Original article

Recovery from hyponatremia in acute phase is associated with better in-hospital mortality rate in acute heart failure syndrome

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ABSTRACT

Background: Although hyponatremia on admission is a predictor of poor prognosis in acute heart failure (AHF) patients, little is known about the association between changes in sodium level in acute phase and in-hospital mortality. This study was performed to clarify the impact of sodium level improvement in the early phase on prognosis in AHF patients.
Methods: A total of 882 consecutive hospitalized AHF patients were retrospectively enrolled in this study. Sodium levels were evaluated on days 1 and 3 of admission, and patients were classified into three groups: patients with hyponatremia on admission and day 3 (hypo-hypo group); patients with hyponatremia on admission and normonatremia on day 3 (hypo-normo group); and patients with normonatremia on admission (normo group).
Results: Hyponatremia (sodium ≤ 135 mEq/L) was observed in 14.3% of cases. In multivariate linear regression analysis, age (standardized beta = 0.084), male gender (standardized beta = −0.072), history of ischemic heart disease (standardized beta = −0.069), baseline sodium level (standardized beta = −0.435), and tolvaptan use (standardized beta = 0.093) were independent determinants of changes in sodium level from day 1 to day 3. In-hospital mortality rates were significantly higher in the hypo-hypo group (23.7%) and hypo-normo group (9.7%) than the normo group (6.9%) ($p < 0.001$). After adjustment for covariates, both hypo-normo (OR: 0.28, 95% CI: 0.08–0.93, $p = 0.038$) and normo (OR: 0.42, 95% CI: 0.20–0.88, $p = 0.022$) groups showed significantly lower in-hospital mortality rates than the hypo-hypo group.
Conclusion: Early recovery from hyponatremia in AHF patients is associated with lower in-hospital mortality rate.

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Introduction

The prognosis of patients with acute heart failure (AHF) is poor, with an in-hospital mortality rate of 3–4% and rate of mortality and/or rehospitalization within 60–90 days after discharge of 35–50% [1–5]. Hyponatremia is a common disorder in AHF patients [6], and many studies have demonstrated that hyponatremia on admission is a predictor of poorer prognosis [7–11]. Furthermore, previous clinical trials and analyses have focused on the relationships between changes in serum sodium level and outcome in AHF patients. However, most of these studies focused on post-discharge outcomes, and it remained unclear whether changes in serum sodium levels during hospitalization were correlated with in-hospital mortality rate [12,13]. As hyponatremia in AHF patients has

been shown to be a consequence of neurohormonal activation, improvement of hyponatremia in the acute phase could be preferable from the viewpoint of prognosis. Therefore, we postulated that recovery from hyponatremia at the early phase after admission may be related to better in-hospital mortality rate.

Methods

Patient population

The study population consisted of consecutive AHF patients aged >18 years old diagnosed by the attending cardiologists according to the Framingham criteria [14] presenting with acute onset or worsening of symptoms and admitted to one of three participating hospitals—Kameda Medical Center, Awa Regional Medical Center, and Kawasaki Medical School Hospital—between January 2011 and July 2013. AHF patients with acute coronary syndrome, primary pulmonary hypertension, pericardial disease, or with a history of maintenance hemodialysis were excluded. On analysis, cases with B-type natriuretic peptide (BNP) < 100 pg/mL on admission were also excluded because the primary diagnosis of these cases may not have been heart failure [15,16]. Medical records were reviewed by the attending cardiologists, and baseline data, including patient characteristics, medical history, and all initial treatments provided from day 1 (admission day) to day 3, were collected. The values of all biomarkers on admission were also collected. We also collected data regarding amount of intravenous sodium infusion from day 1 to day 3. Estimated glomerular filtration rate (eGFR) was calculated by the Japanese coefficient-modified Chronic Kidney Disease Epidemiology Collaboration equation [17]. Hyponatremia was defined as serum sodium ≤135 mEq/L [9,18], and the whole cohort was divided into three groups according to serum sodium levels on days 1 and 3: hypo-hypo group, patients with hyponatremia on admission and day 3; hypo-normo group, patients with hyponatremia on admission and normonatremia on day 3; and normo group, patients with normonatremia on admission. The primary outcome in this study was all-cause in-hospital mortality. This study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee and institutional review board of each participating hospital. Due to the retrospective and observational nature of the present study, written informed consent was not required under current Japanese guidelines.

Statistical analysis

Data are expressed as the means ± standard deviation for normally distributed variables, and as the median with interquartile range for non-normally distributed data. The distribution of data was tested by the Kolmogorov–Smirnov test, and variables were transformed for further analyses when necessary. Categorical data are expressed as numbers and percentages. Baseline characteristics were compared between the three groups by one-way analysis of variance (ANOVA), Kruskal–Wallis test, or chi-squared test where appropriate. We performed univariate and multivariate linear regression analysis to identify independent determinants of changes in sodium level. We also calculated the odds ratio (OR) with 95% confidence interval (95% CI) derived from the logistic regression model to evaluate the prognostic effect of hyponatremia. All baseline variables were evaluated in univariate analysis, and multivariate logistic regression analyses were performed using all variables with $p < 0.1$ on univariate analysis with backward elimination by using the Akaike Information Criterion (AIC) statistic. Statistical analyses were performed using R version 3.1.2 (R foundation for Statistical Computing, Vienna, Austria) and the graphical user interface EZR

[19]. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

Results

Fig. 1 shows the study cohort. Of the total of 1278 AHF patients admitted to one of the three participating hospitals during the study period, 143 patients were excluded because of their comorbidities (120 patients with acute coronary syndrome, 5 patients with primary pulmonary hypertension or pericardial disease, and 18 patients with a history of maintained hemodialysis). A total of 231 patients, including two patients who died before day 3, were excluded because sodium levels on admission and/or day 3 were unavailable. We also excluded 22 patients because their BNP at admission was <100 pg/mL or missing. Finally, 882 patients were included in the analyses. The mean age of the whole cohort was 78.0 years old and 50.2% were male. The mean serum sodium level on admission was 139.6 ± 4.5 mEq/L, and 126 (14.3%) patients were diagnosed with hyponatremia on admission. The whole cohort was divided into three groups according to the presence or absence of hyponatremia on admission and day 3 (Table 1). According to the above definitions, the hypo-hypo group consisted of 64 (7.3%) patients, the hypo-normo group consisted of 62 (7.0%) patients, and the remaining 756 (85.7%) patients formed the normo group. The patients in the hypo-hypo group showed hypotension on admission, low serum albumin level, high blood urea nitrogen level, and poor renal function. The hypo-normo group received greater amounts of sodium infusion and showed
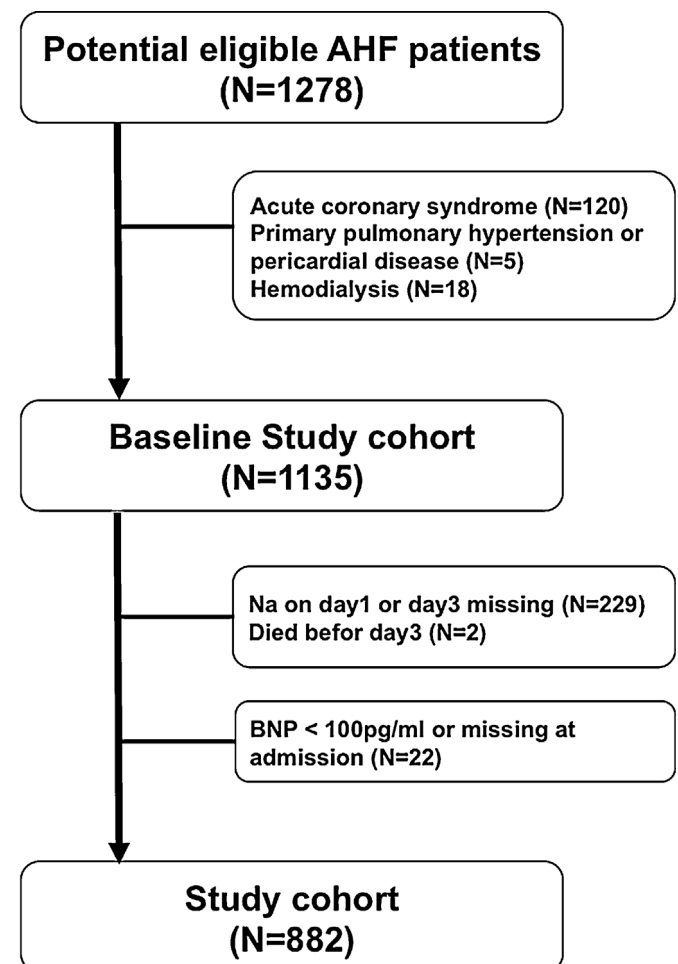

Fig. 1. Study cohort. AHF, acute heart failure; BNP, B-type natriuretic peptide.