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ORIGINAL ARTICLE

Prognostic significance of serum chloride level in heart failure patients with preserved ejection fraction

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Abstract

Aims The prognostic value of serum chloride level has been reported primarily in patients with heart failure with reduced ejection fraction, and hence, there is limited evidence in patients of heart failure with preserved ejection fraction (HFpEF). This study was conducted to clarify the relationship between serum chloride level and clinical outcomes in patients with HFpEF with acute decompensated heart failure (ADHF).

Methods and results Patient data were extracted from The Prospective mUlticenteR obServational stUdy of patIenTs with Heart Failure with Preserved Ejection Fraction (PURSUIT HFpEF) study, a prospective multicentre observational registry for ADHF-HFpEF in Osaka. The data of 870 patients were analysed after excluding patients with in-hospital death, missing follow-up data, missing data of serum chloride level, or on chronic dialysis therapy. The primary endpoint of this study was all-cause mortality. At discharge, right ventricular systolic dysfunction was significantly associated with the lowest tertile of serum chloride level after multivariable adjustment (P = 0.0257). During a mean follow-up period of 1.8 ± 1.0 years, 186 patients died. Cox multivariable analysis showed that serum chloride level at discharge (P = 0.0017) was independently associated with all-cause mortality after multivariable adjustment of major confounders, whereas serum sodium level was no longer significant (P = 0.6761). Kaplan–Meier survival curve analysis revealed a significantly increased risk of mortality stratified by the tertile of serum chloride level [29% vs. 19% vs. 16%, P = 0.0002; hazard ratio (HR): 2.09 (95% confidence interval, CI: 1.31 to 3.34), HR: 1.03 (95% CI: 0.65 to 1.64)].

Conclusions Serum chloride level was useful for the prediction of poor outcome in ADHF patients with preserved ejection fraction.

Keywords Heart failure with preserved ejection fraction; Serum chloride level; Risk stratification

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The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their interpretation.

Introduction

Electrolyte abnormalities are frequently observed in patients with heart failure (HF).[1] This is induced by activated renin-angiotensin-aldosterone system (RAAS) and arginine vasopressin system in these patients, along with decongestion therapy using loop and thiazide diuretics.[2] Although hyponatraemia has been reported to be a strong prognostic factor for a long time,[3,4] hypochloraemia has recently received increased attention due to its wide variety of functions, such as the maintenance of acid–base homeostasis, the activation of RAAS, and the regulation of the transporters in the kidney that are acted upon by loop and thiazide diuretics.[2,5–9]

Previous studies regarding the prognostic significance of hypochloraemia have been conducted primarily in patients with HF with reduced ejection fraction (HFrEF).[2,10] Although a previous study had shown the prognostic relevance of hypochloraemia in patients with HF with preserved ejection fraction (HFpEF), it included only patients with HFpEF and chronic stable condition from North America.[11] Because HFpEF is a syndrome with a wide diversity and regionality, the phenotype of HFpEF could be different according to the geographical differences.[12,13] Therefore, we aimed to investigate the prognostic significance of hypochloraemia in patients with HFpEF with acute decompensated heart failure (ADHF), using real-world multicentre ADHF-HFpEF registry data in Japan.

Methods

Subjects

Patient data were obtained from The Prospective mUlticenteR obServational stUdy of patIenTs with Heart Failure with Preserved Ejection Fraction (PURSUIT HFpEF) study. The PURSUIT-HFpEF study is a prospective multicentre observational study in which collaborating hospitals in Osaka record the clinical, echocardiographic, and outcome data of patients with ADHF and preserved left ventricular ejection fraction (LVEF $\geq$ 50%) (UMIN-CTR ID: UMIN000021831).[14] Consecutive patients with ADHF and preserved ejection fraction were prospectively registered and consented to be followed up for the collection of outcome data. ADHF was diagnosed based on the following criteria: (i) clinical symptoms and signs according to the Framingham Heart Study criteria and (ii) serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level of $\geq$400 pg/mL or brain natriuretic peptide level of $\geq$100 pg/mL. We enrolled the patients between June 2016 and February 2020 after excluding those with in-hospital death, missing chloride data, missing follow-up data, or on chronic dialysis therapy. All patients provided written informed consent for participation in this study, which was approved by the ethics committee of each participating hospital. This study conformed to the ethical guidelines outlined in the Declaration of Helsinki.

Data collection

The exact data collection procedure has been described elsewhere.[14–17] Briefly, baseline patient characteristics, laboratory tests including serum chloride level, echocardiography findings, and medication details were obtained at discharge. Because the present study focused on the prognostic impact of serum chloride level after discharge, we used laboratory data and echocardiography data at the time of discharge (after the completion of decongestion and in stable condition).

Clinical outcomes

After discharge, all patients were followed up in each hospital. Survival data were obtained by dedicated coordinators and investigators through direct contact with patients and their physicians at the hospital or in an outpatient setting, or through a telephone interview with their families or by mail. The primary endpoint of this study was all-cause mortality. The secondary endpoints were cardiovascular death and hospitalization for worsening HF.

Statistical analyses

All continuous variables were expressed as mean (standard deviation) or median (25th–75th percentile) as appropriate, and categorical variables were expressed as percentage. Patients were stratified according to the tertile of serum chloride level. Differences in normally distributed continuous variables were compared using one-factor ANOVA, and those in non-normally distributed data were compared using the Kruskal–Wallis rank sum test. The χ^2 test was used to compare between-group differences in categorical variables. A multivariable logistic regression model, which was composed from echocardiographic parameters, renal function, sodium level, and diuretic use, was constructed to elucidate the associated factors associated with the lowest tertile of serum chloride level. The primary and secondary endpoints were estimated using Kaplan–Meier method, the log-rank test, and the Gray test. Cox proportional-hazards regression models and the Fine–Gray model were used to identify patients at risk of the primary and secondary endpoints as appropriate to calculate the multivariate-adjusted hazard ratio (HR) and 95% confidence interval (CI). The multivariable model included age, sex, body mass index (BMI), and haemoglobin, sodium, albumin, creatinine, and log-transformed NT-proBNP levels. The predictive power of serum chloride level was investigated using receiver-operating characteristic curve analysis. Moreover, to clarify the incremental prognostic value of serum chloride level over a multivariable clinical risk model (including age, sex, BMI, and haemoglobin, sodium, albumin, creatinine, and log-transformed NT-proBNP levels), the c-statistics of the clinical model and clinical model plus chloride were compared according to the method described by DeLong *et al*.[18] that were used to perform all statistical analyses. All statistical analyses were performed using MedCalc Version 17.11.564 bit (MedCalc software bvba) and EZR Version 1.03 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). A P value of <0.05 was considered to be statistically significant.

Results

Baseline patient characteristics

Between June 2016 and February 2020, after excluding patients with in-hospital death (n = 16), missing chloride data (n = 9), missing follow-up data (n = 44), or on chronic dialysis therapy (n = 15), 870 patients with ADHF were analysed in this study. The mean age of the patients was 81 years and 45% of them were male patients.

The median value (interquartile range) of serum chloride level was 103 U/L (100–106 mEq/L). The distribution of the chloride levels was shown in *Figure 1*. The study population (n = 870) was categorized by tertile of chloride levels as follows: low chloride tertile 73–101 mEq/L (n = 314), middle chloride tertile 102–104 mEq/L (n = 243), and high chloride tertile 105–119 mEq/L (n = 313).The patients' baseline characteristics stratified according to the tertile of serum chloride level were shown in *Table 1*. Patients with lower serum chloride level had lower BMI, lower systolic blood pressure, higher heart rate, higher prevalence of atrial fibrillation, lower prevalence of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use, and higher prevalence of aldosterone blocker use. Regarding laboratory data, patients with lower serum chloride level had higher haemoglobin and haematocrit level, higher platelet count, lower sodium level, higher estimated glomerular filtration rate, higher blood urea nitrogen level, and higher NT-proBNP level. No significant difference was found between the tertiles of chloride levels in terms of age, sex, New York Heart Association class, and the prevalence of loop diuretic use.

Regarding echocardiographic data, patients with lower serum chloride level had significantly smaller left ventricular diastolic dimension (LVDd), stroke volume, cardiac output, cardiac index, and tricuspid annular plane systolic excursion (TAPSE) and greater tricuspid regurgitation pressure gradient (TRPG), but LVEF was not different among patients with lowest, middle, and highest tertiles of serum chloride levels. The multivariate logistic regression analysis revealed that TAPSE (P = 0.0257) was significantly and independently associated with the lowest tertile of serum chloride level, independently of serum creatinine level (P = 0.0010), sodium level ($P < 0.0001$), and thiazide diuretic usage (P = 0.0231) (*Table 2*).

Clinical outcomes and prognostic analysis

During a mean follow-up period of 1.8 ± 1.0 years, 186 patients died. There were 81 cardiovascular deaths and 250 HF rehospitalization. The Kaplan–Meier analysis revealed that patients with low chloride levels had a significantly greater risk of all-cause mortality than those with middle or high chloride levels (29% vs. 19% vs. 16%, P = 0.0002) (*Figure 2*). Furthermore, patients with low chloride levels had a greater risk of cardiovascular mortality than those with middle or high chloride level (13% vs. 10% vs. 5%, P = 0.0070). Regarding the outcome of HF rehospitalization, the Gray test showed no statistical significance (31% vs. 29% vs. 27%, P = 0.8040).

The results of the multivariable Cox proportional hazards analysis for the prediction of all-cause mortality, cardiovascular mortality, and HF rehospitalization were shown in *Table 3*. Serum chloride level (as continuous variable) was significantly

Figure 1 Distribution of serum chloride level.

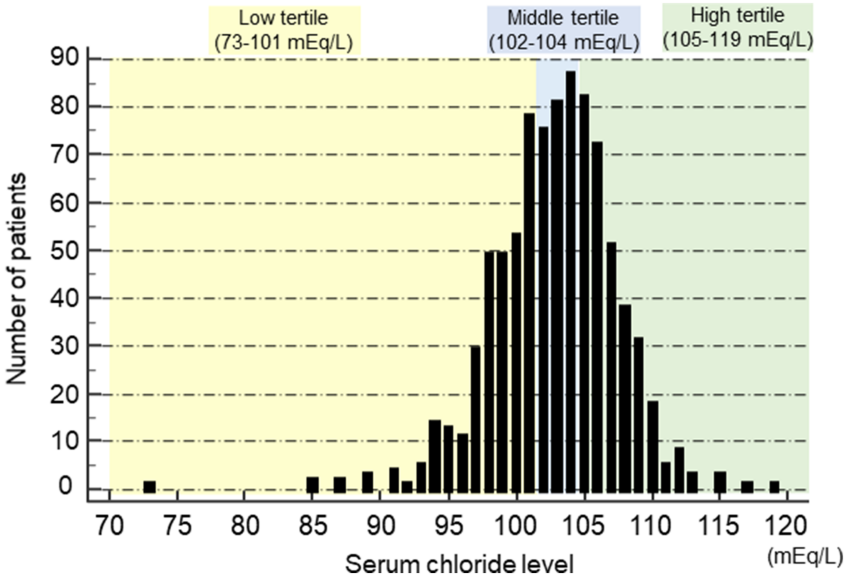


Table 1 Baseline characteristics of the patients with acute decompensated heart failure stratified by the tertile of serum chloride level

	Overall (n = 870)	Lowest tertile Cl level ≤ 101 (n = 314)	Middle tertile 101 < Cl level ≤ 104 (n = 243)	Highest tertile 104 < Cl level (n = 313)	P value
Clinical data					
Age (years)	81 ± 9	82 ± 9	81 ± 9	81 ± 9	0.236
Sex (male, %)	45	45	47	42	0.577
BMI (kg/m^2)	22.0 ± 4.4	21.3 ± 4.3	22.1 ± 4.4	22.6 ± 4.4	0.001
NYHA class III or IV (%)	7	7	5	8	0.247
SBP (mmHg)	120 ± 18	117 ± 17	119 ± 17	123 ± 18	<0.001
Heart rate (b.p.m.)	71 ± 13	73 ± 14	71 ± 12	69 ± 13	0.009
Atrial fibrillation (%)	39	45	41	32	0.005
Hypertension (%)	85	80	88	88	0.011
Diabetes mellitus (%)	33	33	33	32	0.970
Dyslipidaemia (%)	41	36	43	44	0.068
COPD (%)	7	6	10	6	0.193
OMI (%)	7	7	5	8	0.264
Prior HF hospitalization (%)	25	27	24	24	0.654
Medications at discharge					
ACEI or ARB (%)	54	47	54	62	0.002
Beta-blocker (%)	55	57	54	54	0.701
Loop diuretics (%)	96	97	98	95	0.233
Thiazide (%)	8	11	6	6	0.050
Aldosterone blocker (%)	39	43	45	30	<0.001
Tolvaptan (%)	20	20	16	22	0.246
Acetazolamide (%)	0	0	0	0	n.s.
Statin (%)	33	30	32	37	0.194
Laboratory data					
Haemoglobin (g/dL)	11.5 ± 2.0	11.8 ± 2.0	11.6 ± 2.0	11.1 ± 2.0	<0.001
Haematocrit (%)	35 ± 6	36 ± 6	35 ± 6	34 ± 6	<0.001
Platelet count (10^4/mL)	22.3 ± 8.5	23.4 ± 8.7	22.2 ± 8.6	21.4 ± 8.1	0.010
Sodium (mEq/L)	139 ± 3	137 ± 4	139 ± 2	141 ± 2	<0.001
Potassium (mEq/L)	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	0.573
Creatinine (mg/dL)	1.10 (0.90–1.50)	1.00 (0.80–1.50)	1.10 (0.90–1.40)	1.20 (0.90–1.60)	0.178
BUN (mg/dL)	28 ± 14	30 ± 16	27 ± 13	27 ± 14	0.025
eGFR	43 ± 19	45 ± 21	44 ± 17	41 ± 18	0.020
Uric acid (mg/dL)	6.8 ± 1.9	6.9 ± 2.0	7.0 ± 1.9	6.6 ± 1.9	0.036
Albumin (g/dL)	3.4 ± 0.5	3.4 ± 0.5	3.4 ± 0.5	3.3 ± 0.4	0.010
Total cholesterol (mg/dL)	162 ± 35	166 ± 37	161 ± 37	158 ± 32	0.042
C-reactive protein (mg/dL)	0.28 (0.11–0.78)	0.34 (0.13–1.01)	0.22 (0.10–0.69)	0.23 (0.10–0.64)	0.008
NT-proBNP (pg/mL)	1070 (480–2386)	1315 (562–2740)	906 (437–2005)	965 (481–2330)	0.019
AST (U/L)	23 (17–29)	24 (18–30)	23 (18–30)	21 (17–28)	0.004
ALT (U/L)	15 (10–23)	15 (11–21)	16 (11–23)	14 (10–23)	0.279
GGTP (U/L)	32 (20–57)	34 (21–66)	30 (20–56)	31 (17–51)	0.032
ALP (U/L)	249 (198–309)	264 (207–330)	255 (205–303)	230 (192–294)	0.001
Total bilirubin (mg/dL)	0.60 (0.40–0.80)	0.60 (0.50–0.90)	0.60 (0.40–0.80)	0.50 (0.40–0.70)	<0.001
Cholinesterase (U/L)	215 ± 67	209 ± 70	220 ± 68	217 ± 63	0.170
Echocardiography					
LVEF (%)	61 ± 8	60 ± 8	61 ± 8	61 ± 8	0.143
LVDd (mm)	46 ± 6	45 ± 7	45 ± 6	47 ± 6	<0.001
LVEDV (mL)	98 ± 32	93 ± 32	97 ± 29	104 ± 33	<0.001

(*Continues*)

Table 1 (continued)

	Overall (n = 870)	Lowest tertile Cl level ≤ 101 (n = 314)	Middle tertile 101 < Cl level ≤ 104 (n = 243)	Highest tertile 104 < Cl level (n = 313)	P value
LVESV (mL)	36 ± 17	35 ± 18	34 ± 15	38 ± 17	0.059
LAD (mm)	44 ± 8	44 ± 9	44 ± 7	44 ± 8	0.802
LAVI (mL/m^2)	51 (37–66)	51 (37–68)	52 (38–65)	39 (35–66)	0.679
E/e'	14 ± 7	14 ± 7	14 ± 7	14 ± 6	0.685
Stroke volume (mL)	59 ± 20	55 ± 20	58 ± 19	63 ± 21	<0.001
Cardiac output (L/min)	4.0 ± 1.3	3.7 ± 1.4	4.0 ± 1.3	4.3 ± 1.4	<0.001
Cardiac index (L/min/m^2)	2.7 ± 0.9	2.6 ± 0.9	2.7 ± 0.9	2.9 ± 0.9	0.002
TAPSE (mm)	18 ± 5	16 ± 4	18 ± 4	19 ± 5	<0.001
RVDd (mm)	32 ± 7	33 ± 7	33 ± 7	32 ± 7	0.209
TRPG (mmHg)	28 ± 9	29 ± 10	29 ± 10	27 ± 9	0.047
IVC diameter (mm)	14 ± 5	14 ± 5	14 ± 5	15 ± 5	0.122

ACEI, angiotensin-converting enzyme inhibitor; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GGTP, gamma-glutamyl transpeptidase; HF, heart failure; IVC, inferior vena cava; LAD, left atrial dimension; LAVI, left atrial volume index; LVDd, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; OMI, old myocardial infarction; RVDd, right ventricular end-diastolic dimension; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

associated with the all-cause mortality (P = 0.0017) and cardiovascular mortality (P = 0.0015) after multivariable adjustment, whereas serum sodium level was no longer associated with all-cause mortality (P = 0.6761) or cardiovascular mortality (P = 0.6001).

Patients with low tertile of chloride level had approximately two-fold increased risk of all-cause mortality and cardiovascular mortality compared with those with high chloride level after the Cox multivariable adjustment [all-cause mortality: adjusted HR: 2.09 (1.31 to 3.34), P = 0.0019; cardiovascular mortality: adjusted HR: 2.29 (1.08 to 4.87), P = 0.0304]. On the other hand, there was no greater risk of HF rehospitalization in patients with low chloride level.

The results of the receiver-operating characteristic analysis for identification of all-cause mortality are depicted in *Figure 3*. The area under the curve of chloride level was 0.597 (95% CI: 0.564 to 0.630) (*Figure 3A*). Furthermore, the C-statistics of the clinical model + chloride was significantly higher than that of clinical model alone [clinical model + chloride: 0.757 (95% CI: 0.724 to 0.787) vs. clinical model alone: 0.742 (95% CI: 0.709 to 0.774), P = 0.0494] (*Figure 3B*).

Discussion

The primary findings of the present study were as follows. First, a significant association was observed between serum chloride level and clinical outcomes in the Japanese multicentre ADHF-HFpEF cohort. Second, in consistent with the previous studies, hyponatraemia was no longer associated with clinical outcomes after multivariable adjustment including the serum chloride level.

Comparison with previous studies

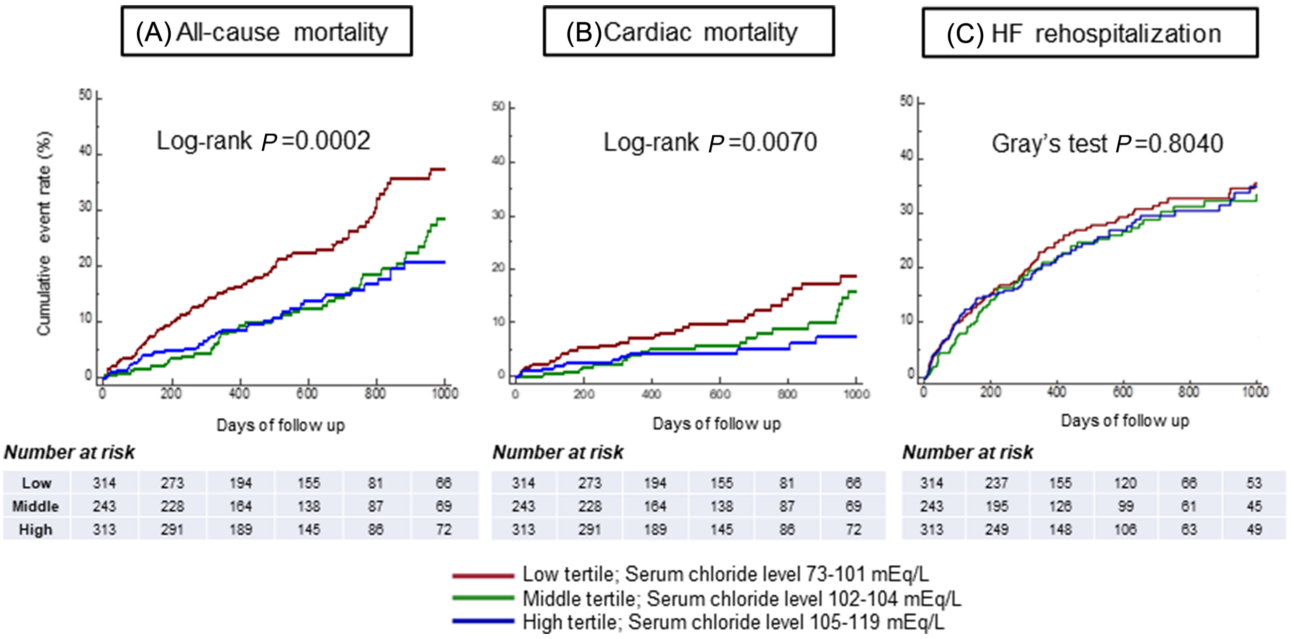
Compared with the post hoc analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT),[11] our study subjects were older in age and comprised more women and had considerably lower BMI and more severely impaired renal function. Regarding the usage of diuretics, the rate of thiazide prescription was considerably lower and, instead, tolvaptan was used in 20% of patients. Despite these different baseline characteristics, the primary results were similar in terms of the significant associations between hypochloraemia and all-cause mortality and cardiovascular mortality, but not HF rehospitalization. This result indicated that the clinical significance of chloride homeostasis of Asian HFpEF patients was similar to that of TOPCAT subjects, which were mainly comprised from HFpEF patients in North America.

Table 2 Multivariable logistic regression models for the identification of the lowest tertile of serum chloride level

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
TAPSE (mm)	0.911 (0.879–0.944)	<0.0001	0.943 (0.896–0.993)	0.0257
TRPG (mmHg)	1.012 (0.997–1.028)	0.1245	1.015 (0.992–1.038)	0.2132
IVC diameter (mm)	0.970 (0.940–1.001)	0.0561	0.949 (0.905–0.996)	0.0331
LVEF (%)	0.981 (0.965–0.997)	0.0210	0.977 (0.953–1.001)	0.0616
Cardiac index (L/min/m^2)	0.779 (0.654–0.927)	0.0049	0.844 (0.662–1.077)	0.1728
Creatinine (mg/dL)	0.956 (0.799–1.144)	0.6217	0.534 (0.368–0.776)	0.0010
Serum sodium level (mEq/L)	0.669 (0.627–0.712)	<0.0001	0.643 (0.589–0.702)	<0.0001
Loop diuretics (%)	1.042 (0.466–2.328)	0.9211	2.091 (0.671–6.517)	0.2033
Thiazide diuretics (%)	1.927 (1.128–3.292)	0.0163	2.404 (1.128–5.122)	0.0231
Aldosterone blocker (%)	1.318 (0.994–1.748)	0.0548	0.787 (0.509–1.216)	0.2798
Atrial fibrillation (%)	1.458 (1.100–1.933)	0.0088	1.773 (1.122–2.802)	0.0141

CI, confidence interval; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

Figure 2 Cumulative event rate curves with patients stratified by the tertile of serum chloride level [(A) all-cause mortality, (B) cardiovascular mortality, and (C) heart failure (HF) rehospitalization].



Possible mechanism

Lower serum chloride levels could be the consequence of the homeostatic change in HF, such as increased water reabsorption by excess arginine vasopressin cascade and RAAS. Chloride depletion by diuretics can also be a cause of hypochloraemia. In the present study, the prevalence of ACEI or ARB use was significantly low, and the thiazide use tended to be high in the subgroup of the low serum chloride group. This result suggests that the low chloride level was the consequence of the inadequate RAAS suppression or chloride depletion by diuretics. Moreover, approximately 20% of patients were prescribed tolvaptan, which is one of the characteristics of this cohort. Hence, the dilutional mechanism of hypochloraemia by the excess arginine vasopressin cascade could be attenuated, compared with the previous study.[11]

The previous study reported the association between lower serum chloride level and diuretic resistance.[19,20] Because our cohort lacked data on the dose of diuretics, it was difficult to describe the association between hypochloraemia and diuretic resistance in the present study. Nevertheless, higher haemoglobin, haematocrit, and platelet levels were observed in the low chloride group, suggesting the condition of haemoconcentration in this group. This is

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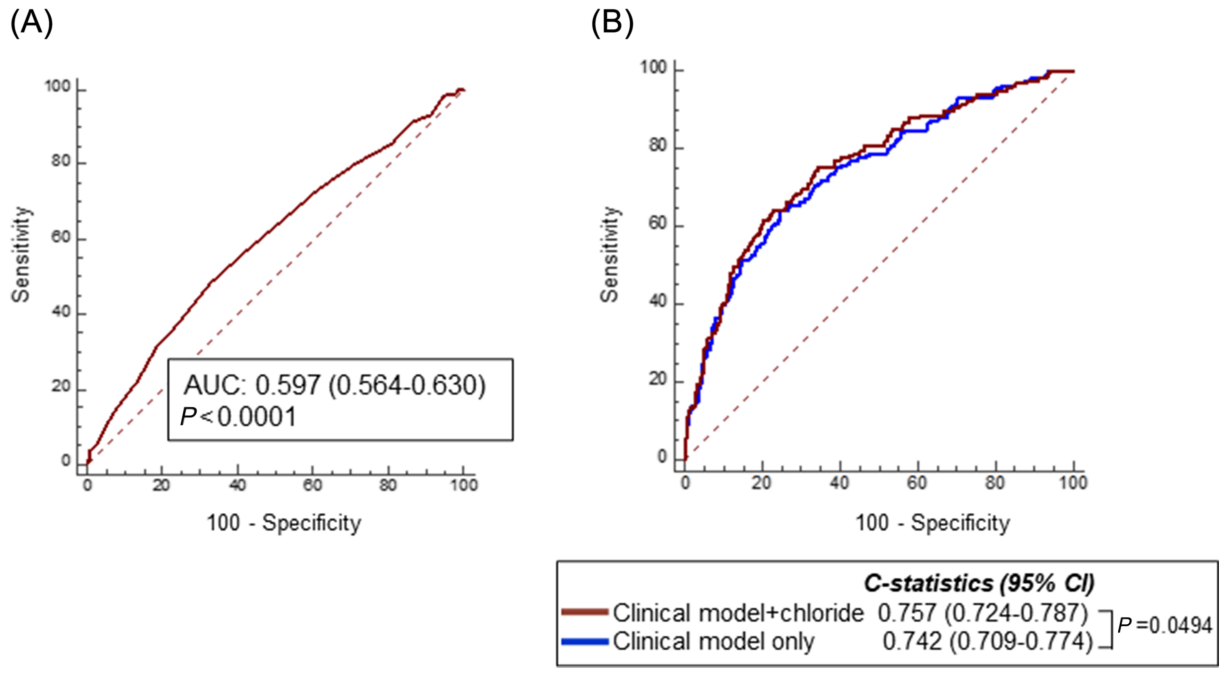
Table 3 Cox multivariable proportional hazard models of serum chloride level for the prediction of all-cause mortality, cardiovascular mortality, and heart failure rehospitalization

	All-cause mortality		Cardiovascular mortality		HF rehospitalization	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Chloride level (continuous variable)	0.93 (0.89–0.97)	0.0017	0.90 (0.84–0.96)	0.0015	0.98 (0.95–1.02)	0.3900
High chloride level (105–119 mEq/L)	Reference		Reference		Reference	
Middle chloride level (102–104 mEq/L)	1.03 (0.65–1.64)	0.9073	1.34 (0.64–2.78)	0.4350	0.92 (0.64–1.31)	0.6300
Low chloride level (73–101 mEq/L)	2.09 (1.31–3.34)	0.0019	2.29 (1.08–4.87)	0.0304	1.03 (0.70–1.50)	0.8900

CI, confidence interval; HR, hazard ratio.
Serum chloride level was adjusted by age, sex, body mass index, haemoglobin, sodium, albumin, creatinine, and log-transformed N-terminal pro-brain natriuretic peptide.

Figure 3 Receiver-operating characteristic (ROC) curve analysis of serum chloride level for the prediction of cardiac events (A) and ROC curve analysis of clinical model plus chloride level and clinical model only (B). AUC, area under the curve.



possibly derived from a high-dose loop or thiazide diuretics. It can also be speculated that chloride depletion and haemoconcentration by diuretics could easily occur in patients with preserved renal function, considering the fact that renal function was better in the low chloride subgroup. Furthermore, this haemoconcentration may explain the reason for the lack of association between chloride level and HF rehospitalization by the euvolaemic status.[21]

Based on the echocardiographic data, patients in low chloride group had lower stroke volume and cardiac index along with lower TAPSE (*Table 1*). In the previous study, Grodin *et al*. reported that lower chloride level was associated with lower cardiac index based on the neurohormonal activation.[22] Although their study was conducted on patients with HFrEF, a similar result was observed in the present study. In addition, the decreased cardiac output in the low chloride group may have been derived from impaired right ventricular (RV) function, not from LV function in patients with HFpEF because LVEF was not different among the three groups. Furthermore, lower TAPSE was significantly associated with lower chloride level after multivariable adjustment, while LVEF was not (*Table 2*). These results could indicate that decreased RV systolic function, which causes decreased cardiac output, RAAS activation, and systemic congestion requiring higher doses of diuretics, would be one of the possible mechanisms of hypochloraemia in patients with HFpEF. This is one of the new findings of the present study because the previous studies, which were primarily conducted in patients with HFrEF, lacked the data of RV systolic function.

Clinical implications

According to the results of the present study, patients with low chloride level had two-fold increased risk of mortality compared with those with high chloride level (*Table 2*). Moreover, incorporating the serum chloride level into a clinical model improved the risk prediction (*Figure 3B*). Thus, physicians should focus on the serum chloride level in daily practice in patients with HFpEF as well.

Although the causal relationship between hypochloraemia and diuretic use was not clear in the present study, we should at least avoid the decongestive therapies that induce hypochloraemia, such as high-dose loop diuretics or thiazide usage. In fact, thiazide usage was significantly associated with hypochloraemia in the present study (*Table 2*). When physicians need to reinforce a decongestive therapy, tolvaptan or sodium-glucose cotransporter 2 (SGLT-2) inhibitor usages could be a possible alternative. Acetazolamide could also be a therapeutic option for patients with a complication of hypochloraemia. Acetazolamide exerts an effect of diuresis and reverse hypochloraemia by increasing bicarbonate excretion and renal chloraemia reabsorption.[23,24] Although the clinical utility of acetazolamide remains to be clarified, the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial would clarify whether adding acetazolamide to loop diuretics can improve the clinical outcome.[25]

Study limitations

Several limitations of this study should be acknowledged. First, because of the observational nature of the study, it was difficult to clarify whether hypochloraemia was a marker of disease severity or therapeutic target. Considering the wide range of functions of chloride in the maintenance of homeostasis, hypochloraemia itself could be a therapeutic target. However, further interventional studies are required to clarify this question. Second, it is important to consider ethnic differences when generalizing our results to non-Japanese populations. Third, the data of bicarbonate, which is an important factor related to acid–base homeostasis, were not included in the present study. Therefore, it was difficult to discuss the association between serum chloride level and metabolic alkalosis. Finally, data regarding the dose of diuretics were not available in the present study. Thus, the causal relationship between hypochloraemia and diuretic resistance could not be clarified.

Conclusions

Serum chloride level was useful for the prediction of poor outcome in ADHF patients with preserved ejection fraction.

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Conflict of interest

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Appendix A

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