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DIAGNOSTIC VALUE OF SYNDECAN-1 FOR EARLY DETECTION OF RENAL DYSFUNCTION AND ITS ASSOCIATION WITH CARDIAC HEMODYNAMIC AND BIOCHEMICAL PARAMETERS IN HEART FAILURE

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Abstract. Background. Renal dysfunction substantially worsens the prognosis of patients with heart failure (HF). Endothelial glycocalyx degradation has recently emerged as a key mechanism underlying cardiorenal syndrome, while syndecan-1 has gained attention as a circulating biomarker of endothelial injury. However, its relationship with renal dysfunction and cardiac hemodynamics in HF remains insufficiently characterized.

Objective. To evaluate the association between serum syndecan-1 concentrations and cystatin C-based renal function, cardiac hemodynamic parameters, inflammatory biomarkers, and to determine its diagnostic value for the early detection of renal dysfunction in patients with chronic heart failure (CHF).

Methods. This prospective observational study included 100 patients with New York Heart Association (NYHA) class II–III CHF and 32 age- and sex-matched healthy controls. Renal function was assessed using cystatin C-based estimated glomerular filtration rate (eGFR), and patients were stratified into two groups (eGFR 60–89 and ≥ 90 mL/min/1.73 m²). Serum syndecan-1, N-terminal pro-B-type natriuretic peptide (NT-proBNP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and echocardiographic parameters were evaluated. Correlation and receiver operating characteristic (ROC) analyses were performed.

Results. Serum syndecan-1 concentrations were significantly higher in patients with reduced renal function than in those with preserved renal function (103.3 ± 2.02 vs. 71.1 ± 0.55 ng/mL, $P < 0.001$). Syndecan-1 showed strong positive correlations with cystatin C ($r = 0.67$), IL-6 ($r = 0.58$), NT-proBNP ($r = 0.59$), and E/e' ratio ($r = 0.44$), and inverse correlations with eGFR ($r = -0.65$) and left ventricular ejection fraction ($r = -0.42$) (all $P < 0.01$). ROC analysis demonstrated excellent diagnostic performance for identifying early renal dysfunction (AUC=0.898), with an optimal cutoff value of 78.3 ng/mL, sensitivity of 88.0%, and specificity of 92.0%.

Conclusions. Syndecan-1 is strongly associated with renal impairment, endothelial injury, inflammation, and cardiac dysfunction in CHF. Its excellent diagnostic accuracy suggests that syndecan-1 may serve as a valuable adjunctive biomarker for the early detection of cardiorenal syndrome and improved risk stratification in patients with chronic heart failure.

Keywords: chronic heart failure; cardiorenal syndrome; syndecan-1; endothelial glycocalyx; cystatin C; renal dysfunction; NT-proBNP; biomarkers.

Introduction.

Heart failure is a complex clinical syndrome characterized by high morbidity, frequent hospitalizations, and increased mortality among cardiovascular diseases. Despite substantial advances in the management of HF over recent years, progressive deterioration of renal function remains closely associated with adverse clinical outcomes, increased rates of hospitalization, and reduced quality of life. Renal dysfunction is a key pathophysiological component of cardiorenal syndrome, and its early detection remains one of the major challenges in contemporary cardiology

and nephrology. In this context, the identification of novel biomarkers that reflect the pathophysiological interplay between the heart and kidneys has attracted considerable scientific and clinical interest [2,3,4,14,15].

Assessment of renal function in patients with HF is traditionally based on serum creatinine concentration and the estimated glomerular filtration rate (eGFR) derived from creatinine-based equations. However, the diagnostic sensitivity of creatinine is limited, particularly during the early stages of renal function decline, because its concentration is substantially influenced by age, sex, muscle mass, nutritional status, and other non-renal factors. In contrast, cystatin C is a low-molecular-weight protein that is constitutively produced by all nucleated cells, freely filtered by the glomeruli, and almost completely reabsorbed and catabolized in the proximal tubules. Consequently, circulating cystatin C levels more accurately reflect even subtle changes in glomerular filtration. Accordingly, recent international guidelines recommend the use of cystatin C-based eGFR, either alone or in combination with creatinine, to improve the assessment of renal function and enable earlier stratification of cardiorenal risk in patients with HF. [1,9,14,15].

In recent years, increasing attention has been directed toward the role of endothelial dysfunction and microvascular injury in the pathogenesis of cardiorenal syndrome. The endothelial glycocalyx is a critical functional component of the vascular endothelium that plays a pivotal role in maintaining vascular permeability, mechanotransduction, nitric oxide bioavailability, regulation of inflammatory responses, and microvascular homeostasis. Degradation of the endothelial glycocalyx, primarily driven by oxidative stress and inflammation, promotes endothelial dysfunction, impairs tissue perfusion, and contributes to the progression of cardiorenal syndrome [7,10,11].

In recent years, increasing attention has been directed toward the role of endothelial dysfunction and microvascular injury in the pathogenesis of cardiorenal syndrome. The endothelial glycocalyx is a critical functional component of the vascular endothelium that plays a pivotal role in maintaining vascular permeability, mechanotransduction, nitric oxide bioavailability, regulation of inflammatory responses, and microvascular homeostasis. Degradation of the endothelial glycocalyx, primarily driven by oxidative stress and inflammation, promotes endothelial dysfunction, impairs tissue perfusion, and contributes to the progression of cardiorenal syndrome [15,16].

Nevertheless, comprehensive studies evaluating the relationship between syndecan-1, a circulating biomarker of endothelial glycocalyx degradation, and cystatin C-based renal function, NT-proBNP and intracardiac hemodynamic parameters in patients with chronic HF remain limited. In particular, the diagnostic performance of syndecan-1 for the early detection of renal dysfunction and its potential role as an early biomarker of cardiorenal syndrome have not yet been fully elucidated.

Therefore, the present study aimed to investigate the association of syndecan-1 with cystatin C-based renal function, NT-proBNP, and intracardiac hemodynamic parameters in patients with New York Heart Association (NYHA) class II–III chronic HF, as well as to evaluate its diagnostic value for the early detection of renal dysfunction.

Objective. The aim of this study was to evaluate the association between circulating syndecan-1, a biomarker of endothelial glycocalyx injury, and cystatin C-based estimated glomerular filtration rate (eGFR), intracardiac hemodynamic parameters, and renal function in patients with New York Heart Association (NYHA) class II–III chronic heart failure, and to determine its diagnostic value for the early detection of renal dysfunction.

Materials and Methods.

Study Design and Participants

This prospective, single-center, observational study was conducted between 2024 and 2025 at the Department of Internal Diseases, Family Medicine No. 2, Tashkent Medical University, and the National Medical Center.

A total of 100 patients with New York Heart Association (NYHA) class II–III chronic heart failure secondary to ischemic heart disease and/or arterial hypertension were enrolled. The control

group comprised 32 age- and sex-matched apparently healthy individuals without clinical evidence of heart failure or renal dysfunction.

The diagnosis of chronic HF was established according to the 2021 European Society of Cardiology (ESC) Guidelines and the 2023 Focused Update. Renal function was assessed using cystatin C-based estimated glomerular filtration rate (eGFR) calculated with the CKD-EPI Cystatin C equation. Accordingly, patients were stratified into two groups: Group I (eGFR 60–89 mL/min/1.73 m², n = 50) and Group II (eGFR ≥90 mL/min/1.73 m², n = 50).

Inclusion and Exclusion Criteria

Eligible participants were adults (≥18 years) with clinically stable New York Heart Association (NYHA) class II–III chronic heart failure and chronic kidney disease (CKD) categories G2–G5, classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline, who provided written informed consent prior to enrollment.

Patients were excluded if they had acute coronary syndrome, acute decompensated heart failure, acute kidney injury, active infectious or inflammatory diseases, autoimmune disorders, malignant neoplasms, severe hepatic insufficiency, or were pregnant or breastfeeding.

Clinical Assessment

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

Echocardiographic Assessment

Transthoracic echocardiography was performed in all patients according to the recommendations of the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). The following parameters were assessed: left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left atrial volume, left ventricular ejection fraction (LVEF), transmitral E and A wave velocities, tissue Doppler-derived e' velocity, and the E/e' ratio. Left ventricular diastolic function was evaluated according to current international recommendations.

Laboratory Measurements

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

Routine hematological and biochemical analyses were performed using standardized automated laboratory methods. Serum concentrations of creatinine, urea, electrolytes, lipid profile components, cystatin C, NT-proBNP, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and syndecan-1 (SDC-1), a biomarker of endothelial glycocalyx injury, were determined.

Serum concentrations of NT-proBNP, cystatin C, IL-6, and TNF-α were measured by enzyme-linked immunosorbent assay (ELISA) according to the manufacturers' instructions. NT-proBNP and IL-6 assays were performed using commercial kits supplied by Vector-Best (Novosibirsk, Russia), whereas TNF-α concentrations were quantified using a Mindray MR-96A microplate reader.

Serum syndecan-1 concentrations were determined using a commercially available Human Syndecan-1 ELISA Kit (DRG Instruments GmbH, Germany; REF: EIA-1299) based on a quantitative sandwich ELISA method, following the manufacturer's protocol. Optical density was measured at 450 ± 2 nm, and serum syndecan-1 concentrations were calculated from a standard calibration curve.

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.

Data distribution was assessed using the Shapiro–Wilk test. Normally distributed variables are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are expressed as median and interquartile range (IQR).

Between-group comparisons were performed using the independent-samples Student's *t*-test for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. Categorical variables were compared using Pearson's χ^2 test. Associations between continuous variables were evaluated using Spearman's rank correlation analysis.

The diagnostic performance of syndecan-1 for the early detection of renal dysfunction was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC), optimal cutoff value determined by the Youden index, sensitivity, and specificity were calculated. All statistical tests were two-sided, and a *P* value <0.05 was considered statistically significant.

Ethical Considerations

All participants received detailed information regarding the objectives of the study, study procedures, and the intended scientific use of the collected data before enrollment. Written informed consent was obtained from each participant prior to participation. The confidentiality of participants' personal information was strictly maintained, and all data were used exclusively for scientific research purposes.

Results

Baseline Clinical and Demographic Characteristics of the Study Population

A total of 100 patients with New York Heart Association (NYHA) class II–III chronic heart failure secondary to ischemic heart disease and arterial hypertension, together with 32 control participants, were included in the study. Based on cystatin C-derived estimated glomerular filtration rate (eGFR), patients were stratified into two groups: 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 summarized in Table 1.

Table 1.

Characteristics of the Study Cohort Baseline Clinical and Demographic Characteristics of the Study Population

Variable	Group I (eGFR 60–89 mL/min/1.73 m ²)(<i>n</i> =50)	Group II (eGFR ≥90 mL/min/1.73 m ²)(<i>n</i> =50)	Control Group(<i>n</i> =32)	<i>P</i> value / χ^2
Age, years	67.98 ± 1.3	65.0 ± 1.5	65.9 ± 0.18	<i>P</i> 1>0.05; <i>P</i> 2>0.05; <i>P</i> 3>0.05
Sex: Male	20 (40.0%)	20 (40.0%)	14 (43.7%)	χ^2 1=0.11; <i>P</i> 1>0.05; χ^2 2=0.11; <i>P</i> 2>0.05; χ^2 3=0.00; <i>P</i> 3>0.05
Sex: Female	30 (60.0%)	30 (60.0%)	18 (56.2%)	
Body mass index (BMI), kg/m ²	28.8 ± 0.7	28.3 ± 0.8	26.99 ± 0.48	<i>P</i> 1>0.05; <i>P</i> 2>0.05; <i>P</i> 3>0.05
Blood pressure, systolic (mmHg)	135.2 ± 2.8	139.1 ± 2.8	128.2 ± 2.6	<i>P</i> 1>0.05; <i>P</i> 2>0.05; <i>P</i> 3>0.05
Blood pressure, diastolic (mmHg)	83.8 ± 1.2	83.5 ± 1.4	78.43 ± 1.25	<i>P</i> 1>0.05; <i>P</i> 2>0.05; <i>P</i> 3>0.05

Obesity, n (%)	14 (28%)	17 (34%)	6 (18.75%)	$\chi^2_1=0.92$; P1>0.05; $\chi^2_2=2.20$; P2>0.05; $\chi^2_3=0.44$; P3>0.05
Family history, n (%)	27 (54%)	19 (38%)	10 (31.25%)	$\chi^2_1=4.24$; P1<0.05; $\chi^2_2=0.38$; P2>0.05; $\chi^2_3=2.57$; P3>0.05

Notes: eGFR, estimated glomerular filtration rate; BMI, body mass index. P1: Group I vs Group II; P2: Group I vs Control; P3: Group II vs Control.

According to the data presented in Table 1, no statistically significant differences were observed among Groups I and II and the control group with respect to age, sex distribution, body mass index (BMI), or blood pressure (all $P > 0.05$).

Analysis of cardiovascular risk factors demonstrated that a positive family history was more prevalent in Group I than in the control group (54.0% vs. 31.3%; $\chi^2 = 4.24$, < 0.05). However, no significant differences were observed between Groups I and II or between Group II and the control group ($P > 0.05$). Likewise, the prevalence of obesity was comparable across all three groups, with no statistically significant between-group differences (all $P > 0.05$).

Overall, the patient and control groups were well matched with respect to their baseline clinical and demographic characteristics.

In our study, biochemical parameters and renal functional status were comparatively evaluated according to the estimated glomerular filtration rate (eGFR).

Table 2.

Biochemical parameters in patients with NYHA class II–III chronic heart failure according to estimated glomerular filtration rate (eGFR)

Parameter	Group I (eGFR 60–90 mL/min/1.73 m ²)(n=50)	Group II (eGFR >90 mL/min/1.73 m ²)(n=50)	Control group(n=32)	P value
Alanine aminotransferase (ALT), U/L	22.4 ± 1.05	23.4 ± 0.99	23.3 ± 0.57	p1>0.05; p2>0.05; p3>0.05
Aspartate aminotransferase (AST), U/L	23.4 ± 1.6	24.1 ± 1.6	21.8 ± 0.42	p1>0.05; p2>0.05; p3>0.05
Total protein, g/L	69.4 ± 0.7	69.2 ± 0.8	73.9 ± 0.34	p1<0.01; p2<0.01; p3>0.05
Total cholesterol, mmol/L	4.3 ± 0.1	4.5 ± 0.1	4.9 ± 0.03	p1<0.05; p2<0.05; p3>0.05
High-density lipoprotein (HDL), mmol/L	1.2 ± 0.03	1.3 ± 0.02	1.41 ± 0.01	p1<0.05; p2<0.05; p3>0.05

Low-density lipoprotein (LDL), mmol/L	2.96 ± 0.06	3.17 ± 0.07	2.7 ± 0.12	$p1 < 0.05$; $p2 < 0.001$; $p3 < 0.05$
Triglycerides, mmol/L	1.8 ± 0.03	1.8 ± 0.02	1.3 ± 0.03	$p1 < 0.01$; $p2 < 0.01$; $p3 > 0.05$
Cystatin C, mg/L	1.05 ± 0.02	0.76 ± 0.01	0.70 ± 0.03	$p1 < 0.001$; $p2 < 0.01$; $p3 < 0.001$
eGFR calculated using cystatin C, mL/min/1.73 m ²	72.9 ± 1.3	101.8 ± 1.3	106.8 ± 1.5	$p1 < 0.001$; $p2 < 0.05$; $p3 < 0.001$

Note: p1 indicates the significance of differences between Group I and the control group; p2 indicates the significance of differences between Group II and the control group; p3 indicates the significance of differences between Group I and Group II.

According to the data presented in Table 2, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels did not differ significantly among Groups I and II and the control group (all $P > 0.05$).

Total serum protein concentrations were comparable between Groups I and II ($P > 0.05$); however, both patient groups exhibited significantly lower values than the control group ($P < 0.01$).

Analysis of the lipid profile demonstrated no significant differences between Groups I and II in total cholesterol, high-density lipoprotein cholesterol (HDL-C), or triglyceride concentrations (all $P > 0.05$). Nevertheless, these parameters were significantly lower in both patient groups than in the control group ($P < 0.05$). In contrast, low-density lipoprotein cholesterol (LDL-C) levels were significantly higher in Group II than in Group I (3.17 ± 0.07 vs. 2.96 ± 0.06 mmol/L, $p < 0.05$) and also differed significantly from those observed in the control group.

Analysis of renal function markers demonstrated that serum cystatin C concentrations were significantly higher in Group I than in Group II (1.05 ± 0.02 vs. 0.76 ± 0.01 mg/L, $P < 0.001$). Accordingly, cystatin C-based estimated glomerular filtration rate (eGFR) was significantly lower in Group I than in Group II (72.9 ± 1.3 vs. 101.8 ± 1.3 mL/min/1.73 m², $P < 0.001$). Compared with the control group, both patient groups also exhibited significant differences in serum cystatin C concentrations and eGFR.

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).

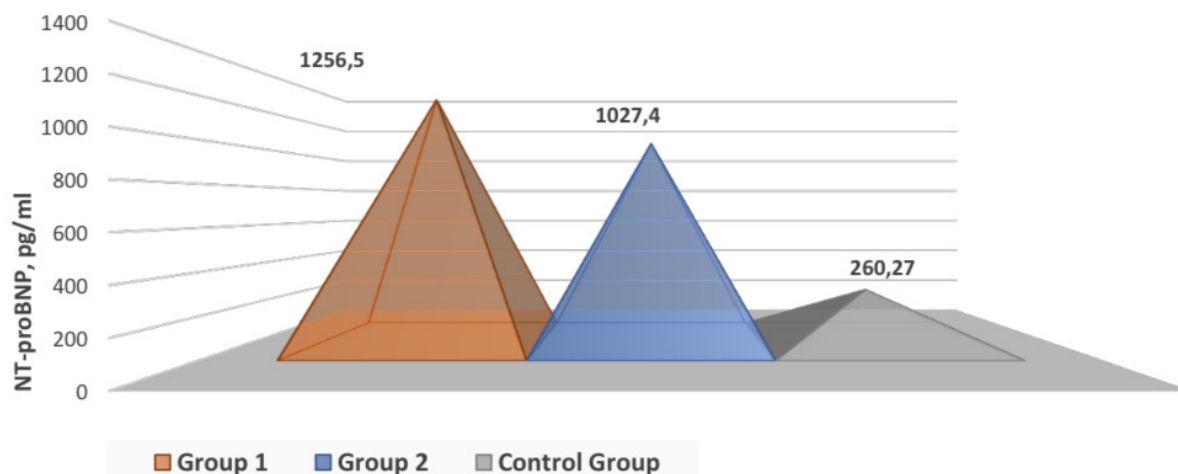


Figure 1. Comparison of Serum NT-proBNP Concentrations Among the Study Groups

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 ($P_3 < 0.001$).

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).

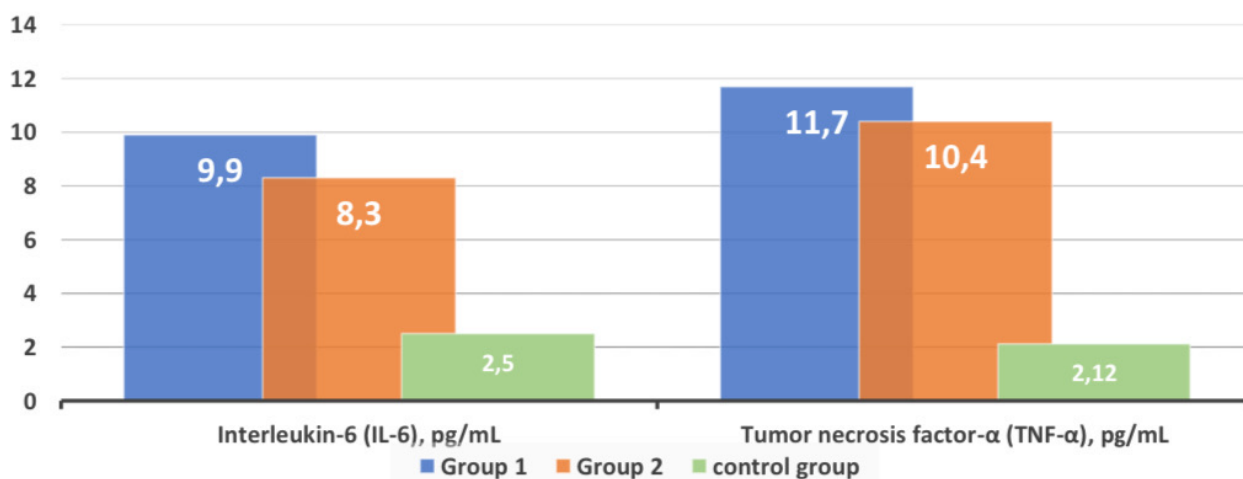


Figure 2. Comparison of Serum Interleukin-6 (IL-6) and Tumor Necrosis Factor- α (TNF- α) Levels in Patients with Heart Failure Stratified by Estimated Glomerular Filtration Rate

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 ($P > 0.05$).

Serum concentrations of syndecan-1, a biomarker of endothelial glycocalyx injury, were compared among the study groups (Figure 3).

The mean serum syndecan-1 concentration was 103.3 ± 2.02 ng/mL in Group I, 71.1 ± 0.55 ng/mL in Group II, and 22.05 ± 1.10 ng/mL in the control group. Syndecan-1 levels were significantly higher in both patient groups than in the control group (both $P < 0.001$). Furthermore, serum syndecan-1 concentrations were significantly higher in Group I than in Group II ($P < 0.001$) (Figure 3).

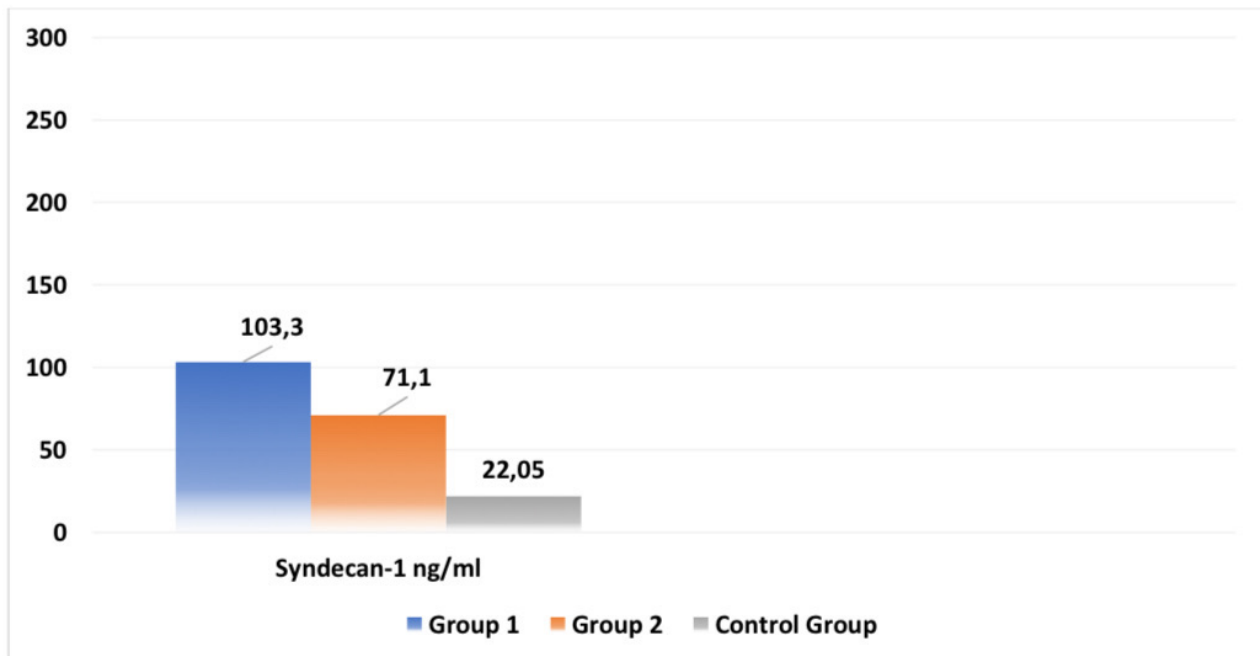


Figure 3. Comparison of Serum Heparan Sulfate and Syndecan-1 Levels in Patients with Chronic Heart Failure Stratified by Estimated Glomerular Filtration Rate

Note: For both biomarkers, serum concentrations were significantly higher in Groups I and II than in the control group ($P_1 < 0.001$ and $P_2 < 0.001$, respectively). In addition, both heparan sulfate and syndecan-1 levels were significantly higher in Group I than in Group II ($P_3 < 0.001$).

According to the analysis, the mean serum syndecan-1 concentration was 103.3 ± 2.02 ng/mL in Group I, 71.1 ± 0.55 ng/mL in Group II, and 22.05 ± 1.10 ng/mL in the control group. Serum syndecan-1 levels were significantly higher in both patient groups than in the control group (both $P < 0.001$). Furthermore, Group I exhibited significantly higher serum syndecan-1 concentrations than Group II ($P < 0.001$).

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 m ²)(n=50)	Group II (eGFR ≥90 mL/min/1.73 m ²)(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	P ₁ >0.05; P ₂ >0.05; P ₃ >0.05
Left ventricular end-systolic diameter, cm	3.97 ± 0.13	3.83 ± 0.09	3.30 ± 0.03	P ₁ <0.001; P ₂ <0.001; P ₃ >0.05
Left ventricular end-diastolic volume, mL	129.1 ± 5.1	128.1 ± 7.2	114.9 ± 1.31	P ₁ <0.05; P ₂ <0.05; P ₃ >0.05
Left ventricular end-systolic volume, mL	66.5 ± 4.6	66.7 ± 5.9	41.7 ± 0.65	P ₁ <0.001; P ₂ <0.001; P ₃ >0.05
Left ventricular ejection fraction (LVEF), %	49.6 ± 1.6	51.3 ± 1.2	62.2 ± 0.44	P ₁ <0.001; P ₂ <0.001; P ₃ >0.05
E/A ratio	0.9 ± 0.04	0.9 ± 0.07	1.04 ± 0.01	P ₁ <0.05; P ₂ <0.05; P ₃ >0.05
E/e' ratio	15.2 ± 0.25	10.5 ± 0.21	7.24 ± 0.07	P ₁ <0.001; P ₂ <0.001; P ₃ <0.001
Interventricular septal thickness, cm	1.2 ± 0.02	1.2 ± 0.02	0.97 ± 0.11	P ₁ <0.05; P ₂ <0.05; P ₃ >0.05
Left ventricular posterior wall thickness, cm	1.17 ± 0.02	1.18 ± 0.02	0.96 ± 0.10	P ₁ <0.05; P ₂ <0.05; P ₃ >0.05
Left ventricular mass, g	261.4 ± 4.5	261.9 ± 4.6	180.03 ± 1.61	P ₁ <0.001; P ₂ <0.001; P ₃ >0.05

Note: P₁ indicates the comparison between Group I and the control group; P₂ indicates the comparison between Group II and the control group; and P₃ 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 $P < 0.001$).

To investigate the relationship between endothelial glycocalyx injury and renal dysfunction, correlation analyses were performed between serum syndecan-1 concentrations and renal function markers (cystatin C and cystatin C-based estimated glomerular filtration rate [eGFR]). In addition, correlations with inflammatory biomarkers (IL-6 and TNF- α), the cardiac biomarker NT-proBNP, and echocardiographic parameters (left ventricular ejection fraction [LVEF] and E/e' ratio) were evaluated to determine whether endothelial glycocalyx degradation is associated with systemic inflammation, cardiac dysfunction, and cardiorenal interactions in patients with chronic heart failure.

Table 4.
Correlation Analysis Between Serum Syndecan-1 and Clinical, Biochemical, Inflammatory, and Echocardiographic Parameters in Patients with Chronic Heart Failure

Variable	Group I (eGFR 60–89)r	P value	Group II (eGFR ≥ 90)r	P value
Cystatin C	0.67	<0.001	0.50	<0.001
eGFR	-0.65	<0.001	-0.48	<0.001
Interleukin-6 (IL-6)	0.58	<0.001	0.47	<0.001
Tumor necrosis factor- α (TNF- α)	0.44	<0.001	0.40	<0.001
NT-proBNP	0.59	<0.001	0.57	<0.001
Left ventricular ejection fraction (LVEF)	-0.42	<0.01	-0.40	<0.01
E/e' ratio	0.44	<0.01	0.44	<0.01

As presented in Table 4, serum syndecan-1 showed significant correlations with renal function, inflammatory biomarkers, cardiac biomarkers, and echocardiographic parameters in both study groups.

Among renal function markers, syndecan-1 demonstrated a strong positive correlation with serum cystatin C in both Group I ($r = 0.67$, $P < 0.001$) and Group II ($r = 0.50$, $P < 0.001$). Conversely, syndecan-1 was inversely correlated with cystatin C-based estimated glomerular filtration rate (eGFR), with a stronger association observed in Group I ($r = -0.65$, $P < 0.001$) than in Group II ($r = -0.48$, $P < 0.001$).

Significant positive correlations were also identified between syndecan-1 and inflammatory biomarkers. Syndecan-1 correlated positively with IL-6 in Group I ($r = 0.58$, $P < 0.001$) and Group II ($r = 0.47$, $P < 0.001$). Similarly, positive correlations were observed between syndecan-1 and TNF- α in Group I ($r = 0.44$, $P < 0.001$) and Group II ($r = 0.40$, $P < 0.001$).

With respect to cardiac biomarkers, syndecan-1 demonstrated significant positive correlations with NT-proBNP in both Group I ($r = 0.59$, $P < 0.001$) and Group II ($r = 0.57$, $P < 0.001$), indicating that increasing endothelial glycocalyx injury was associated with greater cardiac wall stress and neurohormonal activation.

Correlation analysis of echocardiographic parameters revealed significant inverse associations between syndecan-1 and left ventricular ejection fraction (LVEF) in Group I ($r = -0.42$, $P < 0.01$) and Group II ($r = -0.40$, $P < 0.01$). In contrast, syndecan-1 exhibited significant positive correlations with the E/e' ratio in both Group I ($r = 0.44$, $P < 0.01$) and Group II ($r = 0.44$, $P < 0.01$), suggesting that higher circulating syndecan-1 concentrations were associated with elevated left ventricular filling pressures and impaired diastolic function.

ROC Analysis

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the investigated biomarkers for identifying renal dysfunction (eGFR 60–89 mL/min/1.73 m²) in patients with chronic heart failure (Table 5).

Table 5.

Diagnostic Performance of Biomarkers for Detecting Renal Dysfunction in Patients with Chronic Heart Failure (ROC Analysis)

Biomarker	AUC	Optimal cutoff	Sensitivity (%)	Specificity (%)
Syndecan-1	0.898	78.3 ng/mL	88.0	92.0
NT-proBNP	0.945	1196.1 pg/mL	78.0	94.0
Interleukin-6 (IL-6)	0.756	9.1 pg/mL	72.0	68.0
Tumor necrosis factor- α (TNF- α)	0.601	10.8 pg/mL	58.0	60.0

Note: AUC, area under the receiver operating characteristic curve; optimal cutoff determined using the Youden index.

ROC curve analysis demonstrated that NT-proBNP exhibited the highest diagnostic performance for identifying renal dysfunction, with an AUC of 0.945. The optimal cutoff value was 1196.1 pg/mL, providing a sensitivity of 78.0% and a specificity of 94.0%.

Syndecan-1 also demonstrated excellent diagnostic performance, with an AUC of 0.898. The optimal cutoff value was 78.3 ng/mL, corresponding to a sensitivity of 88.0% and a specificity of 92.0%.

Among the inflammatory biomarkers, IL-6 showed moderate diagnostic accuracy (AUC = 0.756), with an optimal cutoff value of 9.1 pg/mL, a sensitivity of 72.0%, and a specificity of 68.0%. In contrast, TNF- α demonstrated relatively poor diagnostic performance, with an AUC of 0.601.

Discussion.

The principal finding of the present study is that serum syndecan-1, a circulating biomarker of endothelial glycocalyx degradation, is closely associated with early renal dysfunction, cardiac structural and functional remodeling, and neurohormonal activation in patients with New York Heart Association (NYHA) class II–III chronic heart failure. Our results demonstrated that patients with mildly impaired renal function (eGFR 60–89 mL/min/1.73 m²) exhibited significantly higher serum syndecan-1 concentrations than those with preserved renal function (103.3 ± 2.02 vs. 71.1 ± 0.55 ng/mL, $P < 0.001$). These findings suggest that endothelial glycocalyx injury may occur before clinically apparent deterioration of renal function becomes evident. Consequently, the endothelial glycocalyx should be regarded as a dynamic structure that reflects early pathophysiological alterations during the progression of chronic heart failure, rather than merely a consequence of advanced cardiovascular or renal injury [11,12].

In the present study, serum syndecan-1 demonstrated a strong positive correlation with cystatin C ($r = 0.67$, $P < 0.001$) and a strong inverse correlation with eGFR ($r = -0.65$, $P < 0.001$). These findings indicate that endothelial glycocalyx degradation is closely associated with impaired glomerular filtration capacity. Notably, elevated serum syndecan-1 concentrations were also observed in patients with relatively preserved renal function, suggesting that endothelial injury may precede

alterations detectable by conventional laboratory markers of renal function. This observation supports the emerging concept that endothelial glycocalyx degradation represents an early pathophysiological event in the development of cardiorenal syndrome [11].

Furthermore, serum syndecan-1 demonstrated a moderate positive correlation with NT-proBNP ($r = 0.59$, $P < 0.001$), a significant inverse correlation with LVEF ($r = -0.42$, $P < 0.01$), and a positive correlation with the E/e' ratio ($r = 0.44$, $P < 0.01$). These findings indicate that endothelial glycocalyx degradation is associated not only with renal dysfunction but also with myocardial remodeling, diastolic dysfunction, and increased cardiac hemodynamic load. Therefore, syndecan-1 should be considered not merely as a biomarker of endothelial injury but also as an integrative biomarker reflecting the complex pathophysiological interplay between the heart and the kidneys. This interpretation is consistent with recent evidence highlighting the central role of endothelial glycocalyx dysfunction in the pathogenesis of CHF [7,11,15].

In the present study, ROC curve analysis demonstrated the high diagnostic performance of syndecan-1 for identifying early renal dysfunction, with an area under the curve (AUC) of 0.898. These findings suggest that syndecan-1 may serve as a promising adjunctive biomarker that complements currently available laboratory markers for the early assessment of renal dysfunction in patients with CHF. Nevertheless, prospective multicenter studies involving larger and more diverse populations are warranted to validate these findings externally and to further establish the clinical utility of syndecan-1 in routine cardiorenal risk assessment.

In the present study, serum syndecan-1 concentrations demonstrated a strong positive correlation with cystatin C ($r = 0.67$, $P < 0.001$) and a strong inverse correlation with eGFR ($r = -0.65$, $P < 0.001$). These findings indicate that endothelial glycocalyx injury is closely associated with the earliest stages of renal function decline. Moreover, our results support the concept that endothelial glycocalyx degradation is not merely a consequence of cardiorenal syndrome but may represent one of its key pathophysiological mechanisms [16,18].

The endothelial glycocalyx is a complex proteoglycan–glycosaminoglycan matrix that covers the luminal surface of the vascular endothelium and plays a pivotal role in mechanotransduction, nitric oxide (NO) bioavailability, regulation of capillary permeability, and maintenance of endothelial barrier integrity. Under conditions of oxidative stress, persistent inflammatory cytokine activation, and chronic neurohormonal stimulation, the glycocalyx undergoes degradation, leading to the shedding of syndecan-1, its principal transmembrane proteoglycan, into the circulation. Consequently, elevated circulating syndecan-1 concentrations are considered one of the most sensitive biomarkers of endothelial injury [2,3,5].

Notably, serum syndecan-1 concentrations remained significantly higher than those in the control group even among patients with relatively preserved renal function ($\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$). This finding suggests that endothelial injury may develop before abnormalities become detectable by conventional laboratory indices of renal function. Therefore, relying solely on serum creatinine or estimated glomerular filtration rate may be insufficient for identifying the earliest stages of cardiorenal syndrome. In this context, the combined assessment of cystatin C and biomarkers of endothelial glycocalyx injury may improve the early detection of renal dysfunction [9].

In the present study, serum syndecan-1 concentrations, a biomarker of endothelial glycocalyx degradation, were significantly higher in patients with impaired renal function than in those with preserved renal function (103.3 ± 2.02 vs. $71.1 \pm 0.55 \text{ ng/mL}$, $P < 0.001$). Furthermore, syndecan-1 demonstrated a strong positive correlation with cystatin C ($r = 0.67$, $P < 0.001$) and a strong inverse correlation with estimated glomerular filtration rate (eGFR) ($r = -0.65$, $P < 0.001$). These findings indicate that endothelial glycocalyx degradation occurs during the earliest stages of renal dysfunction and support the concept proposed by Catherine A. and et al. which highlights the pivotal role of the endothelial glycocalyx in regulating microvascular homeostasis, tissue perfusion, and organ function [7].

Serum syndecan-1 concentrations were also closely associated with markers of cardiac function. Specifically, syndecan-1 demonstrated moderate positive correlations with NT-proBNP in

both Group I ($r = 0.59$, $P < 0.001$) and Group II ($r = 0.57$, $P < 0.001$). In contrast, significant inverse correlations were observed between syndecan-1 and left ventricular ejection fraction (LVEF) (Group I: $r = -0.42$, $P < 0.01$; Group II: $r = -0.40$, $P < 0.01$). Furthermore, syndecan-1 was positively correlated with the E/e' ratio in both groups ($r = 0.44$, $P < 0.01$), indicating an association between endothelial glycocalyx degradation, elevated left ventricular filling pressures, and impaired diastolic function. Collectively, these findings suggest that endothelial glycocalyx injury is closely linked not only to renal dysfunction but also to myocardial remodeling and cardiac functional impairment. Similar conclusions were reported by Jeremy Lagrange and et al., who identified endothelial glycocalyx dysfunction as a central pathophysiological mechanism linking microvascular impairment with multiorgan injury in patients with chronic heart failure [11,16].

Our findings are also consistent with those reported by Radu S. Miftode, Ioana I. Costache, Andreea O. Petriș, et al. Although these authors demonstrated that elevated syndecan-1 concentrations were associated with greater heart failure severity and an unfavorable clinical prognosis, renal function in their study was assessed primarily using conventional biomarkers. In contrast, the present study evaluated renal function using cystatin C-based estimated glomerular filtration rate and simultaneously examined the relationships between endothelial glycocalyx degradation, renal function, neurohormonal activation, and cardiac hemodynamics. This comprehensive approach provides more robust evidence supporting the role of syndecan-1 as an integrative biomarker reflecting the complex pathophysiological interactions underlying the cardiorenal syndrome [15].

In the present study, syndecan-1 also demonstrated excellent diagnostic performance for the early identification of renal dysfunction. ROC curve analysis yielded the AUC of 0.898. The optimal cutoff value was 78.3 ng/mL, corresponding to a sensitivity of 88.0% and a specificity of 92.0%. These findings indicate that syndecan-1 possesses high discriminative ability for detecting early renal function impairment in patients with chronic heart failure. Although most previous studies have primarily focused on the prognostic significance of syndecan-1, its diagnostic utility for the early detection of renal dysfunction has received considerably less attention. Therefore, our findings expand the current body of evidence and provide a rationale for future large-scale multicenter prospective studies aimed at validating the clinical applicability of syndecan-1 as a diagnostic biomarker in patients with chronic heart failure.

In the present study, serum syndecan-1 concentrations demonstrated significant correlations with cystatin C ($r = 0.67$, $P < 0.001$), eGFR ($r = -0.65$, $P < 0.001$), NT-proBNP ($r = 0.59$, $P < 0.001$), LVEF ($r = -0.42$, $P < 0.01$), and the E/e' ratio ($r = 0.44$, $P < 0.01$). These findings indicate that syndecan-1 reflects not only endothelial dysfunction but also multiple pathophysiological components of the cardiorenal interaction, including renal impairment, neurohormonal activation, myocardial remodeling, and diastolic dysfunction. Therefore, the combined assessment of syndecan-1 together with NT-proBNP, cystatin C, and echocardiographic parameters may improve the early identification of patients at high cardiorenal risk.

Therefore, our findings suggest that syndecan-1 should not be regarded as a replacement for established laboratory and instrumental diagnostic methods but rather as a complementary biomarker that enhances their diagnostic value. Its combined assessment with cystatin C, NT-proBNP, and echocardiographic parameters may facilitate earlier identification of patients at increased cardiorenal risk and improve risk stratification in chronic heart failure.

Scientific Novelty, Clinical Implications, and Study Limitations

The findings of the present study further support the concept that endothelial glycocalyx degradation represents one of the earliest pathophysiological events in the development of cardiorenal syndrome in patients with CHF. Previous studies have primarily evaluated syndecan-1 in the settings of acute heart failure, sepsis, or acute kidney injury, whereas data regarding its association with early renal dysfunction in chronic heart failure remain limited [15,16]. Our results extend the existing evidence by demonstrating that syndecan-1 is also an important biomarker reflecting cardiorenal interactions in patients with chronic heart failure.

A major strength of the present study is the comprehensive evaluation of the relationships between syndecan-1 and multiple components of the cardiorenal syndrome. Specifically, syndecan-1 was significantly associated with renal function parameters, cardiac hemodynamic indices, and neurohormonal activation. These findings suggest that endothelial glycocalyx degradation represents a central pathophysiological link connecting cardiac and renal dysfunction. Accordingly, syndecan-1 may be considered an integrative biomarker of the cardiorenal system rather than merely a marker of isolated endothelial injury.

Of particular clinical importance, elevated serum syndecan-1 concentrations were observed even in patients with relatively preserved renal function ($\text{eGFR} > 90 \text{ mL/min/1.73 m}^2$), and significant correlations with both eGFR and NT-proBNP remained evident. These findings suggest that endothelial injury may precede detectable abnormalities in conventional laboratory markers and support the potential role of syndecan-1 as an early biomarker of cardiorenal dysfunction. This interpretation is consistent with the concept of endothelial glycocalyx dysfunction proposed by Lagrange J. et al. [10,11,17].

Several limitations of the present study should be acknowledged. First, this was a single-center study with a relatively limited sample size. Second, longitudinal changes in serum syndecan-1 during treatment were not evaluated, and its association with long-term clinical outcomes was not investigated. Third, direct visualization of the endothelial glycocalyx using dedicated imaging techniques, such as GlycoCheck, was not performed. Therefore, future multicenter prospective studies involving larger patient populations and longitudinal assessment of syndecan-1 during treatment are warranted to further validate and extend the present findings.

Overall, our findings demonstrate that endothelial glycocalyx degradation is an important early pathophysiological process underlying the development of renal dysfunction in patients with chronic heart failure. The close associations between syndecan-1, renal function, cardiac hemodynamics, and neurohormonal activation support its potential role as a promising biomarker for the early detection of cardiorenal syndrome and for improving cardiorenal risk stratification.

Conclusion.

The present study demonstrated that serum syndecan-1, a biomarker of endothelial glycocalyx degradation, is closely associated with renal dysfunction and cardiac hemodynamic abnormalities in patients with CHF. Significantly elevated syndecan-1 concentrations in patients with impaired renal function, together with its strong correlations with cystatin C, estimated glomerular filtration rate (eGFR), N-terminal pro-B-type natriuretic peptide (NT-proBNP), the E/e' ratio, and left ventricular ejection fraction (LVEF), indicate that endothelial glycocalyx degradation plays an important role in the development of cardiorenal syndrome.

These findings suggest that syndecan-1 may serve as a valuable biomarker for the early detection of renal dysfunction and may improve risk assessment in patients with CHF.

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