Relationship Between Serum Sodium Level Within the Low-Normal Range on Admission and Long-Term Clinical Outcomes in Patients with Acute Decompensated Heart Failure

Masaru Hiki,1 MD, Takatoshi Kasai,1,2 MD, Shoichiro Yatsu,1 MD, Azusa Murata,1 MD, Hiroki Matsumoto,1,2 MD, Takao Kato,1 MD, Shoko Suda,1,2 MD, Tetsuro Miyazaki,1 MD, Atsutoshi Takagi,1 MD and Hiroyuki Daida,1 MD

Summary

Although hyponatremia during hospitalization for acute decompensated heart failure (ADHF) is reportedly related with poor prognosis, there is a lack of data regarding the impact of serum sodium level within the low-normal range at admission on clinical events in patients with ADHF. We studied eligible patients admitted to our institution in 2007-2011. All the patients were categorized into 3 groups according to the admission serum sodium levels of < 135 mmol/L (hyponatremia), ≥ 135 and < 140 mmol/L (low-normal range), or ≥ 140 mmol/L (normal range). The association between admission serum sodium levels and long-term clinical events, a composite of all-cause deaths and re-hospitalizations for ADHF, was assessed by multivariable Cox proportional analysis.

Of the 584 eligible patients, 208 (35.6%) were in the low-normal range and 99 (16.9%) had hyponatremia on admission. On multivariable analysis, compared with those with a sodium level ≥ 140 mmol/L, patients with hyponatremia were at increased risk for clinical events (hazard ratio [HR], 1.53; \( P = 0.041 \)), whereas the HR of those in the low-normal range was attenuated and insignificant (HR, 1.08; \( P = 0.625 \)). However, the HR of each category increased significantly as sodium level decreased (HR trend, 0.024). In addition, when serum sodium level was treated as a continuous variable, the lower the serum sodium level, the greater the risk of clinical events (HR, 0.012). The cut-off value of serum sodium level to predict mortality was < 138 mmol/L.

In conclusion, a low serum sodium level on admission for ADHF, even if low-normal, can increase the risk of long-term mortality and/or re-hospitalization for ADHF.

Key words: Congestion, Re-hospitalization, Hyponatremia, Acute heart failure

Despite the recent advances in treatments for heart failure (HF),1 it remains one of the leading causes with increased hospitalization and mortality.2 Acute decompensated HF (ADHF) often requires hospital admission and each episode of ADHF itself is associated with progression and the resulting poor clinical outcomes.3 Each ADHF episode can impair the renal function or alter the cardiovascular physiology and biomarkers4 in association with neurohumoral overactivation,5 which may play a role in HF progression and poor clinical outcomes.

Hyponatremia, mainly caused by dilution and associated with neurohumoral overactivation in patients with HF,3,4 has recently gained focus. Hyponatremia is commonly defined as a serum sodium level < 135 mmol/L3 and several clinical studies have shown that hyponatremia defined as a serum sodium level < 135 mmol/L is a powerful prognostic factor of mortality and re-hospitalization in cases of stable HF.6,10 Hyponatremia at hospital admission due to worsening HF is an independent predictor of mortality and/or re-hospitalization after ADHF.11-17

In patients with ADHF from Western countries, admission serum sodium level as a continuous variable was also associated with poor clinical outcomes and an increased hazard ratio (HR) as admission serum sodium level decreased.11,14,15,16,19 However, in Japanese patients with ADHF, the association between the admission serum sodium level as a continuous variable and poor long-term clinical outcomes remains unclear. Some studies showed that the HR for all-cause mortality increased as admission

From the 1Department of Cardiovascular Medicine, Juntendo University School of Medicine, Tokyo, Japan and 2Cardiovascular Respiratory Sleep Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan.

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Address for correspondence: Takatoshi Kasai, MD, Department of Cardiovascular Medicine, Juntendo University School of Medicine, Cardiovascular Respiratory Sleep Medicine, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. E-mail: kasai-t@mx6.nisq.net

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A admission sodium level and outcomes in ADHF

Methods

Subjects: Patients who were admitted to the cardiac intensive care unit in Juntendo University Hospital (Tokyo, Japan) with a diagnosis of ADHF between January 2007 and December 2011 were included in the present study. ADHF was defined based on modified Framingham criteria.21 Patients who had acute coronary syndrome and/or underwent cardiac surgery during the previous 4 weeks or during the initial hospitalization as well as those with a life-threatening malignancy were excluded from the study. In addition, patients without documented admission serum sodium levels were excluded.

The Institutional Review Board of Juntendo University Hospital approved the study protocol, which complied with the Declaration of Helsinki. Informed consent was obtained from all the patients.

Data collection: The baseline data were prospectively collected at the time of initial hospital admission. The medical history was obtained from a review of the patients’ clinical charts. Complete two-dimensional echocardiography was performed on each patient. The left ventricular ejection fraction (LVEF) was calculated according to the modified Simpson method. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation with a Japanese coefficient from baseline serum creatinine levels.22

Further uni- and multivariable analyses, including a binary categorical variable such as serum sodium level > 135 mmol/L to predict clinical events. In addition, the best cut-off value of serum sodium level to predict the risk of occurrence of clinical events was obtained through receiver operating characteristic (ROC) curve analysis and was identified as the value that minimized the expression ((1-sensitivity)² + (1-specificity)²).24

Further uni- and multivariable analyses including a binary categorical variable such as serum sodium level ≥ or < 140 mmol/L were performed, to determine the cut-off value of serum sodium level > 135 mmol/L to predict clinical events. In addition, the best cut-off value of serum sodium level to predict the risk of occurrence of clinical events was obtained through receiver operating characteristic (ROC) curve analysis and was identified as the value that minimized the expression ((1-sensitivity)² + (1-specificity)²).24

Further uni- and multivariable analyses including a binary categorical variable such as serum sodium level ≥ or < the best cut-off of serum sodium level determined ROC curve analysis were also performed. The assumption of proportional hazards was assessed using a log-minus-log survival graph. A P value < 0.05 was considered statistically significant. SPSS version 23 (SPSS Inc., Chicago, IL, USA) was used to perform all the analyses.

Results

Patient characteristics: Overall, 751 patients were admitted to our institution with ADHF between 2007 and 2011. Among them, 160 patients with concomitant acute coronary syndrome and/or who had undergone cardiac surgery during the previous 4 weeks or during initial hospitalization as well as those who had a life-threatening malignancy were initially excluded, and 7 patients without a serum sodium value on admission were then excluded. Fi-
nally, of the 584 patients, 208 patients (35.6%) were identified as having a serum sodium level ≥ 140 mmol/L and 99 patients (16.9%) were identified as having a serum sodium level < 135 mmol/L on admission.

Table I shows the patients’ baseline characteristics classified into 3 groups by serum sodium level. Patients with a low serum sodium level were likely to be older and have a lower BMI and lower systolic and diastolic BP. The hemoglobin levels and eGFR were lower but the CRP levels were higher in patients with low serum sodium levels than in the other patients. In the patients with a low serum sodium level, the serum potassium level was higher. The patients with a normal to high serum sodium level were less likely to have aldosterone blockers than the other patients.

**Clinical outcomes:** At mean and maximum follow-up durations of 1.4 and 6.3 years, respectively, there were 321 clinical events (55.0%): 141 (50.9%) consisted of 60 deaths (21.6%), including 38 (13.7%) due to cardiovascular causes, and 81 re-hospitalizations (29.2%) in patients with serum sodium level ≥ 140 mmol/L; 116 (55.8%) consisted of 54 deaths (26.0%), including 37 (17.8%) due to cardiovascular causes, and 62 re-hospitalizations (29.8%) in those with a low-normal serum sodium level; and 64 (64.6%) consisted of 36 deaths (36.4%), including 18 (18.2%) due to cardiovascular causes, and 28 re-hospitalizations (28.3%) in those with hyponatremia.

The Figure shows the Kaplan-Meier event-free survival curves of the 3 groups. The patients with low serum sodium levels were more likely to have a high cumulative incidence of clinical events. In the univariable analysis, the patients with a serum sodium level < 135 mmol/L were at an increased risk of clinical events compared to those with a serum sodium level ≥ 140 mmol/L (hazard ratio [HR], 1.91; 95% confidence interval [CI], 1.42-2.57; *P* < 0.001) (Table II). However, among each serum sodium level category, the HR for clinical events increased significantly as the sodium level decreased (*P* value for HR trend, < 0.001). In addition, continuous values of serum sodium were also significantly related to the risk of clinical events (HR, 0.95; 95% CI, 0.93-0.97; *P* < 0.001 per 1-unit increase), suggesting that there was a dose-dependent relationship between serum sodium level and clinical outcomes (Table II). Table II summarizes other variables with a value of *P* < 0.1 on univariable analysis.

Table III shows the results of the primary multivariable regression analysis. Even in the multivariable analysis, patients with a serum sodium level < 135 mmol/L...
were at an increased risk for clinical events compared to those with a serum sodium level ≥140 mmol/L (HR, 1.53; 95% CI, 1.02-2.30; \(P = 0.041\)), whereas the HR of those with a serum sodium level of 135-140 mmol/L was attenuated and remained insignificant (Table III). However, even on multivariable analysis, the HR of each sodium level category increased significantly as the sodium level decreased from ≥140 mmol/L to 135-140 mmol/L to <135 mmol/L (\(P\) value for HR trend, 0.024; Table III) along with ischemic etiology and decreased hemoglobin level. Similarly, the results of the secondary multivariable analysis in which serum sodium level was treated as a continuous variable indicated that the lower the serum sodium level, the greater the risk of all-cause mortality and/or re-hospitalization for HF (Table III).

To determine the cut-off value of serum sodium level for predicting clinical events above the hyponatremia cut-off value (i.e., 135 mmol/L), additional uni- and multivariable analyses, including a categorical variable of serum sodium level ≥ or < 140 mmol/L were performed. In the
univariable analysis, patients with a serum sodium level < 140 mmol/L were at an increased risk of experiencing clinical events compared to those with a serum sodium level ≥ 140 mmol/L (HR, 1.31; 95% CI, 1.05-1.64; P = 0.015). However, in the multivariable analysis, the HR of patients with a serum sodium level of < 140 mmol/L was no longer significant and was excluded from the final model. The ROC analysis determined a serum sodium level ≥ or < 138 mmol/L as the best cut-off level to predict clinical events (sensitivity 62.1, specificity 66.9). Indeed, in the univariable analysis, patients with a serum sodium level < 138 mmol/L were at an increased risk of experiencing clinical events compared to those with a serum sodium level ≥ 138 mmol/L (HR, 1.46; 95% CI, 1.17-1.83; P = 0.001). The HR of patients with a serum sodium level of <138 mmol/L continued to remain significant in the multivariable analysis (HR, 1.23; 95% CI, 1.05-1.44; P = 0.012) (Table IV).

Discussion

The study findings provide novel insights into the relationship between serum sodium level and clinical outcomes in Japanese patients with ADHF. First, consistent with findings from a previous study,13 hyponatremia, defined as serum sodium level < 135 mmol/L on admission, was associated with poor long-term clinical outcomes including all-cause mortality and/or re-hospitalization in patients with ADHF. Second, the risk of clinical events in patients with a low-normal sodium level on admission defined as a serum sodium level of 135-140 mmol/L was not significantly greater than those with a serum sodium level ≥ 140 mmol/L, although there was a significant increasing trend in the risk of clinical events as serum sodium levels decreased, even on multivariable analysis. Third, an inverse relationship between admission serum sodium level as a continuous variable and the risk of clinical events (i.e., the lower the serum sodium level on admission, the greater the risk of clinical events) was clearly shown in the Japanese patient population. Fourth, the cut-off value of serum sodium levels for predicting mortality above the hyponatremia level was < 138 mmol/L, rather than < 140 mmol/L. These findings suggest that, in Japanese patients with ADHF, although admission hyponatremia can be an independent predictor of all-cause mortality and/or re-hospitalization for ADHF, a low-normal serum sodium level on admission may not be an independent predictor. However, considering that significant increasing trend of the risk of clinical events as serum sodium level decreased from ≥ 140 mmol/L to 135-140 mmol/L to < 135 mmol/L and the inverse dose-response association between serum sodium level and the risk of clinical events, we must consider that low serum sodium levels on admission, even within the low-normal clinical range, may increase the risk of long-term clinical events and be a potential target for intervention to improve clinical outcomes in patients after ADHF. Indeed, in the present study, the cut-off value of the serum sodium levels on admission to predict mortality was < 138 mmol/L, which is within the low-normal clinical range.

Several clinical studies have shown that admission hyponatremia, defined as a serum sodium level < 135 mmol/L on admission, is an independent predictor of mortality and/or re-hospitalization following ADHF.12,13,17,23 Among them, some studies of Western countries also reported that the admission serum sodium level, when treated as a continuous variable, was also associated with clinical outcomes, i.e., the lower the admission serum sodium level, the greater the risk of mortality and/or re-hospitalization.11,14,15,18-19 Gheorghiade and colleagues showed that the risk of death or re-hospitalization during 60-90 days following ADHF increased by 8% for each 3-mmol/L decrease in patients with an admission serum sodium < 140 mmol/L.14 Similarly, Deubner and colleagues reported that prognosis was the best for patients with a high normal sodium level defined as 140-145 mmol/L, while the HR for all-cause mortality increased as the admission serum sodium level decreased to below the low-normal sodium level (i.e., < 140 mmol/L).19 Considering these findings, in addition to the hyponatremia defined as a serum sodium level < 135 mmol/L, the prognostic impact of a low-normal serum sodium level (≥ 135 mmol/L

<table>
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<th>95% CI</th>
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<td>-</td>
<td>-</td>
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<td>0.93-0.99</td>
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<td>1.02-2.30</td>
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<td>P value for HR trend</td>
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<td>CI indicates confidence interval; and HR, hazard ratio.</td>
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Table III. Results of Multivariable Forward Stepwise Analyses for Clinical Events

Table IV. Results of Multivariable Forward Stepwise Analyses for Clinical Events Including a Serum Sodium Level ≥ Or < 138 mmol/L
but < 140 mmol/L) should be the focus. From this perspective, Kusaka and colleagues investigated the impact of a low-normal serum sodium level (i.e., ≥ 135 mmol/L but < 140 mmol/L) at hospital discharge separately from hyponatremia (i.e., < 135 mmol/L) on clinical outcomes in a mixture of acute- and chronic-phase HF patients with a preserved ejection fraction. In their study, although the multivariable analysis results were not provided, a low-normal serum sodium level (≥ 135 mmol/L but < 140 mmol/L) was associated with HF-related events on Kaplan-Meier analysis. In the present study, the prognostic impact of a low-normal serum sodium level at hospital admission due to ADHF, independent of hyponatremia, was specifically and primarily assessed. Although there was an increasing trend of HR as the serum sodium level decreased, even on multivariable analysis, the HR of a low-normal serum sodium level did not indicate a significant increased risk of clinical events. When the serum sodium level was treated as a continuous variable, there was a significant inverse relationship between the serum sodium level and the risk of clinical events, and the cut-off value of serum sodium level predicting poor clinical outcomes was determined as < 138 mmol/L. Thus, the present study showed, for the first time, that in Japanese patients with ADHF, the serum sodium level at admission can be a significant predictor for poor long-term clinical outcomes even when the cut-off value within a low-normal serum sodium level (i.e., < 138 mmol/L) is utilized.

The pathogenesis of hyponatremia in ADHF is generally considered multifactorial; however, it has been implicated that neurohumoral activation in association with ADHF plays an important role. The reduction in cardiac output in association with ADHF leads to decreased renal perfusion and consequently increased reabsorption in the proximal tubule. This leads to reduced sodium and water delivery to the diluting sites, which may stimulate water reabsorption at those sites. On the other hand, decreases in cardiac output and effective circulating volume also lead to reflex activation of the neurohumoral factors including arginine vasopressin (AVP) in addition to the sympathetic nervous system and renin-angiotensin-aldosterone system. Enhanced AVP secretion and binding to the V2 receptor enhances free water reabsorption in the distal nephron and consequently contribute to hyponatremia. Thus, in patients with ADHF, serum sodium level may enhance neurohumoral overactivation. Considering this and the findings of the present study in which a significant increasing trend of the risk of clinical events as the serum sodium level decreased and the inverse dose-response association between the serum sodium level and the risk of clinical events were observed, even patients with a low-normal serum sodium level, especially < 138 mmol/L, have some sort of neurohumoral overactivity and a consequent risk of worsening HF.

It is not clear whether hyponatremia is just a comprehensive marker of ADHF severity or a therapeutic target for improving clinical outcomes. Limited information is available regarding the impact of the correction of serum sodium levels on clinical outcomes. In a retrospective observational study of patients admitted with a diagnosis of ADHF, patients whose admission hyponatremia (< 135 mmol/L) was corrected to the normal range (≥ 135 mmol/L) over the course of hospitalization showed better 30-day readmission or mortality rates compared to those with persistent hyponatremia. In terms of increasing serum sodium levels, the vasopressin V2 receptor antagonist tolvaptan is the reasonable option since it acts directly against ADHF-associated enhanced AVP secretion. Indeed, in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST), tolvaptan significantly increased the serum sodium concentration in hyponatremic patients hospitalized with ADHF.

In a post hoc analysis of the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure trial in which patients hospitalized for ADHF were randomized to placebo or one of 3 tolvaptan doses to investigate its effects on 60-day mortality, hyponatremic patients with a serum sodium improvement (≥ 2 mmol/L increased from admission to discharge) had better 60-day mortality rates compared to those showing no improvement, suggesting the therapeutic potential of tolvaptan on admission hyponatremia in patients hospitalized with ADHF. In an analysis of the EVEREST database among patients with hyponatremia at study entry, treatment with tolvaptan led to a correction of serum sodium levels and a lower rate of HF worsening compared to the placebo group. Furthermore, in patients with marked hyponatremia (i.e., < 130 mmol/L; n = 92), tolvaptan use was significantly associated with reduced cardiovascular morbidity and mortality after discharge (P = 0.04). A further randomized study revealed that the effect of tolvaptan versus other interventions for hyponatremia and/or low-normal serum sodium levels is needed.

Our study is subject to some limitations. First, it was limited to a single academic center and included only a Japanese patient population. Our findings must be examined in a larger sample size. Second, since the present study was observational in nature, even after the adjusted analysis, other confounders affecting the results cannot be ruled out. Despite these limitations, our study highlights that the lower the serum sodium level on admission in ADHF patients, the poorer the long-term outcomes.

In conclusion, serum sodium level at the time of admission in patients with ADHF can be a predictor of long-term mortality and/or re-hospitalization for ADHF. Physicians should consider that low serum sodium levels at admission, even when the cut-off value within the low-normal clinical range such as < 138 mmol/L is utilized, are associated with an increased risk of poor long-term clinical outcomes. Further studies are needed to determine whether targeted therapy for this variable will improve the long-term clinical outcomes of patients with ADHF.

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Disclosures


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