 m²) was evaluated using receiver operating characteristic curve analysis. The area under the curve and its 95% confidence interval were calculated. The optimal cutoff value was determined using the Youden index, and the corresponding sensitivity and specificity were reported. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the Ethics Committee of Tashkent State Medical University. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants were informed about the objectives, procedures, potential risks, and intended scientific use of the collected data. Written informed consent was obtained from all participants before enrollment. Participant confidentiality was maintained throughout the study.

Results

Baseline clinical and demographic characteristics

A total of 100 patients with New York Heart Association (NYHA) functional class II–III chronic heart failure secondary to ischemic heart disease and/or arterial hypertension and 32 control participants were included in the study. Based on cystatin C-derived estimated glomerular filtration rate (eGFR), patients with chronic heart failure were stratified into Group I (eGFR 60–89 mL/min/1.73 m²; n = 50) and Group II (eGFR ≥ 90 mL/min/1.73 m²; n = 50). The baseline clinical and demographic characteristics of the study groups are presented in Table 1.

Table 1. Baseline clinical and demographic characteristics of the study groups

Variable	Group I, eGFR 60–89 mL/min/1.73 m² (n = 50)	Group II, eGFR ≥ 90 mL/min/1.73 m² (n = 50)	Control group (n = 32)	Statistical comparison
Age, years	68.0 ± 1.3	65.0 ± 1.5	65.9 ± 0.2	$P_1 = 0.540$; $P_2 = 0.891$; $P_3 = 0.202$
Male sex, n (%)	20 (40.0)	20 (40.0)	14 (43.7)	$\chi^2_1 = 0.113$, $P_1 = 0.737$; $\chi^2_2 = 0.113$, $P_2 = 0.737$; $\chi^2_3 = 0.000$, $P_3 = 1.000$
Body mass index, kg/m²	28.8 ± 0.7	28.3 ± 0.8	27.0 ± 0.5	$P_1 = 0.225$; $P_2 = 0.455$; $P_3 = 0.862$
Systolic blood pressure, mmHg	135.2 ± 2.8	139.1 ± 2.8	128.2 ± 2.6	$P_1 = 0.227$; $P_2 = 0.030$; $P_3 = 0.551$
Diastolic blood pressure, mmHg	83.8 ± 1.2	83.5 ± 1.4	78.4 ± 1.3	$P_1 = 0.021$; $P_2 = 0.031$; $P_3 = 0.984$
Obesity, n (%)	14 (28.0)	17 (34.0)	6 (18.8)	$\chi^2_1 = 0.905$, $P_1 = 0.341$; $\chi^2_2 = 2.249$, $P_2 = 0.134$; $\chi^2_3 = 0.421$, $P_3 = 0.516$
Positive family history, n (%)	27 (54.0)	19 (38.0)	10 (31.3)	$\chi^2_1 = 4.078$, $P_1 = 0.043$; $\chi^2_2 = 0.389$, $P_2 = 0.533$; $\chi^2_3 = 2.576$, $P_3 = 0.108$

Data are presented as mean ± standard error of the mean or number (percentage). Continuous variables were compared using one-way analysis of variance followed by Tukey–Kramer post-hoc comparisons. Categorical variables were compared using Pearson's χ^2 test. eGFR, estimated glomerular filtration rate. P_1 and χ^2_1, Group I versus the control group; P_2 and χ^2_2, Group II versus the control group; P_3 and χ^2_3, Group I versus Group II.

No statistically significant differences were observed among the groups in age, sex distribution, body mass index, or prevalence of obesity.

Systolic blood pressure was higher in Group II than in the control group (139.1 ± 2.8 vs. 128.2 ± 2.6 mmHg; P = 0.030), whereas no significant difference was observed between Group I and the control group or between the two heart failure groups.

Diastolic blood pressure was higher in both Group I and Group II than in the control group (83.8 ± 1.2 vs. 78.4 ± 1.3 mmHg, P = 0.021; and 83.5 ± 1.4 vs. 78.4 ± 1.3 mmHg, P = 0.031, respectively). No significant difference was observed between Group I and Group II (P = 0.984).

A positive family history was more prevalent in Group I than in the control group (54.0% vs. 31.3%; χ^2 = 4.078; P = 0.043). However, no statistically significant difference was observed between Group II and the control group or between Group I and Group II.

Biochemical and renal parameters

Biochemical parameters and renal functional status were compared among the study groups according to cystatin C-based estimated glomerular filtration rate (eGFR). The results are presented in Table 2.

Table 2. Biochemical and renal parameters according to cystatin C-based eGFR

Parameter	Group I, eGFR 60–89 mL/min/1.73 m² (n = 50)	Group II, eGFR ≥ 90 mL/min/1.73 m² (n = 50)	Control group (n = 32)	Statistical comparison
Alanine aminotransferase, U/L	22.4 ± 1.05	23.4 ± 0.99	23.3 ± 0.57	P_1 = 0.813; P_2 = 0.997; P_3 = 0.721
Aspartate aminotransferase, U/L	23.4 ± 1.6	24.1 ± 1.6	21.8 ± 0.42	P_1 = 0.757; P_2 = 0.564; P_3 = 0.934
Total protein, g/L	69.4 ± 0.7	69.2 ± 0.8	73.9 ± 0.34	P_1 < 0.001; P_2 < 0.001; P_3 = 0.976
Total cholesterol, mmol/L	4.3 ± 0.1	4.5 ± 0.1	4.9 ± 0.03	P_1 < 0.001; P_2 = 0.014; P_3 = 0.246
High-density lipoprotein cholesterol, mmol/L	1.20 ± 0.03	1.30 ± 0.02	1.41 ± 0.01	P_1 < 0.001; P_2 = 0.008; P_3 = 0.006
Low-density lipoprotein cholesterol, mmol/L	2.96 ± 0.06	3.17 ± 0.07	2.70 ± 0.12	P_1 = 0.075; P_2 < 0.001; P_3 = 0.113
Triglycerides, mmol/L	1.80 ± 0.03	1.80 ± 0.02	1.30 ± 0.03	P_1 < 0.001; P_2 < 0.001; P_3 = 1.000
Cystatin C, mg/L	1.05 ± 0.02	0.76 ± 0.01	0.70 ± 0.03	P_1 < 0.001; P_2 = 0.100; P_3 < 0.001
Cystatin C-based eGFR, mL/min/1.73 m²	72.9 ± 1.3	101.8 ± 1.3	106.8 ± 1.5	P_1 < 0.001; P_2 = 0.041; P_3 < 0.001

Data are presented as mean ± standard error of the mean. Comparisons were performed using one-way analysis of variance followed by Tukey–Kramer post-hoc comparisons. eGFR, estimated glomerular filtration rate. P_1, Group I versus the control group; P_2, Group II versus the control group; P_3, Group I versus Group II.

Serum alanine aminotransferase and aspartate aminotransferase concentrations did not differ significantly among the three groups (all P > 0.05).

Total serum protein concentrations were lower in Group I and Group II than in the control group (both P < 0.001), whereas no significant difference was observed between the two heart failure groups (P = 0.976).

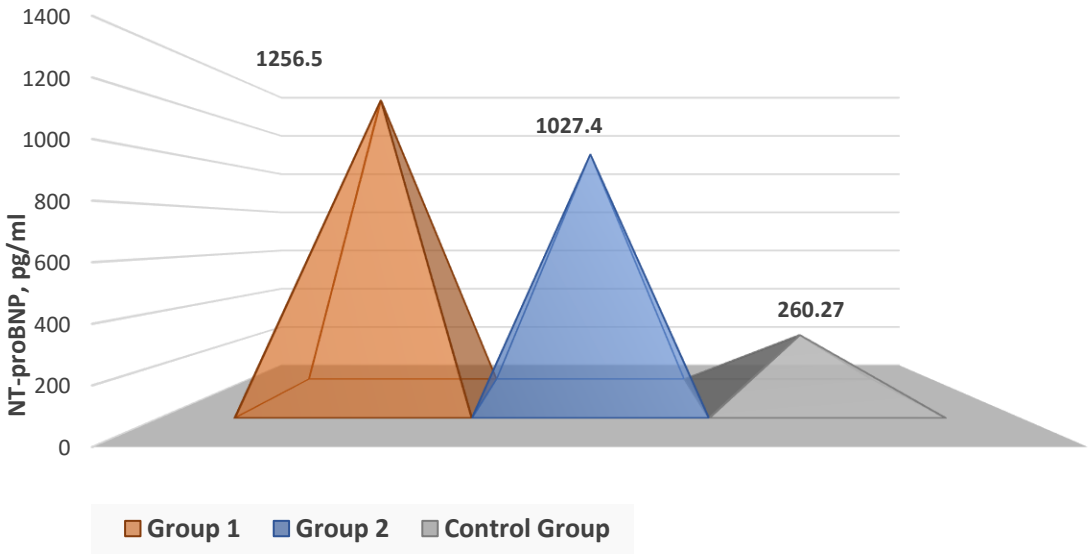
Total cholesterol was lower in Group I and Group II than in the control group (P < 0.001 and P = 0.014, respectively), with no significant difference between the two heart failure groups (P = 0.246). High-density lipoprotein cholesterol was also lower in Group I and Group II than in the control group (P < 0.001 and P = 0.008, respectively). In addition, Group I had lower high-density lipoprotein cholesterol than Group II (1.20 ± 0.03 vs. 1.30 ± 0.02 mmol/L; P = 0.006).

Low-density lipoprotein cholesterol was higher in Group II than in the control group (3.17 ± 0.07 vs. 2.70 ± 0.12 mmol/L; P < 0.001). However, no significant difference was observed between Group I and the control group (P = 0.075) or between Group I and Group II (P = 0.113). Triglyceride concentrations were higher in both heart failure groups than in the control group (both P < 0.001), whereas the two heart failure groups did not differ from each other (P = 1.000).

Serum cystatin C was higher in Group I than in Group II and the control group (both P < 0.001). No significant difference in cystatin C was observed between Group II and the control group (P = 0.100).

Correspondingly, cystatin C-based eGFR was lower in Group I than in Group II and the control group (both P < 0.001). Group II also had a slightly lower eGFR than the control group (101.8 ± 1.3 vs. 106.8 ± 1.5 mL/min/1.73 m²; P = 0.041).

The concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP), one of the principal biomarkers reflecting the severity of heart failure and the degree of neurohormonal activation, was compared across all three groups (Figure 1).



Note: P_1 indicates the comparison between Group I and the control group ($P_1 < 0.001$); P_2 indicates the comparison between Group II and the control group ($P_2 < 0.001$); and P_3 indicates the comparison between Groups I and II ($P_3 < 0.001$).

Figure 1. Comparison of Serum NT-proBNP Concentrations Among the Study Groups

As shown in Figure 1, the mean serum NT-proBNP concentration was 1256.5 ± 14.64 pg/mL in Group I, 1027.4 ± 15.44 pg/mL in Group II, and 260.27 ± 8.50 pg/mL in the control group.

Serum NT-proBNP levels were significantly higher in Group I than in Group II (P < 0.001). Furthermore, both patient groups demonstrated significantly higher NT-proBNP concentrations than the control group (both P < 0.001).

To evaluate systemic inflammatory activity, serum concentrations of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were comparatively analyzed across the study groups (Figure 2).

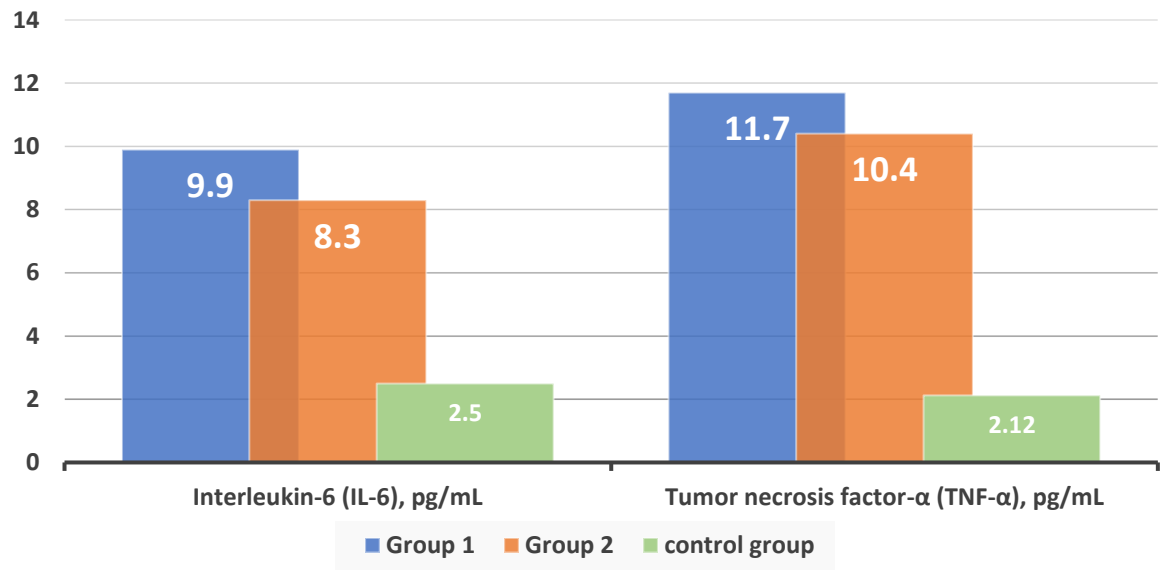


Figure 2. Comparison of Serum Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) Levels in Patients with Heart Failure Stratified by Estimated Glomerular Filtration Rate

According to the analysis, the mean serum IL-6 concentration was 9.9 ± 0.3 pg/mL in Group I, 8.3 ± 0.4 pg/mL in Group II, and 2.5 ± 0.2 pg/mL in the control group. Serum IL-6 levels were significantly higher in both patient groups than in the control group (both $P < 0.001$). In addition, Group I exhibited significantly higher IL-6 concentrations than Group II ($P < 0.01$).

The mean serum TNF-α concentration was 11.7 ± 0.5 pg/mL in Group I, 10.4 ± 0.5 pg/mL in Group II, and 2.12 ± 0.15 pg/mL in the control group. TNF-α levels were significantly higher in both patient groups than in the control group (both $P < 0.001$). However, no statistically significant difference in TNF-α concentrations was observed between Groups I and II ($P > 0.05$).

Following the assessment of neurohormonal and systemic inflammatory activity, serum heparan sulfate concentrations were analyzed as a circulating marker of endothelial glycocalyx degradation. Serum heparan sulfate levels differed significantly among the three study groups. The mean concentration was 236.2 ± 5.5 ng/mL in Group I and 176.7 ± 1.5 ng/mL in Group II, with a highly significant difference between the two CHF groups ($P_3 < 0.001$). In the control group, the mean serum heparan sulfate concentration was 63.1 ± 2.8 ng/mL. Compared with the control group, heparan sulfate levels were significantly elevated in both Group I and Group II ($P_1 < 0.001$ and $P_2 < 0.001$, respectively). Thus, the highest circulating heparan sulfate concentration was observed in patients with CHF and mildly reduced eGFR (60–89 mL/min/1.73 m²).

A comparative analysis of echocardiographic parameters in patients with chronic heart failure and different levels of renal function is presented in Table 3.

Table 3 Echocardiographic and Cardiac Hemodynamic Parameters in Patients with Chronic Heart Failure Stratified by Estimated Glomerular Filtration Rate

Variable	Group I (eGFR 60–89 mL/min/1.73 m²) (n=50)	Group II (eGFR ≥90 mL/min/1.73 m²) (n=50)	Control Group (n=32)	P value
Left ventricular end-diastolic diameter, cm	5.17 ± 0.09	5.08 ± 0.08	5.11 ± 0.03	P1>0.05; P2>0.05; P3>0.05
Left ventricular end-systolic diameter, cm	3.97 ± 0.13	3.83 ± 0.09	3.30 ± 0.03	P1<0.001; P2<0.001; P3>0.05

Left ventricular end-diastolic volume, mL	129.1 ± 5.1	128.1 ± 7.2	114.9 ± 1.31	P1<0.05; P2<0.05; P3>0.05
Left ventricular end-systolic volume, mL	66.5 ± 4.6	66.7 ± 5.9	41.7 ± 0.65	P1<0.001; P2<0.001; P3>0.05
Left ventricular ejection fraction (LVEF), %	49.6 ± 1.6	51.3 ± 1.2	62.2 ± 0.44	P1<0.001; P2<0.001; P3>0.05
E/A ratio	0.9 ± 0.04	0.9 ± 0.07	1.04 ± 0.01	P1<0.05; P2<0.05; P3>0.05
E/e′ ratio	15.2 ± 0.25	10.5 ± 0.21	7.24 ± 0.07	P1<0.001; P2<0.001; P3<0.001
Interventricular septal thickness, cm	1.2 ± 0.02	1.2 ± 0.02	0.97 ± 0.11	P1<0.05; P2<0.05; P3>0.05
Left ventricular posterior wall thickness, cm	1.17 ± 0.02	1.18 ± 0.02	0.96 ± 0.10	P1<0.05; P2<0.05; P3>0.05
Left ventricular mass, g	261.4 ± 4.5	261.9 ± 4.6	180.03 ± 1.61	P1<0.001; P2<0.001; P3>0.05

Note: P_1 indicates the comparison between Group I and the control group; P_2 indicates the comparison between Group II and the control group; and P_3 indicates the comparison between Groups I and II.

A comparative analysis of echocardiographic parameters in patients with chronic heart failure and different levels of renal function is presented in Table 3.

As shown in Table 3, no statistically significant differences were observed between Groups I and II in left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular end-diastolic volume, left ventricular end-systolic volume, or left ventricular ejection fraction (LVEF) (all $P > 0.05$). However, left ventricular end-systolic diameter, end-diastolic and end-systolic volumes, and LVEF differed significantly between both patient groups and the control group ($P < 0.05$–0.001).

Interventricular septal thickness, left ventricular posterior wall thickness, and left ventricular mass were also significantly greater in both patient groups than in the control group ($P< 0.05$–0.001). In contrast, no statistically significant differences in these parameters were observed between Groups I and II (all $P > 0.05$).

Analysis of left ventricular diastolic function demonstrated that the E/A ratio was significantly lower in both patient groups than in the control group ($P < 0.05$), whereas no significant difference was observed between Groups I and II ($P > 0.05$). In contrast, the mean E/e′ ratio was 15.2 ± 0.25 in Group I, 10.5 ± 0.21 in Group II, and 7.24 ± 0.07 in the control group. The E/e′ ratio was significantly higher in both patient groups than in the control group and was also significantly higher in Group I than in Group II (all $P < 0.001$).

Beyond the observed between-group differences in serum heparan sulfate levels and echocardiographic parameters, we further investigated whether circulating heparan sulfate was associated with renal function, systemic inflammation, neurohormonal activation, and cardiac hemodynamic status. Spearman correlation analysis demonstrated that, in Group I, serum heparan sulfate was positively correlated with cystatin C ($r_s = 0.68$, $P < 0.001$), IL-6 ($r_s = 0.53$, $P < 0.001$), TNF-α ($r_s = 0.49$, $P < 0.001$), NT-proBNP ($r_s = 0.62$, $P < 0.001$), and E/e′ ($r_s = 0.52$, $P < 0.001$), whereas inverse correlations were observed with eGFR ($r_s = −0.64$, $P < 0.001$) and LVEF ($r_s = −0.48$, $P < 0.001$). Similar statistically significant associations were observed in Group II, although the correlation coefficients were numerically lower: heparan sulfate was positively correlated with cystatin C ($r_s = 0.49$, $P < 0.001$), IL-6 ($r_s = 0.47$, $P < 0.001$), TNF-α ($r_s = 0.45$, $P < 0.001$), NT-proBNP ($r_s = 0.54$, $P < 0.001$), and E/e′ ($r_s = 0.45$, $P < 0.01$) and inversely correlated with eGFR ($r_s = −0.48$, $P < 0.001$) and LVEF ($r_s = −0.41$, $P < 0.01$). Overall, higher serum heparan sulfate concentrations were associated with poorer renal function, greater systemic inflammatory and neurohormonal activity, lower left ventricular systolic function, and higher estimated left ventricular filling pressure (Table 4).

Table 4. Correlations of serum heparan sulfate with renal, inflammatory, neurohormonal, and echocardiographic parameters

Parameter	Group I: eGFR 60–89 mL/min/1.73 m² (n=50), r_s	P value	Group II: eGFR ≥90 mL/min/1.73 m² (n=50), r_s	P value
Cystatin C	0.68	<0.001	0.49	<0.001
eGFR	−0.64	<0.001	−0.48	<0.001
IL-6	0.53	<0.001	0.47	<0.001
TNF-α	0.49	<0.001	0.45	<0.001
NT-proBNP	0.62	<0.001	0.54	<0.001
LVEF	−0.48	<0.001	−0.41	<0.01
E/e′ ratio	0.52	<0.001	0.45	<0.01

Data are presented as Spearman rank correlation coefficients (r_s). eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

In addition to the observed associations between serum heparan sulfate and renal, inflammatory, neurohormonal, and echocardiographic parameters, ROC curve analysis was performed to evaluate its ability to distinguish patients with CHF and mildly reduced eGFR (Group I, 60–89 mL/min/1.73 m²) from those with preserved eGFR (Group II, ≥90 mL/min/1.73 m²). Serum heparan sulfate demonstrated excellent discriminatory performance, with an AUC of 0.968 (95% CI: 0.934–1.000; P < 0.001). The optimal cutoff value determined using the Youden index was ≥191.0 ng/mL. At this threshold, 44 of 50 patients in Group I were correctly identified, corresponding to a sensitivity of 88.0%, whereas 47 of 50 patients in Group II were correctly classified as having preserved eGFR, corresponding to a specificity of 94.0%. Six patients in Group I were classified as false-negative and three patients in Group II as false-positive. These findings suggest that serum heparan sulfate may have potential discriminatory value for identifying mildly reduced eGFR among patients with CHF (Table 5).

Table 5. Receiver Operating Characteristic Curve Analysis of Serum Heparan Sulfate for Patients with Chronic Heart Failure

Parameter	Result
Group I, n	50
Group II, n	50
Group I heparan sulfate, mean ± SEM, ng/mL	236.2 ± 5.5
Group II heparan sulfate, mean ± SEM, ng/mL	176.7 ± 1.5
AUC	0.968
95% CI	0.934–1.000
Optimal cutoff	≥191.0 ng/mL
Sensitivity	88.0%
Specificity	94.0%
Youden index	0.82
P value	<0.001

Discussion

The present study demonstrated that circulating heparan sulfate concentrations were markedly elevated in patients with clinically stable chronic heart failure (CHF) and were associated with renal filtration, systemic inflammation, neurohormonal activation, and echocardiographic abnormalities. Serum heparan sulfate concentrations were 236.2 ± 5.5 ng/mL in patients with an estimated glomerular filtration rate (eGFR) of 60–89 mL/min/1.73 m², 176.7 ± 1.5 ng/mL in those with an eGFR ≥90 mL/min/1.73 m², and 63.1 ± 2.8 ng/mL in controls (all pairwise $P < 0.001$). Thus, the mean concentration in Group I was approximately 33.7% higher than that in Group II and 3.7-fold higher than that in the control group. These findings suggest that increased endothelial glycocalyx shedding may accompany relatively early alterations in renal filtration in clinically stable CHF, even when eGFR remains ≥60 mL/min/1.73 m². Nevertheless, an eGFR of 60–89 mL/min/1.73 m² corresponds to the Kidney Disease: Improving Global Outcomes G2 category and, in the absence of albuminuria or another marker of kidney damage, does not independently establish a diagnosis of chronic kidney disease.

The observed relationship between circulating heparan sulfate and renal filtration is biologically plausible. Heparan sulfate is one of the principal glycosaminoglycan constituents of the endothelial glycocalyx and contributes to the regulation of vascular permeability, mechanotransduction, anticoagulant activity, and leukocyte–endothelial interactions. Inflammation, oxidative stress, altered shear stress, and increased vascular pressure may activate heparanase and other enzymes involved in the degradation and shedding of glycocalyx components [7,8].

In Group I, heparan sulfate correlated positively with cystatin C ($r_s = 0.68$; $P < 0.001$) and inversely with eGFR ($r_s = -0.64$; $P < 0.001$), supporting an association between glycocalyx shedding and mildly reduced renal filtration. Liew et al. similarly found that biochemical markers of glycocalyx damage were highest in dialysis-dependent patients, followed by patients with chronic kidney disease and kidney transplant recipients, and were associated with endothelial dysfunction and the accumulation of uraemic toxins [13]. That study measured syndecan-1 and hyaluronan and included patients with more advanced kidney disease. In contrast, our findings indicate that circulating heparan sulfate may already differ substantially among patients with CHF whose eGFR remains ≥60 mL/min/1.73 m².

However, the relationship between glycocalyx integrity and renal function has not been consistent across all studies. Stougaard et al. observed altered sublingual glycocalyx-related measurements in patients with type 1 diabetes but found no independent association with eGFR or albuminuria [14]. This discrepancy may reflect differences in the study populations and assessment methods. Sublingual imaging provides an indirect structural estimate of glycocalyx dimensions, whereas circulating heparan sulfate reflects the biochemical shedding of a specific glycocalyx constituent. These methods may therefore characterize related but not identical aspects of endothelial injury.

Systemic inflammatory activity was also associated with circulating heparan sulfate. Interleukin-6 (IL-6) concentrations were 9.9 ± 0.3 pg/mL in Group I, 8.3 ± 0.4 pg/mL in Group II, and 2.5 ± 0.2 pg/mL in controls. Tumor necrosis factor-α (TNF-α) concentrations were 11.7 ± 0.5, 10.4 ± 0.5, and 2.12 ± 0.15 pg/mL, respectively. Both inflammatory markers were elevated in the CHF groups compared with controls, although only IL-6 differed significantly between Group I and Group II. Heparan sulfate correlated positively with IL-6 in Group I and Group II ($r_s = 0.53$ and 0.47, respectively; both $P < 0.001$) and with TNF-α ($r_s = 0.49$ and 0.45, respectively; both $P < 0.001$).

These findings are consistent with experimental evidence indicating that IL-6 may contribute to endothelial glycocalyx injury and that inhibition of IL-6 signaling can attenuate glycocalyx damage [15]. However, those findings were obtained in severe acute inflammatory conditions and cannot be directly extrapolated to clinically stable CHF. Moreover, the cross-sectional associations observed in our study do not establish whether systemic inflammation precedes glycocalyx degradation, results from it, or develops concurrently through shared pathophysiological mechanisms.

Cardiac stress and diastolic hemodynamic burden were more pronounced in patients with mildly reduced eGFR. N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were 1256.5 ± 14.64 pg/mL in Group I, 1027.4 ± 15.44 pg/mL in Group II, and 260.27 ± 8.50 pg/mL in controls. Heparan sulfate correlated positively with NT-proBNP in Group I and Group II ($r_s = 0.62$ and 0.54, respectively; both $P < 0.001$).

Left ventricular ejection fraction (LVEF) was 49.6 ± 1.6% in Group I and 51.3 ± 1.2% in Group II, with no significant difference between the two CHF groups, although both values were lower than the control value of 62.2 ± 0.44%. In contrast, E/e′ differed markedly among the groups: 15.2 ± 0.25 in Group I, 10.5 ± 0.21 in Group II, and 7.24 ± 0.07 in controls (all pairwise $P < 0.001$). Heparan sulfate correlated positively with E/e′ (Group I: $r_s = 0.52$, $P < 0.001$; Group II: $r_s = 0.45$, $P < 0.01$) and inversely with LVEF (Group I: $r_s = -0.48$, $P < 0.001$; Group II: $r_s = -0.41$, $P < 0.01$). The absence of a significant difference in LVEF between the CHF groups, despite the higher E/e′ in Group I, suggests that circulating heparan sulfate may be more closely associated with elevated left ventricular filling pressure and diastolic burden than with mean systolic function alone. This interpretation remains exploratory because the relative strengths of these associations were not formally compared.

The relationship between glycocalyx degradation and cardiac hemodynamic abnormalities is supported by the findings of Lagrange et al., who evaluated glycocalyx markers across the STANISLAS, MEDIA-DHF, and BIOSTAT-CHF cohorts. Perlecan was elevated in patients with heart failure with preserved ejection fraction and was associated with E/e′ and left atrial volume index. Patients in the highest perlecan tertile also had greater risks of cardiovascular hospitalization or death in the MEDIA-DHF and BIOSTAT-CHF cohorts [16]. Although perlecan and heparan sulfate are different analytes, their concordant associations with E/e′ support a potential relationship between endothelial glycocalyx degradation and diastolic dysfunction.

Kim et al. evaluated serum glycocalyx markers in individuals without heart failure and in patients with stable chronic or acute decompensated heart failure with reduced ejection fraction. Heparan sulfate concentrations were highest in patients with acute decompensated heart failure, and each doubling of heparan sulfate was independently associated with a 31.5% increase in the relative hazard of all-cause mortality [9].

The absolute heparan sulfate concentrations reported by Kim et al. were substantially higher than those observed in our study. Direct comparison is inappropriate because of differences in assay characteristics, calibration, study population, and heart failure phenotype. Nevertheless, both studies support an association between higher circulating heparan sulfate and greater biological or clinical heart failure burden. Whereas Kim et al. observed the highest concentrations during acute decompensation, our clinically stable CHF cohort demonstrated the highest concentrations among patients with mildly reduced eGFR, higher NT-proBNP, and increased E/e′.

Receiver operating characteristic analysis yielded an area under the curve of 0.968 (95% confidence interval, 0.934–1.000; $P < 0.001$) for distinguishing patients with an eGFR of 60–89 mL/min/1.73 m² from those with an eGFR ≥90 mL/min/1.73 m². A cutoff of ≥191.0 ng/mL provided 88.0% sensitivity and 94.0% specificity. These findings suggest that heparan sulfate may have discriminatory value for identifying mildly reduced renal filtration among patients with CHF. However, the cutoff was derived and evaluated in the same cohort and was not internally or externally validated. It should therefore be considered exploratory rather than an established diagnostic threshold. Whether heparan sulfate provides incremental information beyond cystatin C, NT-proBNP, and conventional clinical parameters requires evaluation using multivariable models and independent validation cohorts.

Clinical implications and study limitations

The integrated assessment of circulating heparan sulfate in relation to renal filtration, systemic inflammation, neurohormonal activation, and cardiac hemodynamics represents an important aspect of this study. Previous clinical investigations have predominantly evaluated glycocalyx degradation in acute heart failure or advanced kidney disease. Our findings extend these observations by showing substantial differences in circulating heparan sulfate among clinically stable patients with CHF whose eGFR remained ≥60 mL/min/1.73 m².

From a clinical perspective, circulating heparan sulfate may provide complementary information about endothelial glycocalyx injury in patients with CHF. Its associations with cystatin C, NT-proBNP, and E/e′ suggest potential value as an integrative research biomarker reflecting interconnected renal, inflammatory, neurohormonal, and cardiac abnormalities. However, heparan sulfate cannot currently replace established renal or cardiac biomarkers, and its incremental clinical value remains unproven.

Several limitations should be acknowledged. First, the observational design precludes conclusions regarding causality or the temporal sequence of glycocalyx degradation, inflammation, cardiac dysfunction, and renal functional alterations. Second, the relatively small sample size and recruitment from two clinical institutions in a single city may limit the generalizability of the findings. Third, circulating heparan sulfate reflects systemic glycocalyx shedding and cannot identify its specific cardiac, renal, or vascular origin. Fourth, albuminuria, direct glycocalyx imaging, heparanase activity, oxidative stress markers, and tubular injury biomarkers were not assessed. In addition, because eGFR was calculated from cystatin C, the associations of heparan sulfate with cystatin C and cystatin C-based eGFR should not be interpreted as independent findings. Fifth, the potential effects of medical therapy, comorbidities, and other confounding variables were not evaluated using multivariable regression. Finally, the receiver operating characteristic cutoff was derived and evaluated in the same cohort without internal resampling or external validation and may therefore overestimate discriminatory performance. Larger prospective multicenter studies incorporating multivariable analysis and independent validation are required to confirm these findings and determine whether heparan sulfate provides clinically meaningful information beyond conventional cardiorenal biomarkers.

Conclusions

Circulating heparan sulfate concentrations were markedly elevated in patients with chronic heart failure and were highest among those with mildly reduced cystatin C-based eGFR. Higher heparan sulfate concentrations were associated with reduced renal filtration, increased systemic inflammatory and neurohormonal activity, lower left ventricular ejection fraction,

and higher estimated left ventricular filling pressure. Receiver operating characteristic analysis also indicated potential discriminatory value for distinguishing mildly reduced from preserved eGFR. These findings suggest that circulating heparan sulfate may represent a candidate integrative biomarker of endothelial glycocalyx injury within the cardiorenal continuum. However, larger prospective multicenter studies incorporating multivariable analysis and external validation are required before its potential diagnostic or risk-stratification value can be established in clinical practice.

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