Prognostic Relevance of Elevated Plasma Osmolality on Admission in Acute Decompensated Heart Failure With Preserved Ejection Fraction: Insights From PURSUIT-HFpEF Registry

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Research Article

Keywords: HFpEF, plasma osmolality, prognosis

Posted Date: December 28th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-131158/v1

Abstract

Background

Complicated pathophysiology makes it difficult to identify the prognosis of heart failure with preserved ejection fraction (HFpEF). While plasma osmolality has been reported to have prognostic importance, mainly in heart failure with reduced ejection fraction (HFrEF), its prognostic meaning for HFpEF has not been elucidated.

Methods

We prospectively studied 960 patients in PURSUIT-HFpEF, a multicenter observational study of acute decompensated HFpEF inpatients. We divided patients into three groups according to the quantile values of plasma osmolality on admission. During a follow-up averaging 366 days, we examined the primary composite endpoint of cardiac mortality or heart failure re-admission using Kaplan-Meier curve analysis and Cox proportional hazard testing.

Results

216 (22.5%) patients reached the primary endpoint. Kaplan-Meier curve analysis revealed that the highest quantile of plasma osmolality on admission (higher than 300.3 mOsm/kg) was significantly associated with adverse outcomes (Log-rank P = 0.0095). Univariable analysis in the Cox proportional hazard model also revealed significantly higher rates of adverse outcomes in the higher plasma osmolality on admission (hazard ratio [HR] 7.29; 95% confidence interval [CI] 2.25–23.92, P = 0.0009). Multivariable analysis in the Cox proportional hazard model also showed that higher plasma osmolality on admission was significantly associated with adverse outcomes (HR 4.70; 95% CI 1.33–17.35, P = 0.0160) independently from other confounding factors such as age, gender, comorbid of atrial fibrillation, hypertension history, diabetes, malnutrition, and N-terminal pro-B-type natriuretic peptide elevation.

Conclusions

Higher plasma osmolality on admission was prognostically important for acute decompensated HFpEF inpatients.

Introduction

There are many common problems in heart failure (HF) that are linked to hospitalization and mortality.(1) Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all HF cases, and this rate is increasing.(2) Because of their pathophysiological complexity(3), the precise mechanisms involved in HFpEF with a poor prognosis are not fully understood.

Plasma osmolality is easily estimated with a blood sample as(4):

2 x [Serum Sodium] + [blood urea nitrogen]/2.8 + [glucose]/18 (1)

Although the components of the formula, namely sodium(5), blood urea nitrogen(6), serum glucose(7), and other parameters interacting with osmolality such as serum albumin(8) and renal function(9) have been proven to affect the prognosis of heart failure, little has been elucidated about the prognostic meaning of osmolality itself in acute decompensated HF (ADHF).

Plasma osmolality has been reported to be influenced by well-known prognostic factors such as arginine vasopressin (AVP), the renin-angiotensin-aldosterone system (RAAS), and natriuretic peptides(10) (11) (12), which suggests that osmolality itself could be also associated with the prognosis of HF. On one hand, Vaduganathan *et al.* reported that lower osmolality was associated with poor outcomes in heart failure with reduced ejection fraction (HFrEF) from a *post hoc* analysis of the EVEREST trial.(13) Kaya *et al.* also reported that low osmolality on admission correlated with a poor prognosis in HFrEF patients.(14) On the other hand, independent from left ventricular ejection fraction (LVEF), Arévalo-Lorido *et al.* reported higher osmolality in ADHF patients could predict worse outcomes accompanied by higher comorbidities through the National Registry of Heart Failure (RICA).(15)

Based on these previous reports, the aim of this study was to investigate further the prognostic meaning of plasma osmolality, particularly in acute decompensated HFpEF patients.

Methods

The PURSUIT-HFpEF registry

This prospective, multicenter, observational cohort study was performed in 1008 consecutive hospitalized HFpEF patients. Details of the PURSUIT-HFpEF (The **P**rospective m**U**lticente**R** ob**S**ervational st**U**dy of pat**I**en**T**s with **H**eart **F**ailure with **p**reserved **E**jection **F**raction) registry have been described previously.(16) Briefly, in collaboration with 31 hospitals in Japan, this large-scale registry aimed to collect and record a comprehensive range of clinical data to define the pathophysiology and prognostic factors of HFpEF patients. Inclusion criteria were acute decompensated HFpEF diagnosed by the Framingham criteria for HF and the following: 1) LVEF ≥ 50% and 2) N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 400 ng/L or brain natriuretic peptide (BNP) ≥ 100 ng/L on admission. Major exclusion criteria were age < 20 years, severe valvular diseases, acute coronary syndrome on admission, life expectancy of < 6 months due to prognosis of non-cardiac diseases, and previous heart transplantation. The anonymized data were transferred to the data center of Osaka University Hospital for analysis via data capturing system connected with electronic medical records.(17) Written informed consent was received from each participating patient. This study, including the procedure for enrollment, conformed to the principles of the Declaration of Helsinki and was approved by the institutional review board of each participating facility, including the official institutional review board committee of Osaka University Hospital (approved on February 24, 2016). It was registered under the Japanese UMIN Clinical Trials Registration (UMIN000021831).

Study population

A total of 1024 inpatients with HFpEF were registered from June 2016 to February 2020. Of all the participants, 16 (1.6%) patients died in hospital. We should unfortunately exclude additional 48 patients due to missing of plasma osmolality on admission (missing of serum sodium; 1, blood urea nitrogen; 2, and glucose; 46). We finally analyzed remaining 960 (93.8%) patients discharged alive whose plasma osmolality was calculated on admission.

Plasma osmolality, nutrition status, plasma volume estimation and echocardiographic measurements

Plasma osmolality was estimated(4) with a blood sample (Equation 1). Nutrition status was estimated with the Geriatric Nutritional Risk Index (GNRI), which was calculated using serum albumin and body mass index as described previously.(18) Systemic plasma volume was estimated with plasma volume status (PVS) using hematocrit and body weight as described previously.(19) Comprehensive echocardiographic examinations were performed by trained cardiac sonographers according to the American Society of Echocardiography guidelines.(20) LVEF was calculated with the biplane Simpson's method using apical two- and four-chamber views.

Follow-up and endpoints

The primary endpoint of the present study was cardiac mortality or re-admission for HF during the follow-up period. The secondary endpoints were defined as respective events of cardiac mortality and HF re-admission. The duration of the follow-up period was calculated from the day of discharge until an endpoint, or at the time of the last patient contact (including teleconferencing).

Statistical analysis

Data are presented as median and interquartile range of 25%–75% for continuous variables and frequency/percentage for categorical variables. Continuous variables were compared using Kruskal–Wallis test (and Steel-Dwass test for between each groups) and categorical variables were compared using Fisher's exact test (with Bonferroni adjustment for between each groups). The distributions of plasma osmolality on admission and at discharge were compared with F-test. The clinical endpoint was assessed with the Kaplan–Meier curve analysis and compared with the log-rank test. Univariable Cox proportional hazards regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (CIs) for each endpoint. Multivariable Cox regression tests for plasma osmolality of our interest were performed using covariates of clinical importance as follows: age, gender, hypertension history, diabetes mellitus, GNRI, and log-transformed NT-proBNP. All statistical tests were 2-sided and $P < 0.05$ was regarded as statistically significant. Statistical analyses were performed using JMP® Pro 13.2.1, (SAS Institute Inc., Chicago IL, USA) or EZR version 1.51 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Characteristics of the study population

Distributions of plasma osmolality on admission and at discharge are shown in *Figure 1*. Compared with the distribution at discharge, that on admission was significantly wide and shifted to higher levels ($P < 0.0001$, F-test). While the normal osmolality range is known to be 275–295 mOsm/kg,(21) the median on admission was 297 mOsm/kg.

Demographic and clinical characteristics of the 960 patients are summarized in the left column of *Tables 1* and *2*. The study population had a median age of 83 years; 55% were female. Hypertension (85%) was the most prevalent comorbidity followed by atrial fibrillation, dyslipidemia, and chronic kidney disease (46%, 41%, and 40%, respectively). The medians of NT-proBNP and estimated glomerular filtration rate (GFR) were 3,250 ng/L and 45 mL/min/1.73 m^2 on admission, respectively. In the first-step treatment, more than half of all patients were treated with a bolus injection of diuretics (57%); non-invasive positive pressure ventilation was used in 13%. The most frequent prescription at discharge was a loop diuretic (79%), which was the most increased treatment during hospitalization.

According to the quantiles of plasma osmolality on admission (293.2 and 300.3 mOsm/kg), we divided patients into three groups. Background and general information on admission are described in the right column of *Table 1*. Among the components for the osmolality calculation (serum sodium, blood urea nitrogen, and glucose), serum sodium and blood urea nitrogen were significantly elevated in accordance with the elevation of plasma osmolality. In the higher osmolality groups, hypertension, diabetes mellitus, dyslipidemia and chronic kidney disease were prevalent. The higher osmolality groups showed renal dysfunction, and NT-proBNP of the highest quantile group (Q3) was significantly higher than those in other groups. Echocardiography on admission showed generally comparable between groups. In acute phase treatment, intravenous usage of carperitide was more frequent in the Q3 group. At discharge (right column of *Table 2*) higher osmolality groups on admission still had higher osmolality at discharge, and the medians plasma osmolality of Q2 and Q3 had decreased to just around the upper limit of normal. The higher osmolality groups also had significantly lower estimated GFR compared with lower osmolality groups.

Plasma osmolality and prognosis

Among 960 patients, 216 patients (22.5%) suffered composite endpoint with a mean ± standard deviation (SD) follow-up of 366 ± 356 days. As far as the secondary endpoint, 62 patients (6.5%) reached cardiac mortality in 444 ± 378 days, 204 (21.3%) re-admitted for HF in 366 ± 356 days. The Kaplan-Meier curves revealed that higher plasma osmolality was significantly associated with the primary endpoint (Log-rank $P = 0.0095$) (*Figure 2*). Univariable Cox regression tests revealed that the significance was observed particularly between the highest osmolality group (Q3) versus the lowest osmolality group (Q1) (HR 1.61; 95% CI 1.16–2.23, $P = 0.0120$) (*Table 3*). Regarding the secondary endpoint, in the Kaplan-Meier curve analyses, HF readmission was also significantly more frequent in the higher osmolality group (Log-rank $P = 0.0425$), which was not in case with cardiac mortality (Log-rank $P = 0.0937$) (*Figure 2*). Through

univariable Cox regression tests for clinically important parameters on admission, higher age, higher NT-proBNP, and higher plasma osmolality were associated with the primary endpoint (left column of *Table 4*). Moreover, these confounders were shown to be independently associated with the primary endpoint through multivariable Cox regression analysis (right column of *Table 4*).

We further examined the event risk of a composite endpoint among the quantiles stratified by plasma osmolality at discharge. The Kaplan–Meier curve showed that the event risk was not associated with the osmolality at discharge in this cohort (Log-rank $P = 0.1976$, *Online Figure S1*).

Discussion

In this study, we showed that higher plasma osmolality on admission was an important prognostic factor for HFpEF patients. Although a few reports have also indicated that plasma osmolality had prognostic meaning for HF patients, their descriptions were so scattered that we were unable to reach a consensus on how to deal with this marker. Thus, our present finding in a prospective cohort that “higher plasma osmolality on admission” impairs prognosis in “hospitalized decompensated HFpEF” patients is notable.

Prognostic difference in plasma osmolality between HFpEF and HFrEF

Though a sub-analysis of the EVEREST trial for HFrEF patients, Vaduganathan *et.al* showed that normal osmolality at discharge was associated with improved outcomes.(13) Kaya *et.al* investigated clinical implication of plasma osmolality on admission for HFrEF patients.(14) They presented the third quartile of normo-to-hyperosmolality (mean of 293 mOsm/kg) as having the smallest adverse outcome rates, while the lowest quartile (mean of 280 mOsm/kg) showed the worst outcomes, followed by the highest quartile (mean of 301 mOsm/kg). According to these studies, plasma osmolality in the normal range seemed to be quite important for HFrEF patients. This finding should also be related to the particular prognostic importance of hyponatremia in HFrEF.(22) Contrary to these reports, Arévalo-Lorido *et.al* reported that the frequency of adverse outcomes increased in accordance with the increase in osmolality on admission in ADHF(15), similarly to our findings. Although their registry did not group subjects by LVEF, about 70% of the patients had LVEFs > 45%, indicating that HFrEF was underrepresented in that cohort. Taken our present findings together with those of Arévalo-Lorido *et.al*, we conclude that the elevation of plasma osmolality on admission raises the predictability of adverse outcomes in decompensated HFpEF patients.

Cause of higher plasma osmolality in HFpEF patients

Different from HFrEF patients, higher plasma osmolality on admission was related to adverse outcomes in HFpEF patients. It should be noted that the plasma osmolality on admission in our HFpEF cohort (median of 297 mOsm/kg, *Table 1*) was generally higher than that of a previous reported HFrEF cohort (median of approximately 290 mOsm/kg).(14) In an experimental study(12), excessive RAAS activation was proven to cause osmolality elevation in the acute phase of a rapid pacing HF model. RAAS activation could cause sodium reabsorption through modulation of the GFR, tubuloglomerular feedback,

glomerulotubular balance, and distal tubular reabsorption(23), which could increase plasma osmolality. Relative hypovolemia in the higher osmolality groups compared with the lower osmolality groups was not likely to be the cause of RAAS activation because PVS was comparable between groups (*Table 1*). AVP is known to be an another cause of volume retention, and increased AVP activity causes a decrease in osmolality accompanied by hyponatremia in HFrEF patients.(24) In contrast, age-related attenuation of the AVP response(25) could be more common in elderly HFpEF patients than in younger HFrEF patients. Excessive RAAS activation compared to AVP activity might contribute to the higher plasma osmolality in HFpEF compared to HFrEF patients.

Prognostic implication of higher plasma osmolality on admission

We showed that higher plasma osmolality on admission was associated with poorer prognosis in HFpEF patients. The prognostic impact of the AVP system in HF has not been fully elucidated. Because of the short half-life of AVP, it is not practical to measure plasma AVP as a prognostic marker. In this point, copeptin has attracted attention owing to its creation from prepro-vasopressin at the same time as AVP and longer half-life.(26) Some reports have shown the prognostic implications of copeptin for HF.(27) (28) Although plasma osmolality on admission is not necessarily determined by the AVP system, there is a report consistent with our findings. Hage *et. al* described the prognostic meaning of copeptin in a prospective HFpEF cohort (KaRen-study) and clarified that copeptin was elevated in HFpEF patients and had partial prognostic implications, which were blunted after adjustment for NT-proBNP.(29) The relevance of neurohormonal balance and pathophysiology in HFpEF should be further investigated.

What are the clinical implications?

The following variables have reported as prognostic markers in the acute phase in HFpEF patients: TRPG(30), lung congestion observed as B-lines (‘comets’) on lung ultrasound(31), soluble suppression of tumorigenesis-2 with NT-proBNP(32) and cystatin C.(33) In addition to these factors, our findings showed that higher plasma osmolality also has important prognostic implications in the acute phase of HFpEF.

The higher osmolality groups presented even higher plasma osmolality than lower osmolality groups at discharge (*Table 2*), which showed those who had extremely elevated osmolality in the acute phase may suffer from some unfavorable factors which permanently raise the plasma osmolality. It is possible that those who have higher osmolality both on admission and at discharge are exposed to excessive RAAS activation, and the immediate and sustainable handling of this overactivation should be considered. Although various RAAS blockers have shown definite clinical benefits in HFrEF patients, including angiotensin converting enzyme inhibitors(34), angiotensin II receptor blockers(35), angiotensin-neprilysin inhibitors(36), and mineral corticoid-receptor antagonists(37), the benefits in HFpEF patients are controversial.(38) We propose that further investigation to determine whether these approaches are particularly favorable to HFpEF patients with higher plasma osmolality is warranted.

Limitations

Several limitations of this study should be mentioned. First, although our results showed that elevated plasma osmolality on admission was associated with poor outcomes, we could not examine whether extremely decreased plasma osmolality affected prognosis because only 42 (4.4%) subjects had < 275 mOsm/kg on admission. Of note, this finding that excessively low plasma osmolality may be rare in acute decompensated HFpEF patients is important. Second, there have been several formulas which are able to calculate plasma osmolality, and Fazekas *et al*. reported a formula developed by Zander showed excellent concordance with measured osmolality.(39) Zander's formula included lactate and bicarbonate to calculate osmolality, however, we have not measured these parameters in our study. We selected the formula consisted of sodium, blood urea nitrogen and glucose, which was also used in the previous article investigated among HFrEF patients.(14) Third, the present study was a multicenter prospective Asian cohort with quite elder patients (median age of as high as 83 years), which would limit the generalizability of the current findings for other races. Fourth, despite multivariable analysis, residual confounding from unmeasured factors may have affected the results. Finally, although we speculated that RAAS activity, and not AVP activity, was responsible for the poor outcomes, we did not measure either urine osmolality or neurohormonal factors substituting for RAAS.

Conclusion

We show here higher plasma osmolality on admission was associated with poor outcomes in HFpEF patients. Further investigation to confirm the results of this small study and to support our understanding of the pathophysiological meaning of plasma osmolality in HFpEF patients is warranted.

Abbreviations

ADHF; acute decompensated HF

AVP; arginine vasopressin

BNP; brain natriuretic peptide

CIs; confidence intervals

GFR; glomerular filtration rate

GNRI; Geriatric Nutritional Risk Index

HF; heart failure

HFpEF; heart failure with preserved ejection fraction

HFrEF; heart failure with reduced ejection fraction

HRs; hazard ratios

LVEF; left ventricular ejection fraction

NT-proBNP; N-terminal pro-B-type natriuretic peptide

PVS; plasma volume status

RAAS; renin-angiotensin-aldosterone system

SD; standard deviation

Declarations

Availability of data and materials

Not applicable.

Acknowledgement

The authors thank all the investigators, clinical research coordinators and data managers involved in the PURSUIT-HFpEF registry for their dedicated contributions. We thank Nagisa Yoshioka, Kyoko Tatsumi, Satomi Kishimoto, Noriko Murakami, and Sugako Mitsuoka for their excellent assistance with data collection. We thank Libby Cone, MD, MA, from DMC Corp. (http://www.dmed.co.jp/) for editing drafts of this manuscript.

Sources of Funding

This work is funded by Roche Diagnostics K.K. and Fujifilm Toyama Chemical Co. Ltd.

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Contributions

Y.S. has the responsibility on the administration of this cohort study, supervised by Y.Y. and T.Y. Patient enrollment and data correction were directed by A.N., C.Y., T.O., J.T., J.Y., S.T., M.Y., T.H., and Y.N. A.N. provided conceptualization, methodology, formal analysis, and original draft writing of the investigation. Critical draft review and editing were added by Y.Y., S.H. and Y.S. Funding acquisition was provided by D.N., S.H., and Y.S. All authors had read and approved the final version of this manuscript.

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Ethics declarations

Ethics approval and consent to participate and publish

This study, including the procedure for enrollment, was approved by the institutional review board of each participating facility, including the official institutional review board committee of Osaka University Hospital (approved on February 24, 2016). Written informed consent, including data publication, was received from each participating patient.

Statement of conflicts of interest

Daisaku Nakatani has received honoraria from Roche Diagnostics. Shungo Hikoso has received personal fees from Daiichi Sankyo Company, Bayer, Astellas Pharma, Pfizer Pharmaceuticals and Boehringer Ingelheim Japan, and received grants from Roche Diagnostics, FUJIFILM Toyama Chemical and Actelion Pharmaceuticals. Yasushi Sakata received personal fees from Otsuka Pharmaceutical, Ono

Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation and Actelion Pharmaceuticals, and received grants form Roche Diagnostic, FUJIFILM Toyama Chemical, Abbott Medical Japan, Otsuka Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation and Biotronik. Other authors have no conflicts of interest to disclose.

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Tables

Table 1. Baseline characteristics and data on admission divided by plasma osmolality

	All patients (n = 960)	Q1 (n = 318) Osm < 293.2	Q2 (n = 322) 293.2 ≦ Osm < 300.3	Q3 (n = 320) 300.3 ≦ Osm	*P*-value
Age, years	83 (77–87)	83 (77–87)	83 (77–87)	83 (77–87)	0.9761
female	524 (55)	178 (56)	179 (56)	167 (52)	0.5709
prior HF hospitalization	244 (26)	63 (20) ‡	84 (26)	97 (31) *	0.0089
comorbidities					
Hypertension	809 (85)	254 (80) ‡	272 (85)	183 (89) *	0.0112
Diabetes	314 (33)	87 (28) ‡	93 (29) ‡	134 (42) *,†	< 0.0001
Dyslipidemia	393 (41)	111 (35) ‡	128 (40)	154 (48) *	0.0036
COPD	73 (8)	25 (8)	21 (7)	27 (9)	0.6247
CKD	384 (40)	97 (31) ‡	118 (37) ‡	169 (53) *,†	< 0.0001
malignancy	112 (12)	36 (12)	33 (10)	43 (14)	0.4165
General condition on admission					
BMI, kg/m^2	23.8 (21.0–26.9)	23.2 (20.6–26.5) ‡	23.7 (20.9–26.8)	24.6 (21.9–27.7) *	0.0022
SBP, mmHg	147 (128–170)	146 (129–166)	149 (127–167)	149 (128–175)	0.3444
DBP, mmHg	80 (66–93)	82 (69–92)	80 (67–94)	76 (64–93)	0.2598
Heart rate	82 (67–100)	82 (68–102)	82 (68–99)	82 (65–100)	0.7596
AF	444 (46)	153 (48)	154 (48)	137 (43)	0.3187
GNRI	98 (90–106)	96 (89–103) ‡	98 (90–106)	100 (92–107) *	0.0110
Laboratory examination on admission					
Hemoglobin, g/dL	11.1 (9.8–12.5)	11.5 (10.1–12.7) ‡	11.4 (10.1–12.7) ‡	10.7 (9.4–12.3) *,†	< 0.0001
Hematocrit, %	34 (30–38)	35 (31–38) ‡	35 (31–38) ‡	33 (29–38) *,†	0.0033
Serum total protein, g/dL	6.7 (6.3–	6.7 (6.3–	6.7 (6.3–	6.7 (6.2–7.1)	0.3454

	7.1)	7.2)	7.2)		
Serum albumin, g/dL	3.5 (3.2–3.8)	3.5 (3.1–3.8)	3.5 (3.2–3.9)	3.5 (3.1–3.8)	0.3340
BUN, mg/dL	22 (16–32)	18 (14–24) †,‡	21 (15–27) *,‡	31 (23–43) *,†	< 0.0001
Creatinine, mg/dL	1.1 (0.8–1.5)	1.0 (0.7–1.2) †,‡	1.0 (0.8–1.3) *,‡	1.4 (0.9–2.0) *,†	< 0.0001
eGFR, mL/min/1.73m^2	45 (30–58)	51 (38–65) †,‡	45 (33–59) *,‡	33 (21–50) *,†	< 0.0001
Serum sodium, mEq/L	140 (137–142)	137 (134–138) †,‡	141 (139–142) *,‡	142 (140–144) *,†	< 0.0001
Serum potassium, mEq/L	4.1 (3.7–4.5)	4.2 (3.8–4.5) †	4.0 (3.7–4.4) *,‡	4.2 (3.7–4.6) †	0.0084
Serum chloride, mEq/L	105 (101–108)	101 (98–105) †,‡	105 (103–108) *,‡	107 (104–110) *,†	< 0.0001
NT-proBNP, ng/L	3250 (1718–6430)	2950 (1637–5281) ‡	2820 (1580–5292) ‡	4805 (2108–10010) *,†	< 0.0001
CRP, mg/dL	0.53 (0.19–1.94)	0.64 (0.21–2.43)	0.46 (0.18–1.47)	0.53 (0.20–2.00)	0.0734
Glucose, mg/dL	122 (103–161)	118 (101–146) ‡	117 (102–147) ‡	133 (112–194) *,†	< 0.0001
PVS, %	8.7 (-0.4–16.8)	8.3 (-0.04–17.4)	7.4 (-1.1–15.6)	9.8 (0.6–17.9)	0.3156
Plasma osmolality, mOsm/kg	297 (291–303)	288 (283–291) †,‡	297 (295–299) *,‡	305 (303–309) *,†	< 0.0001
Echocardiographic variables on admission					
LVDd, mm	46 (42–51)	46 (41–49) ‡	46 (41–51)	47 (43–51) *	0.0066
LVEF, %	60 (56–65)	60 (56–67)	61 (56–65)	60 (55–65)	0.8524
LAD, mm	44 (40–50)	44 (39–49)	45 (40–51)	45 (39–50)	0.1973
E/A	1.0 (0.7–1.5)	1.1 (0.7–1.5)	1.1 (0.7–1.7)	0.9 (0.7–1.5)	0.4369
E/e'	16 (12–21)	16 (12–20) ‡	16 (12–21)	17 (13–22) *	0.0311
TRPG, mmHg	36 (28–45)	36 (28–45)	36 (29–45)	36 (29–45)	0.9959
IVC max, mm	19 (15–22)	18 (15–22)	18 (15–22)	19 (16–22) †	0.0548

			‡		
IVC collapsibility	0.44 (0.28–0.57)	0.38 (0.23–0.55) †	0.48 (0.30–0.59) *	0.44 (0.29–0.56)	0.0009
Acute phase treatment					
NIPPV usage	121 (13)	36 (11) ‡	26 (8) ‡	59 (19) *,†	0.0003
intubation	16 (1.7)	3 (0.9)	2 (0.6) ‡	11 (3) †	0.0094
DOA (continuous injection)	1 (0.1)	0 (0)	0 (0)	1 (0.3)	0.3663
DOB (continuous injection)	17 (1.7)	2 (0.6)	7 (2)	8 (3)	0.1591
NAD (continuous injection)	10 (1.0)	3 (0.9)	3 (0.9)	4 (1.3)	0.9018
PDE3I (continuous injection)	3 (0.3)	0 (0)	2 (0.6)	1 (0.3)	0.3717
carperitide (continuous injection)	207 (22)	54 (17) ‡	66 (21)	87 (27) *	0.0063
nitrates (continuous injection)	264 (28)	85 (27)	80 (25)	99 (31)	0.1989
Ca channel blocker (continuous injection)	77 (8)	18 (6) ‡	23 (7)	36 (11) *	0.0255
Nicorandil (continuous injection)	6 (0.6)	1 (0.3)	3 (0.9)	2 (0.6)	0.6125
diuretics (continuous injection)	310 (32)	103 (32)	100 (31)	107 (34)	0.7970
diuretics (bolus injection)	549 (57)	176 (55)	178 (55)	195 (61)	0.2296
Prescription before admission					
Antiplatelet	292 (30)	91 (29)	95 (30)	106 (33)	0.4225
ACE inhibitor or ARB	481 (50)	149 (47)	156 (48)	176 (55)	0.0924
calcium channel blocker	489 (51)	148 (47)	162 (50)	179 (56)	0.0575
β−blocker	444 (46)	136 (43)	155 (48)	153 (48)	0.3031
loop diuretics	483 (50)	133 (42) ‡	165 (51)	185 (58) *	0.0003
thiazide	72 (8)	33 (10) †	13 (4) *	26 (8)	0.0085
tolvaptan	52 (5)	14 (4)	22 (7)	16 (5)	0.3667
aldosterone antagonist	204 (21)	72 (23)	68 (21)	64 (20)	0.7153

SGLT2 inhibitor	15 (1.6)	6 (1.9)	2 (0.6)	7 (2)	0.2363
anticoagulant	424 (44)	154 (48)	145 (45)	125 (39)	0.0545

Values are given as median (IQR) or n (%).

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; Ca channel, calcium channel; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP,C-reactive protein; DBP, diastolic blood pressure; DOA, dopamine; DOB, dobutamine; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; HF, heart failure; IVC, inferior vena cava; LAD, left atrial dimension; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NAD, noradrenaline; NIPPV, noninvasive positive pressure ventilation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Osm, plasma osmolality (mOsm/kg); PCI, percutaneous catheter intervention; PDE3I,phosphodiesterase-3 inhibitor; PVS, plasma volume status; SBP, systolic blood pressure; SGLT2, sodium glucose cotransporter 2; TRPG, tricuspid regurgitation pressure gradient

Statistical comparisons were performed using Kruskal Wallis test or Fisher's exact test. Statistical significances between each group ($P < 0.05$) using Steel-Dwass test for continuous variables and Fisher's exact test with Bonferroni adjustment for categorical variables are shown as following: significance in versus Q1*, versus Q2†, and versus Q3‡.

Table 2. Clinical and study characteristics at discharge divided by plasma osmolality on admission

general condition at discharge	All patients (n = 960)	Q1 (n = 318) Osm < 293.2	Q2 (n = 322) 293.2 ≤ Osm < 300.3	Q3 (n = 320) 300.3 ≤ Osm	*P*-value
BMI, kg/m^2	21.4 (18.9–24.2)	21.1 (18.4–23.8) ‡	21.2 (18.7–24.3)	21.9 (19.4–24.6) *	0.0150
SBP, mmHg	118 (106–131)	117 (106–128) ‡	118 (106–130)	122 (107–134) *	0.0106
DBP, mmHg	65 (58–73)	65 (58–73)	66 (58–74)	65 (57–73)	0.7041
Heart rate	70 (61–80)	70 (63–80)	70 (61–80)	70 (60–78)	0.5914
AF	365 (38)	124 (39)	131 (41)	110 (34)	0.2242
GNRI	92 (85–99)	91 (84–97)	94 (85–101)	92 (85–99)	0.1277
6MWD, m	260 (155–340)	240 (150–333)	270 (156–352)	260 (160–338)	0.5728
NYHA classification					0.6460
NYHA I	340 (36)	111 (36)	106 (33)	123 (39)	
NYHA II	538 (57)	173 (55)	193 (60)	172 (54)	
NYHA III	67 (7)	26 (8)	20 (6)	21 (7)	
NYHA IV	4 (0.4)	2 (0.6)	1 (0.3)	1 (0.3)	
laboratory examination at discharge					
Hemoglobin, g/dL	11.3 (10.1–12.7)	11.5 (10.3–12.7) ‡	11.6 (10.4–13.1) ‡	10.8 (9.5–12.2) *,†	< 0.0001
Hematocrit, %	34 (31–39)	35 (32–38) ‡	35 (32–39) ‡	33 (30–37) *,†	< 0.0001
Serum total protein, g/dL	6.6 (6.2–7.1)	6.8 (6.3–7.2) ‡	6.8 (6.3–7.2) ‡	6.5 (6.1–7.0) *,†	0.0009
Serum albumin, g/dL	3.4 (3.1–3.7)	3.4 (3.1–3.7)	3.4 (3.2–3.8) ‡	3.3 (3.1–3.6) †	0.0104
BUN, mg/dL	25 (18–34)	22 (16–28) †,‡	25 (18–33) *,‡	29 (21–42) *,†	< 0.0001
Creatinine, μmol/L	1.1 (0.9–1.5)	1.0 (0.8–1.2) †,‡	1.1 (0.9–1.5) *,‡	1.3 (1.0–2.1) *,†	< 0.0001
eGFR, mL/min/1.73m^2	42 (30–55)	50 (37–60) †,‡	42 (32–54) *,‡	33 (21–49) *,†	< 0.0001
Serum sodium, mEq/L	139 (137–141)	138 (135–140) †,‡	140 (138–141) *,‡	140 (138–142) *	< 0.0001

Serum potassium, mEq/L	4.3 (3.9–4.6)	4.3 (3.9–4.6)	4.3 (4.0–4.6)	4.3 (3.9–4.6)	0.8271
Serum chloride, mEq/L	103 (100–106)	102 (99–105) †,‡	103 (100–105) *,‡	104 (101–107) *,†	< 0.0001
NT–proBNP, ng/L	1112 (478–2550)	993 (497–2190) ‡	952 (439–2025) ‡	1437 (510–3770) *,†	0.0010
CRP, mg/dL	0.29 (0.11–0.90)	0.34 (0.11–1.01)	0.28 (0.11–0.77)	0.26 (0.11–0.93)	0.4804
Glucose, mg/dL	98 (88–117)	97 (87–114)	98 (88–117)	101 (89–120)	0.3746
PVS, %	11.5 (1.9–19.6)	9.9 (1.9–20.0)	9.6 (0.9–17.9) ‡	13.4 (3.1–21.2) †	0.0411
Plasma osmolality, mOsm/kg	294 (289–299)	290 (286–295) †,‡	294 (290–299) *,‡	297 (293–302) *,†	< 0.0001
Prescription at discharge					
Antiplatelet	278 (29)	82 (26)	93 (29)	103 (32)	0.1946
ACE inhibitor or ARB	510 (53)	157 (49)	168 (52)	185 (58)	0.0935
calcium channel blocker	458 (48)	135 (42) ‡	149 (46)	174 (55) *	0.0076
β–blocker	526 (55)	167 (53)	181 (56)	178 (56)	0.5896
loop diuretics	754 (79)	243 (76)	254 (79)	257 (80)	0.4793
thiazide	62 (6)	18 (6)	16 (5)	28 (9)	0.1165
tolvaptan	156 (16)	39 (12) ‡	54 (17)	63 (20) *	0.0377
aldosterone antagonist	383 (40)	125 (39)	141 (44)	117 (37)	0.1683
SGLT2 inhibitor	50 (5)	13 (4)	12 (4)	25 (8)	0.0356
anticoagulant	571 (59)	206 (65) ‡	198 (61)	167 (52) *	0.0035

Values are given as median (IQR) or n (%).

Abbreviations: 6MWD, 6-minute walk distance; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York heart failure functional class; Osm, plasma osmolality (mOsm/kg); PVS, plasma volume status; SBP, systolic blood pressure; SGLT2, sodium glucose cotransporter 2

Statistical comparisons were performed using Kruskal Wallis test or Fisher's exact test. Statistical significances between each group ($P < 0.05$) using Steel-Dwass test for continuous variables and Fisher's

exact test with Bonferroni adjustment for categorical variables are shown as following: significance in versus Q1*, versus Q2†, and versus Q3‡.

Table 3. Cox regression models for prognostic prediction, divided with the internal quantile ranges of plasma osmolality on admission

	Unadjusted HR (95% CI)	*P*-value
Composite endpoint		
Q2 versus Q1	1.13 (0.80–1.60)	1.0000
Q3 versus Q1	1.61 (1.16–2.23)	0.0120
Q3 versus Q2	1.42 (1.03–1.96)	0.0954
Cardiac mortality		
Q2 versus Q1	0.85 (0.42–1.66)	1.0000
Q3 versus Q1	1.59 (0.89–2.88)	0.3531
Q3 versus Q2	1.88 (1.01–3.61)	0.1338
HF re-admission		
Q2 versus Q1	1.12 (0.79–1.60)	1.0000
Q3 versus Q1	1.50 (1.08–2.11)	0.0504
Q3 versus Q2	1.34 (1.08–2.11)	0.2454

Cox proportional hazard models for composite endpoint, cardiac mortality and heart failure re-admission. Composite endpoint was defined as cardiac mortality or heart failure re-admission. P-value was corrected with Bonferroni adjustment.

Abbreviations: HF, heart failure; HR, hazard ratio; Q1, plasma osmolality on admission < 293.2 mOsm/kg; Q2, plasma osmolality on admission ≥ 293.2 and < 300.3 mOsm/kg; and Q3, plasma osmolality on admission ≥ 300.3 mOsm/kg

Table 4. Cox regression models for prognostic prediction of the primary endpoint

	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Age	5.86 (1.88–19.32)	0.0019	5.94 (1.69–22.44)	0.0050
Female	1.20 (0.91–1.58)	0.1897	1.16 (0.85–1.59)	0.3512
AF	0.96 (0.74–1.26)	0.7902	1.05 (0.77–1.43)	0.7605
HT	0.94 (0.77–1.15)	0.5207	0.89 (0.57–1.43)	0.6064
Diabetes	0.94 (0.80–1.10)	0.4475	1.20 (0.86–1.64)	0.2787
GNRI	0.40 (0.10–1.57)	0.1907	0.78 (0.26–2.37)	0.6668
Log NT-proBNP	15.04 (1.93–60.70)	0.0139	3.53 (1.05–2.22)	0.0283
Plasma Osmolality	7.29 (2.25–23.92)	0.0009	4.70 (1.33–17.35)	0.0160
BUN	6.87 (3.36–13.52)	< 0.0001		
Serum sodium	1.18 (0.39–3.81)	0.7755		
Glucose	1.58 (0.46–4.66)	0.4447		

Composite endpoint was defined as cardiac mortality or heart failure re-admission.

Abbreviations: AF, atrial fibrillation; BUN, blood urea nitrogen; GNRI, Geriatric Nutritional Risk Index, HT, Hypertension; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Figures

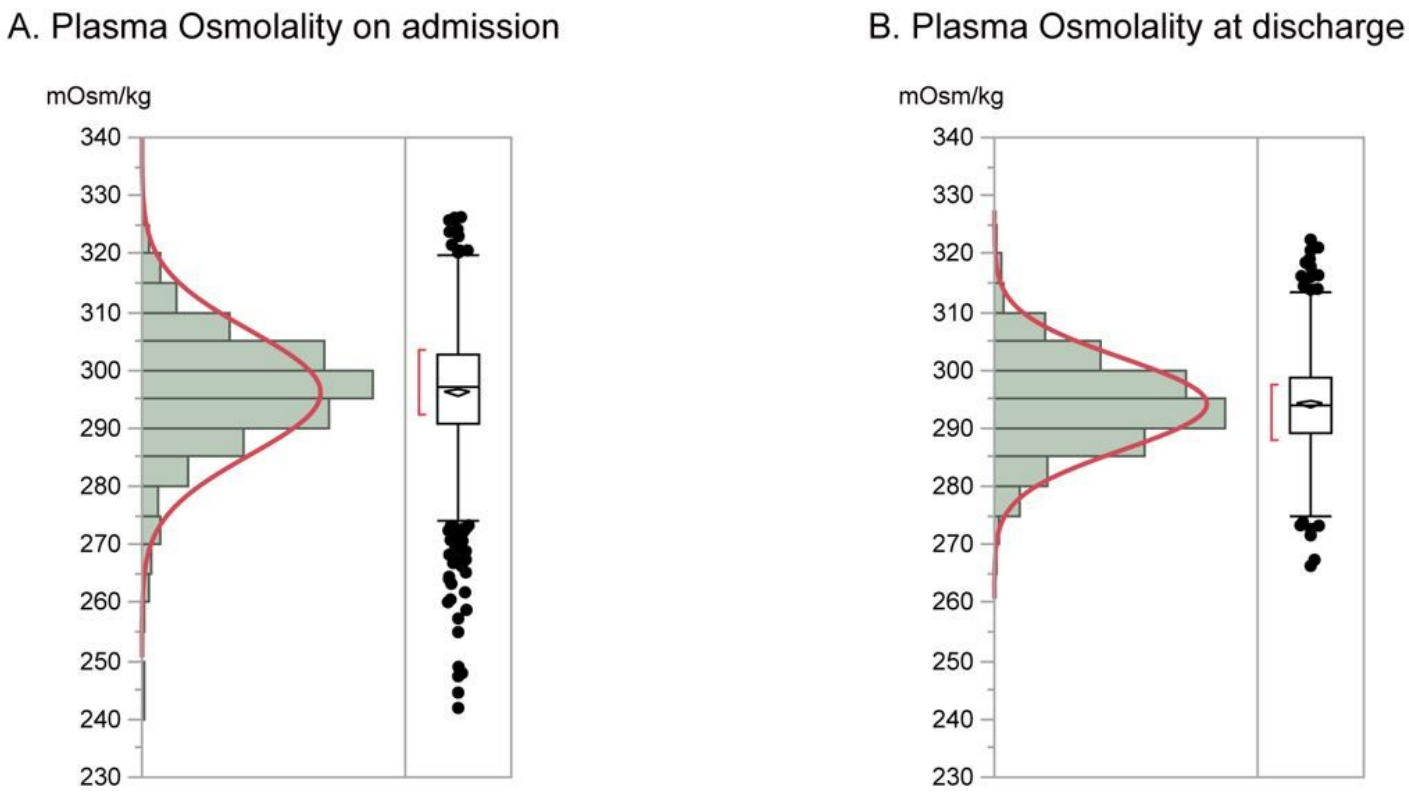

Figure 1

The distributions of plasma osmolality. Distributions of plasma osmolality on admission (A) and at discharge (B). F-test revealed that the distributions were significantly different between on admission and at discharge ($P < 0.0001$).

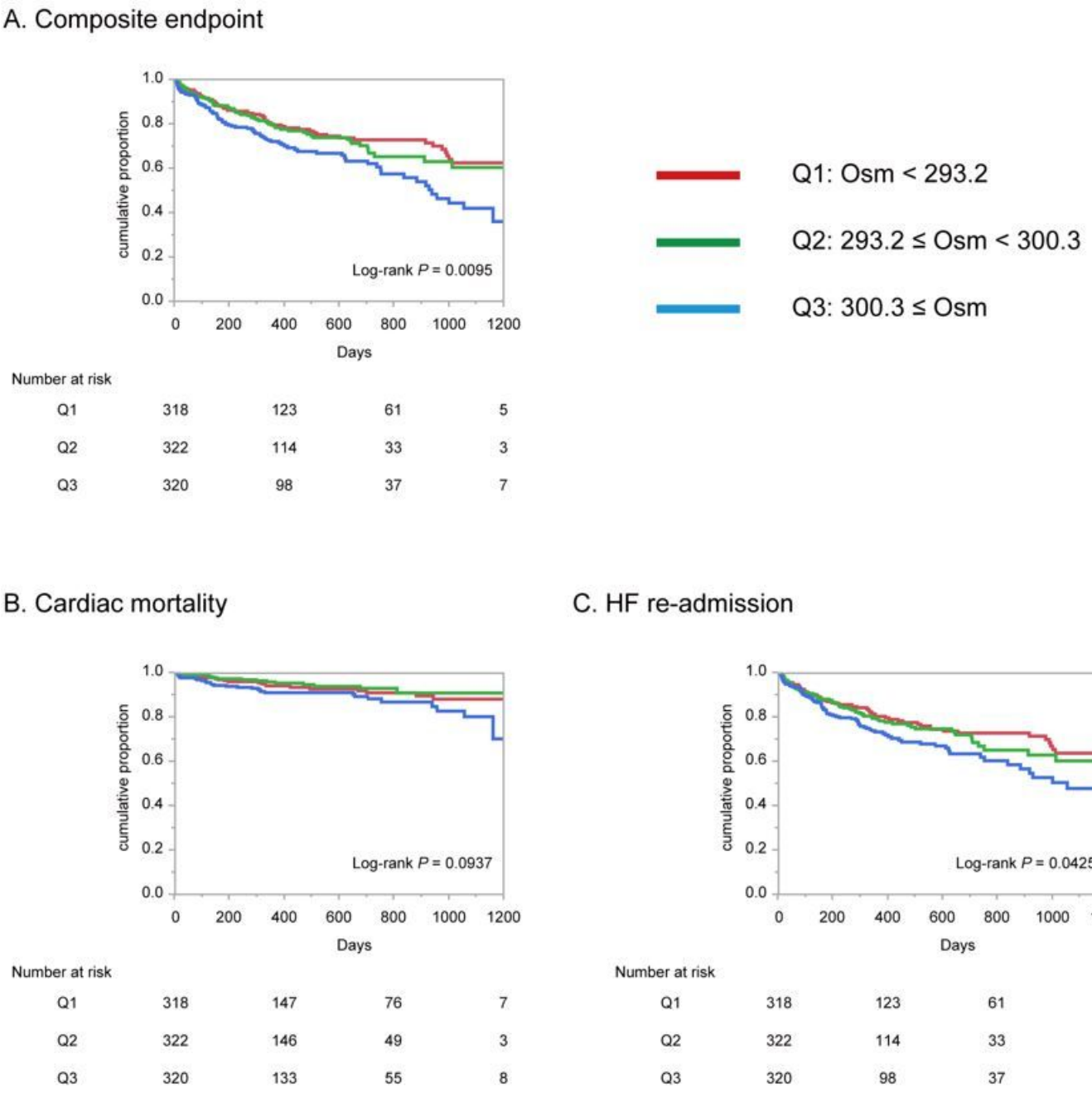

Figure 2

Kaplan-Meier survival curves stratified with quantiles of plasma osmolality on admission Composite endpoint was defined as cardiac mortality or heart failure re-admission. Kaplan-Meier survival curves for composite endpoint (A), cardiac mortality (B) and heart failure re-admission (C) Abbreviations: HF, heart failure; Osm, plasma osmolality (mOsm/kg) on admission