ESC HEART FAILURE
*ESC Heart Failure* 2023; **10**: 255–263
Published online 3 October 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14187

ORIGINAL ARTICLE

# Association between serum sodium level trajectories and survival in patients with heart failure

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## Abstract

**Aims** The effect of changes in serum sodium levels on the survival of patients with heart failure (HF) is unclear. We aimed to analyse the impact of serum sodium level trajectories on survival in intensive care unit (ICU) patients with HF.

**Methods** A total of 4760 patients diagnosed with HF between 2001 and 2012 from the Medical Information Mart for Intensive Care III (MIMIC-III) database were extracted. Of these patients, 1132 patients who died within 48 h of ICU admission were excluded, and 3628 patients were included in this retrospective cohort study. Sodium levels were measured at baseline, 6, 12, 18, 24, 30, 36, 42, and 48 h. Patients were divided into hyponatremia, normal, and hypernatremia groups based on baseline sodium levels, and trajectory modelling was performed for each group separately. Group-based trajectory model (GBTM) method was utilized to identify serum sodium levels trajectories.

**Results** The number of patients with hyponatremia (<135 mmol/L), normal sodium levels (135–145 mmol/L), and hypernatremia (>145 mmol/L) at baseline were 594 (16.37%), 2,738 (75.47%), and 296 (8.16%), respectively. A total of seven trajectory groups were identified, including hyponatremia-slow rise group [initial levels (IL), 128.48 ± 5.42 mmol/L; end levels (EL), 131.23 ± 3.83 mmol/L], hyponatremia-rapid rise to normal group (IL, 132.13 ± 2.18 mmol/L; EL, 137.46 ± 3.68 mmol/L), normal-slow decline group (IL, 137.65 ± 2.15 mmol/L; EL, 134.50 ± 2.54 mmol/L), normal-steady-state group (IL, 139.20 ± 2.26 mmol/L; EL, 139.04 ± 2.58 mmol/L), normal-slow rise group (IL, 140.94 ± 2.37 mmol/L; EL, 143.43 ± 2.89 mmol/L), hypernatremia-rapid decline to normal group (IL, 146.31 ± 1.98 mmol/L; EL, 140.71 ± 3.61 mmol/L), and hypernatremia-slow decline group (IL, 148.89 ± 5.54 mmol/L; EL, 146.28 ± 3.90 mmol/L). The results showed that hyponatremia-slow rise group [hazard ratio (HR) = 1.35; 95% confidence interval (CI), 1.01–1.80, $P$ = 0.040], hyponatremia-rapid rise to normal group (HR = 1.37; 95% CI, 1.11–1.71, $P$ = 0.004), hypernatremia-rapid decline to normal group (HR = 1.46; 95% CI, 1.08–1.97, $P$ = 0.014), and hypernatremia-slow decline group (HR = 1.49; 95% CI, 1.07–2.07, $P$ = 0.018) trajectories were associated with an increased risk of 1-year mortality in HF patients compared with normal-steady-state group. After adjustment for all confounders, hyponatremia-rapid rise to normal group (HR = 1.26, 95% CI; 1.01–1.57, $P$ = 0.038) and hypernatremia-rapid decline to normal group (HR = 1.36; 95% CI, 1.01–1.84, $P$ = 0.047) trajectories were still related to an increased risk of 1-year mortality in patients with HF.

**Conclusions** Serum sodium level trajectories were associated with mortality in patients with HF. Association between serum sodium level trajectories and prognosis in patients with HF deserve further study.

**Keywords** Heart failure; Sodium levels; Trajectory; Survival; Hyponatremia; Hypernatremia

*Received: 30 May 2022; Revised: 15 September 2022; Accepted: 19 September 2022*
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## Introduction

Heart failure (HF) is the most common cardiovascular cause of hospitalization among individuals over 60 years of age, with costly, disabling, and increasing characteristics.[1] The global prevalence and mortality of HF in 2020 were reported to be 6.11 million and 0.37 million, respectively.[2] Factors contributing to the increased prevalence of HF include an

ageing population and increased population of associated risk factors (hypertension, diabetes, and obesity), and treatment prolongs survival in HF patients.[3,4] Mortality in HF patients is high, exceeding 56% within 5 years of diagnosis,[5] and more than 30% of patients require readmission within 90 days of discharge.[6] Several studies indicated that serum sodium levels were associated with the prognosis of HF patients.[7,8]

Hyponatremia (serum sodium levels <135 mmol/L) is observed in approximately 20–30% of hospitalized patients with HF.[9,10] Numerous studies demonstrated that both hyponatremia and hypernatremia (serum sodium levels >145 mmol/L) are associated with poor prognosis in patients admitted to intensive care units (ICU).[11–13] However, these studies typically only assessed the effect of serum sodium levels at admission or discharge on patient prognosis. The trajectory of serum sodium changes in patients after admission may be more clinically valuable for monitoring prognosis. Matsue *et al*. found that the trajectory of sodium levels in the acute phase was related to prognosis in patients with acute HF, but not with baseline sodium levels.[14] Inadequately, previous study focused on the impact of sodium dipping (a fall below the sodium level at admission/baseline) and excluded patients with hypernatremia, without exploring the effect of different sodium trajectories at baseline on outcomes in patients with HF. Different serum sodium levels at admission may correspond to different trajectories, and the impact of these trajectories on the prognosis of patients with HF has not been reported.

Herein, we aimed to group HF patients according to their baseline serum sodium levels. Changes in serum sodium levels in different groups of patients were identified, and the impact of different sodium level trajectories on patient survival was explored.

# Methods

## Data source and patients

Data used in this retrospective cohort study were extracted from the Medical Information Mart for Intensive Care III (MIMIC-III) database between 2001 and 2012. MIMIC-III is a large single-centre database containing hospital-related information on 53 423 adult patients (16 years or older) admitted to the ICU between 2001 and 2012. Data includes demographics, clinical measurement, intervention, medical history, clinical laboratory tests and medical data. HF was identified by the International Classification of Diseases, ninth revision (ICD-9) codes (4280 to 4289 and 39891) in the MIMIC-III database. Patients who met the following criteria were included: (i) diagnosed as HF at ICU admission; (ii) aged ≥18; and (iii) taken serum sodium measurements at least nine times within 48 h of ICU admission. The exclusion criteria were as follows: (i) missing survival information and (ii) dying within 48 h of ICU admission. For patients with multiple admissions during the study period, only data from the first hospital admission were collected for analysis. All included patients had nine measurements of serum sodium levels, the initial serum sodium measurements before ICU admission, and the eight serum sodium levels measurements within 48 h of ICU admission. Serum sodium values were measured every 6 h for 48 h after admission to the ICU (at 6, 12, 18, 24, 30, 36, 42, and 48 h). MIMIC-III database was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. The requirement for individual patient consent was waived as the relevant content of the database did not affect clinical care and all protected health information was de-identified.[15]

## Variables

Patient demographic, laboratory test results, medications use, and medical history were collected, including age (≥18 years), sex (male and female), ethnicity (Asian, Hispanic, black, white, and others), body mass index (BMI), respiratory rate, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), partial pressure of oxygen ($PO_2$), partial pressure of carbon dioxide ($PCO_2$), saturation of peripheral oxygen ($SPO_2$), total bilirubin, base excess, sodium, potassium, lactate, white blood cells (WBC), haemoglobin, Glasgow Coma Scale (GCS), Oxford Acute Severity of Illness (OASIS), beta-blocker (yes and no), angiotensin-converting enzyme inhibitor (ACEI, yes and no), angiotensin receptor blocker (ARB, yes and no), digoxin (yes and no), diuretics (yea and no), implantable cardioverter-defibrillator (ICD, yes and no), cardiac resynchronization therapy (CRT, yes and no), Charlson co-morbidity index (CCI), and follow-up time. Serum sodium levels can be divided into hyponatremia (<135 mmol/L), normal sodium levels (135–145 mmol/L), and hypernatremia (>145 mmol/L).[16]

## Sodium level trajectories grouping

The group-based trajectory model (GBTM) method was utilized to identify serum sodium levels with similar developmental trajectories.[17] Patients were divided into three groups according to their serum sodium levels before admission to the ICU: hyponatremia, normal sodium levels, and hypernatremia. The number of trajectories in each group was confirmed using GBTM method. The detailed process was as follows. The number of groups and the order of the survey wave polynomial functions were determined by constructing a base model with no covariates. The model with

**Table 1** Baseline characteristics of all included patients

| Variables | Total ($n$ = 3628) | 1-year survival ($n$ = 2755) | 1-year mortality ($n$ = 873) | Statistics | $P$ |
|---|---|---|---|---|---|
| Age, years, mean ± SD | 70.69 ± 13.53 | 69.62 ± 13.77 | 74.09 ± 12.13 | t = −9.19 | <0.001 |
| Sex, $n$ (%) | | | | $\chi^2$ = 1.090 | 0.296 |
| Female | 1698 (46.80) | 1276 (46.32) | 422 (48.34) | | |
| Male | 1930 (53.20) | 1479 (53.68) | 451 (51.66) | | |
| Ethnicity, $n$ (%) | | | | $\chi^2$ = 3.283 | 0.512 |
| Asian | 65 (1.79) | 51 (1.85) | 14 (1.60) | | |
| Hispanic | 76 (2.09) | 58 (2.11) | 18 (2.06) | | |
| Black | 284 (7.83) | 224 (8.13) | 60 (6.87) | | |
| White | 2648 (72.99) | 1991 (72.27) | 657 (75.26) | | |
| Others | 555 (15.30) | 431 (15.64) | 124 (14.20) | | |
| BMI, mean ± SD | 28.99 ± 8.66 | 28.74 ± 8.48 | 29.79 ± 9.14 | t = −3.02 | 0.003 |
| Respiratory rate, M ($Q_1$, $Q_3$) | 18.00 (14.00, 23.00) | 18.00 (14.00, 23.00) | 19.00 (15.00, 24.00) | Z = 3.838 | <0.001 |
| Heart rate, mean ± SD | 90.27 ± 20.30 | 90.20 ± 20.03 | 90.47 ± 21.13 | t = −0.33 | 0.738 |
| SBP, mmHg, mean ± SD | 121.59 ± 26.20 | 121.88 ± 26.12 | 120.65 ± 26.45 | t = 1.21 | 0.225 |
| DBP, M ($Q_1$, $Q_3$) | 60.00 (50.00, 71.00) | 60.00 (51.00, 72.00) | 59.00 (49.00, 71.00) | Z = -1.862 | 0.063 |
| $PO_2$, M ($Q_1$, $Q_3$) | 109.00 (72.00, 240.00) | 113.00 (73.00, 259.00) | 98.00 (68.00, 196.00) | Z = -4.566 | <0.001 |
| $PCO_2$, M ($Q_1$, $Q_3$) | 41.00 (35.00, 48.00) | 41.00 (36.00, 47.00) | 41.00 (35.00, 49.00) | Z = 0.337 | 0.736 |
| $SPO_2$, mean ± SD | 96.71 ± 5.92 | 96.74 ± 6.22 | 96.64 ± 4.89 | t = 0.48 | 0.633 |
| Base excess, M ($Q_1$, $Q_3$) | 0.00 (−3.00, 3.00) | 0.00 (−3.00, 3.00) | 0.00 (−3.00, 3.00) | Z = -1.480 | 0.139 |
| Total bilirubin, mg/dL, M ($Q_1$, $Q_3$) | 0.60 (0.40, 1.00) | 0.60 (0.40, 1.00) | 0.60 (0.40, 1.00) | Z = -0.756 | 0.450 |
| Sodium, mmol/L, mean ± SD | 138.04 ± 5.24 | 138.18 ± 5.12 | 137.61 ± 5.61 | t = 2.66 | 0.008 |
| Potassium, mmol/L, mean ± SD | 4.38 ± 0.86 | 4.34 ± 0.83 | 4.51 ± 0.95 | t = −4.78 | <0.001 |
| Lactate, mmol/L, M ($Q_1$, $Q_3$) | 1.70 (1.20, 2.50) | 1.60 (1.20, 2.50) | 1.70 (1.20, 2.50) | Z = 0.871 | 0.384 |
| WBC, k/uL, M ($Q_1$, $Q_3$) | 10.30 (7.30, 14.40) | 10.20 (7.30, 14.20) | 10.30 (7.30, 14.80) | Z = 0.472 | 0.637 |
| Haemoglobin, g/dl, mean ± SD | 11.53 ± 2.20 | 11.68 ± 2.22 | 11.04 ± 2.06 | t = 7.83 | <0.001 |
| OASIS, mean ± SD | 24.89 ± 7.04 | 24.62 ± 7.03 | 25.77 ± 7.01 | t = −4.24 | <0.001 |
| GCS, M ($Q_1$, $Q_3$) | 11.00 (6.00, 15.00) | 11.00 (5.00, 15.00) | 12.00 (7.00, 15.00) | Z = 2.641 | 0.008 |
| Beta-blocker, $n$ (%) | | | | $\chi^2$ = 21.685 | <0.001 |
| No | 2256 (62.18) | 1655 (60.07) | 601 (68.84) | | |
| Yes | 1372 (37.82) | 1100 (39.93) | 272 (31.16) | | |
| ACEI, $n$ (%) | | | | $\chi^2$ = 11.215 | <0.001 |
| No | 2459 (67.78) | 1827 (66.32) | 632 (72.39) | | |
| Yes | 1169 (32.22) | 928 (33.68) | 241 (27.61) | | |
| ARB, $n$ (%) | | | | $\chi^2$ = 0.000 | 0.990 |
| No | 3449 (95.07) | 2619 (95.06) | 830 (95.07) | | |
| Yes | 179 (4.93) | 136 (4.94) | 43 (4.93) | | |
| Diuretics, $n$ (%) | | | | $\chi^2$ = 13.639 | <0.001 |
| No | 727 (20.04) | 514 (18.66) | 213 (24.40) | | |
| Yes | 2901 (79.96) | 2241 (81.34) | 660 (75.60) | | |
| Digoxin, $n$ (%) | | | | $\chi^2$ = 14.755 | <0.001 |
| No | 3247 (89.50) | 2496 (90.60) | 751 (86.03) | | |
| Yes | 381 (10.50) | 259 (9.40) | 122 (13.97) | | |
| ICD, $n$ (%) | | | | $\chi^2$ = 6.235 | 0.013 |
| No | 3558 (98.07) | 2693 (97.75) | 865 (99.08) | | |
| Yes | 70 (1.93) | 62 (2.25) | 8 (0.92) | | |
| CRT, $n$ (%) | | | | $\chi^2$ = 0.014 | 0.906 |
| No | 3602 (99.28) | 2735 (99.27) | 867 (99.31) | | |
| Yes | 26 (0.72) | 20 (0.73) | 6 (0.69) | | |
| CCI, mean ± SD | 3.54 ± 2.01 | 3.49 ± 1.99 | 3.72 ± 2.06 | t = −2.95 | 0.003 |
| Hyponatremia (0 h), mean ± SD | 130.92 ± 3.97 | 130.97 ± 4.13 | 130.79 ± 4.13 | t = 0.54 | 0.586 |
| Normal sodium (0 h), mean ± SD | 139.21 ± 2.55 | 139.24 ± 2.52 | 139.09 ± 2.63 | t = 1.27 | 0.204 |
| Hypernatremia (0 h), mean ± SD | 147.43 ± 4.14 | 147.42 ± 4.14 | 14.47 ± 4.18 | t = −0.09 | 0.925 |
| Sodium 0 h, mmol/L, mean ± SD | 138.52 ± 5.02 | 138.58 ± 4.89 | 138.35 ± 5.40 | t = 1.11 | 0.265 |
| Sodium 6 h, mmol/L, mean ± SD | 138.57 ± 5.02 | 138.62 ± 4.90 | 138.42 ± 5.39 | t = 0.96 | 0.336 |
| Sodium 12 h, mmol/L, mean ± SD | 138.69 ± 4.83 | 138.71 ± 4.70 | 138.64 ± 5.22 | t = 0.33 | 0.741 |
| Sodium 18 h, mmol/L, mean ± SD | 138.76 ± 4.64 | 138.75 ± 4.55 | 138.80 ± 4.94 | t = −0.27 | 0.791 |
| Sodium 24 h, mmol/L, mean ± SD | 138.74 ± 4.64 | 138.72 ± 4.54 | 138.82 ± 4.92 | t = −0.53 | 0.596 |
| Sodium 30 h, mmol/L, mean ± SD | 138.61 ± 4.65 | 138.54 ± 4.60 | 138.82 ± 4.79 | t = −1.58 | 0.114 |
| Sodium 36 h, mmol/L, mean ± SD | 138.56 ± 4.64 | 138.49 ± 4.59 | 138.79 ± 4.79 | t = −1.64 | 0.100 |
| Sodium 42 h, mmol/L, mean ± SD | 138.59 ± 4.61 | 138.51 ± 4.58 | 138.82 ± 4.70 | t = −1.74 | 0.082 |
| Sodium 48 h, mmol/L, mean ± SD | 138.67 ± 4.68 | 138.56 ± 4.66 | 138.99 ± 4.72 | t = −2.34 | 0.020 |
| Follow time, days, M (Q1, Q3) | 365.00 (365.00, 365.00) | 365.00 (365.00, 365.00) | 123.91 (72.10, 220.33) | Z = -59.473 | <0.001 |
| Trajectories, $n$ (%) | | | | $\chi^2$ = 19.529 | 0.003 |
| Group 1 | 197 (5.43) | 141 (5.12) | 56 (6.41) | | |
| Group 2 | 397 (10.94) | 284 (10.31) | 113 (12.94) | | |

(*Continues*)

**Table 1** (continued)

| Variables | Total ($n$ = 3628) | 1-year survival ($n$ = 2755) | 1-year mortality ($n$ = 873) | Statistics | $P$ |
|---|---|---|---|---|---|
| Group 3 | 737 (20.31) | 578 (20.98) | 159 (18.21) | | |
| Group 4 | 1,331 (36.69) | 1,042 (37.82) | 289 (33.10) | | |
| Group 5 | 670 (18.47) | 504 (18.29) | 166 (19.01) | | |
| Group 6 | 167 (4.60) | 117 (4.25) | 50 (5.73) | | |
| Group 7 | 129 (3.56) | 89 (3.23) | 40 (4.58) | | |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCI, Charlson co-morbidity index; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; ICD, implantable cardioverter-defibrillator; OASIS, Oxford Acute Severity of Illness; $PCO_2$, partial pressure of carbon dioxide; PO2, partial pressure of oxygen; SBP, systolic blood pressure; $SPO^2$, saturation of peripheral oxygen; WBC, white blood cells.
Trajectory group 1, hyponatremia-slow rise group; group 2, hyponatremia-rapid rise to normal group; group 3, normal-slow decline group; group 4, normal-steady state group; group 5, normal-slow rise group; group 6, hypernatremia-rapid decline to normal group; group 7, hypernatremia-slow decline group.

the highest probability of trajectories and based on the goodness-of-fit statistic by the Bayesian information criterion (BIC, BIC absolute value closest to zero) was determined to be the best fit model. Assign each patient to the matched trajectory groups based on maximum likelihood estimation to estimate the probability of variance of serum sodium value in each group.

### Statistical analysis

Normality of data distribution was evaluated by the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range [M (Q1, Q3)], and the *t*-test or Wilcoxon rank-sum test was used for comparison between groups. Categorical variables were reported as number and percentage [n (%)], and the chi-square test was utilized for comparison between groups. The Kaplan–Meier curves were used to compare differences in survival between trajectories groups. Variables found to be predictive of mortality with $P < 0.05$ at the univariable analysis were introduced into the multivariable Cox regression analysis (stepwise regression). The following models were used in the Cox regression analysis: (i) unadjusted model and (ii) multivariable model that adjusted for age, BMI, respiratory rate, $PO_2$, potassium, haemoglobin, OASIS score, beta-blocker, diuretics, and digoxin. Hazard ratio (HR) and 95% confidence interval (CI) were used for results evaluation. A two-side *P*-value $< 0.05$ was considered statistically significant. All analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

## Results

### Baseline characteristics of patients

A total of 4760 patients diagnosed with HF between 2001 and 2012 were extracted from the MIMIC-III database. One thousand one hundred thirty-two patients who died within 48 h of ICU admission were excluded, and 3628 patients were eventually included in the study. *Table 1* displays the baseline characteristics of included patients. The mean age and BMI of patients were 70.69 ± 13.53 years and 28.99 ± 8.66 kg/$m^2$, respectively. The number of male patients was 1930 (53.20%). The mean Charlson co-morbidity index of patients was 3.54 ± 2.01. The mean serum sodium levels in patients with hyponatremia (<135 mmol/L), normal sodium levels (135–145 mmol/L), and hypernatremia (>145 mmol/L) at baseline were 130.92 ± 3.97 mmol/L, 139.21 ± 2.55 mmol/L, and 147.43 ± 4.14 mmol/L, respectively. The numbers of patients with hyponatremia, normal sodium levels, and hypernatremia at baseline were 594 (16.37%), 2,738 (75.47%), and 296 (8.16%), respectively. At the end of the 1-year follow-up period, 873 (24.06%) patients died, and the median follow-up time was 123. 91 (72.10, 220.33) days.

Analysis of differences between survival and death patients displayed that significant differences were observed in age, BMI, respiratory rate, $PO_2$, sodium, potassium, haemoglobin, OASIS score, GCS score, beta-blocker, ACEI, diuretics, digoxin, ICD, and follow-up time (all $P < 0.05$; *Table 1*).

### Serum sodium levels trajectory groups

The numbers of trajectories in the hyponatremia group, normal sodium levels group, and hypernatremia group were confirmed using the GBTM method. A total of seven trajectory groups were identified, including two trajectories in the hyponatremia group, three trajectories in the normal sodium levels group, and two trajectories in the hypernatremia group (*Table 2* and *Figure 1*): hyponatremia-slow rise group [Group 1; initial levels, 128.48 ± 5.42 mmol/L; end levels, 131.23 ± 3.83 mmol/L; change in sodium levels (Δ), 1.00 (−1.00, 6.00)], hyponatremia-rapid rise to normal group [Group 2; initial levels, 132.13 ± 2.18 mmol/L; end levels, 137.46 ± 3.68 mmol/L; change in sodium levels (Δ), 5.00

**Table 2** Characteristics of serum sodium level trajectory groups

| Variables | Total ($n$ = 3628) | Serum sodium level trajectory groups | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Group 1 ($n$ = 197) | Group 2 ($n$ = 397) | Group 3 ($n$ = 737) | Group 4 ($n$ = 1331) | Group 5 ($n$ = 670) | Group 6 ($n$ = 167) | Group 7 ($n$ = 129) |
| Sodium 0 h, mean ± SD | 138.52 ± 5.02 | 128.48 ± 5.41 | 132.13 ± 2.18 | 137.65 ± 2.15 | 139.20 ± 2.26 | 140.94 ± 2.37 | 146.31 ± 1.98 | 148.89 ± 5.54 |
| Sodium 6 h, mean ± SD | 138.57 ± 5.02 | 129.07 ± 5.22 | 135.58 ± 3.60 | 135.90 ± 3.07 | 138.94 ± 2.36 | 142.57 ± 3.41 | 142.16 ± 3.89 | 148.47 ± 5.56 |
| Sodium 12 h, mean ± SD | 138.69 ± 4.83 | 129.41 ± 4.77 | 136.12 ± 3.45 | 135.57 ± 2.73 | 139.08 ± 2.09 | 143.09 ± 3.15 | 141.65 ± 3.58 | 148.01 ± 4.78 |
| Sodium 18 h, mean ± SD | 138.76 ± 4.64 | 129.70 ± 4.29 | 136.68 ± 3.23 | 135.34 ± 2.53 | 139.08 ± 1.94 | 143.33 ± 2.39 | 141.62 ± 3.36 | 147.83 ± 4.34 |
| Sodium 24 h, mean ± SD | 138.74 ± 4.64 | 130.05 ± 4.07 | 136.96 ± 3.18 | 134.96 ± 2.44 | 139.06 ± 1.83 | 143.65 ± 2.35 | 140.88 ± 3.76 | 147.50 ± 4.16 |
| Sodium 30 h, mean ± SD | 138.61 ± 4.65 | 130.44 ± 3.79 | 137.01 ± 3.26 | 134.49 ± 2.41 | 138.95 ± 1.89 | 143.70 ± 2.34 | 140.41 ± 3.64 | 147.26 ± 4.00 |
| Sodium 36 h, mean ± SD | 138.56 ± 4.64 | 130.58 ± 3.91 | 137.17 ± 3.40 | 134.33 ± 2.39 | 138.90 ± 1.94 | 143.61 ± 2.55 | 140.48 ± 3.13 | 147.02 ± 3.67 |
| Sodium 42 h, mean ± SD | 138.59 ± 4.61 | 130.82 ± 3.63 | 137.27 ± 3.45 | 134.37 ± 2.31 | 138.92 ± 2.09 | 143.56 ± 2.71 | 140.59 ± 3.39 | 146.71 ± 3.58 |
| Sodium 48 h, mean ± SD | 138.67 ± 4.68 | 131.23 ± 3.83 | 137.46 ± 3.68 | 134.50 ± 2.54 | 139.04 ± 2.58 | 143.43 ± 2.89 | 140.71 ± 3.61 | 146.28 ± 3.90 |
| Change in sodium levels (Δ), M (Q1, Q3) | 0.00 (−3.00, 3.00) | 1.00 (−1.00, 6.00) | 5.00 (2.00, 8.00) | −3.00 (−5.00, −1.00) | 0.00 (−2.00, 2.00) | 2.00 (0.00, 5.00) | −5.00 (−8.00, −2.00) | −1.00 (−4.00, 1.00) |

Trajectory group 1, hyponatremia-slow rise group; group 2, hyponatremia-rapid rise to normal group; group 3, normal-slow decline group; group 4, normal-steady state group; group 5, normal-slow rise group; group 6, hypernatremia-rapid decline to normal group; group 7, hypernatremia-slow decline group.

(2.00, 8.00)], normal-slow decline group [Group 3; initial levels, 137.65 ± 2.15 mmol/L; end levels, 134.50 ± 2.54 mmol/L; change in sodium levels (Δ), −3.00 (−5.00, −1.00)], normal-steady-state group [Group 4; initial levels, 139.20 ± 2.26 mmol/L; end levels, 139.04 ± 2.58 mmol/L; change in sodium levels (Δ), 0.00 (−2.00, 2.00)], normal-slow rise group [Group 5; initial levels, 140.94 ± 2.37 mmol/L; end levels, 143.43 ± 2.89 mmol/L; change in sodium levels (Δ), 2.00 (0.00, 5.00)], hypernatremia-rapid decline to normal group [Group 6; initial levels, 146.31 ± 1.98 mmol/L; end levels, 140.71 ± 3.61 mmol/L; change in sodium levels (Δ), −5.00 (−8.00, −2.00)], and hypernatremia-slow decline group [Group 7; initial levels, 148.89 ± 5.54 mmol/L; end levels, 146.28 ± 3.90 mmol/L; change in sodium levels (Δ), −1.00 (−4.00, 1.00)].

## Effect of serum sodium level trajectory groups on 1-year survival in patients with HF

The association between serum sodium level trajectories and 1-year survival of HF patients was shown in *Table 3*. Because the sodium trajectory group 4 was a steady-state group with normal sodium levels, it was used as the reference group. The results indicated that hyponatremia-slow rise group (Group 1; HR = 1.35; 95% CI, 1.01–1.80), hyponatremia-rapid rise to normal group (Group 2; HR = 1.37; 95% CI, 1.11–1.71), hypernatremia-rapid decline to normal group (Group 6; HR = 1.46; 95% CI, 1.08–1.97), and hypernatremia-slow decline group (Group 7; HR = 1.49; 95% CI, 1.07–2.07) trajectories were associated with an increased risk of 1-year mortality in HF patients compared with the Group 4. After adjustment for age, BMI, respiratory rate, $PO_2$, potassium, haemoglobin, OASIS score, beta-blocker, diuretics, and digoxin, hyponatremia-rapid rise to normal group (Group 2; HR = 1.26; 95% CI, 1.01–1.57) and hypernatremia-rapid decline to normal group (Group 6; HR = 1.36; 95% CI, 1.01–1.84) trajectories were still related to an increased risk of 1-year mortality in patients with HF.

*Figure 2* shows the 1-year cumulative mortality rate for different serum sodium level trajectory groups. The results indicated that patients with the hypernatremia-slow decline group (Group 7) and hypernatremia-rapid decline to normal group (Group 6) trajectories had the highest 1-year cumulative mortality rate than those in other groups. Patients with the hyponatremia-rapid rise to normal group (Group 2) and hyponatremia-slow rise group (Group 1) trajectories also had a higher 1-year cumulative mortality rate than that of the normal group (Group 4). Furthermore, the 1-year cumulative mortality rate of patients in the normal-slow decline group (Group 3) trajectory was the same as in the normal-steady-state group (Group 4).

**Figure 1** Serum sodium level trajectories in patients with heart failure (HF).

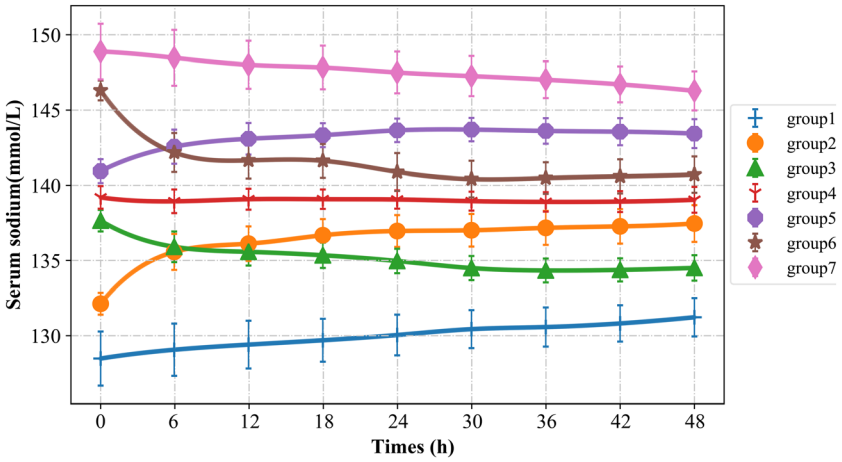



**Table 3** Association between serum sodium level trajectories and 1-year survival of heart failure (HF) patients

| Trajectory groups | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | HR (95% *CI*) | *P* value | HR (95% CI) | *P* value |
| Group 4 | Ref | | Ref | |
| Group 1 | 1.35 (1.01–1.80) | 0.040 | 1.20 (0.90–1.60) | 0.222 |
| Group 2 | 1.37 (1.11–1.71) | 0.004 | 1.26 (1.01–1.57) | 0.038 |
| Group 3 | 0.99 (0.82–1.21) | 0.946 | 1.03 (0.85–1.26) | 0.738 |
| Group 5 | 1.17 (0.97–1.42) | 0.106 | 1.05 (0.87–1.27) | 0.614 |
| Group 6 | 1.46 (1.08–1.97) | 0.014 | 1.36 (1.01–1.84) | 0.047 |
| Group 7 | 1.49 (1.07–2.07) | 0.018 | 1.05 (0.75–1.47) | 0.764 |

95% CI, confidence interval; HR, hazard ratio.
Group 1, hyponatremia-slow rise group; group 2, hyponatremia-rapid rise to normal group; group 3, normal-slow decline group; group 4, normal-steady state group; group 5, normal-slow rise group; group 6, hypernatremia-rapid decline to normal group; group 7, hypernatremia-slow decline group; model 1, unadjusted model; model 2, adjusted for age, BMI, respiratory rate, $PO_2$, potassium, haemoglobin, OASIS score, beta-blocker, diuretics, and digoxin.

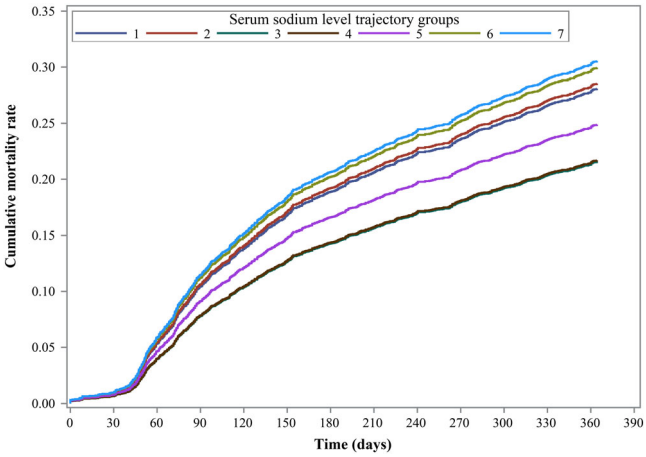
## Discussion

In this study, we analysed the impact of serum sodium level trajectories on survival in HF patients with hyponatremia, normal sodium levels, and hypernatremia before admission. A total of seven serum sodium level trajectories were identified, of which hyponatremia-slow rise group, hyponatremia-rapid rise to normal group, hypernatremia-rapid decline to normal group, and hypernatremia-slow decline group trajectories were associated with an increased risk of 1-year mortality. After adjustment for all confounders, trajectories of hyponatremia-rapid rise to normal group and hypernatremia-rapid decline to normal group were still associated with an increased risk of 1-year mortality in patients with HF.

The sodium ion is the main component that affects the effective osmotic pressure of the extracellular fluid. Serum sodium levels are regulated by thirst and renal mechanisms, including arginine vasopressin and tonicity-responsive element binding protein.[18,19] Several mechanisms by which hyponatremia contributes to poor outcomes in patients with HF have been reported.[20,21] First, hyponatremia may directly reflect reduced cardiac output.[22] Reduced cardiac output decreases renal perfusion and glomerular filtration rates, which are associated with poor outcomes in patients with HF.[23–25] Second, hormonal abnormalities play an important role in the relationship between heart failure and hyponatremia. The renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) are activated in HF patients,[26] resulting in renal vasoconstriction and reduced glomerular filtration rate. In addition, abnormalities of these hormones increase sodium and water retention in the body and increase the release of arginine vasopressin (AVP). The release of AVP increases vascular resistance and free water retention.[27,28] Third, diuretic use may also lead to hyponatremia and adverse outcomes in patients with HF.[29,30] Diuretic resistance does not adequately increase fluid and sodium output to relieve volume overload, oedema, or congestion and is a major cause of repeated hospitalizations in patients with chronic HF.[30]

A recent study found that changes in serum sodium levels within 48 h before admission were more strongly associated with mortality risk.[13] Our study explored the association between changes in serum sodium levels and mortality in patients with HF based on the sodium level trajectory within 48 h after admission to the ICU. Our results found that both hyponatremia-related and hypernatremia-related trajectories of sodium levels were associated with increased 1-year mortality risk in patients with HF. Previous studies also demonstrated that hyponatremia or hypernatremia are independent

**Figure 2** The 1-year cumulative mortality rate for different serum sodium level trajectory groups in patients with HF.




predictors of short-term and long-term mortality in adult patients.[13,31,32] A meta-analysis indicated that hyponatremia is an important determinant of mortality in HF patients regardless of ejection fraction.[32] Thongprayoon *et al*. indicated that patients with hyponatremia or hypernatremia had increased hospitalization rates and 1-year mortality compared with patients with normal serum sodium levels.[13] In addition, a retrospective secondary analysis based on a randomized controlled trial showed that the trajectory of sodium levels in the acute phase was a better indicator of prognosis in patients with acute HF than baseline sodium levels.[14] However, their study focused on the impact of sodium dipping and excluded patients with hypernatremia. Our study more comprehensively analysed the serum sodium trajectories of patients with hyponatremia, normal sodium levels, and hypernatremia at baseline. Our results further found that trajectories of hyponatremia-rapid rise to normal group and hypernatremia-rapid decline to normal group were associated with an increased risk of 1-year mortality in HF patients after adjustment for all confounders. These results suggested that rapid intervention with sodium levels in hyponatremia or hypernatremia patients may increase the mortality risk. However, there are significant differences in the management and correction rates between acute and chronic hyponatremia.[33] For example, chronic hyponatremia should be corrected at a rate sufficient to relieve symptoms, not at an excessive rate.[34] The effect of serum sodium level correction rate on the prognosis of patients with HF may require further study. Our study developed serum sodium trajectories based on serum sodium level measurements taken every 6 h within 48 h of admission. Intensive measurements can fully demonstrate the true sodium level changes in HF patients, but this may be difficult to achieve in practice. It may be possible to refer to the sodium level trajectories in this study and select a small number of sodium measurements such as the sodium level every 12 h to reflect the patient's serum sodium trajectories in clinical practice.

Our study analysed the effect of serum sodium level trajectories on survival in patients within 48 h of ICU admission based on a large sample of the MIMIC-III database. Patients were grouped according to their serum sodium levels at baseline (hyponatremia, normal sodium levels, and hypernatremia), and the serum sodium level trajectories of different groups of patients were identified separately. A total of seven sodium level trajectories were identified, and their impact on survival was analysed. However, some limitations should be acknowledged. First, the sodium intake of each patient could not be assessed, especially by intravenous sodium intake. Second, although we attempted to adjust for confounders as much as possible, a potential unadjusted confounding could remain. Third, patients with acute and chronic dysnatraemia had different correction rates, which may affect the grouping of trajectories. Fourth, the study period was 13 years (2001–2012), which may present a time bias in the treatment of HF, as new treatment modalities, protocols, and drugs were introduced. Fifth, our study did not explore the effect of serum sodium level trajectories on different left ventricular ejection fraction (LVEF) patients due to the lack of LVEF data in the MIMIC-III database. Sixth, a total of 1132 patients who died within 48 h of admission were excluded, which may underestimate the impact of serum sodium trajectories on mortality in HF patients.

## Conclusions

A total of seven trajectories of sodium levels in HF patients were identified based on changes in sodium levels within

48 h of ICU admission. Trajectories of hyponatremia-rapid rise to normal group and hypernatremia-rapid decline to normal group were associated with an increased risk of 1-year mortality in patients with HF. These results suggested that rapid intervention with sodium levels in hyponatremia or hypernatremia patients may increase the mortality risk. Confirmed evidence may require further study.

## Conflict of interest

None declared.

## Funding

None.

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