Original article

Hyponatremia is an independent predictor of adverse clinical outcomes in hospitalized patients due to worsening heart failure

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ABSTRACT

Background and purpose: Hyponatremia is common and is associated with poor in-hospital outcomes in patients hospitalized with heart failure (HF). However, it is unknown whether hyponatremia is associated with long-term adverse outcomes. The purpose of this study was to clarify the characteristics, clinical status on admission, and management during hospitalization according to the serum sodium concentration on admission, and determine whether hyponatremia was associated with in-hospital as well as long-term outcomes in 1677 patients hospitalized with worsening HF on index hospitalization registered in the database of the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD).
Methods and subjects: We studied the characteristics and in-hospital treatment in 1659 patients hospitalized with worsening HF by using the JCARE-CARD database. Patients were divided into 2 groups according to serum sodium concentration on admission <135 mEq/mL (*n* = 176; 10.6%) or ≥135 mEq/mL (*n* = 1483; 89.4%).
Results: The mean age was 70.7 years and 59.2% were male. Etiology was ischemic in 33.9% and mean left ventricular ejection fraction was 42.4%. After adjustment for covariates, hyponatremia was independently associated with in-hospital death [adjusted odds ratio (OR) 2.453, 95% confidence interval (CI) 1.265–4.755, *p* = 0.008]. It was significantly associated also with adverse long-term (mean 2.1 ± 0.8 years) outcomes including all-cause death (OR 1.952, 95% CI 1.433–2.657), cardiac death (OR 2.053, 95% CI 1.413–2.983), and rehospitalization due to worsening HF (OR 1.488, 95% CI 1.134–1.953).
Conclusions: Hyponatremia was independently associated with not only in-hospital but also long-term adverse outcomes in patients hospitalized with worsening HF.
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Introduction

Hyponatremia, usually defined as a serum sodium concentration <135 mEq/L, has been observed in ~20% and consistently an independent risk for all-cause mortality as well as longer length of stay in hospitalized patients with worsening heart failure (HF) [1–4]. However, most of these studies have been focused on short-term outcome with up to 90 days of follow-up. A recent study using a large individual patient data meta-analysis demonstrated that hyponatremia is a determinant of all-cause death during the follow-up of 3 years [3]. This study analyzed only all-cause death and could not include cardiac death or hospitalization due to worsening HF for an inherent limitation of meta-analysis using the incorporated data from both randomized trials and observational studies [3]. Therefore, little information has been available regarding the relationship between serum sodium concentration and adverse outcomes including cardiac death and hospitalization due to worsening HF. Moreover, most of these previous studies were performed mainly in the USA and Europe. Therefore, the impact of hyponatremia on outcomes has not been assessed in a broad cohort of HF patients encountered in routine clinical practice in Japan.

The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) studied the characteristics, management, and the outcomes including death and rehospitalization in a broad sample of patients hospitalized with worsening HF in Japan [5–13]. The

JCARE-CARD prospectively enrolled patients admitted with worsening HF in a web-based registry at 164 participating hospitals.

The objectives of this study were to clarify the characteristics of patients, clinical status on admission, and management during hospitalization according to the serum sodium concentration on admission, and determine whether hyponatremia was associated with in-hospital as well as long-term outcomes in 1677 patients hospitalized with worsening HF on index hospitalization registered in the JCARE-CARD database [14,15].

Materials and methods

The details of the JCARE-CARD have been described previously [5,8–10,14,15]. Briefly, it registered the patients hospitalized due to worsening HF as the primary cause of admission. The study hospitals were encouraged to register the patients as consecutively as possible. For each patient, baseline data included (1) demography; (2) causes of HF; (3) precipitating causes; (4) comorbidities; (5) complications; (6) clinical status; (7) electrocardiographic and echocardiographic findings; (8) laboratory data; and (9) treatments including discharge medications. The data were entered using a web-based electronic data capture (EDC) system licensed by the JCARE-CARD (www.jcare-card.jp).

Using the database of 1677 patients registered in JCARE-CARD [14,15], the present study analyzed the data of (1) patient demographics, clinical characteristics, vital signs, and laboratory data on admission [age, sex, cause of HF, medical history, prior hospitalization due to HF, New York Heart Association (NYHA) functional class, symptoms and signs, vital signs, laboratory data including serum sodium concentration, and echocardiographic parameters], (2) medication use before admission [angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), βblocker, diuretics, digitalis, Ca channel blocker, nitrate, antiarrhythmics, aspirin, warfarin, and statin], (3) in-hospital management (diuretics, inotropic agents, vasodilator agents, and non-pharmacological procedures), (4) clinical status during index hospitalization [admission from emergency room, stay at coronary care unit (CCU), length of CCU stay, length of stay, and in-hospital death], and (5) long-term outcomes (all-cause death, cardiac death, and rehospitalization due to HF). Eighteen (1.1%) patients were excluded with missing data of serum sodium concentration on admission, resulting in 1659 patients included in this analysis. Hyponatremia was defined as a serum sodium concentration on admission <135 mEq/L.

Statistical analysis

Patient characteristics and treatments were compared using Pearson chi-square test for categorical variables, Student's *t*-test for normally distributed continuous variables, and Mann–Whitney *U* test for continuous variables not normally distributed. Multivariable logistic regression was performed to determine the odds of in-hospital mortality. The covariates including medical history [hypertension, diabetes mellitus, ventricular tachycardia/ventricular fibrillation (VT/VF)], NYHA functional class on admission, medication use before hospitalization (ACE inhibitor, diuretics, aldosterone antagonist, and warfarin), laboratory data on admission [estimated glomerular filtration rate (eGFR), hemoglobin, and plasma B-type natriuretic peptide (BNP)] were used in developing the multivariable logistic regression model. The relationship between serum sodium concentration and long-term outcomes was evaluated among patients with the post-discharge Cox proportional hazard models. Relative risk was calculated after adjustment with covariables including age, ischemic etiology, medical history (hypertension, diabetes mellitus, sustained VT/VF, and prior stroke), NYHA functional class on admission, medication use

on admission (ACE-inhibitor or ARB, βblocker, diuretics, aldosterone antagonist, and warfarin), and laboratory data on admission (eGFR, hemoglobin, and plasma BNP). SPSS version 16.0 J for Windows (Chicago, IL, USA) was used for all statistical analyses.

Results

Patient characteristics

The distribution of serum sodium concentration on admission in the total cohort of study patients is shown in Fig. 1. The mean and median serum sodium concentrations on admission were 139.6 ± 4.5 mEq/L and 140.0 mEq/L, respectively, ranging from 114.0 to 156.0 mEq/L. Out of 1659 patients, 176 patients (10.6%) had hyponatremia, defined as serum sodium concentration on admission <135 mEq/L.

Clinical characteristics for the total cohort of patients and those classified into 2 groups according to the presence or absence of hyponatremia are shown in Table 1. The mean age was 70.7 ± 13.5 years and 59.3% were men. The causes of HF were ischemic heart disease in 33.9%, valvular heart disease in 28.1%, hypertensive heart disease in 26.4%, and dilated cardiomyopathy in 16.9%. As expected, mean serum sodium concentration was 130.4 mEq/L in patients with hyponatremia and 140.7 mEq/L without it.

The mean age and causes of HF were comparable between 2 groups. Patients with hyponatremia more frequently had diabetes mellitus, prior stroke, sustained VT/VF, and prior hospitalization due to HF, but less hypertension. They had worse NYHA functional class and lower blood pressure on admission. eGFR and hemoglobin concentration were significantly lower in these patients and plasma BNP levels were significantly higher. Echocardiographic parameters including left ventricular ejection fraction (LVEF) were comparable between groups.

Medication use before hospitalization was compared between groups of patients (Table 2). The use of ACE inhibitor, ARB, and βblocker was comparable between groups. The use of loop diuretics, aldosterone antagonist, antiarrhythmics, and warfarin was significantly higher in patients with hyponatremia.

In-hospital management

The use of thiazide and spironolactone was significantly higher in patients with hyponatremia. Patients with hyponatremia were more often treated with catecholamines, PDE III inhibitor, and carperitide. Mechanical ventilation, PCI, and hemodialysis were also more frequently used in them (Table 3).
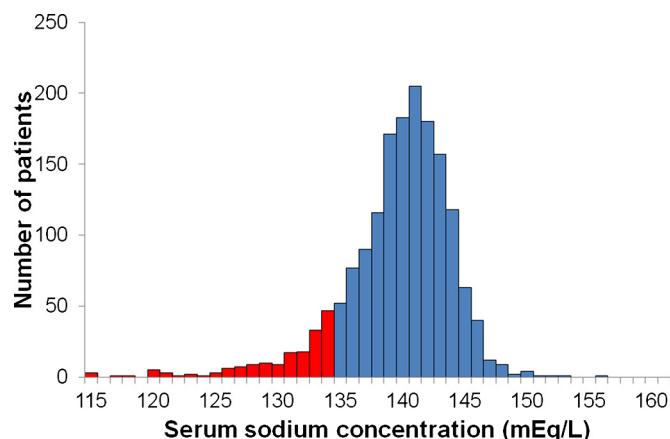

Fig. 1. Distribution of serum sodium concentration on admission in patients hospitalized with worsening heart failure.