ORIGINAL ARTICLE

Hyponatremia on admission and its impact on clinical outcomes in patients hospitalized for heart failure

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Abstract: Background – Hyponatremia is a common electrolyte disorder among patients with heart failure and associated with poor clinical outcomes. This study aims to assess the prevalence and clinical outcomes in hyponatremia compared to normonatremia patients hospitalized for heart failure. **Methods –** This was a cohort retrospective study using medical record of patients hospitalized for heart failure between January and December 2015 in Adam Malik Hospital, Medan, Indonesia. Patients were assigned to one of two groups; hyponatremia with admission serum sodium <135 mg/dl or normonatremia with admission serum sodium ≥135 mg/dl. Differences in variables between two groups were evaluated using chi-square test for categorical variables and independent samples *t* test or Mann Whitney U test for continuous variables. Furthermore, hyponatremia group was classified into mild, moderate and severe to analyses outcomes based on severity of hyponatremia. **Results –** Of 497 patients, hyponatremia was present in 230 patients (46.27%) with mean admissions serum sodium 129.16±5.17 mg/dl. Patients with hyponatremia had significantly higher in-hospital mortality (p=0.034, OR=1.999, 95% CI 1.044-3.828) and longer hospital stays (p=0.023) compared to normonatremia but no difference in readmission rate was observed between groups (p=0.414). Among hyponatremia groups, severe hyponatremia had worse clinical outcomes, with highest in-hospital mortality (19.35%) and longest length of stays (11.16±8.04 days). **Conclusions –** Hyponatremia was a relatively common condition found in patients hospitalized for heart failure and associated with higher in-hospital mortality and longer hospital stays. Poorer clinical outcomes were observed in severe hyponatremia group.

Keywords: Hyponatremia; heart failure; in-hospital mortality; length of stays; readmission.

INTRODUCTION

Hyponatremia defined as serum sodium concentration <135 mEq/L is one of the major electrolyte disorders in-hospitalized patients[1]. Prevalence of hyponatremia in heart failure patients ranges from 4-45%[2], in the *Organized Program to initiate Lifesaving Treatment in-hospitalized Patients with Heart Failure* (OPTIMIZE-HF) study 20% of patients present with hyponatremia while in *Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure* (ACTIV in CHF) trial 21% heart failure patients hospitalized with hyponatremia[2].

Hyponatremia has repeatedly been shown to be a marker of increased morbidity and mortality in heart failure population. Several previous study demonstrated that both admission and hospitalized acquired hyponatremia are associated with and increase adverse outcomes including prolonged hospital length of stays, frequent rehospitalization, and associated with increased in-hospital and post discharge mortality[3].

In daily clinical practice, hyponatremia has not been considered significant unless the serum sodium was <125 mg/dl. However, in heart failure population even mild hyponatremia has been recognized as a risk factors for poor prognosis[4]. Therefore this study aims to assess the prevalence and severity of hyponatremia and evaluate the relationship among admission serum sodium, patients characteristic and clinical outcomes among patients hospitalized for heart failure.

MATERIAL AND METHODS

This was a cohort retrospective study using medical record of patients hospitalized for heart failure between January and December 2015 in Adam Malik Hospital, Medan, Indonesia. Eligible patients were enrolled if they were at least 18 years and diagnosed with heart failure according to the clinical practice guidelines of *European Society of Cardiology* based on the presence of heart failure symptoms and signs[5]. Detailed clinical data were collected regarding patients characteristics,

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laboratories, echocardiography variables and co morbidities.

Serum sodium concentration was recorded at the day of hospital admission. Patients were categorized to one of two groups; hyponatremia with admission serum sodium <135 mg/dl or normonatremia with admission serum sodium ≥135 mg/dl. Furthermore, hyponatremia group was classified into mild (serum sodium 130-134 mg/dl), moderate (serum sodium 125-129 mg/dl) and severe (serum sodium <125 mg/dl) to analyses outcomes based on severity of hyponatremia.

Means, standard deviations and percentages were used to describe the characteristics of study population. Differences in variables between groups were evaluated using chi-square test for categorical variables and independent samples *t* test or Mann Whitney U test for continuous variables. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 610 patients diagnosed with heart failure during period of study, of which 113 patients were excluded do to missing data. From 497 patients eligible for this study, hyponatremia was present in 230 patients (46.27%) with mean admissions serum sodium 129.16±5.17 mg/dl. Patients mean age were similar in the two groups (51.74 and 52.86; p=0.290) and no gender predominance were found between groups. Patients in hyponatremia groups were statistically had lower serum chloride and higher blood urea nitrogen. No difference in ejection fraction were found between groups, both groups had ejection fraction <50% (p=0.096). Anemia was more profound in hyponatremia groups, while coronary artery disease frequently found in normonatremia groups. Analysis of other cardiovascular risk factor and co morbidities revealed no statistically significant differences. The characteristics of two groups are shown in Table 1.

Hyponatremia was associated with higher in-hospital mortality (p=0.034, OR=1.999, 95% CI 1.044-3.828) and longer hospital stays (p=0.023) compared to normonatremia. No difference in readmission rate was observed between groups (p=0.414, HR 1.163, 95% CI 0.809-1.673) as shown in Table 2.

Among hyponatremia groups, severe hyponatremia had worse clinical outcomes, with highest in-hospital mortality (19.35%) and longest length of stays (11.16±8.04 days) as shown in Table 3.

DISCUSSIONS

Heart failure represent a major public health problem due to high in-hospital and post discharge mortality, longer length of stay, frequent hospital readmission and that has significant association with higher medical cost. Several prognostic markers has been associated with poor adverse outcomes in heart failure patients such as age, functional class of heart failure, low blood pressure, higher blood urea nitrogen (BUN) and hyponatremia[6,7]. Identification of these predictors could potentially aid in making clinical decision and help pa-

Table 1. Baseline characteristics by admission serum sodium groups

Variables	Hyponatremia (n=230)	Normonatremia (n=267)	P
Age, years (SD)	51.74 (13.19)	52.85 (14.04)	0.290
Female, n (%)	102 (44.34)	123 (46.06)	0.701
Mean serum sodium on admission, mg/dl (SD)	129.16 (5.17)	138.48 (3.38)	<0.0001
Mean serum potassium on admission, mg/dl (SD)	4.05 (0.93)	3.98 (0.67)	0.536
Mean serum chloride on admission, mg/dl (SD)	99.14 (6.49)	104.47 (4.59)	<0.0001
Mean serum BUN on admission, mg/dl (SD)	30.00 (26.51)	23.29 (18.85)	0.001
Mean serum creatinine on admission, mg/dl (SD)	2.09 (2.73)	1.77 (2.35)	0.215
Mean eGFR, (SD)	65.44 (44.31)	68.78 (43.72)	0.300
Mean LVEF, % (SD)	46.80 (17.02)	49.28 (16.76)	0.096
Co morbidity			
DM, n (%)	54 (23.47)	44 (16.47)	0.051
Anemia, n (%)	60 (26.08)	47 (17.60)	0.022
Hypertension, n (%)	85 (36.95)	92 (34.45)	0.562
Dyslipidemia, n (%)	21 (9.13)	22 (8.23)	0.725
CKD, n (%)	36 (15.65)	27 (10.11)	0.064
CAD, n (%)	68 (29.56)	102 (38.20)	0.043
VHD, n (%)	32 (13.91)	51 (19.10)	0.122
Cardiomyopathy, n (%)	5 (2.17)	5 (1.87)	0.812

SD, standard deviation; BUN, Blood Urea Nitrogen; eGFR, estimated glomerular filtration rate using Modification of Diet in Renal Disease (MDRD) Study equation; DM, diabetes mellitus; CKD, chronic kidney disease; CAD, coronary artery disease; VHD, valvular heart disease

Table 2. Clinical outcomes by admission serum sodium groups					
	Hyponatremia n=230	**Normonatremia n=267**	**P**	**OR**	**95% CI**
In-hospital mortality, n (%)	26 (11.30)	16 (5.99)	0.034	1.999	1.044-3.828
	Hyponatremia n=204[a]	Normonatremia n=251[a]		HR	
Mean length of stay, days (SD)	9.75 (5.70)	8.54 (5.41)	0.023		
Readmission, n (%)	60 (29.41)	59 (23.50)	0.414	1.163	0.809-1.673
SD, standard deviation; OR, odds ratio; HR, Hazard ratio; CI, confidence interval [a] patients died were excluded from analyses of length of stay and readmission					

Table 3. Clinical outcomes by severity of hyponatremia			
	Mild n=140	**Moderate n=59**	**Severe n=31**
In-hospital mortality, n (%)	12 (8.57)	8 (13.55)	6 (19.35)
	Mild n=128[a]	Moderate n=51[a]	Severe n=25a
Mean length of stay, days (SD)	9.67 (5.25)	9.25 (5.47)	11.16 (8.04)
Readmission, n (%)	36 (28.12)	17 (28.81)	7 (22.58)
SD, standard deviation; [a] patients died were excluded from analyses of length of stay and readmission			

tients who might benefit from aggressive monitoring and intervention[7,8].

Hyponatremia on hospital admission is a relatively common condition in patients hospitalized for heart failure. Previous studies reported 19-25% of heart failure patients have hyponatremia, while this study found 46.27% of patients in hyponatremia groups[2]. Hyponatremia often parallels the severity of cardiac dysfunction while this study was conducted in a tertiary hospital which received referral patients with severe conditions could explain higher prevalence of hyponatremia found in this study.

OPTIMIZE-HF study reported that patients in hyponatremia groups were clinically similar with patients in normonatremia groups in terms of age, gender, heart failure etiology, diabetes, heart rate, ejection fraction and symptom of congestion[9]. Previous study by Lu D, et al found that patients with hyponatremia were older, more likely to have diabetes, hypertension and stroke but no difference in sex distribution, left ventricular ejection fraction and presence of coronary artery disease[10]. Baseline characteristic of age, gender, ejection fraction and creatinine in this study were not significantly different between hyponatremia and normonatremia groups. Hyponatremia groups were more likely to have higher blood urea nitrogen, lower serum chloride, higher cases of anemia but fewer cases of coronary artery disease.

This study found that blood urea nitrogen was higher in hyponatremia group compared to normonatremia. Lower serum sodium was associated with more severe heart failure which also correlated with higher blood urea nitrogen. Reduction in renal perfusion, renin angiotensin aldosterone and sympathetic activation lead to increased sodium and water reabsorption that is coupled with enhanced urea reabsorption in proximal tubules[7]. Vasopressin on binding to V2 receptors in the inner medullary collecting ducts increases urea permeability though activation of urea transporter which enables its reabsorption[7].

Admission chloride levels were directly correlated to admission sodium levels as we found in this study. Serum chloride act as a buffer for cations including acid and sodium therefore had a role in the kidney's ability to eliminate salt and water. Although not completely understood, chloride might represent the downstream effect of adverse prognostic maladaptive neurohormonal, renal and acid base disturbance in heart failure[11].

In this study, hyponatremia groups had higher anemia cases than normonatremia groups. Renal dysfunction, neurohormonal and proinflammatory cytokine activation found in heart failure participate in the development of anemia. While on the other hand anemia increases myocardial workload and worsen cardiac dysfunction[12].

This study demonstrated that the more severe the hyponatremia, the poorer the outcome. This findings were similar with the result of OPTIMIZE-HF registry which conclude that hyponatremia is associated with longer hospital stays and higher in-hospital mortality and early post discharge mortality[9]. In the OPTIMIZE-HF, the in-hospital and post discharge mortality risk

increased 19.5% and 10.0% for each 3 mg/dl decreased in serum sodium up to 140 mg/dl after adjustment for other prognostic variables[9].

The underlying pathophysiology of hyponatremia related to mortality is still unclear, whether hyponatremia is an active contributor to poor clinical outcomes in heart failure or it is simply reflects a more advanced disease. Decrease stimulation of mechanoreceptors in the left ventricle, carotid sinus, aortic arch and renal afferent arterioles in heart failure patients leads to increased neurohormonal activation such as sympathetic nervous system, renin angiotensin aldosterone system and non osmotic release of vasopressin[8,7]. Increased sympathetic drive contributes to sodium and water retention through renal vasoconstriction, stimulation of renin angiotensin aldosterone system and direct effect on the proximal convulated tubules. Increase angiotensin II and aldosterone levels lead to decreased sodium and water delivery to the collecting duct which combined with resistance to the action of natriuretic peptides, results in impairment of free water excretion and hyponatremia[3,7]. The non osmotic stimulation of vasopressin released results in an increased number of aquaporin water channels in the collecting duct of the kidney that promote abnormal free water retention and contribute to the development of hyponatremia. This raised the hypothesis that low serum sodium may be a marker of neurohormonal activation reflecting the severity of heart failure. Moreover, this study adds the information that poorer clinical outcomes found in a more severe hyponatremia state.

There were several limitations in the present study. First, this study conducted in a single tertiary hospital which may led to selection bias given that patients were more likely in severe conditions. Second, patient's clinical characteristics and medication history were not recorded in this present study. Third, this study could not differentiate patient's fluid and hyponatremia status, whether in euvolemic, hypervolemic or normovolemic state[3].

CONCLUSIONS

Hyponatremia was a relatively common condition found in patients hospitalized for heart failure and associated with higher in-hospital mortality and longer hospital stays. Poorer clinical outcomes were observed in severe hyponatremia group.

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