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Title

Hyponatremia at Discharge is Associated with Adverse Prognosis in Hospitalized Heart Failure Patients with Preserved Ejection Fraction

-A Report from the JASPER Registry-

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Keywords: Heart failure with preserved ejection fraction; prognosis; hyponatremia, sodium

Short title: Hyponatremia in hospitalized HFpEF patients

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Abstract

Introduction: Hyponatremia is a major predictor of adverse prognosis in patients with heart failure (HF). However, the differences in the prognostic impact of hyponatremia on admission and at discharge, especially in hospitalized patients with HF with preserved ejection fraction (HFpEF), have not been fully examined.

Methods and Results: The Japanese Heart Failure Syndrome with Preserved Ejection Fraction (JASPER) registry is a nationwide, observational, prospective registration of consecutive Japanese hospitalized HFpEF patients with LVEF ≥50%. There were 523 consecutive patients enrolled in this analysis. We divided the patients into two groups based on their sodium serum levels at discharge: hyponatremia group (sodium <135 mEq/L, n = 55, 10.5%), and control group (sodium ≥135 mEq/L, n = 468, 89.5%). We compared the patients' demographic data, laboratory and echocardiographic data, in-hospital treatment, length of hospital stay, and prognosis after discharge. This present analysis had two primary endpoints: 1) all-cause death and 2) all-cause death and rehospitalization for HF. The hyponatremia group showed a higher prevalence of prior HF admission (52.9%, vs. 36.0%, P = 0.018). At discharge, the hyponatremia group had lower systolic blood pressure (110.0 mmHg vs. 114.0 mmHg, P = 0.029), lower levels of hemoglobin (10.6 g/dL vs. 11.4 g/dL, P = 0.027) and higher levels of urea nitrogen (32.8 mg/dl vs. 24.9 mg/dL, P = 0.024). Additionally, the length of hospital stay was longer in the hyponatremia group (18 days vs. 15 days, P = 0.037). In the Kaplan-Meier analysis, more patients in the hyponatremia group reached the primary endpoints than those in the control group (all-cause death, Log-Rank <0.001; all-cause death and rehospitalization for HF, Log-Rank 0.004). In contrast, there were no significant relationships between

hyponatremia on admission and the endpoints. In the univariable Cox proportional hazard analysis, hyponatremia at discharge was a predictor of the two endpoints (all-cause death, hazard ratio 2.657, 95% confidence interval 1.574–4.486, P <0.001; all-cause death and rehospitalization for HF, hazard ratio 1.774, 95% confidence interval 1.192–2.641, P = 0.005).

Conclusion: Hyponatremia at discharge, not on admission, is associated with adverse prognosis in hospitalized patients with HFpEF.

Introduction

Heart failure (HF) is a major cause of death among the elderly in many countries and has become a significant public health issue[1, 2] Especially, heart failure with preserved ejection fraction (HFpEF) is a increasing public health problem.[3-6] Hyponatremia, which is usually defined as sodium serum levels <135 mEq/L, is a well-known predictor of adverse prognosis in hospitalized patients with heart failure with reduced ejection fraction (HFrEF).[7-10] In contrast, 1) the prognostic impact of hyponatremia in patients with HFpEF and 2) the differences in the prognostic impact of hyponatremia on admission and at discharge have not been fully examined. Thus, the aim of this present analysis was to compare the prognostic impact of hyponatremia on admission and at discharge in patients enrolled in the Japanese Heart Failure Syndrome with Preserved Ejection Fraction (JASPER) registry, a HFpEF-specific nationwide cohort study in hospitalized patients for acute decompensated HF.[11]

Methods

Patient recruitment

The JASPER registry[11] is a multicenter, observational, prospective cohort that includes consecutive patients aged ≥20 years who require hospitalization after being diagnosed as having acute HF according to the Framingham criteria[12] by at least two experienced cardiologists. Preserved left ventricular (LV) systolic function was defined as LV ejection fraction (LVEF) ≥50% by the modified Simpson method or LV fractional shortening ≥25% by echocardiography. Patients with acute coronary syndrome, receiving hemodialysis or with a history of heart transplantation were excluded. The patients' demographic data, including comorbid conditions, clinical signs, laboratory and echocardiographic data, and length of hospital stay, were obtained. Follow-up was performed at discharge, as well as at 12 and 24 months after discharge by coordinators and investigators, as follows: direct contact with patients or their physicians at the hospital or outpatient clinic; telephone interview of patients or, if deceased, family members; or by mail.[11]

In the current study, because patient information was anonymized and de-identified prior to the analyses, written informed consent was not obtained from each patient. However, the study was publicized by posting a summary of the protocol on the National Cerebral and Cardiovascular Center website, where a notice clearly informed patients of their right to refuse enrollment. These procedures for informed consent and enrollment were in accordance with detailed regulations regarding informed consent described in the guidelines, and this study, including the procedure for enrollment, was approved by the Institutional Review Board of each site and registered under the Japanese

UMIN Clinical Trials Registration (UMIN000010601).[11]

The patient flow chart of the present analysis is shown in **Figure 1**. Of 535 patients enrolled in the JASPER registry, seven patients who died during the first hospitalization and five patients with unknown serum levels of sodium were excluded. Finally, 523 patients were enrolled in this present analysis. We divided these patients into two groups based on sodium serum levels at discharge: hyponatremia group (sodium <135 mEq/L, n = 55, 10.5%) and control group (sodium ≥135 mEq/L, n = 468, 89.5%). We compared the patients' demographic data, laboratory and echocardiographic data, in-hospital treatment, length of hospital stay, and prognosis after discharge between the groups. This present analysis had two primary endpoints: 1) all-cause death and 2) all-cause death and rehospitalization for HF.

Statistical analysis

Normality was confirmed using the Shapiro-Wilk test in each group. Parametric variables were presented as mean ± standard deviation, non-parametric variables were presented as a median (interquartile range), and categorical variables were expressed as numbers and percentages. Parametric variables were compared using Student's t-test, non-parametric variables were compared using the Mann-Whitney U test, and the chi-square test was used for comparisons of categorical variables. The Kaplan-Meier analysis was used for presenting all-cause death, and the log-rank test was used for initial comparisons. The proportional hazards assumption for the model was checked by examining log minus-log transformed data. The curves helped in identifying the non-proportionality patterns in hazard function such as convergence (the difference in risk between the two groups

decreases with time), divergence or crossing of the curves. We conducted subgroup analyses to assess the potential heterogeneity of associations between hyponatremia and 1) all-cause mortality and 2) all-cause mortality or rehospitalization for HF. Interactions between hyponatremia and clinically relevant variables including age, sex, New York Heart Association (NYHA) functional class, systoloc blood pressure, presence of prior myocardial infarction, atrial fibrillation, diabetes mellitus, chronic kidney disease, use of loop diuretics and β blockers, length of hospital stay, hemoglobin, blood urea nitrogen (BUN), C-reactive protein (CRP), and LVEF were estimated by the Cox proportional hazards regression model. A P-value of <0.05 was considered statistically significant for all comparisons. All analyses were performed using a statistical software package (SPSS ver. 25, IBM, Armonk, NY, USA).

Results

Of the 523 enrolled patients, 47 (9.0%) patients had serum sodium levels less than 135 mEq/L on admission, 16 (3.1%) of whom had sustained hyponatremia, while 31 (5.9%) had corrected serum sodium levels at discharge (**Figure 1**). On the other hand, 39 (7.5%) patients newly developed hyponatremia during hospitalization (**Figure 1**). At discharge (**Figure 1**), 55 (10.5%) patients had hyponatremia. First, we compared the prognostic impact of sodium serum levels on admission and at discharge using the Kaplan-Meier analysis (**Figures 2 and 3**). The existence of hyponatremia on admission was not significantly associated with all-cause death (**Figure 2A**, Log-Rank 0.088) and the composite endpoint of all-cause death and rehospitalization for HF (**Figure 3A**, Log-Rank 0.411). On the other hand, the hyponatremia group at discharge showed higher all-cause death and reached the composite endpoint more often than the control group. (all-cause death, **Figure 2B**, Log-Rank <0.001; all-cause death and rehospitalization for HF, **Figure 3B**, Log-Rank 0.004).

Next, we compared patients' characteristics and treatment between the two groups (**Table 1**). There were no statistical differences in age, sex, body mass index, and NYHA functional class between the two groups, while the hyponatremia group demonstrated lower systolic blood pressure at discharge (110.0 mmHg vs. 114.0 mmHg, P = 0.029) compared to the control group. The prevalence of prior HF admission was more common (52.9% vs. 36.0%, P = 0.018) in the hyponatremia group. The usage of tolvaptan, an arginine vasopressin (AVP) V_2 receptor antagonist, was comparable between the two groups. Both groups obtained similar initial treatments, whereas length of hospital stay was longer in the hyponatremia group (18.0 days vs. 15.0 days, P = 0.037). Echocardiographic parameters including LVEF, LV outflow tract velocity time integral,

inferior vena cava diameter, and tricuspid regurgitation pressure gradient were comparable between the two groups.

Laboratory data are summarized in **Table 2**. The median sodium serum levels were 138.0 mEq/L on admission and 132.0 mEq/L at discharge in the hyponatremia group, which were significantly lower than those in the control group (P <0.001, respectively). There was no significant difference in levels of B-type natriuretic peptide (BNP), potassium, and creatinine between the two groups both on admission and at discharge. At discharge, hemoglobin levels were lower (P = 0.027), BUN, BUN/creatinine ratio, and CRP were higher in the hyponatremia group compared to the control group (P<0.05, respectively). In the multivariable logistic regression analysis (**Table 3**), systolic blood pressure and CRP at discharge were associated with hyponatremia at discharge (systolic blood pressure at discharge, odds ratio 0.978, 95% confidence interval (CI) 0.957–1.000, P = 0.045; CRP at discharge, odds ratio 1.225, 95% CI, 1.036–1.450, P = 0.018).

In the univariable Cox proportional hazard analysis (**Tables 4 and 5**), hyponatremia at discharge was associated with all-cause death (hazard ratio (HR) 2.657, 95% CI 1.574–4.486, P <0.001) and the composite endpoint of all-cause death and rehospitalization for HF (HR 1.774, 95% CI 1.192–2.641, P = 0.005). The subgroup analysis (**Tables 4 and 5**) revealed the association between hyponatremia and 1) all-cause death and 2) all-cause death and rehospitalization for HF in subgroups after adjusting for interactions between hyponatremia and prespecified clinically important variables. To predict all-cause death, and the composite endpoint of all-cause death and rehospitalization for HF, there were no interactions between hyponatremia and

prespecified clinically important variables.

Discussion

To the best of our knowledge, this analysis is the first to clarify the prognostic impact of hyponatremia in hospitalized HFpEF patients taking account of the timing of measurement. Namely, the existence of hyponatremia at discharge, rather than on admission, was associated with significantly higher all-cause mortality and rehospitalization rate due to HF after discharge. Patients in the hyponatremia group showed lower systolic blood pressure, higher levels of BUN and BUN/creatinine ratio, longer length of hospital stay, and had a higher prevalence of prior HF admission.

The underlying mechanisms of hyponatremia in acute decompensated HF have been reported as follows: activation of the renin-angiotensin-aldosterone system (RAAS); stimulation of the sympathetic nervous system (SNS); and baroreceptor-mediated non-osmotic AVP release due to arterial underfilling caused by decreased cardiac output.[13, 14] Serum sodium levels are reported to be slightly lower in patients with HFrEF than those with HFpEF,[15] but the prevalence of hyponatremia (sodium <135 mEq/L) is equivalent in HFrEF and HFpEF patients.[10, 16] In addition, side effects of HF medication such as diuretics may worsen hyponatremia.[14] In the present analysis, decreased systemic blood pressure and increased levels of BUN and BUN/creatinine ratio supported the pathophysiology of arterial underfilling, activated RAAS and SNS, and AVP release.[17, 18] The prognostic difference between hyponatremia on admission and at discharge was probably due to the change in RAAS/SNS/AVP activation during hospitalization. Of the patients with hyponatremia on admission, 66.0% had corrected serum sodium levels during hospitalization, suggesting that their neurohormonal activation improved. Conversely, 8.2% of patients without hyponatremia on admission developed

hyponatremia during hospitalization along with exacerbation of neurohormonal factors. Our results were similar to a previous study enrolling HFrEF patients with persistent hyponatremia.[19] Even though RAAS, SNS and AVP are important compensatory mechanisms in critical conditions including blood loss and low cardiac output, sustained activation of these systems have potential adverse effects on prognosis in HF patients by increased afterload and myocardial oxygen consumption, and induced cardiomyocyte remodeling.[20-23] Thus, an increase in BUN is reported to independently be associated with adverse prognosis in hospitalized HF patients.[24]

In this present analysis, patients in the hyponatremia group showed lower systemic blood pressure, had a higher prevalence of prior HF admission, higher serum levels of BUN at discharge, and longer length of hospital stay. These results suggest that HFpEF patients with hyponatremia have severe or advanced HF.[24, 25] There was no difference in BNP plasma levels, which is one of the strongest predictors of death in patients with HF,[26] between the two groups. However, BNP is mainly secreted by LV stretch and diastolic wall stress, and is generally lower in patients with HFpEF than in those with HFrEF.[27-29] The discrepancy can be explained from the structural features that LV diastolic diameter and LV wall thickness were comparable between the two groups.[30] These results suggest that the reliability of BNP plasma levels in HFpEF patients with hyponatremia is relatively lower than that in patients with HFrEF.

To date, the treatment methods of HFpEF patients with hyponatremia have remained unclear. Considering the increased neuro-hormonal activation described above, neuro-hormonal antagonists are likely to show a desirable prognostic impact as is in the case of patients with HFrEF.[1, 2] However, angiotensin-converting enzyme inhibitors,[31]

angiotensin receptor blockers,[32, 33] and β blockers[34] have failed to improve clinical outcomes in previous studies with patients with HFpEF, whereas a significant effect is evident in patients with HFrEF.[1, 2] Diuretics may relieve symptoms,[35] but at the same time, potentially worsen neuro-hormonal activation and lower serum sodium levels.[14] At the moment, mineralocorticoid receptor antagonists[36] and angiotensin receptor blockers[33] are expected to reduce hospitalization for HF. Although AVP V_2 receptor antagonists did not improve the prognosis in patients with HFrEF,[37] they also have been reported to reduce hospitalization in patients with HFpEF.[38]

Study strengths and limitations

There were several strengths in the present analysis. First, we analyzed observational and prospective data from multicenters in Japan. HF was restricted to acute HFpEF requiring hospitalization and the diagnosis was made by at least two experienced cardiologists. Second, sodium serum levels both on admission and at discharge were available in the JASPER registry. We were able to compare the prognostic impact of hyponatremia at two different times. On the other hand, there were some limitations in this present analysis. The general limitations of the JASPER registry were described in the previous article.[11] Regarding sodium, the change in serum levels after discharge could not be determined. Since the number of participants enrolled in the JASPER registry was relatively smaller, there was a possibility that the impact of hyponatremia on admission could not be detected.

Conclusion

Hyponatremia at discharge, not admission, is associated with adverse prognosis in hospitalized patients with HFpEF.

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Figure legends

Figure 1. Patient flow chart

Figure 2. Comparisons of all-cause death

Figure 3. Comparisons of all-cause death and rehospitalization for heart failure

Figure 1. Patient flow chart

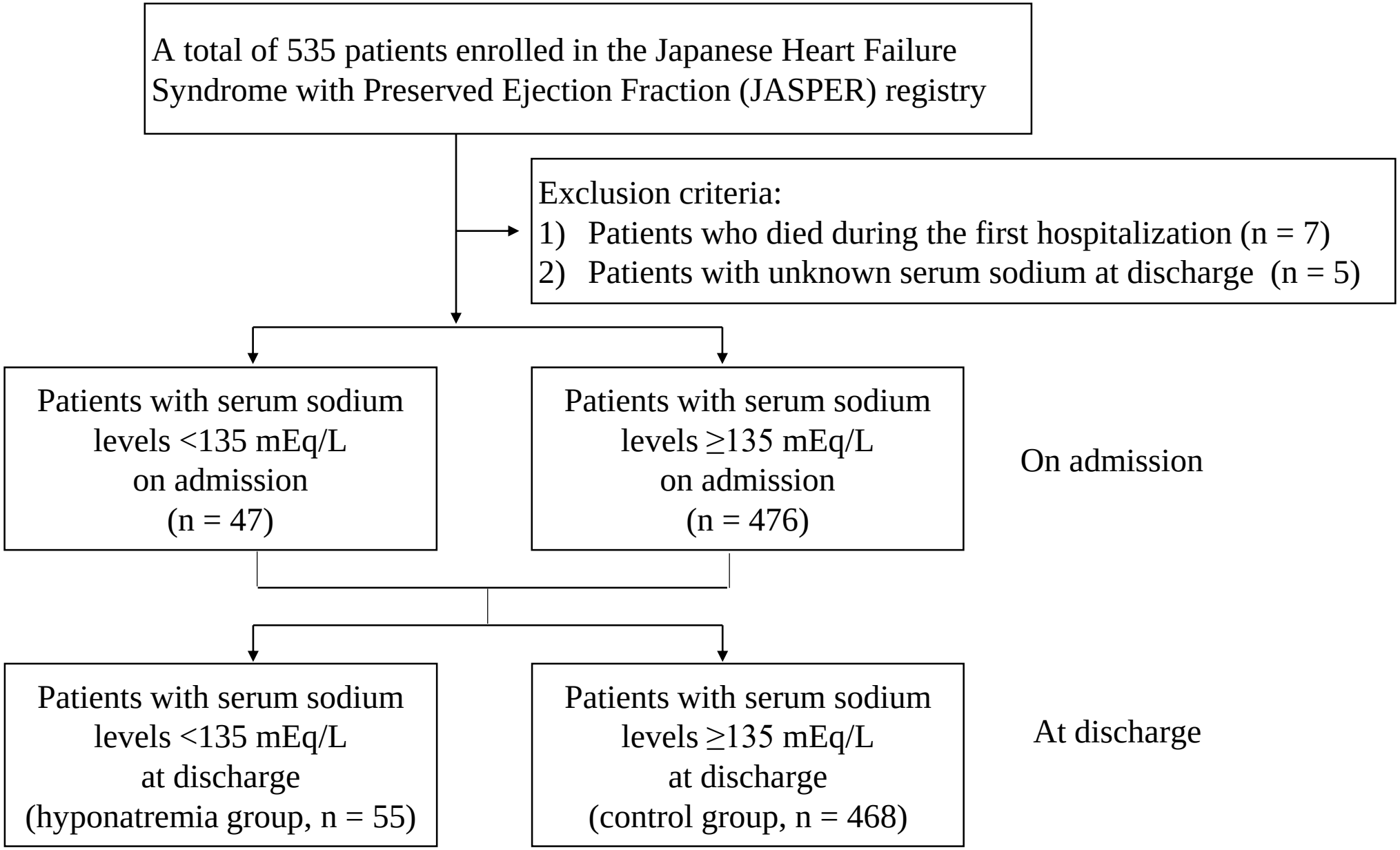
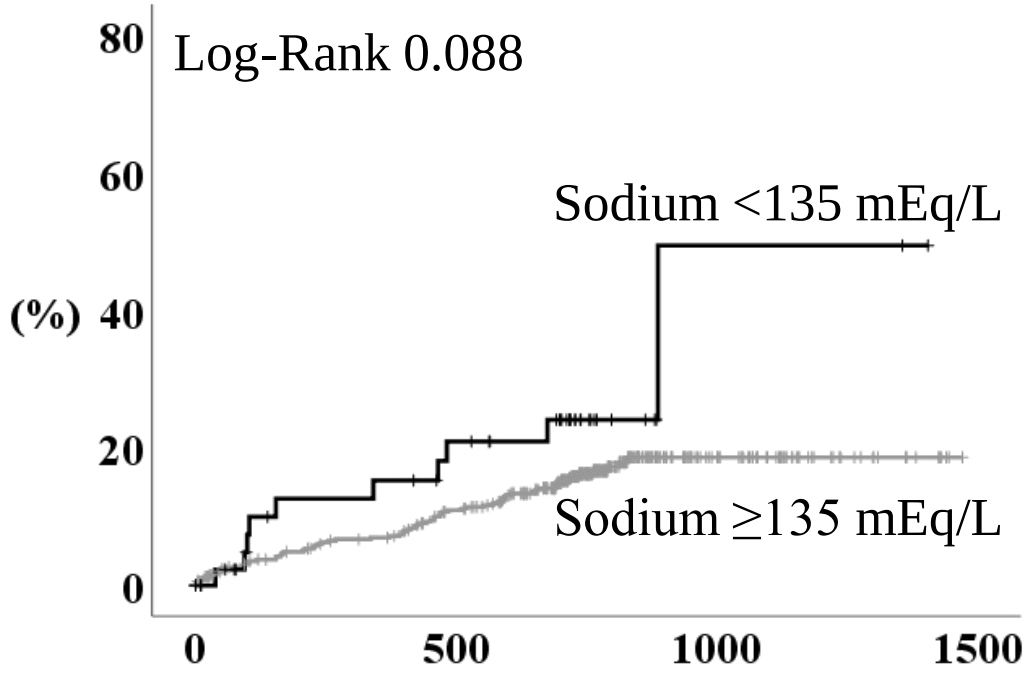


Figure 2. All-cause death

A) Classification on admission



Number at risk

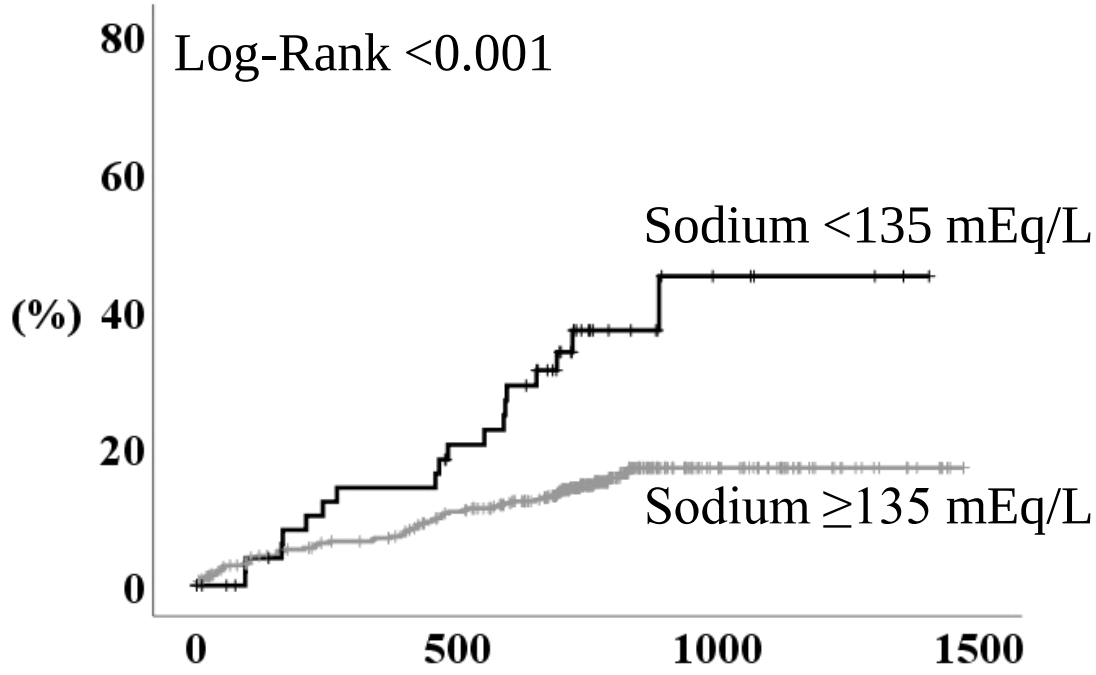
Patients with serum sodium levels <135 mEq/L

47 33 28 11 2 2 0

Patients with serum sodium levels ≥135 mEq/L

476 409 375 209 51 14 0

B) Classification at discharge



Number at risk

Patients with serum sodium levels <135 mEq/L

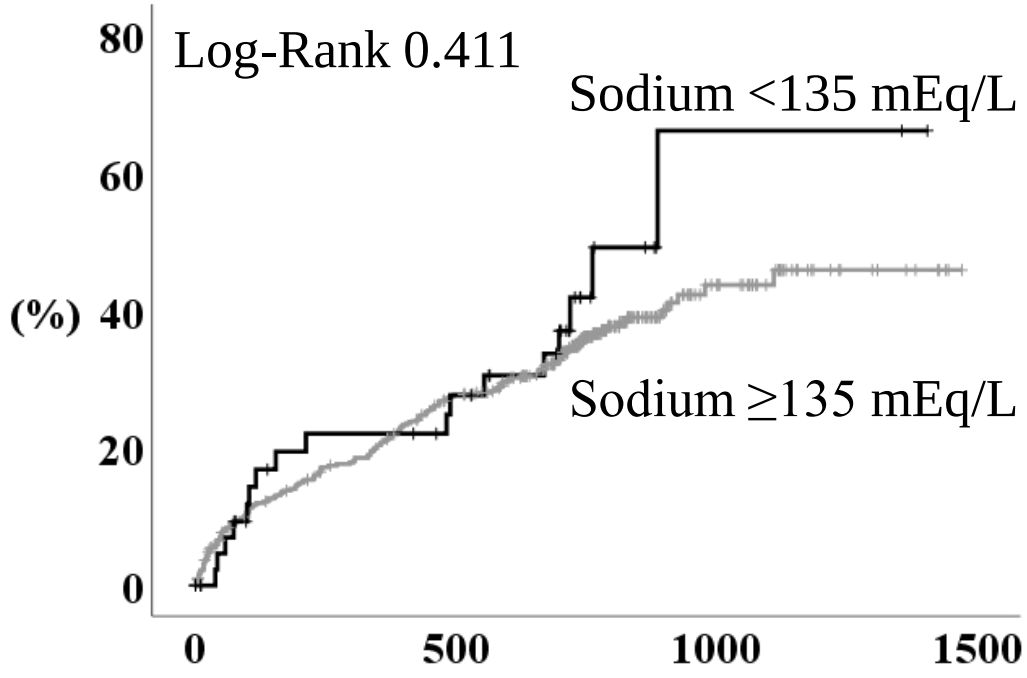
55 43 37 16 5 3 0

Patients with serum sodium levels ≥135 mEq/L

468 399 366 204 48 13 0

Figure 3. All-cause death and rehospitalization for heart failure

A) Classification on admission



Number at risk

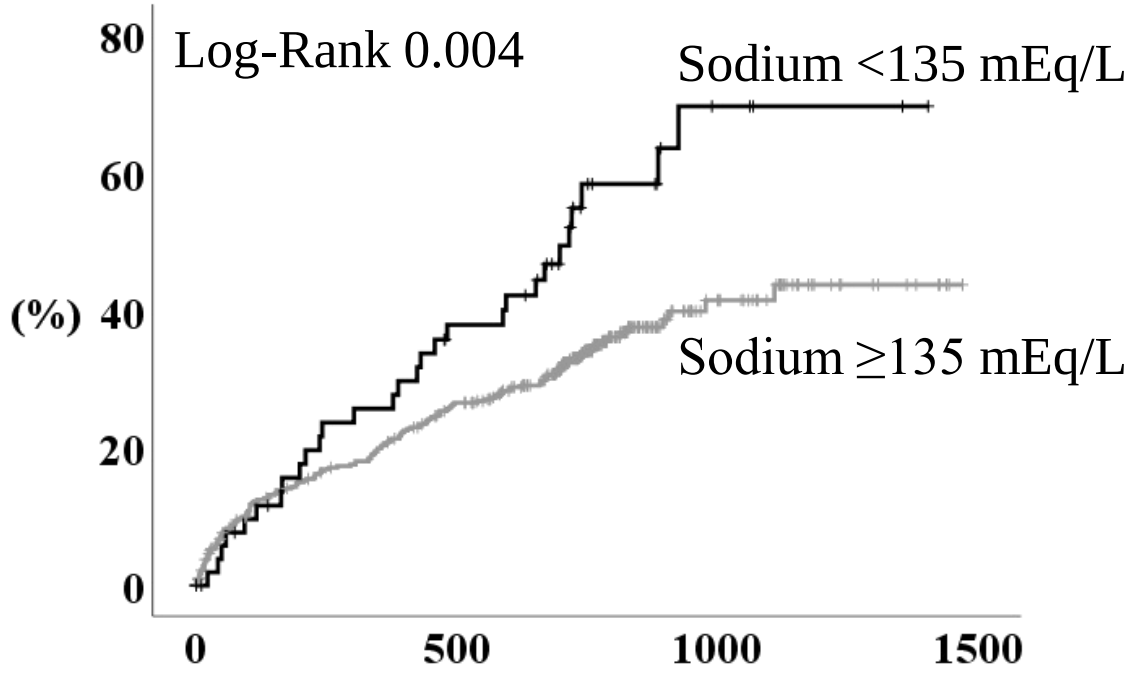
Patients with serum sodium levels <135 mEq/L

47 30 26 9 2 2 0

Patients with serum sodium levels ≥135 mEq/L

476 364 309 165 38 9 0

B) Classification at discharge



Number at risk

Patients with serum sodium levels <135 mEq/L

55 38 29 12 4 2 0

Patients with serum sodium levels ≥135 mEq/L

468 356 306 162 36 9 0

Table 1. Baseline patient characteristics between control and hyponatremia groups

	Control (n = 468)	Hyponatremia (n = 55)	P value	Missing (%)
Age (years)	80.0 (73.0–84.0)	80.0 (72.5–85.0)	0.780	0 (0)
Male sex (%)	231 (49.4)	29 (52.7)	0.636	0 (0)
Body mass index (kg/m^2)	21.6 (19.6–24.2)	21.6 (18.4–23.9)	0.512	23 (4.4)
NYHA functional class III or IV (n, %) at discharge	24 (5.6)	6 (11.8)	0.088	46 (8.8)
Vital signs at discharge				
Heart rate (beats/min)	66.0 (60.0–74.0)	68.0 (60.0–74.0)	0.844	3 (0.6)
SBP (mmHg)	114.0 (103.0–125.0)	110.0 (100.5–118.0)	0.029	2 (0.4)
DBP (mmHg)	60.0 (53.0–68.0)	60.0 (56.0–68.0)	0.776	3 (0.6)
Past history				
Smoking history (n, %)	201 (44.6)	28 (50.9)	0.372	17 (3.3)
Prior HF admission (n, %)	164 (36.0)	27 (52.9)	0.018	17 (3.3)
Prior myocardial infarction (n, %)	60 (13.0)	5 (9.1)	0.410	6 (1.1)
Prior angina pectoris (n, %)	103 (22.3)	11 (20.4)	0.741	8 (1.5)
Atrial fibrillation (n, %)	286 (61.8)	36 (66.7)	0.482	6 (1.1)
DM/IGT (n, %)	180 (38.7)	22 (40.0)	0.853	3 (0.6)
Hypertension (n, %)	365 (78.3)	41 (74.5)	0.523	2 (0.4)
Dyslipidemia (n, %)	202 (43.4)	21 (36.4)	0.316	3 (0.6)
Chronic kidney disease (n, %)	240 (51.5)	28 (50.9)	0.934	2 (0.4)
Medications at discharge				
β blockers (n, %)	310 (66.2)	28 (50.9)	0.024	0 (0)
ACEIs/ARBs (n, %)	335 (71.6)	36 (65.5)	0.344	0 (0)
Spironolactone (n, %)	124 (26.5)	14 (25.5)	0.868	0 (0)

CCB (n, %)	250 (53.4)	26 (47.3)	0.388	0 (0)
Loop diuretics (n, %)	345 (73.7)	42 (76.4)	0.672	0 (0)
Tolvaptan (n, %)	17 (3.6)	5 (9.1)	0.070	0 (0)
Initial treatments during hospitalization				
Intravenous diuretics (n, %)	380 (81.2)	43 (78.2)	0.591	0 (0)
Vasodilators (n, %)	286 (61.1)	31 (56.4)	0.495	0 (0)
Inotropes (n, %)	20 (4.3)	2 (3.6)	0.587	0 (0)
Digitalis (n, %)	25 (5.3)	1 (1.8)	0.218	0 (0)
NIPPV (n, %)	90 (19.2)	9 (16.4)	0.608	0 (0)
IPPV (n, %)	8 (1.7)	1 (1.8)	0.635	0 (0)
Length of hospital stay (days)	15.0 (11.0–23.0)	18.0 (14.0–23.0)	0.037	0 (0)
Echocardiographic data				
LAD (mm)	45.0 (41.0–50.0)	45.0 (40.0–48.0)	0.608	192 (36.7)
IVSD (mm)	10.0 (9.0–12.0)	10.0 (9.0–11.0)	0.345	190 (36.3)
LVPWD (mm)	10.0 (9.0–11.4)	10.0 (9.5–11.0)	0.523	191 (36.5)
LVDD (mm)	46.4±6.7	46.7±5.7	0.761	186 (35.6)
LVSD (mm)	29.5 (26.0–34.9)	30.4 (26.0–33.0)	0.982	188 (35.9)
LVEF (%)	60.0 (54.7–65.0)	61.0 (55.0–69.0)	0.765	192 (36.7)
LVOT-VTI (cm)	18.9 (15.5–22.8)	23.1 (17.5–24.7)	0.585	351 (67.1)
IVCD (mm)	16.0 (12.0–20.0)	17.0 (14.0–20.7)	0.887	187 (35.8)
TR-PG (mmHg)	27.5 (21.9–34.0)	28.0 (22.0–37.0)	0.369	214 (40.9)

NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HF, heart failure; DM, diabetes mellitus; IGT, impaired glucose tolerance; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; NIPPV, non-invasive positive pressure ventilation; IPPV, invasive positive pressure ventilation; LAD, left atrial dimension; IVSD, intraventricular septum diameter; LVPWD, left ventricular (LV) posterior wall diameter; LVDD, LV diastolic diameter; LVSD, LV systolic diameter; LVEF, LV ejection fraction; LVOT-VTI, LV outflow tract velocity

time integral; IVCD, inferior vena cava diameter; TR-PG, tricuspid regurgitation pressure gradient.

Table 2. Laboratory data (n = 523)

	Control (n = 468)	Hyponatremia (n = 55)	P value	Missing (%)
Laboratory data on admission				
BNP (pg/mL)	423.6 (229.4–679.8)	331.0 (233.0–645.8)	0.457	9 (1.7)
Hemoglobin (g/dL)	11.0 (9.8–12.7)	10.8 (9.4–12.0)	0.182	0 (0)
Sodium (mEq/L)	141.0 (138.0–142.0)	138.0 (133.0–140.3)	<0.001	0 (0)
Potassium (mEq/L)	4.1 (3.8–4.6)	4.3 (3.6–4.6)	0.626	0 (0)
Albumin (g/dL)	3.7 (3.3–4.0)	3.6 (3.3–4.0)	0.479	31 (5.9)
Total bilirubin (mg/dL)	0.7 (0.5–1.0)	0.7 (0.5–1.1)	0.701	6 (1.1)
BUN (mg/dL)	22.0 (16.0–31.0)	25.0 (15.8–33.5)	0.544	0 (0)
Creatinine (mg/dL)	1.04 (0.76–1.45)	1.18 (0.73–1.65)	0.865	0 (0)
BUN/Creatinine ratio	20.6 (16.0–26.5)	20.9 (17.4–29.3)	0.295	0 (0)
CRP (mg/dL)	0.40 (0.13–1.34)	0.42 (0.17–1.75)	0.369	8 (1.5)
Laboratory data at discharge				
BNP (pg/mL)	162.1 (76.0–305.8)	118.5 (73.1–225.3)	0.199	91 (17.4)
Hemoglobin (g/dL)	11.4 (10.1–12.8)	10.6 (9.9–12.1)	0.027	1 (0.2)
Sodium (mEq/L)	140.0 (138.0–142.0)	132.0 (130.0–134.0)	<0.001	0 (0)
Potassium (mEq/L)	4.3 (4.0–4.6)	4.4 (4.1–4.8)	0.149	0 (0)
Albumin (g/dL)	3.6 (3.4–3.9)	3.6 (3.2–4.0)	0.545	102 (19.5)
Total bilirubin (mg/dL)	0.6 (0.5–0.8)	0.6 (0.4–0.8)	0.985	29 (5.5)
BUN (mg/dL)	24.9 (18.3–36.3)	32.8 (20.0–48.5)	0.024	0 (0)
Creatinine (mg/dL)	1.08 (0.84–1.58)	1.15 (0.90–1.65)	0.370	0 (0)
BUN/Creatinine ratio	22.6 (17.9–27.9)	27.3 (18.9–34.2)	0.015	0 (0)
CRP (mg/dL)	0.21 (0.08–0.79)	0.43 (0.12–1.07)	0.039	40 (7.6)

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein.

Table 3. Logistic regression analysis for hyponatremia at discharge

	Univariable		Multivariable	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age	0.999 (0.973–1.026)	0.969	0.994 (0.966–1.024)	0.713
Male sex	1.144 (0.654–2.002)	0.637	1.088 (0.588–2.016)	0.788
SBP at discharge	0.979 (0.960–0.997)	0.025	0.978 (0.957–1.000)	0.045
Prior HF admission	1.996 (1.115–3.573)	0.020	1.676 (0.865–3.246)	0.126
Hemoglobin at discharge	0.843 (0.720–0.986)	0.033	0.885 (0.728–1.076)	0.220
BUN at discharge	1.016 (1.003–1.029)	0.015	1.010 (0.995–1.026)	0.195
CRP at discharge	1.182 (1.016–1.376)	0.030	1.225 (1.036–1.450)	0.018
LVEF at discharge	1.023 (0.981–1.066)	0.291	NS	-

CI, confidence interval; SBP, systolic blood pressure; HF, heart failure; BUN, blood urea nitrogen; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NS, not selected.

Table 4. Subgroup analysis for all-cause death: impact of hyponatremia at discharge

Factor	Subgroup	N	HR	95% CI	P value	Interaction P value
Total		523	2.657	1.574–4.486	<0.001	-
Age	≥80 years	272	2.898	1.486–5.652	0.002	0.824
	<80 years	251	2.586	1.109–6.031	0.028	
Sex	Male	260	2.330	1.121–4.844	0.023	0.615
	Female	263	3.104	1.464–6.585	0.003	
NYHA functional class at discharge	I or II	447	2.545	1.347–4.806	0.004	0.919
	III or IV	30	2.202	0.643–7.539	0.209	
SBP at discharge	≥113 mmHg	267	1.593	0.622–4.083	0.332	0.181
	<113 mmHg	254	3.553	1.853–6.815	<0.001	
Prior myocardial infarction	Yes	65	3.623	0.778–16.863	0.101	0.806
	No	452	2.669	1.525–4.671	0.001	
Atrial fibrillation	Yes	322	3.143	1.708–5.784	<0.001	0.443
	No	195	1.885	0.649–5.474	0.244	
DM/IGT	Yes	202	2.410	0.979–5.928	0.056	0.734
	No	318	2.876	1.508–5.487	0.001	
Chronic kidney disease	Yes	268	2.759	1.370–5.555	0.004	0.867
	No	253	2.543	1.154–5.602	0.021	
Use of loop diuretics at discharge	Yes	387	2.329	1.267–4.280	0.007	0.326
	No	136	4.074	1.432–11.587	0.008	
Use of β blockers at discharge	Yes	338	2.497	1.219–5.117	0.012	0.692
	No	185	3.030	1.370–6.703	0.006	
Length of hospital stay	≥16 days	263	2.773	1.494–5.146	0.001	0.499
	<16 days	260	1.892	0.663–5.396	0.233	
Hemoglobin at discharge	≥11.4 g/dL	261	3.580	1.433–8.948	0.006	0.362
	<11.4 g/dL	261	2.114	1.114–4.011	0.022	
BUN at discharge	≥25.0 mg/dL	267	2.561	1.390–4.720	0.003	0.719
	<25.0 mg/dL	256	2.104	0.731–6.053	0.168	
CRP at discharge	≥0.24 mg/dL	243	2.268	1.208–4.255	0.011	0.718
	<0.24 mg/dL	240	2.818	1.066–7.450	0.037	

LVEF at discharge	≥60.0%	202	2.584	1.160–5.759	0.020	0.301
	<60.0%	129	4.853	1.901–12.388	0.001	

HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; SBP, systolic blood pressure; DM, diabetes mellitus; IGT, impaired glucose tolerance; BUN, blood urea nitrogen; CRP, C-reactive protein; LVEF, left ventricular ejection fraction.

Table 5. Subgroup analysis for all-cause death and rehospitalization for HF: impact of hyponatremia at discharge

Factor	Subgroup	N	HR	95% CI	P value	Interaction P value
Total		523	1.774	1.192–2.641	0.005	-
Age	≥80 years	272	2.037	1.212–3.424	0.007	0.572
	<80 years	251	1.630	0.877–3.032	0.123	
Sex	Male	260	1.989	1.139–3.472	0.016	0.585
	Female	263	1.576	0.892–2.784	0.117	
NYHA functional class at discharge	I or II	447	1.585	0.998–2.516	0.051	0.532
	III or IV	30	1.088	0.387–3.060	0.872	
SBP at discharge	≥113 mmHg	267	1.268	0.635–2.531	0.501	0.211
	<113 mmHg	254	2.268	1.380–3.726	0.001	
Prior myocardial infarction	Yes	65	1.497	0.450–4.984	0.511	0.821
	No	452	1.832	1.200–2.798	0.005	
Atrial fibrillation	Yes	322	1.706	1.056–2.758	0.029	0.871
	No	195	1.760	0.831–3.727	0.140	
DM/IGT	Yes	202	1.084	0.518–2.265	0.831	0.082
	No	318	2.351	1.460–3.786	<0.001	
Chronic kidney disease	Yes	268	1.572	0.892–2.769	0.118	0.602
	No	253	2.004	1.144–3.510	0.015	
Use of loop diuretics at discharge	Yes	387	1.679	1.065–2.646	0.026	0.599
	No	136	2.106	0.927–4.788	0.075	
Use of β blockers at discharge	Yes	338	1.733	1.024–2.933	0.040	0.695
	No	185	2.032	1.091–3.782	0.025	
Length of hospital stay	≥16 days	263	1.881	1.149–3.079	0.012	0.543
	<16 days	260	1.511	0.756–3.020	0.242	
Hemoglobin at discharge	≥11.4 g/dL	261	2.370	1.275–4.404	0.006	0.214
	<11.4 g/dL	261	1.374	0.817–2.309	0.231	
BUN at discharge	≥25.0 mg/dL	267	1.495	0.921–2.426	0.103	0.546
	<25.0 mg/dL	256	1.962	0.972–3.960	0.060	
CRP at discharge	≥0.24 mg/dL	243	1.555	0.930–2.599	0.092	0.715

	<0.24 mg/dL	240	1.845	0.947–3.594	0.072	
LVEF at discharge	≥60.0%	202	1.888	1.032–3.456	0.039	0.479
	<60.0%	129	2.637	1.279–5.436	0.009	

HF, heart failure; HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; SBP, systolic blood pressure; DM, diabetes mellitus; IGT, impaired glucose tolerance; BUN, blood urea nitrogen; CRP, C-reactive protein; LVEF, left ventricular ejection fraction.