INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND DENTAL HEALTH
(ISSN: 2454-4191)
www.ijmsdh.org (2026)

Received: 07 Aug 2026
Revised: 21 Aug 2026
Accepted: 04 Sep 2026
Published: 26 Sep 2026

Volume 12 Issue 09, 2026
Page No - 253-265
DOI - 10.55640/ijmsdh-12-09-31

Article Citation: Gadaev, A., Rakhimova , M., & Muzaffarov, J. (2026). Kallikrein Activation and Its Association with NT-proBNP, Cystatin C–Derived eGFR, and Cardiac Remodeling in Patients with Chronic Heart Failure and Early Cardiorenal Syndrome. International Journal of Medical Science and Dental Health, 12(09), 253-265. https://doi.org/10.55640/ijmsdh-12-09-31

Kallikrein Activation and Its Association with NT-proBNP, Cystatin C–Derived eGFR, and Cardiac Remodeling in Patients with Chronic Heart Failure and Early Cardiorenal Syndrome

Abdigaffar Gadaev
Department of Internal Diseases in Family Medicine No. 2, Tashkent State Medical University, Tashkent 100109, Uzbekistan

Matluba Rakhimova
Department of Internal Diseases in Family Medicine No. 2, Tashkent State Medical University, Tashkent 100109, Uzbekistan

Jahongir Muzaffarov
Department of Internal Diseases, Alfraganus University, Tashkent 100190, Uzbekistan

Corresponding author
Jahongir Muzaffarov
Department of Internal Diseases, Alfraganus University
Tashkent, Uzbekistan
Email: muzaffarovjahongir93@gmail.com

Abstract

Background: Neurohormonal activation plays a central role in the progression of chronic heart failure (CHF) and in the development of cardiorenal syndrome (CRS). However, the role of the kallikrein–kinin system in early CRS remains insufficiently investigated.

Objective: To evaluate the association between serum kallikrein concentrations and NT-proBNP, cystatin C–derived estimated glomerular filtration rate (eGFR), and cardiac remodeling parameters in patients with New York Heart Association (NYHA) class III CHF and early CRS, and to assess the effect of guideline-directed medical therapy.

Methods: This study included 85 patients with NYHA class III CHF (mean age 66.7 ± 1.0 years) and 40 healthy controls. Patients were stratified according to left ventricular ejection fraction (LVEF ≥40% and <40%). Serum kallikrein, NT-proBNP, aldosterone, and cystatin C concentrations were measured, and eGFR was calculated using the CKD-EPI cystatin C equation. Correlations were evaluated, and biomarker dynamics were

reassessed after six months of four-component guideline-directed medical therapy.

Results: Patients with LVEF <40% had significantly lower kallikrein concentrations (448.6 ± 9.6 vs. 581.0 ± 10.7 ng/mL; P < 0.001), higher NT-proBNP concentrations (1123.3 ± 77.7 vs. 547.8 ± 46.5 pg/mL; P < 0.001), and lower eGFR (47.3 ± 0.8 vs. 56.2 ± 1.1 mL/min/1.73 m²; P < 0.001) than patients with LVEF ≥40%. Kallikrein correlated positively with eGFR (r = 0.55; P < 0.001) and inversely with NT-proBNP (r = −0.51; P < 0.001). After six months of therapy, kallikrein concentrations increased significantly and cardiac and renal parameters improved, with a more pronounced effect in patients receiving eplerenone.

Conclusion: Serum kallikrein is associated with both cardiac and renal function in early cardiorenal syndrome and may serve as a candidate biomarker of neurohormonal adaptation and therapeutic response in patients with chronic heart failure.

Keywords: chronic heart failure; cardiorenal syndrome; kallikrein; NT-probnp; cystatin C; estimated glomerular filtration rate; cardiac remodeling; mineralocorticoid receptor antagonists

Introduction

Background

Chronic heart failure (CHF) is one of the most common and progressive cardiovascular disorders and is associated with poor clinical outcomes, impaired quality of life, and high mortality. It is regarded as the final stage of the cardiovascular continuum and carries a markedly increased risk of death [1].

Reported prevalence estimates range from 1–2.6% in European countries to approximately 2.2% in the United States and 7–10% in the Russian Federation, and CHF accounts for up to 5% of all hospital admissions in Europe [1]. Comorbidities are common, occurring in 60–70% of patients with CHF and exceeding 90% in some series, and more than half of patients exhibit renal dysfunction [2–4].

The frequent coexistence of heart failure and kidney disease has been described as two parallel epidemics and has led to the concept of cardiorenal syndrome (CRS), characterized by simultaneous dysfunction of the heart and kidneys [5]. The mechanisms underlying CRS extend beyond reduced renal perfusion and venous congestion and include neurohormonal activation—particularly of the renin–angiotensin–aldosterone system (RAAS), the kallikrein–kinin system (KKS), and the sympathetic nervous system—together with endothelial dysfunction, inflammation, oxidative stress, and altered natriuretic peptide activity [6–9].

Among these mechanisms, the contribution of the kallikrein–kinin system to CRS associated with CHF remains insufficiently characterized [10]. Several studies suggest that the KKS counterbalances RAAS activation and may contribute to disease stabilization through vasodilatory, natriuretic, and antifibrotic effects [11]. Despite growing interest in the protective role of kallikrein in cardiac and renal dysfunction, important questions remain unresolved [12]. In particular, limited data are available regarding the interaction of kallikrein with natriuretic peptides and its behaviour in patients receiving mineralocorticoid receptor antagonists such as spironolactone or eplerenone as part of contemporary CHF therapy [13–16].

Mineralocorticoid receptor antagonists exert well-established cardiovascular and renal effects, and examining their influence in parallel with KKS activity may provide additional insight into the complex pathophysiology of CRS [17,18]. Similarly, sacubitril/valsartan and sodium–glucose cotransporter-2 (SGLT2) inhibitors modulate neurohormonal and renal pathways relevant to the cardiorenal continuum [19–23]. However, the associations of kallikrein with cystatin C–based eGFR, NT-proBNP, aldosterone, and echocardiographic indices of cardiac remodeling have not been comprehensively evaluated within a single clinical study [24,25].

Therefore, this study aimed to evaluate serum kallikrein concentrations in patients with NYHA class III CHF and early cardiorenal syndrome, stratified according to left ventricular ejection fraction, and to determine their associations with renal function, NT-proBNP, aldosterone, and cardiac remodeling parameters, as well as their dynamics after six months of guideline-directed medical therapy including either spironolactone or eplerenone.

Materials and Methods

Study Design and Participants

This study enrolled 85 patients with chronic heart failure (CHF) of New York Heart Association (NYHA) functional class III, developed on the background of ischemic heart disease and arterial hypertension. The mean age was 66.7 ± 1.1 years; 31 patients (36.4%) were men and 54 (63.6%) were women. All patients had confirmed cardiorenal syndrome with chronic kidney disease (CKD) stage I–II, and the estimated glomerular filtration rate (eGFR) calculated from serum creatinine averaged 79.3 ± 1.67 mL/min/1.73 m². The control group comprised 40 apparently healthy individuals (mean age 65.2 ± 5.4 years; 16 men [40%] and 24 women [60%]) who provided informed consent and showed no statistically significant demographic differences from the main group.

Patients were subsequently stratified into two subgroups according to left ventricular ejection fraction (LVEF): LVEF ≥40% (n = 56) and LVEF <40% (n = 29). Mean LVEF values were 52.7 ± 0.7% and 36.2 ± 0.3%, respectively (P < 0.001). Each subgroup was then divided into two equal treatment arms (Ia and Ib; IIa and IIb) according to the mineralocorticoid receptor antagonist prescribed.

Eligibility Criteria

Eligible participants were adults with clinically stable NYHA functional class III CHF secondary to ischemic heart disease and arterial hypertension, with cardiorenal syndrome and CKD stage I–II. Patients with acute coronary syndrome, acute decompensated heart failure, acute kidney injury, active infection or inflammation, or other severe intercurrent illness were not included.

Treatment Protocol and Follow-up

All patients received four-component guideline-directed medical therapy comprising a β-blocker (bisoprolol), sacubitril/valsartan, a mineralocorticoid receptor antagonist, and a sodium–glucose cotransporter-2 (SGLT2) inhibitor (empagliflozin). Patients in subgroups Ia and IIa received spironolactone, whereas patients in subgroups Ib and IIb received eplerenone in place of spironolactone. All participants underwent comprehensive clinical, laboratory, and instrumental evaluation at baseline and after six months of therapy.

Clinical and Instrumental Assessment

Demographic and clinical characteristics, anthropometric measurements, body mass index, cardiovascular risk factors, blood pressure, and heart rate were recorded for all participants. Evaluation at baseline and follow-up included general clinical tests (complete blood count, urinalysis, and blood glucose), electrocardiography, and transthoracic echocardiography.

Echocardiographic Assessment

Transthoracic echocardiography was performed using standard M-mode, two-dimensional, and Doppler techniques. The evaluated parameters included left ventricular end-diastolic and end-systolic diameters (LVEDD, LVESD), left ventricular end-diastolic and end-systolic volumes (EDV, ESV), left ventricular ejection fraction (LVEF), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), early (E) and late (A) transmitral diastolic flow velocities, and the E/A ratio.

Blood Sampling and Biochemical Measurements

Venous blood samples were obtained after an overnight fast. Routine biochemical parameters, including liver transaminases, bilirubin, urea, and creatinine, were measured using standard laboratory methods. Serum cystatin C was measured by immunoassay, and kallikrein, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and aldosterone concentrations were determined using commercially available immunoassay kits according to the manufacturers' instructions.

Estimation of Glomerular Filtration Rate

Cystatin C–based eGFR was calculated using the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C equation, with eGFR expressed in mL/min/1.73 m² and serum cystatin C in mg/L. Renal filtration status derived from cystatin C was used for the comparative and correlation analyses.

Statistical Analysis

Continuous variables are presented as mean ± standard error of the mean, and categorical variables as frequencies and percentages. Between-group comparisons of continuous variables were performed using the Student t-test or analysis of variance, as appropriate, and categorical variables were compared using the χ^2 test. Associations between serum kallikrein concentrations and biochemical and echocardiographic parameters were evaluated using correlation analysis, with correlation coefficients reported as r. Pre- and post-treatment comparisons were performed within each subgroup. A two-sided P value < 0.05 was considered statistically significant.

Ethics Approval and Informed Consent

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants were informed about the objectives, procedures, and intended scientific use of the collected data, and written informed consent was obtained before enrollment. Participant confidentiality was maintained throughout the study.

Results

Baseline clinical and demographic characteristics

A total of 85 patients with NYHA functional class III CHF and 40 control participants were included. The baseline clinical and demographic characteristics of the study groups are presented in Table 1.

Table 1. Baseline characteristics of the study population

No	Parameter	CHF, NYHA class III (n = 85)	Control group (n = 40)	P / χ^2
1	Age, years	66.74 ± 1.05	65.2 ± 5.4	> 0.05
2	Male, n (%)	31 (36.4)	16 (40.0)	χ^2 = 0.144; P > 0.05
3	Female, n (%)	54 (63.6)	24 (60.0)	
4	Body mass index, kg/m²	28.76 ± 0.60	22.32 ± 1.90	< 0.01
5	Systolic blood pressure, mmHg	135.9 ± 2.14	128.3 ± 3.67	> 0.05
6	Diastolic blood pressure, mmHg	83.1 ± 0.97	80.3 ± 3.48	> 0.05
7	Family history, n (%)	40 (47.0)	5 (12.5)	χ^2 = 14.1; P < 0.01
8	Smoking, n (%)	31 (36.5)	6 (15.0)	χ^2 = 6.017; P < 0.05
9	eGFR (creatinine), mL/min/1.73 m²	79.3 ± 1.67	91.5 ± 1.34	< 0.001

Data are presented as mean ± standard error of the mean or number (percentage). CHF, chronic heart failure; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate.

No statistically significant differences were observed between the CHF and control groups in age, sex distribution, or blood pressure. Patients with CHF had a higher body mass index, a more frequent family history of cardiovascular disease, a higher prevalence of smoking, and a lower creatinine-based eGFR than controls.

Biochemical and renal parameters

Selected biochemical parameters according to left ventricular ejection fraction (LVEF) are presented in Table 2.

Table 2. Biochemical parameters in patients with chronic heart failure stratified by left ventricular ejection fraction

No	Parameter	LVEF ≥40% (n = 56)	LVEF <40% (n = 29)	P
1	Cystatin C, mg/L	1.89 ± 0.04	1.97 ± 0.03	> 0.05
2	eGFR (CKD-EPI cystatin C), mL/min/1.73 m²	56.2 ± 1.1	47.3 ± 0.8	< 0.001

No	Parameter	LVEF ≥40% (n = 56)	LVEF <40% (n = 29)	P
3	Kallikrein, ng/mL	581.04 ± 10.74	448.62 ± 9.58	< 0.001
4	NT-proBNP, pg/mL	547.8 ± 46.5	1123.3 ± 77.7	< 0.001
5	Aldosterone, pg/mL	248.3 ± 16.6	368.3 ± 18.2	< 0.001

Data are presented as mean ± standard error of the mean. eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Cystatin C–based eGFR was significantly lower in patients with LVEF <40% than in those with LVEF ≥40% (47.3 ± 0.8 vs. 56.2 ± 1.1 mL/min/1.73 m²; P < 0.001). Serum kallikrein was markedly lower in the LVEF <40% group (448.62 ± 9.58 vs. 581.04 ± 10.74 ng/mL; P < 0.001), whereas NT-proBNP and aldosterone were significantly higher (1123.3 ± 77.7 vs. 547.8 ± 46.5 pg/mL and 368.3 ± 18.2 vs. 248.3 ± 16.6 pg/mL, respectively; both P < 0.001).

Correlations of kallikrein with renal filtration and neurohormonal activation

The relationship between serum kallikrein and cystatin C–based eGFR is shown in Figure 1. In patients with LVEF ≥40%, a moderate positive correlation was observed between kallikrein and eGFR (r = 0.55; P < 0.001), whereas the correlation was weaker in patients with LVEF <40% (r = 0.38; P < 0.05), suggesting a gradual attenuation of kallikrein–kinin system activity as renal function declines.

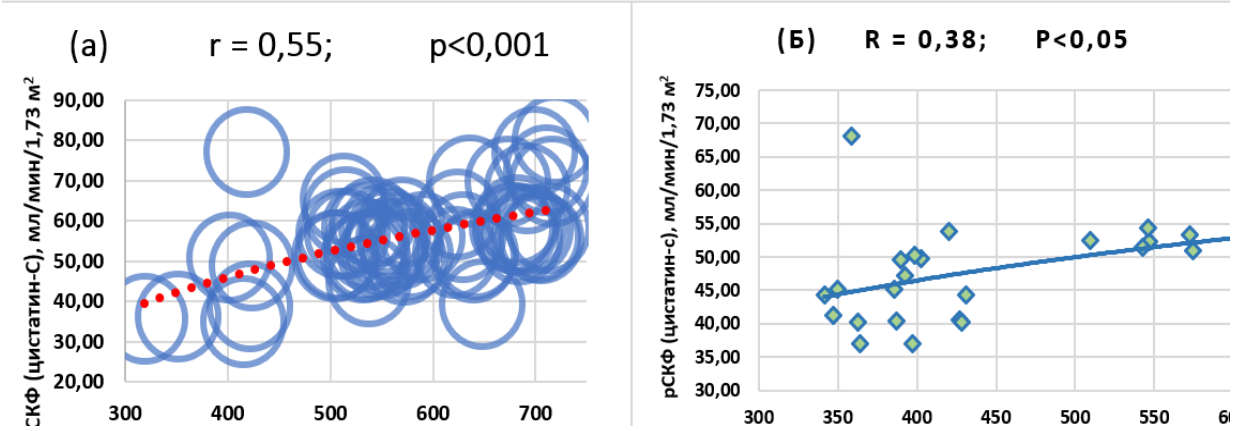

Figure 1. Correlation between serum kallikrein concentrations and cystatin C–based glomerular filtration rate in patients with NYHA class III CHF and left ventricular ejection fraction ≥40% (A) and <40% (B).

The relationship between kallikrein and NT-proBNP is shown in Figure 2. A moderate inverse correlation was observed in patients with LVEF ≥40% (r = −0.51; P < 0.001) and a similar inverse correlation in patients with LVEF <40% (r = −0.45; P < 0.01), indicating a close link between reduced kallikrein concentrations and increased neurohormonal activation.

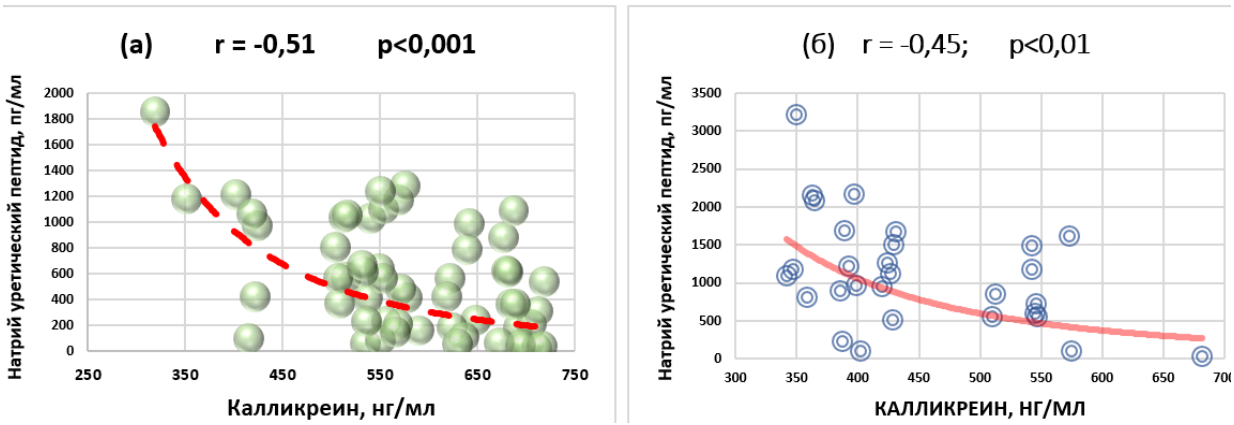

Figure 2. Correlation between serum kallikrein and NT-proBNP concentrations in patients with NYHA class III CHF and left ventricular ejection fraction ≥40% (A) and <40% (B).

Echocardiographic and hemodynamic parameters

A comparative analysis of echocardiographic and hemodynamic parameters is presented in Table 3.

Table 3. Echocardiographic and hemodynamic parameters in patients with chronic heart failure stratified by left ventricular ejection fraction

No	Parameter	LVEF ≥40% (n = 56)	LVEF <40% (n = 29)	P
1	LV end-diastolic diameter (LVEDD), cm	4.99 ± 0.06	5.42 ± 0.08	< 0.001
2	LV end-systolic diameter (LVESD), cm	3.64 ± 0.05	4.47 ± 0.10	< 0.001
3	LV end-diastolic volume (EDV), mL	120.1 ± 3.15	149.5 ± 6.93	< 0.001
4	LV end-systolic volume (ESV), mL	57.18 ± 2.06	88.6 ± 6.2	< 0.001
5	Ejection fraction (EF), %	52.7 ± 0.74	36.2 ± 0.30	< 0.001
6	LV posterior wall thickness (LVPWT), mm	11.7 ± 0.19	11.5 ± 0.20	> 0.05
7	Interventricular septal thickness (IVST), mm	11.8 ± 0.18	11.7 ± 0.20	> 0.05
8	Early diastolic velocity (E wave), m/s	0.72 ± 0.01	0.68 ± 0.03	> 0.05
9	Late diastolic velocity (A wave), m/s	0.81 ± 0.01	0.81 ± 0.01	> 0.05
10	E/A ratio	0.92 ± 0.02	0.66 ± 0.02	< 0.001

Data are presented as mean ± standard error of the mean. LV, left ventricular.

Compared with patients with LVEF ≥40%, those with LVEF <40% demonstrated significantly larger LVEDD, LVESD, EDV, and ESV and lower LVEF (all P < 0.001), consistent with dilatational left ventricular remodeling. Wall thickness (LVPWT and IVST) did not differ significantly between groups, suggesting a predominance of eccentric remodeling. The E/A ratio was significantly lower in the LVEF <40% group (0.66 ± 0.02 vs. 0.92

± 0.02; P < 0.001), indicating more pronounced diastolic dysfunction and elevated left ventricular filling pressures.

Correlations of kallikrein with cardiac parameters

The correlation between kallikrein and LVEF is shown in Figure 3. A statistically significant but moderate positive correlation was observed in patients with LVEF ≥40% (r = 0.40; P < 0.01) and in patients with LVEF <40% (r = 0.29; P < 0.05), indicating that factors in addition to kallikrein contribute to systolic function in this population.

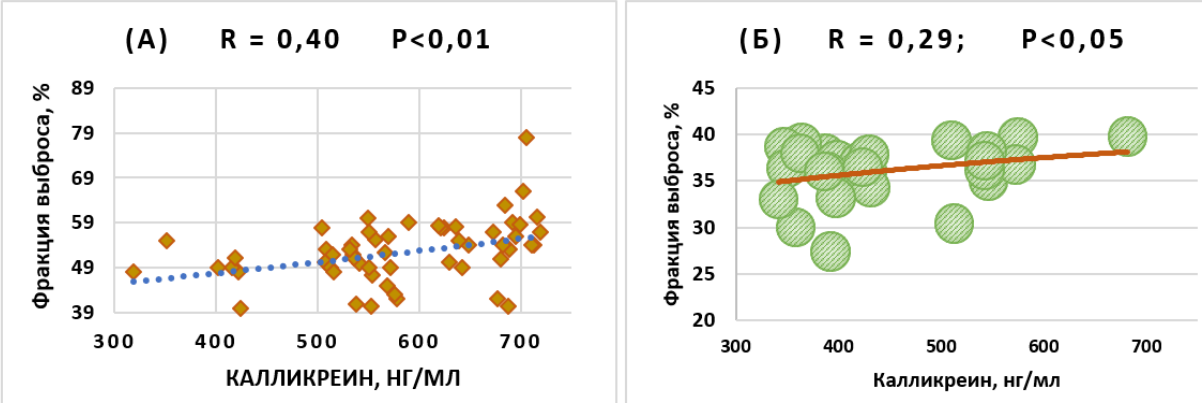

Figure 3. Correlation between serum kallikrein concentrations and left ventricular ejection fraction in patients with NYHA class III CHF and left ventricular ejection fraction ≥40% (A) and <40% (B).

The correlation between kallikrein and the E/A ratio is shown in Figure 4. A moderate positive correlation was observed in patients with LVEF ≥40% (r = 0.62; P < 0.001) and a somewhat weaker correlation in patients with LVEF <40% (r = 0.50; P < 0.001). These findings indicate that kallikrein concentrations more closely reflect the degree of diastolic dysfunction in patients with moderately impaired myocardial function.

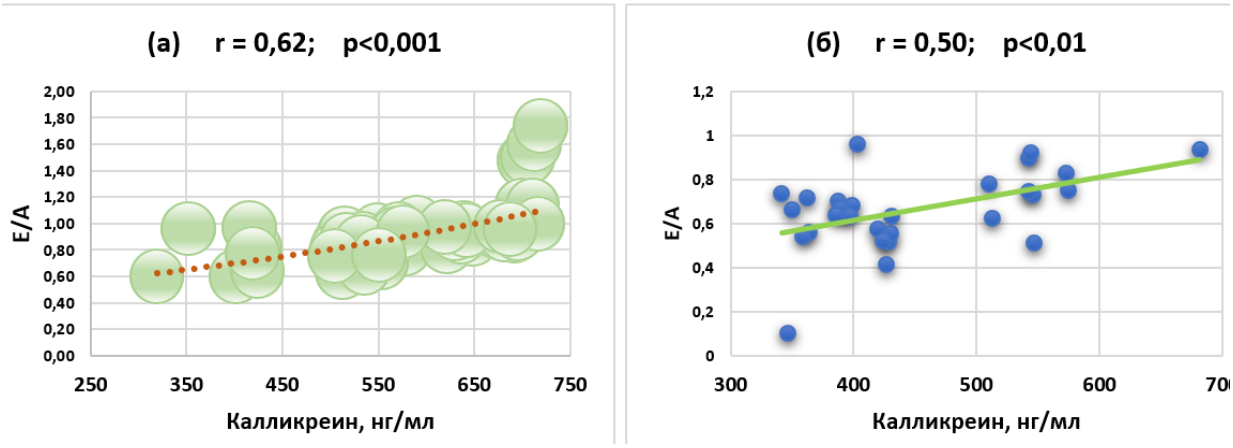

Figure 4. Correlation between serum kallikrein concentrations and the E/A ratio in patients with NYHA class III CHF and left ventricular ejection fraction ≥40% (A) and <40% (B).

Effects of six-month guideline-directed medical therapy

Biochemical parameters before and after six months of therapy in the LVEF ≥40% subgroups (Ia and Ib) are presented in Table 4.

Table 4. Biochemical parameters before and after treatment in patients with LVEF ≥40% (subgroups Ia and Ib)

No	Parameter	Ia (n = 28) Before	Ia (n = 28) After	P_1	Ib (n = 28) Before	Ib (n = 28) After	P_2
1	Cystatin C, mg/L	1.88 ± 0.04	1.65 ± 0.03	< 0.001	1.91 ± 0.03	1.52 ± 0.02	< 0.001
2	eGFR (CKD-EPI cys), mL/min/1.73 m²	55.9 ± 0.9	59.1 ± 1.2	< 0.05	56.2 ± 1.1	63.4 ± 1.4	< 0.001
3	Kallikrein, ng/mL	578.2 ± 11.4	789.5 ± 20.4	< 0.001	582.5 ± 9.2	810.7 ± 24.8	< 0.001
4	NT-proBNP, pg/mL	548.3 ± 42.2	412.6 ± 21.3	< 0.01	547.1 ± 43.8	365.4 ± 19.5	< 0.001
5	Aldosterone, pg/mL	250.4 ± 17.4	241.7 ± 13.8	> 0.05	247.3 ± 15.9	218.5 ± 10.6	> 0.05

Ia, spironolactone-based therapy; Ib, eplerenone-based therapy. P_1 and P_2 denote before- vs. after-treatment comparisons within subgroups Ia and Ib, respectively.

Biochemical parameters before and after treatment in the LVEF <40% subgroups (IIa and IIb) are presented in Table 5.

Table 5. Biochemical parameters before and after treatment in patients with LVEF <40% (subgroups IIa and IIb)

No	Parameter	IIa (n = 14) Before	IIa (n = 14) After	P_1	IIb (n = 14) Before	IIb (n = 14) After	P_2
1	Cystatin C, mg/L	1.98 ± 0.06	1.72 ± 0.03	< 0.001	1.94 ± 0.07	1.58 ± 0.02	< 0.001
2	eGFR (CKD-EPI cys), mL/min/1.73 m²	47.2 ± 0.8	54.7 ± 1.1	< 0.001	47.6 ± 0.9	57.2 ± 1.3	< 0.001
3	Kallikrein, ng/mL	449.4 ± 4.7	694.6 ± 12.3	< 0.001	443.0 ± 7.4	781.2 ± 18.1	< 0.001
4	NT-proBNP, pg/mL	1117.3 ± 69.5	636.5 ± 55.3	< 0.001	1138.5 ± 30.8	512.7 ± 49.6	< 0.001
5	Aldosterone, pg/mL	372.6 ± 16.2	308.4 ± 15.1	< 0.01	363.6 ± 15.4	283.7 ± 14.3	< 0.001

IIa, spironolactone-based therapy; IIb, eplerenone-based therapy. P_1 and P_2 denote before- vs. after-treatment comparisons within subgroups IIa and IIb, respectively.

After six months of four-component therapy, all subgroups showed significant improvements in renal and neurohormonal parameters, with more pronounced changes in patients receiving eplerenone. Cystatin C–based eGFR increased and cystatin C, NT-proBNP, and aldosterone concentrations decreased, while serum kallikrein rose substantially, indicating reactivation of the kallikrein–kinin system. The dynamics of eGFR, kallikrein, NT-proBNP, and aldosterone across the four subgroups are shown in Figures 5–8.

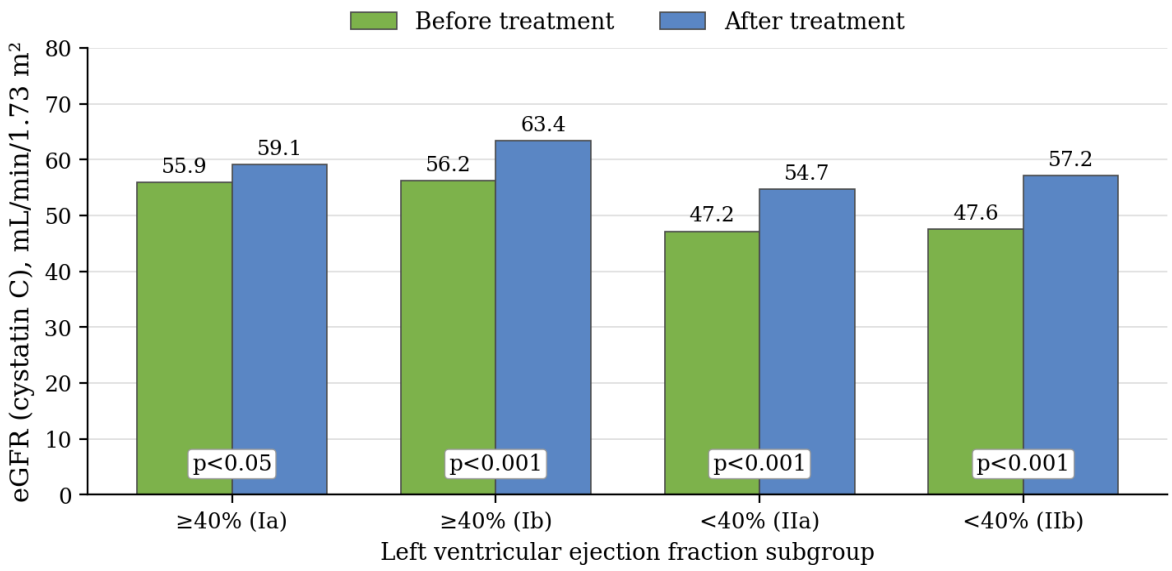

Figure 5. Cystatin C–based eGFR before and after six months of therapy in subgroups Ia, Ib, IIa, and IIb.

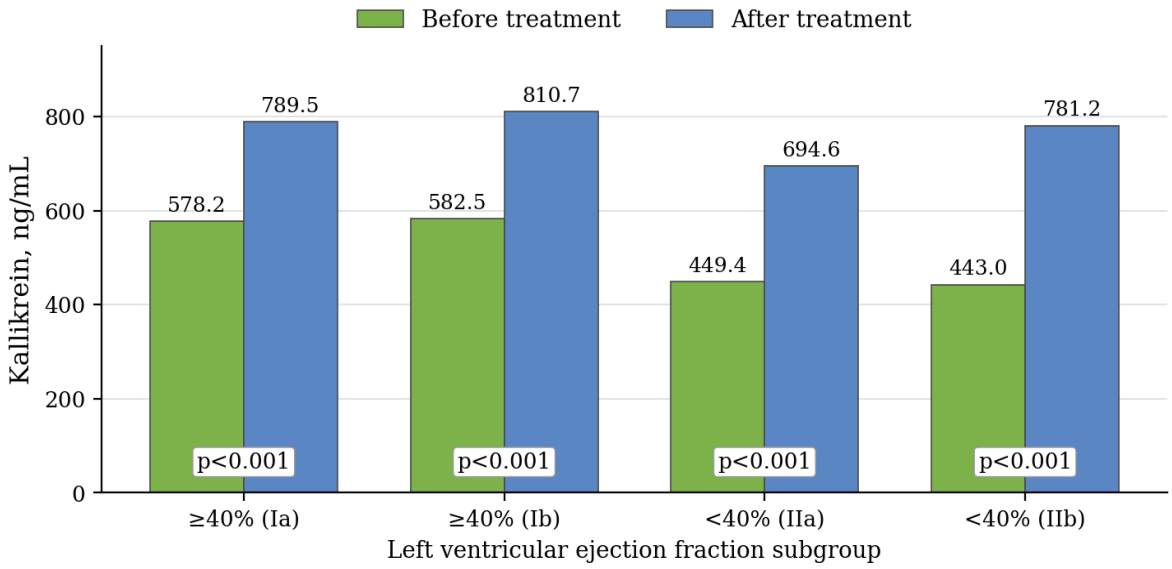

Figure 6. Serum kallikrein concentrations before and after six months of therapy in subgroups Ia, Ib, IIa, and IIb.

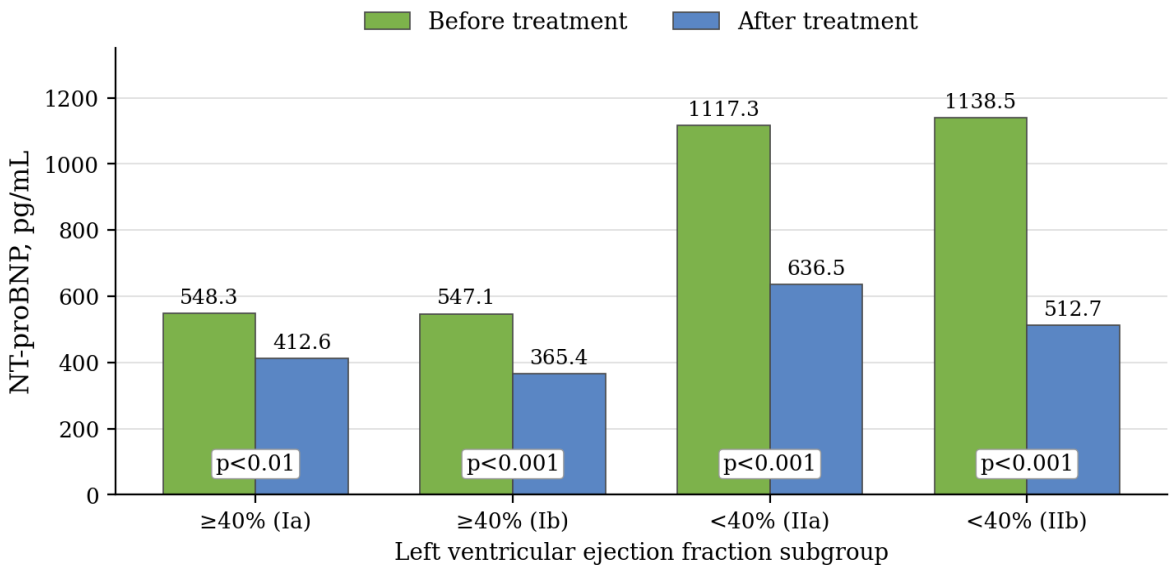

Figure 7. Serum NT-proBNP concentrations before and after six months of therapy in subgroups Ia, Ib, IIa, and IIb.

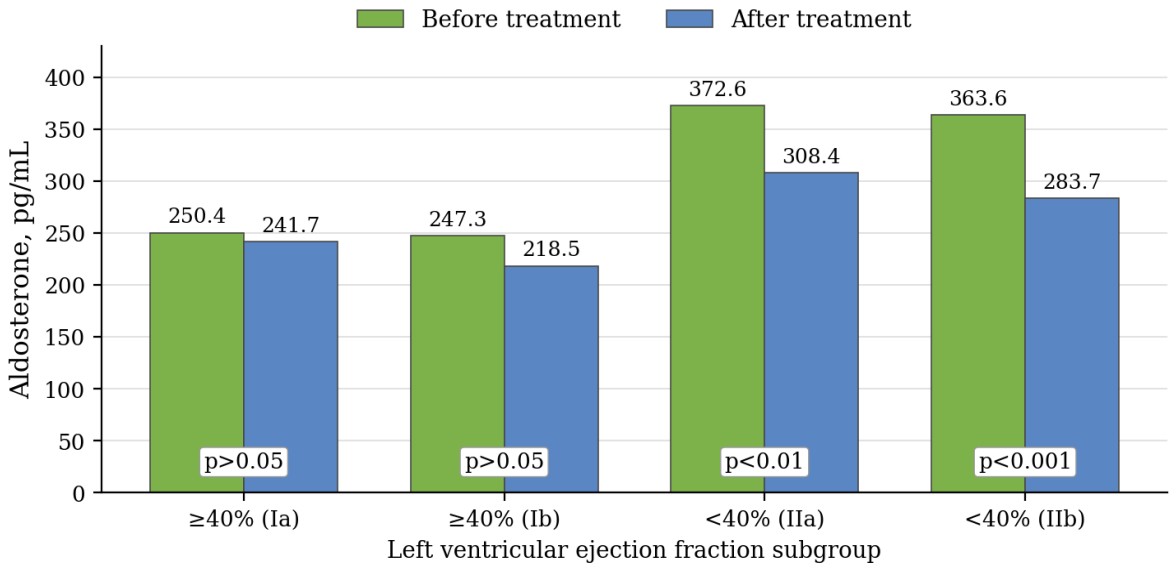

Figure 8. Serum aldosterone concentrations before and after six months of therapy in subgroups Ia, Ib, IIa, and IIb.

Discussion

The present study demonstrated that serum kallikrein concentrations were closely associated with both cardiac and renal function in patients with NYHA class III CHF and early cardiorenal syndrome. Kallikrein was markedly lower in patients with reduced left ventricular ejection fraction (LVEF <40%) than in those with LVEF ≥40% and was accompanied by lower cystatin C–based eGFR and higher NT-proBNP and aldosterone concentrations. These findings support the concept that activation of the kallikrein–kinin system represents a compensatory, protective response that becomes attenuated as cardiac and renal dysfunction progress.

In recent years, cystatin C has been increasingly used for the early detection of glomerular filtration changes because, unlike creatinine, its concentration is less influenced by muscle mass, sex, age, and diet [24–28]. In the present cohort, cystatin C–based eGFR was significantly lower in patients with LVEF <40%, and the positive correlation between kallikrein and eGFR ($r = 0.55$ in patients with LVEF ≥40%) suggests that declining renal filtration is accompanied by reduced kallikrein–kinin system activity. This interpretation is consistent with previous reports describing a protective role of the kallikrein–kinin system in cardiac and renal dysfunction [29,30].

The inverse correlation between kallikrein and NT-proBNP observed in both LVEF strata indicates a close relationship between the kallikrein–kinin system and neurohormonal activation. As natriuretic peptide concentrations rise with worsening heart failure, kallikrein concentrations decline, which may reflect a shift in the balance between the counter-regulatory kallikrein–kinin system and the renin–angiotensin–aldosterone and natriuretic peptide systems [9,12].

Echocardiographic analysis revealed pronounced dilatational and eccentric left ventricular remodeling in patients with LVEF <40%, with significant increases in cavity dimensions and volumes and a lower E/A ratio indicating diastolic dysfunction and elevated filling pressures [31,32]. Kallikrein correlated positively with LVEF and, more strongly, with the E/A ratio, suggesting that kallikrein concentrations more closely reflect diastolic burden in patients with moderately impaired systolic function [33].

After six months of four-component guideline-directed medical therapy—comprising a β-blocker, sacubitril/valsartan, an SGLT2 inhibitor, and a mineralocorticoid receptor antagonist—renal and neurohormonal parameters improved in all subgroups. The reduction in cystatin C and the corresponding increase in eGFR are consistent with the nephroprotective effects reported for SGLT2 inhibitors and mineralocorticoid receptor antagonists [34], while the decline in NT-proBNP mirrors the reduction in neurohormonal activation and filling pressures reported with sacubitril/valsartan [35].

The marked post-treatment increase in serum kallikrein, particularly in patients receiving eplerenone, indicates reactivation of the kallikrein–kinin system, which contributes to vasodilation, natriuresis, and antifibrotic signalling. This may result from suppression of the renin–angiotensin–aldosterone system through mineralocorticoid and angiotensin II type 1 receptor blockade, enhanced natriuresis and vasodilation mediated by empagliflozin, and increased bradykinin availability related to neprilysin inhibition. The more pronounced elevation of kallikrein with eplerenone suggests less inhibition of kinin synthesis compared with spironolactone and may confer additional endothelial-protective effects, in line with the favourable cardiorenal outcomes reported for eplerenone [36,37].

Taken together, these findings indicate that the kallikrein–kinin system, and kallikrein in particular, plays an active role in the pathophysiology of cardiorenal syndrome and may serve as an indicator of neurohormonal adaptation and treatment response.

Clinical implications and study limitations

The integrated assessment of serum kallikrein in relation to renal filtration, neurohormonal activation, and cardiac remodeling represents a distinctive aspect of this study. The associations of kallikrein with cystatin C–based eGFR, NT-proBNP, and the E/A ratio, together with its dynamic response to therapy, suggest potential value as an integrative research biomarker reflecting interconnected renal, neurohormonal, and cardiac alterations in early cardiorenal syndrome, and as a marker for comparing the effects of spironolactone and eplerenone.

Several limitations should be acknowledged. First, the observational design precludes conclusions regarding causality or the temporal sequence of neurohormonal, cardiac, and renal changes. Second, the relatively small sample size and single-center recruitment may limit generalizability. Third, kallikrein was evaluated as a circulating marker and was not compared with established cardiorenal biomarkers using multivariable models. Fourth, the treatment comparison was not randomized, and the potential influence of comorbidities and concomitant therapy was not formally adjusted. Larger prospective, multicenter studies incorporating multivariable analysis and independent validation are required to confirm these findings and to determine whether kallikrein provides clinically meaningful information beyond conventional cardiorenal biomarkers.

Conclusions

In patients with NYHA class III chronic heart failure and early cardiorenal syndrome, serum kallikrein concentrations were closely associated with both cardiac and renal function. Lower kallikrein concentrations accompanied reduced left ventricular ejection fraction, lower cystatin C–based eGFR, and higher NT-proBNP and aldosterone concentrations, whereas six months of four-component guideline-directed medical therapy—particularly with eplerenone—was associated with reactivation of the kallikrein–kinin system and improvement in renal, neurohormonal, and cardiac parameters. These findings suggest that kallikrein may represent a candidate integrative biomarker of neurohormonal adaptation and therapeutic response within the cardiorenal continuum. Larger prospective multicenter studies with multivariable analysis and external validation are needed before its diagnostic or prognostic value can be established in clinical practice.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no conflict of interest related to the publication of this article.

Author Contributions

Abdigaffar Gadaev — study conception and design, scientific supervision, data analysis and interpretation, and critical revision of the manuscript. Matluba Rakhimova — methodology development, clinical data analysis, and manuscript editing. Jahongir Muzaffarov — corresponding author; study coordination, clinical data collection, statistical analysis, manuscript drafting, communication with the journal, and final approval of the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgments

The authors sincerely thank the staff of the Republican Specialized Scientific and Practical Medical Center of Cardiology for their assistance in organizing and conducting the study and in patient recruitment, and the Department of Internal Diseases in Family Medicine No. 2 of Tashkent State Medical University for scientific and methodological support.

References

1. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail. 2020;22(8):1342-1356. doi:10.1002/ejhf.1858.
2. Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, Lerma EV, Mezue K, Molitch M, Mullens W, Ronco C, Tang WHW, McCullough PA. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2019;139(16):e840-e878. doi:10.1161/CIR.0000000000000664.
3. Savira F, Magaye R, Liew D, Reid C, Kelly DJ, Kompa AR, Sangaralingham SJ, Burnett JC, Kaye D, Wang BH. Cardiorenal syndrome: multi-organ dysfunction involving the heart, kidney and vasculature. Br J Pharmacol. 2020;177(13):2906-2922. doi:10.1111/bph.15065.
4. Silva Lopez DE, Calzada Delgado HZ, Junez Villicana IL, et al. Cardio-renal syndrome: a comprehensive review of pathophysiology, clinical subtypes, diagnostic challenges, and therapeutic strategies. Int J Med Sci Clin Res Stud. 2025;5(7):1150-1157. doi:10.47191/ijmscrs/v5-i07-21.
5. Khandait H, Sodhi SS, Khandekar N, Bhattad VB. Cardiorenal syndrome in heart failure with preserved ejection fraction: insights into pathophysiology and recent advances. Cardiorenal Med. 2025;15(1):41-60. doi:10.1159/000542633.
6. Mohammadi K, Shafie D, Ghomashi N, Abdolizadeh A, Sadeghpour M. Kinin-kallikrein system: new perspectives in heart failure. Heart Fail Rev. 2024;29(3):729-737. doi:10.1007/s10741-024-10393-y.
7. Gembillo G, Visconti L, Giusti M, Siligato R, Gallo A, Santoro D, Mattina A. Cardiorenal syndrome: new pathways and novel biomarkers. Biomolecules. 2021;11(11):1581. doi:10.3390/biom11111581.
8. Goffredo G, Barone R, Di Terlizzi V, Correale M, Brunetti ND, Iacoviello M. Biomarkers in cardiorenal syndrome. J Clin Med. 2021;10(15):3433. doi:10.3390/jcm10153433.
9. Okamoto R, Ali Y, Hashizume R, Suzuki N, Ito M. BNP as a major player in the heart-kidney connection. Int J Mol Sci. 2019;20(14):3581. doi:10.3390/ijms20143581.
10. Girolami J, Bouby N, Richer-Giudicelli C, Alhenc-Gelas F. Kinins and kinin receptors in cardiovascular and renal diseases. Pharmaceuticals (Basel). 2021;14(3):240. doi:10.3390/ph14030240.
11. Bekassy Z, Fagerstrom IL, Bader M, Karpman D. Crosstalk between the renin-angiotensin, complement and kallikrein-kinin systems in inflammation. Nat Rev Immunol. 2022;22(7):411-428. doi:10.1038/s41577-021-00634-8.
12. Gallo G, Lanza O, Savoia C. New insight in cardiorenal syndrome: from biomarkers to therapy. Int J Mol Sci. 2023;24(6):5089. doi:10.3390/ijms24065089.
13. Verbrugge FH, Martens P, Ameloot K, Haemels V, Penders J, Dupont M, Tang WHW, Droogne W, Mullens W. Spironolactone to increase natriuresis in congestive heart failure with cardiorenal syndrome. Acta Cardiol. 2019;74(2):100-107. doi:10.1080/00015385.2018.1455947.
14. Chen TH, Ou SM, Lin KH, Ho Y, Tseng WC, Chu YC, Tarng DC. Effect of spironolactone on cardiovascular and renal outcomes in patients with chronic kidney disease. Clin Kidney J. 2025;18(9):sfaf247. doi:10.1093/ckj/sfaf247.
15. Agarwal R, Kolkhof P, Bakris G, Bauersachs J, Haller H, Wada T, Zannad F. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. Eur Heart J. 2021;42(2):152-161. doi:10.1093/eurheartj/ehaa736.
16. Lu T, Zhu W, Yang F, Zhu K, Ren J, Zhu H, Ye B, Sun F, Zhang W, Qiu X. Kallikrein-kinin system as a potential target for the treatment of intervertebral disc degeneration. Eur J Med Res. 2025;30(1):1083. doi:10.1186/s40001-025-03341-5.
17. Cannavo A, Bencivenga L, Liccardo D, Elia A, Marzano F, Gambino G, D'Amico ML, Perna C, Ferrara N, Rengo G, Paolocci N. Aldosterone and mineralocorticoid receptor system in cardiovascular physiology and pathophysiology. Oxid Med Cell Longev. 2018;2018:1204598. doi:10.1155/2018/1204598.
18. Davel AP, Jaffe IZ, Tostes RC, Jaisser F, Belin de Chantemele EJ. New roles of aldosterone and mineralocorticoid receptors in cardiovascular disease: translational and sex-specific effects. Am J Physiol Heart Circ Physiol. 2018;315(4):H989-H999. doi:10.1152/ajpheart.00073.2018.

19. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, Prescott MF, Shi VC, Rouleau JL, Swedberg K, Zile MR, Packer M, Desai AS, Solomon SD, McMurray JJV. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. JACC Heart Fail. 2018;6(6):489-498. doi:10.1016/j.jchf.2018.02.004.
20. Lee W, Liao T, Chen T, Fang H, Fang Y, Chen H, Lin Y, Chang S, Chen M. Sacubitril/valsartan improves all-cause mortality in heart failure patients with reduced ejection fraction and chronic kidney disease. Cardiovasc Drugs Ther. 2023;38(3):505-515. doi:10.1007/s10557-022-07421-0.
21. Kluger AY, Tecson KM, Lee AY, Lerma EV, Rangaswami J, Lepor NE, Cobble ME, McCullough PA. Class effects of SGLT2 inhibitors on cardiorenal outcomes. Cardiovasc Diabetol. 2019;18(1):99. doi:10.1186/s12933-019-0903-4.
22. Salvatore T, Galiero R, Caturano A, Rinaldi L, Di Martino A, Albanese G, Di Salvo J, Epifani R, Marfella R, Docimo G, Lettieri M, Sardu C, Sasso FC. An overview of the cardiorenal protective mechanisms of SGLT2 inhibitors. Int J Mol Sci. 2022;23(7):3651. doi:10.3390/ijms23073651.
23. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. Nat Rev Nephrol. 2021;17(5):319-334. doi:10.1038/s41581-021-00393-8.
24. Benoit SW, Ciccia EA, Devarajan P. Cystatin C as a biomarker of chronic kidney disease: latest developments. Expert Rev Mol Diagn. 2020;20(10):1019-1026. doi:10.1080/14737159.2020.1768849.
25. Chen DC, Potok OA, Rifkin D, Estrella MM. Advantages, limitations, and clinical considerations in using cystatin C to estimate GFR. Kidney360. 2022;3(10):1807-1814. doi:10.34067/KID.0003202022.
26. Prowle JR, Croal B, Abbott TEF, Cuthbertson BH, Wijeysundera DN, Myles PS, et al. Cystatin C or creatinine for pre-operative assessment of kidney function and risk of post-operative acute kidney injury: a secondary analysis of the METS cohort study. Clin Kidney J. 2024;17(1):sfae004. doi:10.1093/ckj/sfae004.
27. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, Tang WHW, Skouri H, Verbrugge FH, Orso F, Hill L, Ural D, Lainscak M, Rossignol P, Metra M, Mebazaa A, Seferovic P, Ruschitzka F, Coats A. Evaluation of kidney function throughout the heart failure trajectory: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2020;22(4):584-603. doi:10.1002/ejhf.1697.
28. Levey AS, Eckardt KU, Dorman NM, Christiansen SL, Hoorn EJ, Ingelfinger JR, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2020;97(6):1117-1129. doi:10.1016/j.kint.2020.02.010.
29. Boulet J, Mehra MR. Left ventricular reverse remodeling in heart failure: remission to recovery. Struct Heart. 2021;5(5):466-481. doi:10.1080/24748706.2021.1954275.
30. Kang E, Lee SW, Ryu H, Kang M, Kim S, Park SK, Jung JY, Lee K, Han SH, Ahn C, Oh KH. Left ventricular diastolic dysfunction and progression of chronic kidney disease: analysis of KNOW-CKD data. J Am Heart Assoc. 2022;11(13):e025554. doi:10.1161/JAHA.122.025554.
31. Yang Y, Li Z, Guo X, Zhou Y, Chang Y, Yang H, Yu S, Ouyang N, Chen S, Sun G, Hua Y, Sun Y. Interventricular septum thickness for the prediction of coronary heart disease and myocardial infarction in a hypertension population: a prospective study. J Clin Med. 2022;11(23):7152. doi:10.3390/jcm11237152.
32. Tile BM, Kumar KS, Sundar R, Kumar P. Echocardiographic assessment of left ventricular diastolic dysfunction in chronic kidney disease. Eur J Cardiovasc Med. 2024;14(6):181-190. doi:10.5083/ejcm.
33. Ahn JM, Zimmermann FM, Arora S, et al. Prognostic value of comprehensive intracoronary physiology assessment early after heart transplantation. Eur Heart J. 2021;42(48):4918-4929. doi:10.1093/eurheartj/ehab568.
34. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303.
35. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Sacubitril-valsartan in heart failure with preserved ejection fraction. N Engl J Med. 2019;381(17):1609-1620. doi:10.1056/NEJMoa1908655.
36. Wang K, Ni G, Wu Q, Zhou Y, Yao W, Zhang H, Li X. Prognostic value of N-terminal pro-B-type natriuretic peptide and glomerular filtration rate in patients with acute heart failure. Front Cardiovasc Med. 2020;7:123. doi:10.3389/fcvm.2020.00123.
37. Vergani M, Cannistraci R, Perseghin G, Ciardullo S. The role of natriuretic peptides in the management of heart failure with a focus on the patient with diabetes. J Clin Med. 2024;13(20):6225. doi:10.3390/jcm13206225.