Circulation Reports
Circ Rep 2020; 2: 409–419
doi:10.1253/circrep.CR-20-0058

ORIGINAL ARTICLE
Heart Failure

# Prognostic Impact of Early Changes in Serum Chloride Concentrations Among Hospitalized Acute Heart Failure Patients

## — A Retrospective Cohort Study —

Satoshi Yamaguchi, MD, PhD; Masami Abe, MD; Kunitoshi Iseki, MD, PhD;
Tomohiro Arakaki, MD; Osamu Arasaki, MD;
Michio Shimabukuro, MD, PhD; Shinichiro Ueda, MD, PhD

***Background:*** Serum electrolyte concentrations on admission and after the administration of loop diuretics may be associated with prognosis in patients hospitalized due to acute heart failure (AHF). This study investigated the prognostic impact of early changes in chloride (Cl) concentrations after diuretic administration, according to stratified Cl concentrations on admission, in AHF.

***Methods and Results:*** In all, 355 consecutive patients hospitalized due to AHF were included in this single-center retrospective cohort study. Patients were divided into 2 groups based on whether Cl decreased (n=196) or not (n=159) during the first 5 days in hospital. These 2 groups were further stratified according to Cl on admission into 4 groups: Group 1, decrease in Cl and no hypochloremia (n=127); Group 2, decrease in Cl and hypochloremia (n=69); Group 3, no decrease in Cl and no hypochloremia (n=50); and Group 4, no decrease in Cl and hypochloremia (n=109). The risk of death was significantly higher in the group without than with a decrease in Cl (all-cause death hazard ratio [HR] 1.79; 95% confidence interval [CI] 1.15–2.78; P=0.009). Group 4 had the worst prognosis and a significantly higher risk of death (all-cause death [vs. Group 1 as a reference], HR 2.51; 95% CI 1.45–4.32; P=0.001).

***Conclusions:*** The absence of an early decline in Cl was associated with poor prognosis in AHF, especially in patients with hypochloremia on admission.

**Key Words:** Acute heart failure; Chloride; Prognosis

Hyponatremia is often observed in patients with heart failure.[1,2] Serum sodium concentrations have been considered to play a central role in fluid homeostasis and the progression of heart failure (HF).[3] However, recent studies have documented that hypochloremia also appears problematic in HF, because this state is reportedly associated with worse prognosis in both chronic and acute HF (AHF),[4,5] partly through diuretic resistance.[6] Hypochloremia in HF could result from the activation of neurohormones, such as the renin-angiotensin-aldosterone system and arginine vasopressin, and could be closely associated with the poor prognosis of HF.[7–9]

Changes in serum electrolyte concentrations may reflect not only the pathophysiological status, but also the efficacy of diuretics in HF patients.[10] Loop diuretics, which are widely used as primary therapy for treating a congestive state, suppress sodium-potassium-chloride (Cl) cotransporters in the loop of Henle.[11] The initial response to loop diuretics could predict the prognosis of AHF patients.[12] When loop diuretics prove effective in AHF, their administration is accompanied by declines in Cl.[11] Therefore, a poor diuretic response of Cl to loop diuretics may predict a poor prognosis in AHF.[12] However, little is known about the prognostic implications of early changes in Cl after the administration of loop diuretics.

The present single-center retrospective cohort study in hospitalized patients with AHF investigated the prognostic value of early changes in Cl after the administration of loop diuretics. Patients were stratified according to Cl concentrations on admission, and the interaction between baseline Cl concentrations and early changes in Cl after the administration of loop diuretics on prognosis was investigated.

Received June 8, 2020; accepted June 8, 2020; J-STAGE Advance Publication released online July 18, 2020 Time for primary review: 1 day

Department of Cardiology, Nakagami Hospital, Okinawa (S.Y.); Department of Cardiology (M.A., T.A., O.A.), Clinical Research Support Center (K.I.), Tomishiro Central Hospital, Okinawa; Department of Clinical Pharmacology and Therapeutics, Graduate School of Medicine, University of the Ryukyus, Okinawa (S.Y., S.U.); and Department of Diabetes, Endocrinology and Metabolism, School of Medicine, Fukushima Medical University, Fukushima (M.S.), Japan

Mailing address: Shinichiro Ueda, MD, PhD, Department of Clinical Pharmacology and Therapeutics, Graduate School of Medicine, University of the Ryukyus, 207 Uehara, Okinawa 903-0125, Japan. E-mail: suedano9@icloud.com


ISSN-2434-0790

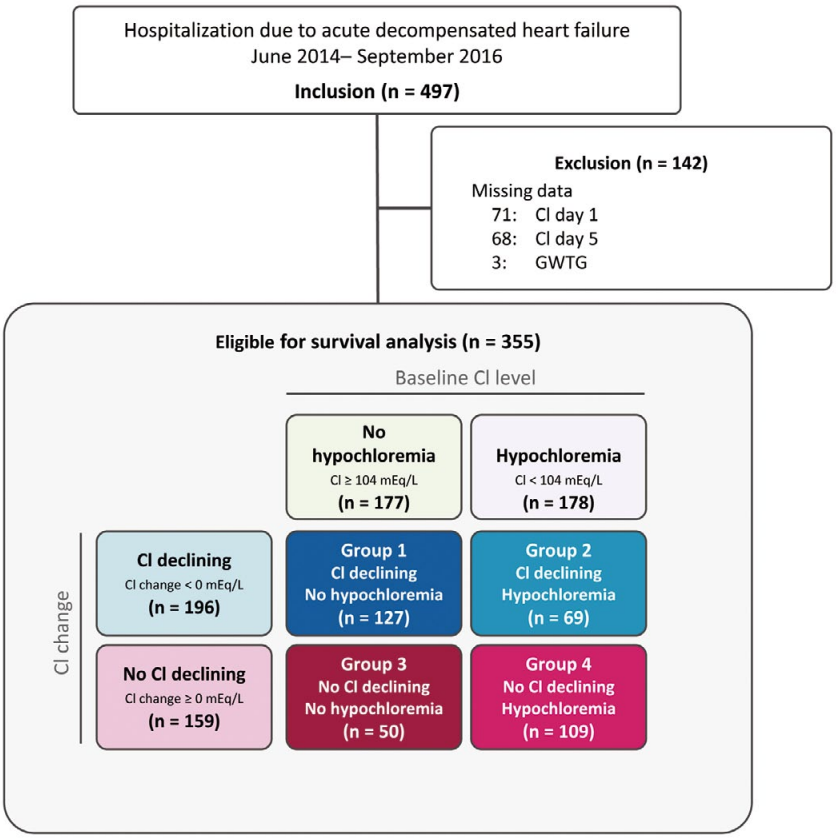



**Figure 1.** Flowchart showing study enrollment. Cl, serum chloride concentrations; GWTG, Get With the Guideline heart failure risk score.

## Methods

### Participants

The present single-center observational study was performed at Tomishiro Central Hospital, Okinawa, Japan. In all, 497 consecutive patients admitted to the cardiology ward due to AHF from June 2014 to September 2016 were recruited to the study. Patients who required cardiac support devices (e.g., intra-aortic balloon pumps or a left ventricular assist device) or mechanical ventilation with intubation were excluded from the study. All diagnoses were based on Framingham criteria and all patients had Class III or IV HF symptoms according to the New York Heart Association functional classification[13] and at least one of the following congestive signs: bilateral shadow on chest X-ray, pitting edema of the lower extremities, a distended jugular vein, and/or pleural effusion. All patients with congestive symptoms were administered intravenous furosemide 20 mg within 6 h of admission to hospital as initial therapy. Of the initial 497 patients, 142 were excluded because of missing values for serum Cl concentration on admission (n=71), serum Cl concentration on Day 5 in hospital (n=68), and Get With The Guideline Heart Failure (GWTG) risk score (n=3). Thus, 355 patients were finally considered eligible for analysis in this study (**Figure 1**).

The present study followed the tenets of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects proposed by the Ministry of Health and Welfare in Japan. The Institutional Ethics Committee at Tomishiro Central Hospital approved this study and waived the requirement for informed consent because of the observational nature of the study. This study was registered with the UMIN Clinical Trials Registry (ID: UMIN000033755).

### Allocation

Patients were allocated into different groups according to: (1) the change in Cl from admission to Day 5 in hospital; (2) Cl on admission; and (3) both Cl on admission and Cl on Day 5 (**Figure 1**). The change in Cl was calculated by subtracting Cl on admission from Cl on Day 5. A decline in Cl during the first 5 days in hospital was defined as a change in Cl change <0 mEq Cl/L (n=196); patients with values for the change in Cl ≥0 mEq/L were defined to having no decrease in Cl (n=159).

Previous reports defined Cl <96 mEq/L as hypochloremia, which was associated with a worse prognosis in AHF.[14] Considering the feasibility in this study for a 4-group comparison, we defined hypochloremia as Cl <104 mEq/L (the median Cl concentration in the study population). Patients were divided into 2 groups based on the median Cl at the time of admission: those with hypochloremia (Cl <104 mEq/L; n=178) and those without hypochloremia (Cl ≥104 mEq/L; n=177).

Finally, patients were divided into 4 groups based on both Cl on admission and the change in Cl as follows: Group 1, decrease in Cl and no hypochloremia on admission (n=127); Group 2, decrease in Cl and hypochloremia (n=69); Group 3, no decrease in Cl and no hypochloremia (n=50); and Group 4, no decrease in Cl and hypochloremia (n=109).

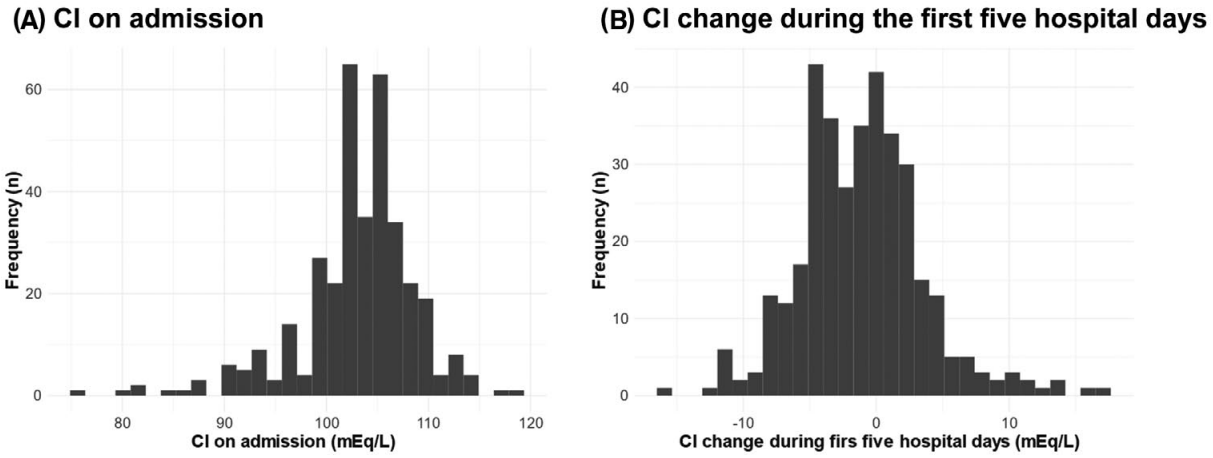



**Figure 2.** Distribution of (**A**) serum chloride concentrations (Cl) on admission and (**B**) early changes in Cl.

### Blood Sampling

All blood samples were obtained from the brachial vein at the time of hospital admission and on Day 5 in hospital and collected in test tubes (Venoject; Terumo, Tokyo, Japan). Blood samples were tested immediately after collection.

### Data Collection

A detailed review was conducted of patients' medical charts to collect demographic characteristics and clinical data. The primary outcome was all-cause death and the secondary outcome was a composite of all-cause death and rehospitalization due to HF. Death was confirmed from medical charts, telephone calls with patients, or obituaries in local newspapers.

### Statistical Analysis

The distribution of continuous variables was checked using histograms. Continuous variables with a normal distribution are presented as the mean±SD, whereas those with a skewed distribution are expressed as the median with interquartile range (IQR). Categorical variables are expressed as n (%).

In 2-group comparisons, the significance of differences for normally distributed continuous variables was determined using Student's t-test, whereas the Mann-Whitney U-test was used for variables with a skewed distribution. The significance of differences between categorical variables was tested using Fisher's exact test.

In 4-group comparisons, continuous variables with a normal distribution were tested using analysis of variance (ANOVA), whereas those with a skewed distribution were tested using the Kruskal-Wallis test. Categorical variables were tested by Fisher's exact test. Holm's test was used for multiple comparisons.

Analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) and EZR (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html), which provides a graphical user interface and functions for biostatistics.[15]

### Survival Analysis

Survival analysis was performed for all-cause death and the composite endpoint of all-cause death and rehospitalization due to HF. Survival was compared between groups with and without changes in Cl during the first 5 days in hospital with time zero ($t_0$) set as the fifth hospital day, as well between groups with and without hypochloremia on admission, with $t_0$ in that case set as the date of admission. Survival was also compared between Groups 1–4, defined on the basis of both Cl concentrations on admission and the change in Cl during the first 5 hospital days; in these analyses, $t_0$ was set as the fifth hospital day. Observations were censored at all-cause death or the composite endpoint of all-cause death and rehospitalization due to HF with events, or last hospital visit without events. Non-informative censoring was used, and no events at the end of follow-up resulted in right censoring as of October 31, 2016. Kaplan-Meier curves were generated and the log-rank test was used to compare survival curves. Holm's test was used for multiple comparisons in 4-group comparisons.

The pooled cause-specific survival using competing risks method was used for survival risk for composite endpoints of all-cause death and rehospitalization due to HF.

### Risk of Change in Cl During the First 5 Hospital Days and Hypochloremia on Admission

Univariate Cox proportional hazard modeling was used to assess the risk of change in Cl during the first 5 hospital days, hypochloremia on admission, and both. We hypothesized that a decline in Cl should represent a diuretic response to the loop diuretics. Thus, to compute the hazard ratios (HRs) of the combination of Cl change and baseline Cl concentration, Group 1 was used as the reference group. In addition, Cox proportional hazard modeling adjusted by the GWTG risk score. The GWTG risk score is an established score for estimating the risk of in-hospital mortality in AHF and predicting long-term prognosis in patients with chronic HF.[16–18] The GWTG risk score is calculated using systolic blood pressure, blood urea nitrogen, serum sodium concentrations, age, heart rate, ethnicity, and the presence or absence of chronic obstructive pulmonary disease. Cox proportional models provided HRs with 95% confidence intervals (CIs).

In addition, the interaction between hypochloremia and

**Table 1. Demographic and Laboratory Data Stratified by Baseline Serum Chloride Concentrations (Cl) on Admission and Changes in Cl During the First 5 Hospital Days**

| | Overall (n=355) | Decline in Cl | | | Hypochloremia | | |
|---|---|---|---|---|---|---|---|
| | | Yes (n=196) | No (n=159) | P-value | Yes (n=178) | No (n=177) | P-value |
| Age (years) | 80±12 | 79±12 | 79±12 | 0.61 | 80±12 | 78±12 | 0.16 |
| No. males | 166 (47) | 101 (52) | 65 (41) | 0.058 | 76 (43) | 90 (51) | 0.15 |
| BMI (kg/m$^2$) | 22.6±4.4 | 22.6±4.3 | 22.7±4.5 | 0.84 | 22.2±4.7 | 23.0±4.0 | 0.069 |
| Body weight (kg) | | | | | | | |
| On admission | 59 [47, 69] | 60 [50, 69] | 56 [46, 70] | 0.3 | 54 [46, 70] | 60 [52, 69] | 0.031 |
| On third hospital day | 55 [45, 65] | 56 [46, 65] | 54 [44, 64] | 0.4 | 51 [43, 64] | 57 [49, 65] | 0.01 |
| At hospital discharge | 53 [44.2, 62.8] | 53 [45, 63] | 53 [44, 62] | 0.45 | 50 [42, 63] | 56 [47, 63] | 0.021 |
| Body weight change (kg) | | | | | | | |
| During first 3 days | −1.6 [−2.9, −0.5] | −1.8 [−3.4, −0.6] | −1.4 [−2.7, −0.3] | 0.024 | −1.4 [2.8, −0.3] | −1.7 [−3.4, −0.8] | 0.082 |
| From admission to discharge | −3.3 [−5.6, −1.8] | −3.6 [−6.1, −2.1] | −3.1 [−4.9, −1.4] | 0.052 | −3.1 [−4.9, −1.4] | −3.6 [−6, −2.3] | 0.037 |
| GWTG HF risk sore | 38±7 | 38±7 | 39±8 | 0.16 | 39±8 | 37±7 | 0.016 |
| HF hospitalization history | 121 (34) | 61 (31) | 60 (38) | 0.23 | 73 (41) | 48 (27) | 0.008 |
| Diabetes | 124 (35) | 63 (32) | 61 (38) | 0.27 | 61 (34) | 63 (36) | 0.088 |
| Old MI | 72 (20) | 36 (18) | 36 (23) | 0.39 | 37 (21) | 35 (20) | 0.92 |
| COPD | 20 (5.6) | 10 (5.1) | 10 (6.3) | 0.80 | 11 (6.2) | 9 (5.1) | 0.83 |
| AF | 110 (31) | 66 (34) | 44 (28) | 0.27 | 54 (30) | 56 (32) | 0.88 |
| LVEF (%) | 45 [29, 58] | 44 [28, 58] | 45 [34, 56] | 0.43 | 45 [31, 58] | 45 [30, 57] | 0.88 |
| Non-invasive PPV use | 71 (20) | 38 (19) | 33 (21) | 0.85 | 36 (20) | 35 (20) | >0.99 |
| Inotropic use | 23 (6.5) | 10 (5.1) | 13 (8.2) | 0.34 | 15 (8.4) | 8 (4.5) | 0.2 |
| Nitrovasodilator infusion | 9 (2.5) | 5 (2.6) | 4 (2.5) | >0.99 | 3 (1.7) | 6 (3.4) | 0.49 |
| Carperitide | 134 (38) | 82 (42) | 52 (33) | 0.098 | 57 (32) | 77 (44) | 0.034 |
| Hospital stay (days) | 13 [9, 21] | 14 [9, 20] | 13 [9, 22] | 0.94 | 15 [10, 23] | 12 [9, 19] | 0.026 |
| Hemodynamic parameters | | | | | | | |
| SBP on admission (mmHg) | 132±25 | 133±25 | 130±26 | 0.22 | 129±25 | 134±25 | 0.058 |
| HR on admission (beats/min) | 78 [69, 93] | 81 [69, 95] | 77 [68, 89] | 0.23 | 78 [70, 92] | 78 [68, 93] | 0.7 |
| SBP at discharge (mmHg) | 120±20 | 119±21 | 120±21 | 0.81 | 117±22 | 122±20 | 0.067 |
| HR at discharge (beats/min) | 75 [67, 86] | 75 [66, 86] | 75 [67, 86] | 0.94 | 75 [68, 86] | 74 [66, 86] | 0.41 |
| Medication on admission | | | | | | | |
| Loop diuretics | 126 (36) | 58 (30) | 68 (43) | 0.014 | 71 (40) | 55 (31) | 0.1 |
| Thiazide | 15 (4.2) | 8 (4.1) | 7 (4.4) | 0.99 | 10 (5.6) | 5 (2.8) | 0.3 |
| ACEI and/or ARB | 95 (27) | 52 (27) | 43 (27) | >0.99 | 44 (25) | 51 (29) | 0.45 |
| Aldosterone antagonist | 70 (20) | 38 (19) | 32 (20) | 0.97 | 36 (20) | 34 (19) | 0.92 |
| β-blocker | 125 (35) | 69 (35) | 56 (35) | >0.99 | 67 (38) | 58 (33) | 0.4 |
| Medication at discharge | | | | | | | |
| Loop diuretics | 145 (41) | 93 (47) | 52 (33) | 0.007 | 60 (34) | 85 (48) | 0.008 |
| Thiazide | 21 (5.9) | 14 (7.1) | 7 (4.4) | 0.39 | 11 (6.2) | 10 (5.6) | >0.99 |
| ACEI and/or ARB | 93 (26) | 56 (29) | 37 (23) | 0.31 | 36 (20) | 57 (32) | 0.014 |
| Aldosterone antagonist | 93 (26) | 57 (29) | 36 (23) | 0.21 | 50 (28) | 43 (24) | 0.49 |
| β-blocker | 138 (39) | 86 (44) | 52 (33) | 0.042 | 59 (33) | 79 (45) | 0.035 |
| Tolvaptan | 30 (8.5) | 21 (11) | 9 (5.7) | 0.13 | 13 (7.3) | 17 (9.6) | 0.56 |
| Cl (mEq/L) | | | | | | | |
| On admission | 103±6 | 105±4 | 100±6 | <0.001 | 99±5 | 107±3 | <0.001 |
| On fifth hospital day | 102±5 | 101±4 | 103±5 | <0.001 | 99±4 | 104±4 | <0.001 |
| Change in Cl over first 5 hospital days (mEq/L) | −1±5 | −4±3 | 3±3 | <0.001 | 0±5 | −3±4 | <0.001 |

(**Table 1** continued the next page.)

| | Overall (n=355) | Decline in Cl | | | Hypochloremia | | |
|---|---|---|---|---|---|---|---|
| | | Yes (n=196) | No (n=159) | P-value | Yes (n=178) | No (n=177) | P-value |
| Laboratory tests on admission | | | | | | | |
| Cr (mg/dL) | 1.14 [0.84, 1.54] | 1.09 [0.79, 1.48] | 1.19 [0.85, 1.65] | 0.056 | 1.16 [0.85, 1.53] | 1.10 [0.82, 1.56] | 0.89 |
| BUN (mg/dL) | 24 [16, 35] | 23 [15, 33] | 25 [17, 37] | 0.049 | 25 [17, 36] | 23 [16, 34] | 0.31 |
| BUN/Cr | 21.6±8.4 | 21.5±9.0 | 21.7±7.6 | 0.88 | 22.5±9.5 | 20.6±7 | 0.034 |
| eGFR (mL/min/1.73 m$^2$) | 42 [29, 58] | 44 [33, 62] | 37 [25, 54] | 0.01 | 39 [30, 56] | 43 [29, 58] | 0.48 |
| Na (mEq/L) | 139±5 | 141±3.3 | 137±6.4 | <0.001 | 137±6 | 142±3 | <0.001 |
| BNP (pg/mL) | 727 [419, 1,269] | 719 [426, 1,187] | 728 [411, 1,440] | 0.87 | 664 [421, 1,497] | 728 [425, 986] | 0.85 |
| Laboratory test on Day 5 in hospital | | | | | | | |
| Cr (mg/dL) | 1.16 [0.88, 1.61] | 1.12 [0.90, 1.48] | 1.21 [0.86, 1.64] | 0.22 | 1.18 [0.84, 1.60] | 1.15 [0.91, 1.63] | 0.66 |
| BUN (mg/dL) | 26 [19, 38] | 25 [19, 35] | 26 [19, 40] | 0.28 | 26 [19, 39] | 25 [19, 37] | 0.68 |
| BUN/Cr | 23.8±9.8 | 23.7±9.4 | 23.9±10.3 | 0.91 | 24.6±10.3 | 22.9±9.3 | 0.13 |
| eGFR (mL/min/1.73 m$^2$) | 40 [27, 56] | 43 [30, 57] | 37 [25, 53] | 0.063 | 38 [27, 57] | 42 [27, 56] | 0.98 |
| Na (mEq/L) | 140±4 | 140±3 | 140±5 | 0.73 | 139±5 | 141±3 | <0.001 |
| Diuretic use in first 5 days | | | | | | | |
| Furosemide (mg) | 120 [60, 120] | 120 [60, 200] | 120 [60, 240] | 0.94 | 120 [55, 225] | 120 [60, 200] | 0.85 |
| Tolvaptan (mg) | 15 [11, 30] | 14 [9, 20] | 15 [14, 24] | 0.74 | 21 [15, 30] | 15 [8, 30] | 0.32 |

Unless indicated otherwise, data are presented as the mean±SD, median [interquartile range], or n (%). A decline in Cl was defined as a change in Cl of <0 mEq/L, whereas no decline in Cl was defined as a change in Cl of ≥0 mEq/L. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; Cr, creatinine; eGFR, estimated glomerular filtration rate; GWTG, Get With the Guidelines; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; Na, serum sodium concentration; PPV, positive pressure ventilation; SBP, systolic blood pressure.

early changes in Cl in AHF was examined using Cox proportional hazard models.

### Sensitivity Analysis

Hypochloremia was defined as Cl <96 mEq/L and was associated with poor survival in a previous study.[14] In the present study, hypochloremia was defined as Cl <104 mEq/L. To confirm the consistency of the effect of hypochloremia on prognosis in AHF between the different definitions of hypochloremia, performed survival analysis was also using the dataset and a definition of hypochloremia of Cl <96 mEq/L.

Cox proportional hazard models adjusted by GWTG risk score and hemoglobin level were used to calculate HRs of no decrease in Cl, hypochloremia, and both.

## Results

### Participants

The overall population for this study comprised 166 men and 189 women, with a mean age of 80±12 years. The GWTG risk score was 38±7. Serum Cl concentrations on admission and on the fifth hospital day were 103±6 and 102±5 mEq/L, respectively, and the mean change in Cl during the first 5 hospital days was −1±5 mEq/L (**Figure 2**). In 2-group comparisons between groups with and without a decrease in Cl concentrations, patients in the group without a decrease in Cl had a lower decrease in body weight, a greater frequency of loop diuretic use on admission, lower Cl on admission, higher Cl on the fifth hospital day, higher blood urea nitrogen, lower estimated glomerular filtration rate, and lower sodium concentrations on admission (**Table 1**).

In 2-group comparisons of patients with and without hypochloremia, those with hypochloremia had a lower body weight both on admission and on the fifth hospital day, a higher GWTG risk score, lower Cl on the fifth hospital day, a lower change in Cl, and lower sodium concentrations on admission and on the fifth hospital day (**Table 1**).

In 4-group comparisons of Groups 1–4, based on serum Cl concentrations on admission and changes in Cl during the first 5 days in hospital, significant differences were seen for serum sodium concentrations on admission and on the fifth hospital day (**Table 2**).

### Survival Analysis

**Comparisons of Patients With and Without Decreases in Cl During the First 5 Hospital Days** During follow-up, 45 of 159 patients (28%) in the group without a decrease in Cl died, compared with 36 of 196 patients (18%) in the group in which Cl decreased ($P_{incidence}$=0.037). Survival analysis revealed a significant difference for all-cause death (log rank, P=0.008; **Figure 3A**).

In univariate Cox proportional hazard modeling, no decrease in Cl was a significant risk factor for all-cause death (HR 1.79; 95% CI 1.15–2.78; P=0.009; **Supplementary Table 1**). In adjusted Cox proportional hazard modeling, no decrease in Cl remained a significant risk factor for all-cause death (HR 1.91; 95% CI 1.23–2.97; P=0.004).

During follow-up, 75 of 159 patients (47%) in the group

**Table 2. Demographic and Laboratory Data Between Groups Defined on the Basis of Serum Chloride Concentrations (Cl) on Admission and Changes in Cl in the First 5 Hospital Days**

| | Group 1 (n=127) | Group 2 (n=69) | Group 3 (n=50) | Group 4 (n=109) | P-value |
|---|---|---|---|---|---|
| Age (years) | 79±12 | 79±11 | 76±12 | 81±12 | 0.24 |
| No. males | 69 (54) | 32 (46) | 21 (42) | 44 (40) | 0.16 |
| BMI (kg/m$^2$) | 22.8±3.8 | 22.2±5.1 | 23.7±4.4 | 22.2±4.4 | 0.19 |
| Body weight (kg) | | | | | |
| On admission | 60 [51, 68] | 56 [47, 70] | 60 [55, 69] | 52 [45, 70] | 0.11 |
| On third hospital day | 57 [49, 64] | 51 [42, 66] | 57 [53, 67] | 50 [43, 63] | 0.059 |
| At hospital discharge | 55 [46, 63] | 50 [42, 63] | 56 [50, 62] | 50 [43, 61] | 0.11 |
| Body weight change (kg) | | | | | |
| During first 3 days | −1.7 [−3.5, −0.9] | −1.8 [−3.0, −0.5] | −1.5 [−2.7, −0.4] | −1.2 [−2.7, 0] | 0.1 |
| From admission to discharge | −3.6 [−6.1, −2.4] | −3.4 [5.6, −1.8] | −3.4 [−5.7, −2] | −3.0 [−4.6, −1.2] | 0.098 |
| GWTG HF risk sore | 37±7 | 38±6 | 37±6 | 40±8 | 0.063 |
| HF hospitalization history | 34 (27) | 27 (39) | 14 (28) | 46 (42) | 0.05 |
| Diabetes | 43 (34) | 20 (29) | 20 (40) | 41 (38) | 0.56 |
| Old MI | 24 (19) | 12 (17) | 11 (22) | 25 (23) | 0.78 |
| COPD | 6 (4.7) | 4 (5.8) | 3 (6.0) | 7 (6.4) | 0.95 |
| AF | 42 (33) | 24 (35) | 14 (28) | 30 (28) | 0.67 |
| LVEF (%) | 44 [29, 57] | 46 [27, 59] | 47 [32, 56] | 45 [34, 57] | 0.86 |
| Non-invasive PPV use | 24 (19) | 14 (20) | 11 (22) | 22 (20) | 0.97 |
| Inotropic use | 6 (4.7) | 4 (5.8) | 2 (4) | 11 (10) | 0.31 |
| Nitrovasodilator infusion | 5 (3.9) | 0 (0) | 1 (2) | 3 (2.8) | 0.41 |
| Carperitide | 58 (46) | 24 (35) | 19 (38) | 33 (30) | 0.15 |
| Hospital stay (days) | 13 [9, 19] | 16 [11, 24] | 11 [9, 18] | 14 [10, 23] | 0.13 |
| Hemodynamic parameters | | | | | |
| SBP on admission (mmHg) | 135±26 | 129±21 | 132±23 | 129±28 | 0.24 |
| HR on admission (beats/min) | 80 [68, 96] | 82 [70, 93] | 77 [68, 89] | 77 [69, 89] | 0.53 |
| SBP at discharge (mmHg) | 120±21 | 119±22 | 126±18 | 117±22 | 0.072 |
| HR at discharge (beats/min) | 74 [66, 86] | 75 [69, 88] | 74 [65, 87] | 75 [67, 85] | 0.87 |
| Medication on admission | | | | | |
| Loop diuretics | 35 (28) | 23 (33) | 20 (40) | 48 (44) | 0.056 |
| Thiazide | 3 (2.4) | 5 (7.2) | 2 (4) | 4 (4.6) | 0.44 |
| ACEI and/or ARB | 35 (28) | 17 (25) | 16 (32) | 27 (25) | 0.77 |
| Aldosterone antagonist | 26 (21) | 12 (17) | 8 (16) | 24 (22) | 0.78 |
| $\beta$-blocker | 38 (30) | 31 (45) | 20 (40) | 36 (33) | 0.16 |
| Medication at discharge | | | | | |
| Loop diuretics | 66 (52) | 27 (39) | 19 (38) | 33 (30) | 0.008 |
| Thiazide | 7 (5.5) | 7 (10) | 3 (6) | 4 (3.7) | 0.36 |
| ACEI and/or ARB | 42 (33) | 14 (20) | 15 (30) | 22 (20) | 0.08 |
| Aldosterone antagonist | 32 (25) | 25 (36) | 11 (22) | 25 (23) | 0.29 |
| $\beta$-blocker | 61 (48) | 25 (36) | 18 (36) | 34 (31) | 0.056 |
| Tolvaptan | 15 (12) | 6 (8.7) | 2 (4) | 7 (6.4) | 0.29 |
| Cl (mEq/L) | | | | | |
| On admission | 108±3 | 102±2*** | 106±2* | 98±6*** | <0.001 |
| On fifth hospital day | 103±3 | 98±3*** | 107±2*** | 101±5*** | <0.001 |
| Change in Cl over first 5 hospital days (mEq/L) | −5±3 | −3±2* | 1±1*** | 3±4*** | <0.001 |

(**Table 2** continued the next page.)

| | Group 1 (n=127) | Group 2 (n=69) | Group 3 (n=50) | Group 4 (n=109) | P-value |
|---|---|---|---|---|---|
| Laboratory tests on admission | | | | | |
| Cr (mg/dL) | 1.09 [0.81, 1.54] | 1.09 [0.77, 1.31] | 1.13 [0.84, 1.59] | 1.21 [0.89, 1.68] | 0.12 |
| BUN (mg/dL) | 22 [16, 33] | 23 [15, 34] | 24 [17, 36] | 26 [17, 39] | 0.24 |
| BUN/Cr | 20.6±7.4 | 23.3±11.2 | 20.8±6.0 | 22.0±8.2 | 0.15 |
| eGFR (mL/min/1.73 m$^2$) | 43 [29, 59] | 46 [34, 66] | 43 [29, 57] | 37 [25, 53] | 0.047 |
| Na (mEq/L) | 142±3 | 139±4*** | 141±3 | 135±7*** | <0.001 |
| BNP (pg/mL) | 727 [403, 1,009] | 645 [498, 1,490] | 737 [561, 800] | 727 [320, 1,633] | 0.95 |
| Laboratory test on Day 5 in hospital | | | | | |
| Cr (mg/dL) | 1.17 [0.92, 1.54] | 1.09 [0.83, 1.44] | 1.12 [0.86, 1.67] | 1.27 [0.85, 1.62] | 0.21 |
| BUN (mg/dL) | 25 [19, 35] | 24 [18, 35] | 25 [19, 41] | 27 [19, 40] | 0.56 |
| BUN/Cr | 23.1±9.6 | 25.0±9.0 | 22.6±8.5 | 24.4±11.1 | 0.48 |
| eGFR (mL/min/1.73 m$^2$) | 42 [28, 55] | 48 [32, 61] | 43 [26, 56] | 36 [24, 52] | 0.1 |
| Na (mEq/L) | 140±3 | 138±4 | 142±4 | 139±5 | <0.001 |
| Diuretic use in first 5 days | | | | | |
| Furosemide (mg) | 120 [75, 205] | 110 [45, 200] | 120 [40, 190] | 140 [60, 270] | 0.88 |
| Tolvaptan (mg) | 15 [8, 30] | 30 [18, 36] | 15 [12, 21] | 17 [14, 24] | 0.56 |

Patients were divided into 4 groups based on Cl at admission and decreases in Cl over the first 5 days in hospital as follows: Group 1, decline in Cl and no hypochloremia; Group 2, decline in Cl and hypochloremia; Group 3, no decline in Cl and no hypochloremia; and Group 4, no decline in Cl and hypochloremia. Unless indicated otherwise, data are presented as the mean±SD, median [interquartile range], or n (%). *P<0.05, ***P<0.001 compared with Group 1. A decline in Cl was defined as a change in Cl of <0 mEq/L, whereas no decline in Cl was defined as a change in Cl of ≥0 mEq/L. Hypochloremia and no hypochloremia were defined as Cl <104 and ≥104 mEq/L at admission, respectively. Abbreviations as in Table 1.

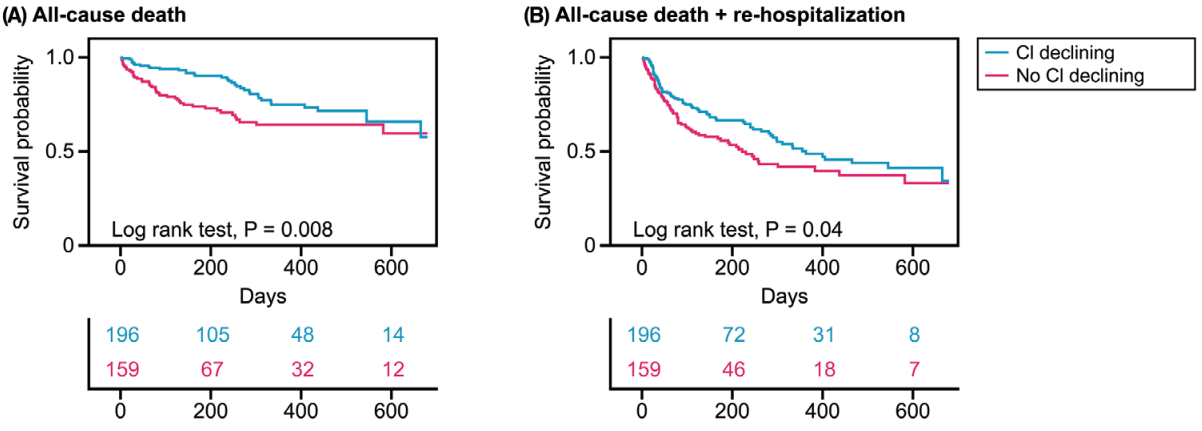



**Figure 3.** Kaplan-Meier curves for (**A**) all-cause death and (**B**) the composite endpoint of all-cause death and rehospitalization for heart failure in groups with and without decreases in serum chloride concentrations (Cl) during the first 5 hospital days. A decline in Cl was defined as a change in Cl <0 mEq/L during the first 5 hospital days; no decline in Cl was defined as a change in Cl change ≥0 mEq/L.

without a decrease in Cl experienced the composite endpoint, compared with 77 of 196 patients (39%) in the group in which Cl decreased ($P_{incidence}$=0.16). A significant difference in survival was seen for the composite endpoint (log rank, P=0.04; **Figure 3B**).

In univariate Cox proportional hazard modeling, no decrease in Cl was a significant risk factor for the composite endpoint (HR 1.39; 95% CI 1.01–1.92; P=0.041; **Supplementary Table 2**). In adjusted Cox proportional hazard modeling, no decrease in Cl remained a significant risk factor for the composite endpoint (HR 1.43; 95% CI 1.04–1.97; P=0.028).

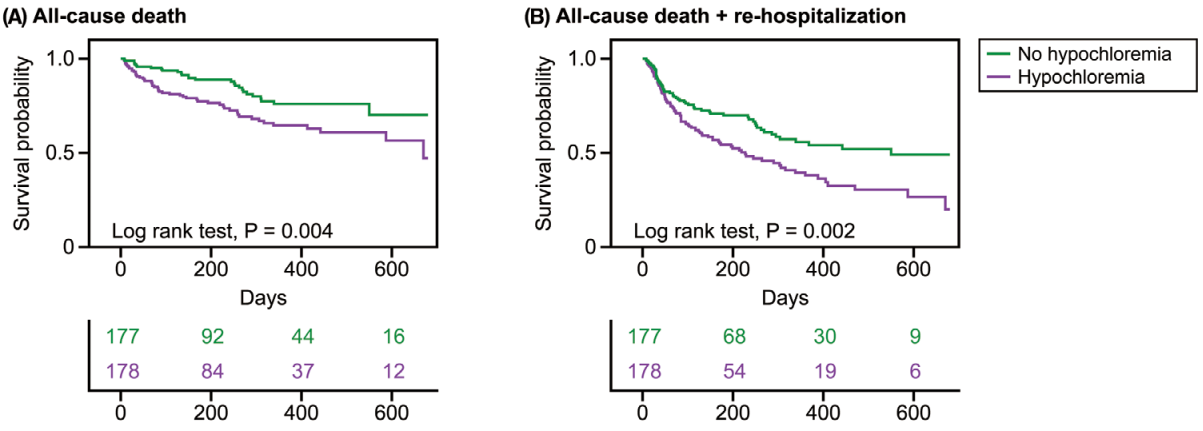
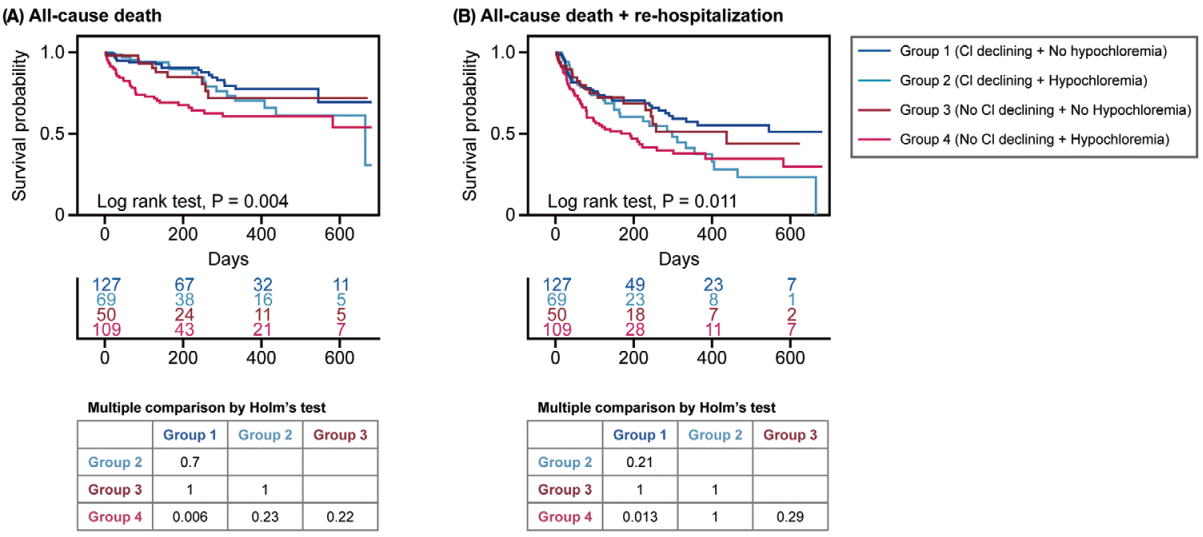



**Figure 4.** Kaplan-Meier curves for (**A**) all-cause death and (**B**) the composite endpoint of all-cause death and rehospitalization for heart failure in groups with and without hypochloremia on admission. Hypochloremia and no hypochloremia were defined as <104 and ≥104 mEq Cl/L on admission, respectively.




Multiple comparison by Holm's test

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Group 2 | 0.7 | | |
| Group 3 | 1 | 1 | |
| Group 4 | 0.006 | 0.23 | 0.22 |

Multiple comparison by Holm's test

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Group 2 | 0.21 | | |
| Group 3 | 1 | 1 | |
| Group 4 | 0.013 | 1 | 0.29 |

**Figure 5.** Kaplan-Meier curves for (**A**) all-cause death and (**B**) the composite endpoint of all-cause death and rehospitalization for heart failure for the 4 groups stratified by serum chloride concentrations (Cl) on admission and changes in Cl during the first 5 hospital days.

**Comparisons Between Groups With and Without Hypochloremia on Admission** During the follow-up period (median 198 days; IQR 90–379 days), 52 of 178 patients (29%) with hypochloremia group died, compared with 29 of 177 patients (16%) without hypochloremia ($P_{incidence}$=0.001). A significant difference in survival analysis was seen for all-cause death (log rank, P=0.004; **Figure 4A**).

In univariate Cox proportional hazard modeling, hypochloremia was a significant risk factor for all-cause death (HR 1.92; 95% CI 1.22–3.02; P=0.005; **Supplementary Table 1**). In adjusted Cox proportional hazard modeling, hypochloremia remained a significant risk factor for all-cause death (HR 1.74; 95% CI 1.10–2.75; P=0.017).

During follow-up, 92 of 178 patients (52%) with hypochloremia and 60 of 177 patients (34%) without hypochloremia experienced the composite endpoint ($P_{incidence}$=0.001). A significant difference in survival was identified for the composite endpoint (log rank, P=0.002; **Figure 4B**).

In univariate Cox proportional hazard modeling, hypochloremia was a significant risk for the composite endpoint (HR 1.67; 95% CI 1.20–2.31; P=0.002; **Supplementary Table 2**). In adjusted Cox proportional hazard modeling, hypochloremia remained a significant risk factor for the composite endpoint (HR 1.62; 95% CI 1.17–2.25; P=0.004).

**Comparisons of Groups 1–4** During follow-up, 20 of 127 patients (16%) in Group 1, 16 of 69 patients (23%) in Group 2, 9 of 50 patients (18%) in Group 3, and 36 of 109 patients (33%) in Group 4 died ($P_{incidence}$=0.013). A significant

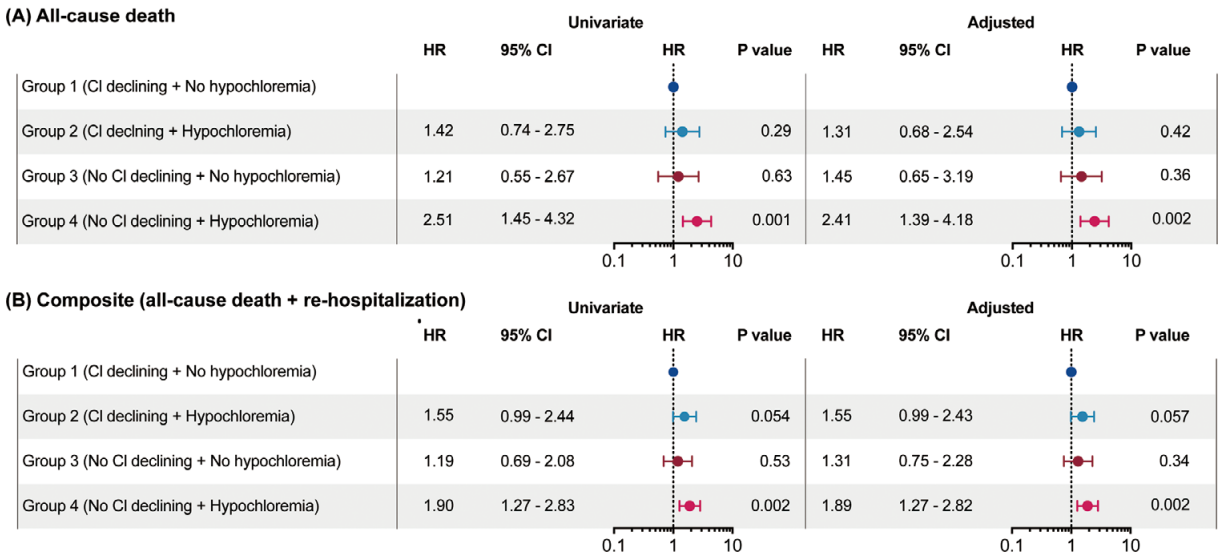



**Figure 6.** Hazard ratios (HRs) of 4 groups stratified by hypochloremia on hospital admission and change in serum chloride concentrations (Cl) during the first 5 hospital days. CI, confidence interval.

difference in survival analysis was seen for all-cause death (log rank, P=0.004; **Figure 5A**). In multiple comparisons, patients in Group 4 had worse survival than those in Group 1 (P=0.006).

In univariate Cox proportional hazard modeling, being in Group 4 was a significant risk factor for all-cause death (HR 2.51; 95% CI 1.45–4.32; P=0.001; **Figure 6A**; **Supplementary Table 1**). In adjusted Cox proportional hazard modeling, being in Group 4 (relative to Group 1) was also a significant risk factor for all-cause death (HR 2.41; 95% CI 1.39–4.18; P=0.002; **Figure 6A**; **Supplementary Table 1**).

During follow-up, 42 of 127 patients (33%) in Group 1, 35 of 69 patients (51%) in Group 2, 18 of 50 patients (36%) in Group 3, and 57 of 109 patients (52%) in Group 4 experienced the composite endpoint ($P_{incidence}$=0.009). A significant difference in survival was identified for the composite endpoint (log rank, P=0.011; **Figure 5B**).

In univariate Cox proportional hazard modeling, being in Group 4 (relative to Group 1) was a significant risk factor for the composite endpoint (HR 1.9; 95% CI 1.27–2.83; P=0.002; **Figure 6B**; **Supplementary Table 2**). In adjusted Cox proportional hazard modeling, being in Group 4 (relative to Group 1) remained a significant risk factor for the composite endpoint (HR 1.89; 95% CI 1.27–2.82; P=0.002; **Figure 6B**; **Supplementary Table 2**).

### Interaction Between Hypochloremia on Admission and Early Changes in Cl

There was a significant interaction between no decrease in Cl and hypochloremia on admission in the Cox proportional hazard model for all-cause death and the composite endpoint (HR 2.50 [95% CI 1.45–4.32; P=0.001] and HR 1.94 [95% CI 1.31–2.90; P=0.001], respectively).

### Sensitivity Analysis With Hypochloremia Defined as Cl <96 mEq/L

Survival analysis was performed defining hypochloremia as Cl <96 mEq/L. In this analysis, Group 2 was excluded because there were only 2 patients in this group (**Supplementary Figure**).

During the follow-up period, 34 of 194 patients (18%) in Group 1, 30 of 129 patients (23%) in Group 3, and 15 of 30 patients (50%) in Group 4 died ($P_{incidence}$<0.001). A significant difference in survival analysis for all-cause death was apparent (log rank, P<0.001; **Supplementary Figure**).

In univariate Cox proportional hazard modeling, being in Group 4 (relative to Group 1) was a significant risk factor for all-cause death (HR 3.7; 95% CI 2.01–6.82; P<0.001). In adjusted Cox proportional hazard modeling, being in Groups 3 and 4 (relative to Group 1) was a significant risk factor for all-cause death (HR 1.67 [95% CI 1.02–2.75; P=0.042] and HR 2.92 [95% CI 1.57–5.41; P<0.001], respectively).

During the follow-up period, 75 of 194 patients (39%) in Group 1, 58 of 129 patients (45%) in Group 3, and 17 of 30 patients (57%) in Group 4 experienced the composite endpoint ($P_{incidence}$=0.14) No significant difference in survival was seen, but a trend was apparent (see **Supplementary Figure**; log rank, P=0.071).

Univariate Cox proportional hazard modeling did not show a significant HR for Group 3 or Group 4 relative to Group 1, trends were apparent (HR 1.36 [95% CI 0.96–1.91; P=0.082] and HR 1.67 [95% CI 0.98–2.84; P=0.057], respectively). Adjusted Cox proportional hazard modeling revealed that being in Group 3 (relative to Group 1) was a significant risk for the composite endpoint (HR 1.49; 95% CI 1.05–2.1; P=0.025).

### Sensitivity Analysis Using Cox Proportional Hazard Models Adjusted by GWTG Risk Score and Hemoglobin Levels

Estimated HRs for all-cause death and the composite

endpoint from Cox proportional hazard models adjusted by the GWTG risk score and hemoglobin levels confirmed that no decrease in Cl, hypochloremia, and both (Group 4) were significant (**Supplementary Tables 1**,**2**).

## Discussion

To the best of our knowledge, the present study is the first to show that an early change in Cl during the first 5 hospital days, which may reflect responses to diuretics, was associated with prognosis in AHF. Patients with no decline in Cl had significantly higher risks for all-cause death and the composite endpoint of all-cause death and rehospitalization for HF than those in whom Cl declined, especially in patients with hypochloremia on admission.

### Early Changes in Cl and Cl Trajectory in HF Hospitalization

The present study focused on relatively early changes in serum Cl because this may reflect responses to diuretics better than changes in Cl from admission to discharge. Another group showed that progression of hypochloremia from normochloremia on admission was associated with worse prognosis.[19] These findings appear inconsistent with those of the present study, but suggest that progression of hypochloremia may reflect persistence of congestion requiring long-term treatment with diuretics or, in contrast, excessive loop diuretic use that could result in enhanced neurohormonal activation.[6,20] In addition, testing the association of time-dependent variables, such as changes in Cl from admission to discharge, with outcomes after discharge may be confounded by definitions of $t_0$.

### Interaction

The prognostic value of Cl on admission in AHF was reported by Grodin et al,[4] with hypochloremia on admission associated with poor long-term survival. The results of the present study are consistent with those of Grodin et al,[4] despite a different definition of hypochloremia (<104 mEq/L) in the present study. Given that the decrease in bodyweight during the first 3 hospital days was less in the hypochloremia than non-hypochloremia group (**Table 1**), hypochloremia was assumed to suppress the response to loop diuretics and may be associated with worse prognosis in our study population. In fact, Hanberg et al[6] reported that hypochloremia was associated with diuretic resistance. However, comparison of the 4 stratified groups suggests a different explanation. The lack of a decline in Cl and the presence of hypochloremia additively or synergistically interacted to increase mortality risk in our population. Factors other than resistance to diuretics, such as neurohormonal activation, may contribute to the higher mortality risk in patients with hypochloremia. Conversely, the poor prognosis in patients with a poor Cl response may be the result of a slow improvement in congestion.

### Study Limitations

The present study has several limitations. Changes in Cl earlier than Day 5 in hospital could not be obtained from the clinical data. Furthermore, we did not obtain data on urine volume or urinalysis, including Cl and sodium levels, and arterial blood gas analysis was not performed. Instead of urine volume, we used body weight change during the first 3 hospital days. The mechanisms underlying the decreases in Cl were assumed to be multifactorial, such as salt intake and diuretic use. Body weight change was used as a surrogate marker for a diuretic response. Thus, the present study could not address the physiological mechanisms underlying the decrease in Cl after AHF hospitalization. Future studies to clarify the relationship between Cl changes and diuretic response are warranted.

## Conclusions

No decrease in serum Cl concentrations (Cl change ≥0 mEq/L) was associated with a poor prognosis in AHF after initial loop diuretic administration. The risk of Cl unresponsiveness was exaggerated particularly in patients with hypochloremia at the time of hospital admission.

### Acknowledgments

The authors thank Chio Iseki, Shimon Toma, and Yoji Takami for data collection. The authors also appreciate the dedicated work of the medical technicians at Tomishiro Central Hospital, who analyzed all the laboratory data for the hospitalized HF patients. The authors thank Atsushi Kakazu, Toshiya Chinen, Masanori, Kakazu, Masahiro Tamashiro, Masaki Tabuchi, Akihiko Yamauchi, Hideaki Sonoi, and Hideki Takaesu for caring for the patients. The authors also thank Syoko Nakaima and Yumi Ikehara for assisting with the writing of this manuscript.

### Sources of Funding

This study did not receive any specific funding.

### Disclosures

S.U. is a member of *Circulation Journal*' Editorial Team. The other authors have no conflicts of interest to declare.

### IRB Information

This study was approved by the local ethics committee of Tomishiro Central Hospital (Reference no. H28R018).

### Data Availability

The data will not be shared.

### References

1. Dunlap ME, Hauptman PJ, Amin AN, Chase SL, Chiodo JA 3rd, Chiong JR, et al. Current management of hyponatremia in acute heart failure: A report from the hyponatremia registry for patients with euvolemic and hypervolemic hyponatremia (HN Registry). *J Am Heart Assoc* 2017; **6:** e005261.
2. Oren RM. Hyponatremia in congestive heart failure. *Am J Cardiol* 2005; **95:** 2B–7B.
3. O'Connor CM, Ahmad T. The role of sodium and chloride in heart failure: Does it take two to tango? *J Am Coll Cardiol* 2015; **66:** 667–669.
4. Grodin JL, Simon J, Hachamovitch R, Wu Y, Jackson G, Halkar M, et al. Prognostic role of serum chloride levels in acute decompensated heart failure. *J Am Coll Cardiol* 2015; **66:** 659–666.
5. Grodin JL, Verbrugge FH, Ellis SG, Mullens W, Testani JM, Tang WH. Importance of abnormal chloride homeostasis in stable chronic heart failure. *Circ Heart Fail* 2016; **9:** e002453.
6. Hanberg JS, Rao V, Ter Maaten JM, Laur O, Brisco MA, Perry Wilson F, et al. Hypochloremia and diuretic resistance in heart failure: Mechanistic insights. *Circ Heart Fail* 2016; **9:** e003180.
7. Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; **342:** 1581–1589.
8. Goldsmith SR, Francis GS, Cowley AW Jr, Levine TB, Cohn JN. Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J Am Coll Cardiol* 1983; **1:** 1385–1390.
9. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation* 1990; **82:** 1724–1729.

10. Clayton JA, Rodgers S, Blakey J, Avery A, Hall IP. Thiazide diuretic prescription and electrolyte abnormalities in primary care. *Br J Clin Pharmacol* 2006; **61:** 87–95.
11. Lim HS. Hypochloremia in acute decompensated heart failure. *J Am Coll Cardiol* 2015; **66:** 2682–2683.
12. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, et al. Diuretic response in acute heart failure: Clinical characteristics and prognostic significance. *Eur Heart J* 2014; **35:** 1284–1293.
13. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed Little, Brown & Co; Boston, Mass: 1994. pp. 253–256.
14. Testani JM, Hanberg JS, Arroyo JP, Brisco MA, Ter Maaten JM, Wilson FP, et al. Hypochloraemia is strongly and independently associated with mortality in patients with chronic heart failure. *Eur J Heart Fail* 2016; **18:** 660–668.
15. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant* 2013; **48:** 452–458.
16. Peterson PN, Rumsfeld JS, Liang L, Albert NM, Hernandez AF, Peterson ED, et al. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association Get With the Guidelines program. *Circ Cardiovasc Qual Outcomes* 2010; **3:** 25–32.
17. Shiraishi Y, Kohsaka S, Abe T, Mizuno A, Goda A, Izumi Y, et al. Validation of the Get With the Guideline-Heart Failure risk score in Japanese patients and the potential improvement of its discrimination ability by the inclusion of B-type natriuretic peptide level. *Am Heart J* 2016; **171:** 33–39.
18. Suzuki S, Yoshihisa A, Sato Y, Kanno Y, Watanabe S, Abe S, et al. Clinical significance of Get With the Guidelines-Heart Failure risk score in patients with chronic heart failure after hospitalization. *J Am Heart Assoc* 2018; **7:** e008316.
19. Kondo T, Yamada T, Tamaki S, Morita T, Furukawa Y, Iwasaki Y, et al. Serial change in serum chloride during hospitalization could predict heart failure death in acute decompensated heart failure patients. *Circ J* 2018; **82:** 1041–1050.
20. Kotchen TA, Luke RG, Ott CE, Galla JH, Whitescarver S. Effect of chloride on renin and blood pressure responses to sodium chloride. *Ann Intern Med* 1983; **98:** 817–822.

## Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-20-0058