Prognostic value of serum hyponatremia for outcomes in patients with heart failure with preserved ejection fraction: An observational cohort study

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Abstract. Hyponatremia is a risk factor associated with poor prognosis in patients with heart failure (HF) with reduced ejection fraction. However, whether hyponatremia has a similar role in patients with HF with preserved ejection fraction (HFpEF) has remained controversial. Therefore, the present study aimed to investigate the clinical characteristics and 24-month prognostic profile of a cohort of patients with HFpEF in China. From a registered observational cohort study on 1,027 subjects with HF, 496 patients with HFpEF were included. The association between baseline hyponatremia on admission and 24-month adverse outcomes (including all-cause mortality, re-hospitalization for HF and stroke) was analyzed using logistic regression with the Cox proportional hazards model. Of the 496 patients with HFpEF with a mean age of 72.8 years and proportion of males of 53.0%, 71 patients were diagnosed with hyponatremia. Furthermore, 29 patients (5.8%) were lost to follow-up. The hyponatremia group had lower blood pressure and serum hemoglobin, higher N-terminal pro B-type natriuretic peptide (NT-proBNP) and D-dimer, more patients with a history of atrial fibrillation and a higher proportion of spironolactone and loop diuretic use. According to a multivariate regression analysis, New York Heart Association functional classes III-IV and a serum NT-proBNP level above the median were risk factors for hyponatremia, while higher systolic blood pressure and β-blocker use were protective factors against hyponatremia. In the Kaplan-Meier analysis, hyponatremia was associated with all-causes of mortality, re-hospitalization for HF and a poor prognosis for patients suffering from strokes (log-rank P<0.05 for all 3 endpoints). On multivariate logistic regression analysis with the Cox proportional hazard model, hyponatremia was an independent predictor of three adverse outcomes [all-cause mortality: Hazard ratio (HR)=1.54, 95% CI=1.07-2.91, P=0.034; re-hospitalization for heart failure: HR=1.28, 95% CI=1.16-2.47, P=0.013; stroke: HR=1.78, 95% CI=1.04-2.89, P=0.016]. Collectively, the present results suggested that hyponatremia on admission was significantly associated with all-cause mortality, re-hospitalization and stroke within 24 months in a cohort of hospitalized patients with HFpEF in China. Thus, hyponatremia should be carefully monitored and frequently adjusted in patients with HFpEF (NCT04062500).

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Introduction

Heart failure (HF) is a clinical syndrome associated with poor quality of life, substantial health-care resource utilization and premature mortality (1). Despite the fact that the division of HF with preserved ejection fraction (HFpEF) varies depending on the cut-off point of the left ventricular ejection fraction (LVEF) used, previous studies have reported that HFpEF accounted for ~50% of patients with HF (2). Unlike HF with reduced EF (HFrEF), HFpEF is characterized by heterogenetic pathophysiology processes and various co-morbidities (3).

Hyponatremia, defined as a serum sodium levels of <135 mmol/l, is one of the major electrolyte disorders in acute hospitalized patients (4), and its prevalence in patients with acute HF (AHF) was estimated to be ≤25% (5-7). HF involves fluid retention in the body and diuretics are normally used to induce a negative balance of sodium in patients with HF, and all of this may lead to hyponatremia. A lower serum sodium level in AHF may indicate poor water excretion attributed to cardio-renal insufficiency, which is linked to a worse clinical outcome. Previous studies have revealed that hyponatremia is an independent predictor of mortality and re-hospitalization

for patients with HFrEF (7,8) and has been demonstrated in HFpEF populations (9,10). However, there is limited data on the burden of hyponatremia and its complications in patients with HFpEF in China and any other Asian countries.

To the best of our knowledge, the prevalence and factors associated with hyponatremia among patients with HFpEF have not been studied in China or other Asian countries. Therefore, the aim of the present study was to examine the clinical characteristics of subjects with hyponatremia via a prospective observational study with a cohort of patients with HFpEF and examine the prognostic value regarding adverse outcomes.

Materials and methods

Study population. In the present prospective observational study, consecutive symptomatic patients with HF hospitalized for the treatment of decompensated HFpEF from Shanghai 10th People's Hospital, Tongji University School of Medicine (Shanghai, China) between July 2017 and December 2018 were enrolled. The study protocol was approved by the Ethics Committee of Shanghai 10th People's Hospital (Shanghai, China). Written informed consent for medical treatment was provided by each patient on admission. The present study was based on a previously registered clinical trial (NCT04062500). Symptomatic HFpEF was defined based on the Framingham criteria (11) and a left ventricular ejection fraction (LVEF) of >50%. In line with previous studies, patients were ≥18 years of age and met the Framingham criteria for the diagnosis of HF (presence of either two major criteria or combination of one major criterion and two minor criteria). Patients with severe liver disease, trauma, infection and recent surgery were excluded. A flow diagram depicting the movement of the patients throughout the study is presented in Fig. 1.

Blood samples and echocardiography were obtained within 24 h of hospitalization of admission before any treatment was given. Echocardiographic parameters were measured by experienced echocardiographic cardiologists according to the recommendations of the American Society of Echocardiography (12). The left atrial diameter, measured as the diameter from the anterior to the posterior side of the left atrium, the left ventricular end-systolic diameter and the left ventricular end-diastolic diameter were determined in the parasternal long-axis view. The left ventricular ejection fraction was calculated using a biplane methods of disc (modified Simpson's rule) in four-chamber view (13).

The patients' medical history and current medical treatment of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blocker, β-blockers, aldosterone antagonists, loop diuretics, antiplatelet agents, oral anticoagulants and calcium channel blockers were collected. Cardiac function was evaluated using the New York Heart Association (NYHA) classification (1).

Data preparation and outcome measures. Patients were categorized depending on their level of sodium on first admission to the center. Each patient was assigned to either the hyponatremia group if serum sodium was <135 mmol/l or the non-hyponatremia group if sodium was ≥135 mmol/l. The follow-up period of the patients was 24 months. Clinical events, including all-cause mortality, re-hospitalization for HF and stroke, were recorded via telephone enquiry and searching of the patients' electronic medical records. The prognostic value of hyponatremia for the outcomes of patients with HFpEF was investigated.

Statistical analysis. Continuous, normally distributed variables are presented as the mean ± standard deviation and non-normally distributed data as the median (interquartile range). Data were compared using the independent-samples Student's t-test or by one-way analysis of variance and the Mann-Whitney U-test, as appropriate. Categorical data are presented as n (%) and compared using Pearson's χ^2-test.

Univariate logistic regression analysis was used to assess the influence of relevant variables on hyponatremia that were derived from a comparison of baseline characteristics and published literature (14). In addition, multivariate logistic regression analysis was performed to determine whether they have a significant influence on the outcomes. Cumulative survival rates were calculated according to the Kaplan-Meier method with the log-rank test used for comparison between hyponatremia and non-hyponatremia groups, setting statistical power by assuming an event rate of 0.3 for all-cause mortality, re-hospitalization for HF and stroke.

Cox-proportional hazards models were used to calculate the hazard ratio (HR) with corresponding 95% CI for occurrence of the primary study end-points (all-cause mortality, re-hospitalization for HF and stroke) associated with each pattern of hyponatremia development. All-cause mortality was adjusted by age, sex, body mass index (BMI), systolic blood pressure (SBP), hyponatremia, N-terminal pro B-type natriuretic peptide (NT-proBNP), NYHA class, atrial fibrillation history, estimated glomerular filtration rate (eGFR) and hemoglobin. Re-hospitalization for HF was adjusted by age, sex, BMI, SBP, hyponatremia, NT-proBNP, NYHA class, atrial fibrillation history, eGFR and hemoglobin. Furthermore, stroke was adjusted by age, sex, SBP, hyponatremia, D-dimer, atrial fibrillation history, anti-platelet use and statin use.

P<0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS v.25 (IBM Corp.).

Results

Baseline clinical characteristics of patients with HFpEF. In total, 496 patients with HFpEF (mean age, 72.8±11.6 years; 53.0% males) were included and the mean serum sodium level was 140.1±4.7 mmol/l. Patients with hyponatremia had a mean sodium level of 131.1±3.6 mmol/l. Baseline characteristics of patients with HFpEF are presented in Table I. The hyponatremia group had a significantly lower blood pressure (SBP, 112.1±13.1 vs. 137.1±22.5 mmHg, P<0.001; diastolic blood pressure (DBP), 67.7±11.6 vs. 76.9±12.4 mmHg, P=0.002) and hemoglobin levels (113.4±14.4 vs. 123.2±22.1 g/l, P<0.001) but higher NT-proBNP [1,168.0 (586.1-3,000.0) vs. 1,046.0 (525.8-2,380.5), P<0.001] and D-dimer levels [0.78 (0.48-1.43) vs. 0.47 (0.27-0.90), P<0.001]. Furthermore, the hyponatremia group contained a larger proportion of patients with a history of atrial fibrillation (49.3 vs. 28.9%, P<0.001). The proportion of patients taking aldosterone antagonists and loop diuretics

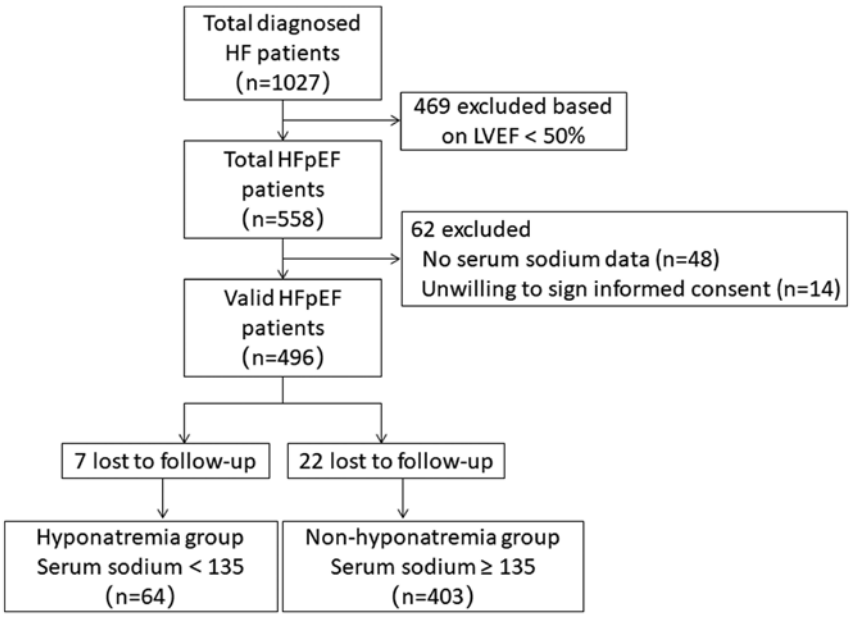

Figure 1. Flow chart of the study. LVEF, left ventricle ejection fraction; HF, heart failure; HFpEF, HF with preserved ejection fraction.

was higher in the hyponatremia group (59.2 vs. 33.4%, P<0.001; 66.2 vs. 40.2%, P<0.001, respectively). Furthermore, there were no differences in age, sex, percentage of NYHA III-IV, eGFR, lipid profile, blood glucose, echocardiographic parameters and other medications that the patients were taking.

Serum sodium distribution of patients with HFpEF and logistic regression analysis for risk factors of hyponatremia. The distribution of serum sodium levels was analyzed in patients with HFpEF and the majority of patients was within the interval of 141.5-142.4 mmol/l (n=56; Fig. S1).

Univariate logistic regression analyses identified that hyponatremia was positively associated with NT-proBNP >median [odds ratio (OR)=6.045, 95% CI=3.41-10.72], NYHA classification III-IV (OR=2.994, 95% CI=1.714-5.057), atrial fibrillation history (OR=2.100, 95% CI=1.233-3.577), loop diuretics (OR=1.875, 95% CI=1.094-3.215) and spironolactone (OR=1.799, 95% CI=1.058-3.058), but it was negatively associated with β-blockers (OR=0.569, 95% CI=0.331-0.981),SBP (OR=0.946, 95% CI=0.930-0.962) and DBP (OR=0.965, 95% CI=0.945-0.986). Multivariate logistic regression analysis demonstrated that in patients with HFpEF, a higher NT-proBNP (above median, OR=4.521, 95% CI=2.450-9.584) or worse cardiac function (OR=2.275, 95% CI=1.207-4.338) were positively associated with hyponatremia. In addition, a higher SBP (OR=0.942, 95% CI 0.920-0.964) and β-blocker use (OR=0.343, 95% CI=0.186-0.675) were negatively associated with hyponatremia (Table II).

Clinical outcomes of patients with HFpEF. In total, 29 (6%) patients were lost to follow-up, mortality occurred in 71 (15.2%) cases in the first 24 months, 129 (27.6%) patients were re-hospitalized for HF and 77 (16.5%) patients had a stroke. Furthermore, the hyponatremia group had a worse prognosis compared with the non-hyponatremia group. All-cause mortality was 39.1% in the hyponatremia group compared with 11.4% in the non-hyponatremia group (P<0.001). In the hyponatremia group, 40.6% of patients were re-hospitalized for HF, as compared with 25.6% in the non-hyponatremia group (P=0.016). Furthermore, the prevalence of stroke was 28.1% in the hyponatremia group as compared with 14.6% in the non-hyponatremia group (P=0.011; Table III).

Survival analysis. The median duration of the follow up of the study participants was 24 months. The number of mortalities in the hyponatremia group was 25 (39.1% of patients) compared with 46 in the non-hyponatremia group (11.4% of patients). Kaplan-Meier survival curves (Fig. 2) indicated that there were significant differences in survival status, re-hospitalization and stroke between the two groups of patients with HFpEF. In addition, patients with sodium levels ≥135 mmol/l had an improved prognosis compared with patients with hyponatremia.

In order to investigate the predictors of adverse events in patients with HFpEF, a multivariate Cox proportion hazard regression model was established for all-cause mortality, re-hospitalization and stroke (Fig. 3). It was indicated that hyponatremia was an independent predictor for three adverse events in patients with HFpEF (all-cause mortality: Adjusted HR=1.54, 95% CI=1.07-2.91, P=0.034; re-hospitalization: Adjusted HR=1.28, 95% CI=1.16-2.47, P=0.013; stroke: Adjusted HR=1.78, 95% CI=1.04-2.89, P=0.016). Another independent predictor for all-cause mortality was older age (adjusted HR=1.07, 95% CI=1.05-1.09, P<0.001). Furthermore, lower SBP (adjusted HR=0.97, 95% CI=0.97-0.98, P<0.001), NT-proBNP >median (adjusted HR=1.62, 95% CI=1.05-3.03, P=0.027), NYHA III-IV (adjusted HR=1.73, 95% CI=1.07-2.81, P=0.021), AF history (adjusted HR=2.69, 95% CI=1.32-3.58, P<0.001) and eGFR<60 ml/min/1.73 m^2 (adjusted HR=0.51, 95% CI=0.28-0.91, P=0.024) were significantly associated with all-cause mortality. Other independent predictors for re-hospitalization were older age (adjusted HR=1.04, 95% CI=1.02-1.07, P=0.008), lower SBP (adjusted HR=0.96, 95% CI=0.95-0.99, P=0.001), NT-proBNP >median

Table I. Baseline clinical characteristics of patients with heart failure with preserved ejection fraction based on serum sodium status.

Item	Normal range	Serum sodium concentration (mmol/l)		P-value
		<135 (n=71)	≥135 (n=425)	
Age (years)	-	73.9±11.8	72.6±11.6	0.381
Male sex	-	31 (43.7)	232 (54.6)	0.104
BMI (kg/m^2)	-	24.1±3.80	23.9±4.16	0.342
SBP (mmHg)	-	112.1±13.1	137.1±22.5	<0.001
DBP (mmHg)	-	67.7±11.6	76.9±12.4	0.002
Heart rate (beats/min)	-	88.3±17.3	89.9±17.5	0.490
NYHA class III-IV	-	65 (91.5)	391 (92.0)	0.761
Medical history				
Diabetes	-	24 (33.8)	153 (36.0)	0.790
Hypertension	-	48 (67.6)	292 (68.7)	0.893
Coronary artery disease	-	43 (60.6)	256 (60.2)	1.000
Atrial fibrillation	-	35 (49.3)	123 (28.9)	<0.001
Laboratory data				
Hemoglobin (g/l)	110-160	113.4±14.4	123.2±22.1	<0.001
CRP (mg/l)	0-10	7.65 (3.02-18.0)	3.23 (3.02-11.9)	0.079
Alb (g/l)	35-50	38.3±5.60	39.7±4.81	0.082
UA (μmol/l)	<420	371.6±73.5	383.1±62.7	0.523
eGFR (ml/min/1.73 m^2)	>90	69.9±23.9	67.1±23.5	0.357
TC (mmol/l)	2.8-5.2	3.75±1.04	3.78±1.14	0.831
LDL-C (mmol/l)	<3.1	1.98±0.86	2.08±1.00	0.442
HDL-C (mmol/l)	0.8-1.8	1.09±0.39	1.14±0.65	0.698
Sodium (mmol/l)	135-145	131.1±3.6	141.6±2.8	<0.001
Potassium (mmol/l)	3.5-5.5	4.19±0.53	3.98±0.54	0.980
HbA1C (%)	4-6	6.42±1.92	6.39±1.60	0.195
NT-proBNP (ng/l)	125 (<75 years) 450 (≥75 years)	1,168.0 (586.1-3,000.0)	1,046.0 (525.8-2,380.5)	<0.001
D-dimer (mg/l)	<0.55	0.78 (0.48-1.43)	0.47 (0.27-0.90)	<0.001
Echocardiographic parameters				
LVEF (%)	-	58.1±4.35	58.9±4.45	0.104
LAD (mm)	-	41.0±6.12	41.1±6.62	0.690
LVeDD (mm)	-	45.4±4.88	45.9±4.99	0.512
Levs (mm)	-	29.7±4.86	29.9±4.80	0.744
Medications				
ACEI/ARB	-	29 (40.8)	170 (40.1)	0.847
Beta-blocker	-	48 (67.7)	302 (71.1)	0.059
Aldosterone blocker	-	42 (59.2)	142 (33.4)	<0.001
Loop diuretic	-	47 (66.2)	171 (40.2)	<0.001
Antiplatelet agent	-	55 (77.5)	345 (81.2)	0.519
Oral anticoagulant	-	26 (36.6)	189 (44.5)	0.248
Calcium channel blocker	-	22 (31.0)	144 (33.9)	0.692
Cost (Yuan)	-	31,140.1±30,503.2	32,583±64,318.6	0.771

Continuous variables are presented as the mean ± standard deviation if they conform to a normal distribution, and otherwise as the median with interquartile range. Categorical variables are presented as n (%). Cost refers to the cost of medical treatment during hospitalized period. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, c-reactive protein; Alb, albumin; UA, uric acid; eGFR, estimated glomerular filtration rate; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1C, glycated hemoglobin A1C; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; Levs, left ventricular end-systolic diameter; LVeDD, left ventricular end-diastolic diameter; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

Table II. Univariate and multivariate logistic regression analysis for the risk factors of hyponatremia.

	Univariate logistic regression			Multivariate logistic regression		
Variable	OR	95% CI	P-value	OR	95% CI	P-value
SBP	0.946	0.930-0.962	<0.001	0.942	0.920-0.964	<0.001
NYHA III-IV	2.994	1.714-5.057	<0.001	2.275	1.207-4.338	0.013
Atrial fibrillation history	2.100	1.233-3.577	0.006	1.831	0.963-3.325	0.057
Beta-blocker	0.569	0.331-0.981	0.043	0.343	0.186-0.675	0.002
Loop diuretic	1.875	1.094-3.215	0.022	1.003	0.476-2.235	0.985
Spironolactone	1.799	1.058-3.058	0.030	0.907	0.422-2.062	0.840
NT-proBNP >median[a]	6.045	3.41-10.72	<0.001	4.521	2.450-9.584	0.001

[a]The median value for NT-proBNP was 2,294 pg/ml. OR, odds ratio; SBP, systolic blood pressure; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

Table III. Outcomes of patients with HF with preserved ejection fraction based on serum sodium status.

		Serum sodium concentration (mmol/l)		
Variable	All patients	<135 (n=64)	≥135 (n=403)	P-value
All-cause mortality	71 (15.2)	25 (39.1)	46 (11.4)	<0.001
Re-hospitalization for HF	129 (27.6)	26 (40.6)	103 (25.6)	0.016
Stroke	77 (16.5)	18 (28.1)	59 (14.6)	0.011

P-values were adjusted for age and sex. HF, heart failure.

(adjusted HR=1.24, 95% CI=1.03-2.08, P=0.042), NYHA III-IV (adjusted HR=2.15, 95% CI=2.02-2.46, P=0.001) and additional AF history (adjusted HR=1.48, 95% CI=1.05-2.20, P=0.003). In addition, other independent predictors for stroke were lower SBP (HR=0.99, 95% CI=0.98-0.99, P=0.042), higher D-dimer levels (HR=1.96, 95% CI=1.30-2.59, P=0.025) and atrial fibrillation history (HR=1.34, 95% CI=1.15-2.47, P=0.018).

Discussion

In the present observational study, it was indicated that hyponatremia was associated with higher all-cause mortality and re-hospitalization for HF in a cohort of patients with HFpEF; these results were consistent with those of previous studies (14-16). Furthermore, patients with HFpEF with hyponatremia had lower blood pressure, higher serum levels of NT-proBNP and D-dimer, serious anemia and atrial fibrillation, as well as higher rate of medication used, such as spironolactone and loop diuretics, which suggested that the disease in those patients was more serious and should be actively treated. To the best of our knowledge, the present study was the first to demonstrate that hyponatremia was an independent predictor of the incidence of stroke in a patient population with HFpEF.

HFpEF is an increasingly prevalent phenotype of HF. Unlike those for HFrEF, the diagnosis and treatment of HFpEF are not well-standardized, rendering numerous patients with HFpEF misdiagnosed or underdiagnosed. In this situation, the disease may further progress due to poor appetite and low-sodium diet (insufficient intake), and a high dose of diuretic agents (excessive loss), leading to electrolyte disorders, particularly hyponatremia (16).

Hyponatremia is the most common electrolyte disorder (17) and is frequently encountered in patients with HF. It may either arise from depletion (excessive sodium depletion), which is caused by extensive administration of diuretics as aforementioned, or dilution, which is caused by impaired glomerular filtration. Therefore, dilutional hyponatremia in patients with HF with impaired renal function likely results in volume overload, which deteriorates the condition and subsequently leads to a worse prognosis (16). Thus, hyponatremia is an adverse marker of a significant underlying disease and may enhance the severity and complexity of HF. The present results suggested a high incidence of hyponatremia of 14.3% in hospitalized patients with HF, which is comparable to that reported by other studies on acute decompensated HF (7,18,19).

The causes of hyponatremia are miscellaneous, as the present results suggested that a higher NYHA class and NT-proBNP levels increase the risk, while usage of renin-angiotensin-aldosterone system (RAAS) inhibitor and β-blockers reduce the risk. On one hand, it has been reported that NYHA class and NT-proBNP correlate with the severity of HF (14). While patients with severe HF require a large dosage of diuretics, this will lead to disturbance of homeostasis and pose a higher risk for hyponatremia. The present results support this concept

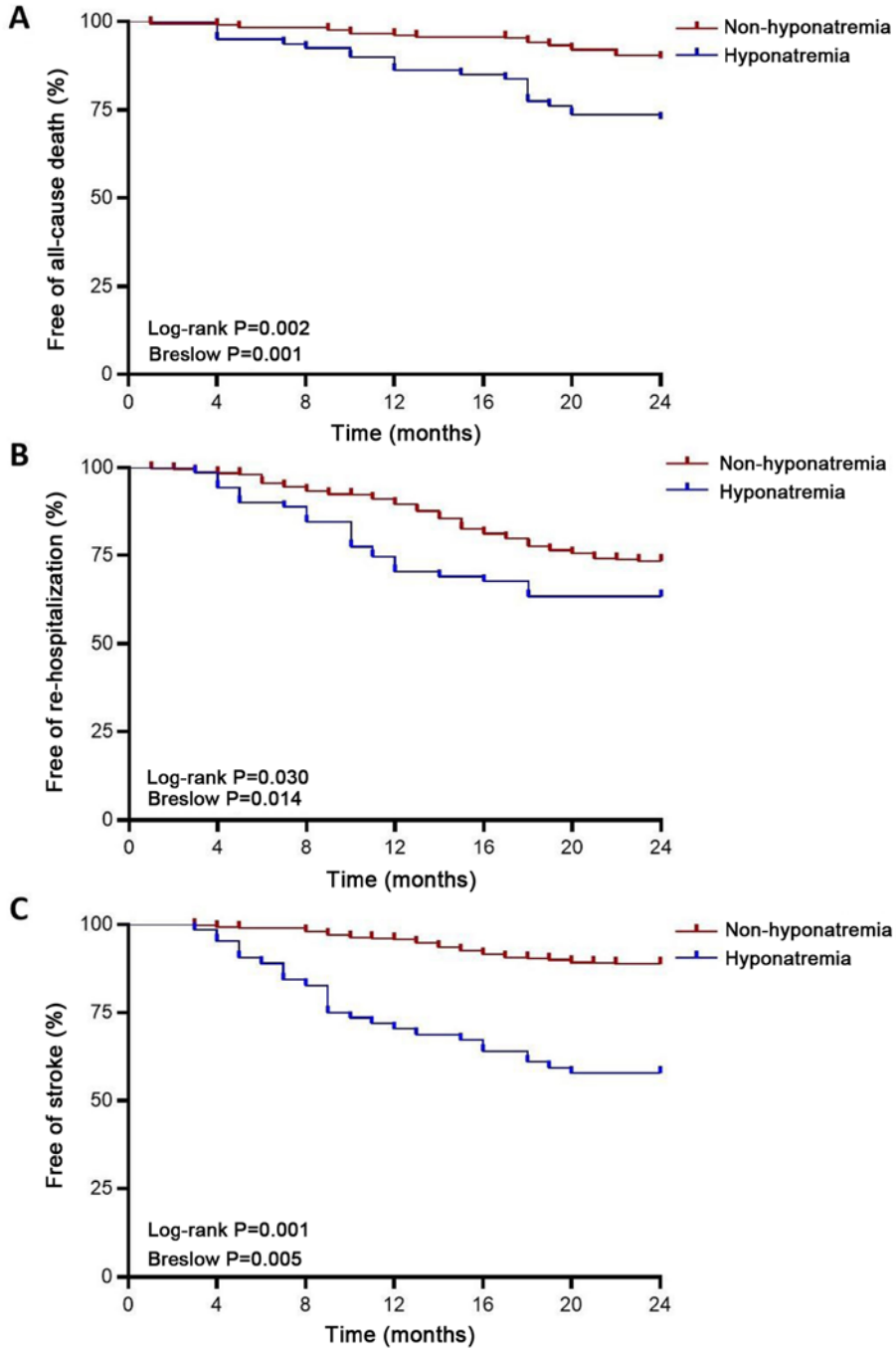

Figure 2. Kaplan Meier survival curves for patients with HFpEF based on the serum sodium status. (A) Rate of survival (no mortality from any cause) in the two groups. (B) Rate of freedom from re-hospitalization in the two groups. (C) Rate of freedom from stroke in the two groups. Patients with hyponatremia had a significantly higher all-cause mortality, re-hospitalization rate and stroke rate (P=0.002, 0.030 and 0.001, respectively). HFpEF, heart failure with preserved ejection fraction.

and are consistent with those of previous studies (20). One the other hand, dilutional hyponatremia resulting from concomitant activation of the RAAS and sympathetic nervous system may be counteracted by the use of RAAS inhibitor or β-blockers (21,22). This is also in line with the present results.

Previous studies have reported that hyponatremia was associated with worse short-term, mid-term and long-term outcomes (1,19,23). In the OPTIMIZE-HF (24) and OPTIME-CHF (19) trials, following a drop in serum sodium levels (per 3 mmol/l decrease from 140 mmol/l), the OR of in-hospital mortality, 60-day mortality and 60-90 day mortality was 1.25, 1.18 and 1.10, respectively. In the present study, all-cause mortality was 13.9% in patients with HFpEF, which is lower than the rates obtained in other trials (OPTIME-CHF, 27%; ACTIV-in-CHF, 21%) (5,19). Furthermore, hyponatremia was associated with a 2-fold increased risk of 24-month all-cause mortality. Hence, hyponatremia is a valuable predictor of prognosis in patients with HF.

A number of factors contribute to the poor outcomes in patients with HFpEF with hyponatremia. For instance, HF progression is closely linked to the activation of the neuroendocrine system, which is classically represented

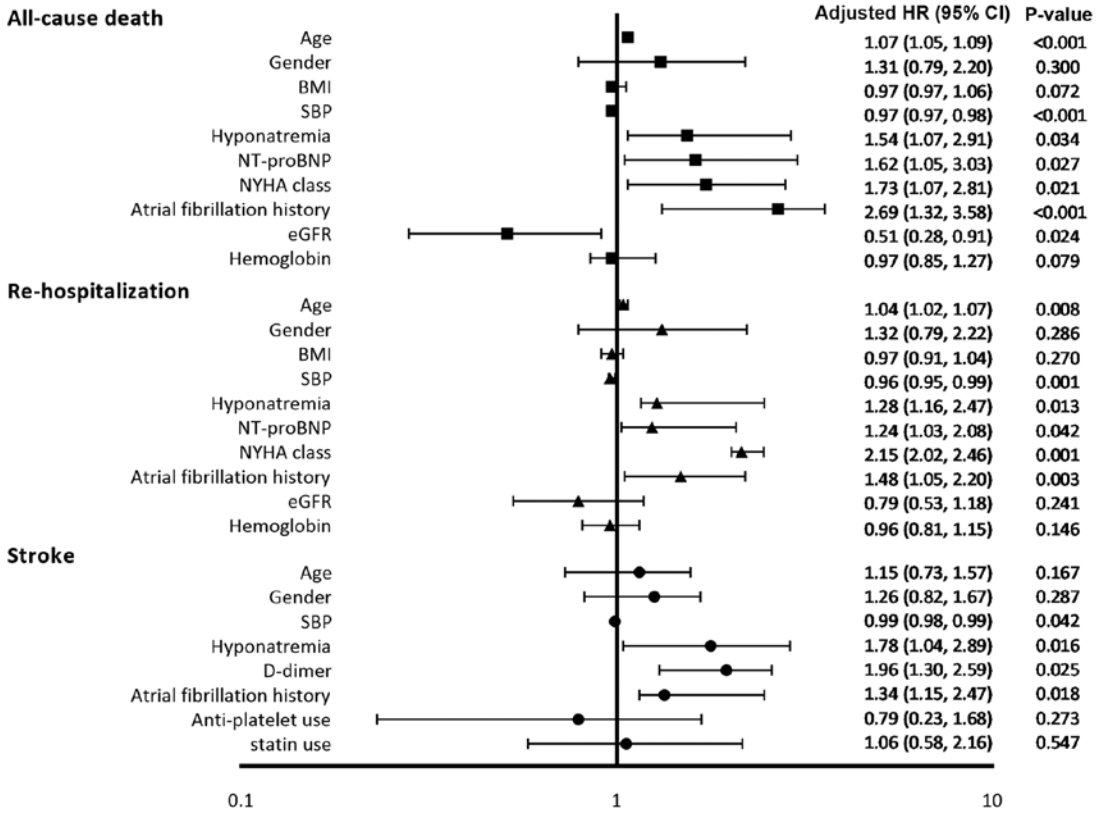

Figure 3. Predictors of all-cause mortality, re-hospitalization and stroke in patients with HFpEF. Logistic regression analysis with the Cox proportional hazard model was performed for the three endpoint events. Univariate analysis was applied prior to the multivariate analysis (data not shown). According to the results of the multivariate analysis, hyponatremia, older age, lower SBP, NT-proBNP above the median, NYHA class III-IV, a history of AF and eGFR<60 ml/min/1.73 m^2 predicted higher all-cause mortality, after adjustment for sex, BMI and hemoglobin. Furthermore, hyponatremia predicted a higher re-hospitalization rate and a higher incidence of stroke. HR, hazard ratio; HFpEF, heart failure with preserved ejection fraction; AF, atrial fibrillation; BMI, body mass index; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

by the RAAS. Furthermore, hyponatremia may directly upregulate the activity of RAAS and arginine vasopressin (AVP), which increase the heart rate, vessel constriction and renal urine reabsorption. However, excessive activation of the neuroendocrine system may result in adverse effects, including increased cardiac afterload and myocardial oxygen consumption, cardiac cell death and myocardial fibrosis (25). However, the amount of BNP secreted into the circulation of patients with exacerbation inhibits the release of aldosterone to facilitate natriuresis (26,27).

To the best of our knowledge, the present study was the first to demonstrate that hyponatremia (OR=1.78, 95% CI=1.04, 2.89, P=0.016) was a stronger predictor of stroke in patients with HFpEF. Furthermore, a previous study reported that hyponatremia was associated with stroke (28). Aberrant serum sodium levels are also considered as a complication of cerebrovascular disease (29), and the possible mechanisms are associated with inappropriate secretion of antidiuretic hormone, frequent use of diuretics, as well as blood concentration and viscosity (30).

Since hyponatremia is independently associated with poor outcomes, correcting hyponatremia in a timely and appropriate manner may improve the prognosis of patients with HFpEF. There are different treatment options, the first of which includes a daily fluid allowance of 800-100 ml. As another option, the addition of furosemide with an ACEI is able to significantly improve the sodium concentration. In addition, arginine vasopressin (AVP) receptor antagonists, which have a central role in regulating water retention via these receptors, may be used. It has been revealed that anemia, NT-proBNP and NYHA cardiac function not only have an impact on the risk of mortality, but also on the incidence of hyponatremia (14,31), which should be corrected as soon as possible.

The present study had several limitations. First, it was designed as an observational study and was potentially open to selection bias, as patients with severe liver disease, trauma, infection and recent surgery were excluded. Furthermore, the etiology of hyponatremia was not surveyed in the patients. The present study did not differentiate true hyponatremia from pseudo-hyponatremia and did not analyze depletion and dilution hyponatremia, but the prognosis and treatment were different between them (32). In addition, tolvaptan and AVP receptor antagonists were not widely used in the current cohort and these should be further examined to assess their effect on patients with HFpEF. Due to potential recall bias when performing the subgroup analysis, the present study did not avoid the influence of the history of atrial fibrillation on the incidence of stroke.

In conclusion, the present results indicated that hyponatremia on admission may be a useful prognostic marker for patients with HFpEF. However, larger studies are required to be performed to confirm these results, as well as to elucidate

the mechanisms of mortality and stroke associated with hyponatremia and identify the potential benefit of correction of hyponatremia in patients with HFpEF.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Conception and design: YS, YL, CY. Clinical support and acquisition of data: YS, YL, CY. Provision of study materials or patients: YS, YL. Collection and collation of data: YS, MM, HZ, XP, XZ and FZ. Data analysis and interpretation: YS, YL. Manuscript writing: YS, MM, HZ, YL, CY. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Research Ethical Committee of Shanghai 10th People's Hospital of Tongji University School of Medicine (Shanghai, China) and conducted according to the principles expressed in the Declaration of Helsinki. The data were retrieved from the hospital's medical record system and therefore, no additional informed consent was required. The institutional review board also waived the need for written informed consent from the participants. The privacy of patients' personal data was protected.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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