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Serum sodium concentration, blood urea nitrogen, and outcomes in patients hospitalized for acute decompensated heart failure

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ABSTRACT

Background: This study investigated the association of a low serum sodium and elevated blood urea nitrogen (BUN) with outcomes in acute decompensated heart failure (HF) patients.
Methods: Of the 4842 patients enrolled in the Acute Decompensated Heart Failure Syndromes (ATTEND) registry, 4438 patients discharged after hospitalization for acute decompensated HF were investigated to assess the association of a low serum sodium and/or elevated BUN at discharge with all-cause mortality. The patients were divided into four groups based on serum sodium (>136 or ≤136 mEq/l) and BUN (<25 or ≥25 mg/dl) at discharge. The median follow-up period after discharge was 517 (381–776) days.
Results: According to multivariate analysis, a low serum sodium (≤136 mEq/l) or an elevated BUN (≥25 mg/dl) was significantly associated with a higher risk of all-cause death compared with patients who had neither (hazard ratio [HR], 1.53; 95% confidence interval [CI], 1.22 to 1.94; $P < 0.001$ and HR, 1.44; 95% CI, 1.19 to 1.73; $P < 0.001$, respectively). Patients with both low serum sodium and elevated BUN had a higher risk of all-cause death relative to patients with neither (HR, 2.64; 95% CI, 2.17 to 3.20; $P < 0.001$) and also relative to patients with either low serum sodium alone or elevated BUN alone (HR, 1.72; 95% CI, 1.36 to 2.18; $P < 0.001$ and HR, 1.84; 95% CI, 1.53 to 2.21; $P < 0.001$, respectively).
Conclusion: These findings demonstrated that a low serum sodium and an elevated BUN may be additive risk factors for postdischarge mortality in acute decompensated HF patients.

1. Introduction

Hyponatremia is a well-known predictor of mortality in patients with heart failure (HF) [1–8]. This is probably because hyponatremia in patients with exacerbation of HF is likely to be related to hypervolemia due to sympathetic nervous overactivity, activation of the renin-angiotensin-aldosterone system (RAAS), and release of arginine vasopressin [2–4]. It was recently suggested that vasopressin enhances urea transport in the renal collecting ducts, thereby increasing blood urea nitrogen (BUN) [9,10]. Elevated BUN levels have been shown to be associated with low blood pressure, low serum sodium, and worse clinical outcomes of HF, indicating that a low serum sodium concentration may be related to an elevated BUN level in HF patients [1,11]. However, the association of serum sodium and BUN levels with outcomes is unclear in HF patients. Furthermore, very few registries of hospitalized HF patients collect data on the outcomes after discharge, although the majority of adverse events are known to occur after patients leave hospital [12,13]. The aim of the present study was to investigate the association of a low serum sodium concentration and/or elevated BUN level at the time of discharge from hospital with outcomes in patients who were discharged after hospitalization for acute decompensated HF.

2. Methods

2.1. Study design and data collection

The Acute Decompensated Heart Failure Syndromes (ATTEND) registry was a nationwide hospital- based prospective observational multicenter cohort study of patients with acute decompensated HF admitted to 53 hospitals in all regions of Japan between April 1, 2007 and December 31, 2011. Patients were enrolled at their first admission and then followed, so that data collection was patient-based and not event-based. The study design, study methods, and patient profile have been described previously [14,15]. Briefly, the ATTEND registry study was designed to clarify the profile of patients with acute decompensated HF, including their demographic and clinical characteristics, treatment, in-hospital mortality, and morbidity/mortality after discharge from hospital. Management

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of acute decompensated HF was not specified, and treatment was selected by the attending physicians. Information obtained for each registered patient included demographic data, medical history, baseline characteristics, initial evaluation, treatment, procedures, hospital course, and disposition. This study was conducted in accordance with the principles of the Declaration of Helsinki. Institutional review board approval was obtained at each participating medical center prior to commencement of the study, and all patients gave written informed consent to enrollment. The endpoint classification committee (two experienced cardiologists who were not investigators) reviewed all endpoint data and asked the primary physician to confirm the cause of death if any problems were encountered.

2.2. Patients and definitions

The ATTEND registry study enrolled consecutive eligible patients with a discharge diagnosis of acute decompensated HF, in whom acute decompensated HF was the primary reason for admission. Acute decompensated HF was defined according to the modified Framingham criteria. Patients aged less than 20 years old, those with acute coronary syndrome, and others considered unsuitable by their attending physicians were excluded from the study. Patients on hemodialysis were also excluded from this analysis. A preserved ejection fraction (EF) was defined as a documented EF >40% at admission, while a reduced EF was defined as an EF ≤40% at admission. Patients were divided into four groups based on their serum sodium and BUN values at discharge. In order to define the optimum cut-off values of serum sodium and BUN for predicting all-cause death after discharge, Receiver operating characteristics (ROC) analysis with the Youden index was employed. As shown in Fig. 1, this analysis demonstrated that the area under the ROC curve (AUC) for serum sodium at discharge was 0.60 and a cut-off value of 136 mEq/l had a sensitivity of 39% and specificity of 77% for predicting all-cause death after discharge. On the other hand, ROC analysis showed that the AUC for BUN at discharge was 0.63 and that a cut-off value of 25 mg/dl had a sensitivity of 60% and specificity of 61% for predicting all-cause death after discharge. In the present study, a low serum sodium concentration was defined as serum sodium ≤136 mEq/l and an elevated BUN level was defined as BUN ≥25 mg/dl. Accordingly, outcomes were evaluated in subgroups stratified by serum sodium >136 or ≤136 mEq/l at discharge and BUN <25 or ≥25 mg/dl at discharge. Patients assigned to group 1 had a serum sodium >136 mEq/l and BUN <25 mg/dl, group 2 had a serum sodium >136 mEq/l and BUN ≥25 mg/dl, group 3 had a serum sodium ≤136 mEq/l and BUN <25 mg/dl, and group 4 had a serum sodium ≤136 mEq/l and BUN ≥25 mg/dl. Using these four groups, we evaluated the association of a low serum sodium and/or an elevated BUN at discharge with outcomes in patients who were discharged after hospitalization for acute decompensated HF. The primary endpoint was all-cause death after discharge, while the secondary endpoints were cardiac death after discharge and a combination of all-cause death and readmission for HF after discharge.

2.3. Statistical analysis

Data are presented as the mean (SD), as the median with interquartile range, or as proportions. ROC curves with the Youden index were constructed to identify the optimum cut-off values of serum sodium and BUN for predicting outcomes after discharge. One-way ANOVA was used for comparison of continuous variables with a normal distribution among the four groups, while the Kruskal-Wallis H-test was used for comparison of skewed continuous variables or discrete variables. The chi-square test was employed to compare nominal scale variables. Cumulative probability of event curves was estimated by the Kaplan–Meier method and was compared with the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed to assess the association of candidate variables with postdischarge outcomes. The multivariate model included variables that were significant predictors of outcomes according to univariate analysis, as well as other factors known to influence postdischarge outcomes, including the age, gender, ischemic etiology, hypertension, diabetes, readmission for HF, left ventricular EF, atrial fibrillation, body mass index, systolic blood pressure, New York Heart Association functional class, hemoglobin, and use of the following drugs at discharge: loop diuretics, spironolactone, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. The proportional hazard assumption was confirmed by calculating the log value (log survival function), and the influence of profile, interaction, and multicollinearity in these models was examined by regression diagnostic analysis. A probability (P) value of less than 0.05 (two-tailed) was considered to indicate statistical significance. An independent statistical data center (STATZ Institute, Inc., Tokyo, Japan) performed all analyses using SAS system ver. 9.3 software (SAS Institute, Cary, NC, USA).

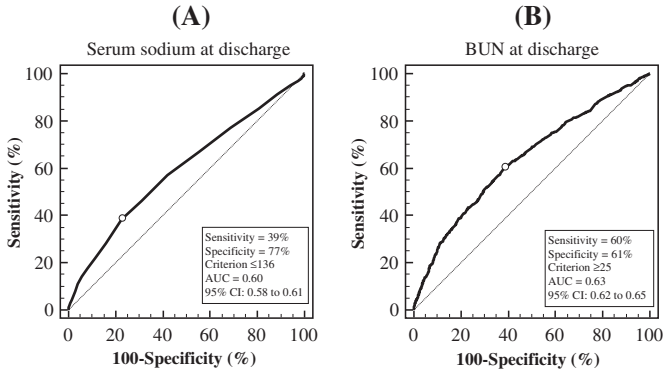

Fig. 1. Receiver-operating characteristic (ROC) curves of serum sodium at discharge (A) and BUN at discharge (B) predicting the all-cause death after discharge. Open circles indicate the optimum cut-off values. BUN = blood urea nitrogen, HF = heart failure, AUC = area under the receiver-operating characteristic curve. CI = confidence interval.

3. Results

3.1. Baseline characteristics of all patients and subgroups stratified by serum sodium and BUN

Among the 4842 patients enrolled in the ATTEND registry, 4530 patients were discharged after hospitalization for acute decompensated HF. Of these 4530 patients, 4438 patients were included in this analysis since data on serum sodium and BUN at discharge were available, as well as postdischarge follow-up data (Table 1). The median follow-up period after discharge was 517 (381–776) days. The all-cause mortality rate after discharge was 19.1%, while the composite endpoint (all-cause mortality and readmission for HF) was reached by 37.4% of patients. Of the 4438 patients analyzed, 1148 patients (25.8%) had a low serum sodium level (≤136 mEq/l) at discharge and 1819 (40.9%) had an elevated BUN level (≥25 mg/dl) at discharge. As shown in Fig. 2, there was a modest inverse correlation between serum sodium and BUN at discharge ($R = -0.18$; $P < 0.001$). The baseline clinical characteristics of the four groups of patients stratified by serum sodium and BUN at discharge are shown in Table 2. In patients with a serum sodium >136 mEq/l (groups 1 and 2) or ≤136 mEq/l (groups 3 and 4), serum sodium concentrations were similar between BUN ≥25 mg/dl and BUN <25 mg/dl. There were no significant differences among the four groups with respect to gender, preserved or reduced EF, and use of beta-blockers at discharge. Patients with a BUN level ≥ 25 mg/dl at discharge (groups 2 and 4) were significantly older, had a higher rate of ischemic or valvular etiology, a higher frequency of a history of hospitalization for HF, were more likely to be using loop or thiazide diuretics at discharge, and had a lower hemoglobin at discharge than the patients with a BUN level < 25 mg/dl (groups 1 and 3). In addition, patients with a serum sodium ≤136 mEq/l (groups 3 and 4) were more likely to have a history of chronic obstructive pulmonary disease, less likely to have a history of hypertension or dyslipidemia, and less likely to be using angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at discharge than the patients with a serum sodium >136 mEq/l (groups 1 and 2).

3.2. Outcomes stratified by serum sodium and BUN at discharge

Fig. 3 shows the unadjusted hazard ratios for the relationship between the serum sodium concentration and all-cause death after discharge in patients with and without elevation of BUN at discharge. There was a significantly higher risk of all-cause death after discharge in patients who had a low serum sodium level (≤136 mEq/l), an elevated BUN level (≥25 mg/dl), or both compared with patients who had neither an elevated BUN level nor a low serum sodium level (Table 2). After adjustment for multiple comorbidities, either a low serum sodium level or an elevated BUN level was still significantly associated with a higher risk of all-cause mortality relative to patients with neither of these parameters (hazard ratio [HR], 1.53; 95% confidence interval [CI], 1.22 to 1.94; P < 0.001, and HR, 1.44; 95% CI, 1.19 to 1.73; P < 0.001, respectively). In addition, the combination of a low serum sodium level and an elevated BUN level was significantly associated with a higher risk of all-cause mortality relative to patients with neither parameter (HR, 2.64; 95% CI, 2.17 to 3.20; P < 0.001), as well as relative to patients with either