Original Paper

Hyponatremia in Acute Heart Failure in Relation to Hematocrit Levels: Clinical Relevance and Prognostic Implication

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Keywords

Hyponatremia · Acute heart failure · Hematocrit · Congestion · Outcome

Abstract

Background: Hyponatremia is the most common electrolyte abnormality found in hospitalized patients with acute heart failure (AHF) and is related to poor prognosis. This study sought to evaluate: (1) the different prognostic impact of dilutional versus depletion hyponatremia, evaluating short- and long-term outcome; (2) the relationship between both types of hyponatremia and intravenous furosemide dose, renal function changes, and persistent congestion at discharge. **Methods:** This retrospective single-center study included 233 consecutive patients with a primary diagnosis of AHF. Hyponatremia was defined as serum sodium <135 mEq/L, which could be either dilutional (hematocrit <35%) or depletion (hematocrit ≥35%). Persistent congestion was defined as a congestion score ≥2 at discharge. Patients were followed 180 days for occurrence of death or rehospitalization for AHF. **Results:** Hyponatremia was present in 68/233 patients with 27 cases classified as dilutional hyponatremia versus 41 as depletion. The proportion of patients with persistent congestion was higher in the dilutional hyponatremia group, but similar in the depletion hyponatremia group (52 vs. 81 vs. 58%; $p = 0.02$). After adjustment for important baseline characteristics, dilutional hyponatremia was significantly associated with the risk of death or rehospitalization for AHF at 60 days (HR 2.17 [1.08–4.37]; $p = 0.03$) and 180 days (HR 1.88 [1.10–3.21]; $p = 0.02$). In contrast, depletion hyponatremia was only significantly associated with the same endpoint at 180 days (HR 1.64 [1.05–2.57]; $p = 0.03$). **Conclusions:** Low hematocrit levels in AHF patients with hyponatremia characterize a population that is more difficult to decongest and has poor clinical outcome. In contrast, patients with hyponatremia but normal hematocrit are better decongested and have better short-term outcome.

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Introduction

Despite new drugs in the treatment of acute heart failure (AHF), 5-year mortality and rehospitalization rates after discharge remain unacceptably high [1, 2]. Loop diuretic therapy is the most common treatment in AHF patients, and intravenous (IV) administration is performed early during hospitalization in 90% of cases. Through inhibition of the $\text{Na}^+/\text{2Cl}^-/\text{K}^+$ cotransporter in the thick ascending loop of Henle, loop diuretics induce natriuresis and diuresis with consequent resolution of pulmonary and systemic congestion. In some patients however, the diuretic response may be insufficient and is related to higher rates of rehospitalization and death [3].

Hyponatremia, defined as serum sodium <135 mEq/L, is a common electrolyte disturbance encountered in 15–25% of patients with AHF before and during decongestion and has been associated with impaired diuretic response and adverse events [4–6]. Hyponatremia may be the result of either effectively low sodium levels, mostly related to intensive use of diuretic therapy (i.e., depletion) or alternatively hemodilution, with the latter reflecting neurohormonal activation and plasma osmolality changes [7]. Indeed, absence of hemoconcentration and persistent hyponatremia may indicate inadequate decongestion, which is related to poor outcomes in AHF [8–10]. The prognostic impact of true depletion hyponatremia has been less investigated in AHF, and more studies should be performed that meticulously assess the cause of hyponatremia, which may guide subsequent loop diuretic titration.

In this study, the association between hyponatremia and outcome in AHF was assessed, comparing dilutional versus depletion hyponatremia defined by low versus high hematocrit values, respectively.

Methods

Study Population

This was a retrospective single-center study, including 233 consecutive subjects from the interventional Diur-HF Trial (NCT01441245) enrolled between January, 2011, and June, 2016. Patients were eligible if they were admitted <24 h with a primary diagnosis of AHF and demonstrated evidence of volume overload [9]. Additional inclusion criteria included: (1) age ≥ 18 years; (2) at least two typical AHF signs and symptoms (third heart sound, pulmonary rales, jugular venous distention, hepatomegaly, peripheral edema, lung congestion on chest X-ray, and B-type natriuretic peptide [BNP] levels >100 pg/dL). Patients were excluded if they had end-stage renal disease defined as serum creatinine levels >4.0 mg/dL or need for renal replacement therapy or ultrafiltration, recent (within 60 days before enrollment) myocardial infarction, systolic blood pressure <90 mm Hg, elevated C-reactive protein levels, severe liver disease, or neoplastic disease (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000490767). Therefore secondary causes of anemia were excluded (gastrointestinal bleeding, secondary to inflammatory or neoplastic diseases, hemolytic anemia, and iron deficiency) by performing specific laboratory and diagnostic tests such as evaluation of MCV, serum iron, serum ferritin, transferrin saturation, C-reactive protein elevation, fecal blood test to exclude gastrointestinal bleeding. All patients underwent an echocardiogram (Hewlett Packard Sonos 5500 Philips) to assess left ventricular ejection fraction (EF) at baseline. Blood samples were acquired on admission and before discharge or at day 7. All patients received IV loop diuretic therapy for a time period ranging from 72 to 120 h. The cumulative daily dose of IV furosemide to be given in the initial 12 h was decided upon by the attending physician. All patients have given their informed consent, and the study protocol has been approved by the local institute's committee on human research (C.E.A.V.S.E.).

Definitions

Hyponatremia was defined as serum sodium <135 mEq/L [11]. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² at baseline [12]. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation [13]. Among hyponatremic patients, persistence of hyponatremia was defined as discharge serum sodium levels <135 mEq/L. Hemo-

concentration was defined as hematocrit increase $\geq 3\%$ from admission to discharge/day 7 [14]. Worsening renal function (WRF) was defined as a serum creatinine increase ≥ 0.3 mg/dL or eGFR decrease $\geq 20\%$ from a blood sample taken at admission and blood samples taken at discharge/day 7 [15]. A congestion score from 1 to 5 was calculated by addressing 1 point for every clinical sign of volume overload: third heart sound, pulmonary rales, jugular venous distension, hepatomegaly, and peripheral edema [16]. Persistent congestion was defined as a congestion score ≥ 2 at discharge. The assessment of congestive signs was performed by the same two physicians who evaluated the patient at admission and at discharge, but both were blinded to the evaluation of the other, and final judgement was done at the end of the study.

Dilutional and Depletional Hyponatremia Definition

We defined hyponatremia on the basis of hematocrit levels as dilutional (hematocrit $< 35\%$) or depletional (hematocrit $\geq 35\%$). We tested preliminarily our formula by the assessment of admission plasma osmolarity levels calculated in 20 hyponatremic patients (patients with serum glucose levels available) with the following formula: serum osmolarity = $([\text{Na}^+] \times 2) + ([\text{BUN}]/2.8) + [\text{serum glucose}]/18$. Serum osmolarity was defined as “low” (≤ 285 mOsm/kg) or “normal” (285–300 mOsm/kg) [8]. Receiving operating characteristics curves were employed to detect the hematocrit cut-off able to predict low plasma osmolarity; a cut-off value $\geq 35\%$ showed a good sensitivity and specificity (80%) to assess AHF patients with normal plasma osmolarity and those patients with depletional hyponatremia (online suppl. Fig. 2A). Moreover, admission plasma osmolarity demonstrated a good correlation with admission hematocrit levels ($r = 0.51$; $p = 0.02$) (online suppl. Fig. 2B).

Endpoints and Study Goals

Clinical outcome was evaluated in terms of death or heart failure rehospitalization at 60 and 180 days. There was a scheduled outpatient visit 2 and 6 months after discharge, with telephone contacts in patients who did not attend. Heart failure rehospitalizations were defined as any hospital admission with a primary or secondary diagnosis of volume overload or low output due to pump failure, acute coronary syndrome complicated by heart failure, ventricular arrhythmia associated with left ventricular dysfunction, or heart failure associated with WRF. The first goal of the study was to assess the different prognostic impact of dilutional versus depletional hyponatremia evaluating short- (2 months) and long-term (6 months) outcome. Secondly, the relationship between both types of hyponatremia and furosemide maintenance dose, renal function, and persistent congestion at discharge was examined.

Statistical Analysis

Continuous variables are expressed as median [interquartile range], while discrete variables are presented as counts with percentages (%). The Mann-Whitney U test and χ^2 test were used as indicated to compare among groups. Cox regression analysis was used to assess the independent relationship between hyponatremia status and clinical outcome and was adjusted for age, gender, CKD, hypertension, diabetes, dyslipidemia, atrial fibrillation, and active smoking. Kaplan-Meier methods were employed to generate survival plots, with the log-rank test used for comparison among groups. Clinical outcome was evaluated in terms of death or heart failure rehospitalization both at 60 and 180 days to better stratify adverse events risk in the two subgroups. All reported probability values were 2-tailed, and $p \leq 0.05$ was considered statistically significant. Statistical analysis was performed using the SPSS 20.0 statistical software package (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics

A total of 245 patients met the inclusion criteria, and 12 were excluded because of incomplete data. Therefore, the final study population consisted of 233 AHF patients having HYHA class III or IV. All patients excluded are shown in online supplementary Figure 1.

Sixty-eight patients (29%) of the included patients had admission hyponatremia, with 27 versus 41 cases classified as dilutional versus depletional hyponatremia, respectively. The median age of the population was 83 [76–88] years, with 51% males. CKD was present in

Table 1. Differences in baseline clinical and laboratory parameters between hyponatremic and normonatremic patients

	No hyponatremia (n = 165)	Hyponatremia (n = 68)	p value
Age, years	83 [77–87]	83 [70–89]	0.91
Males, %	50	51	0.87
EF, %	40 [25–50]	35 [24–45]	0.01
Furosemide home dosage, mg	150 [125–200]	175 [150–200]	<0.001
Laboratory data at admission			
Creatinine, mg/dL	1.27 [1.01–1.60]	1.50 [1.10–1.99]	0.04
eGFR, ml/min/1.73 m ²	49 [38–63]	44 [31–60]	0.10
BUN, mg/dL	65 [46–86]	71 [53–114]	0.07
Serum sodium, mEq/L	140 [138–141]	133 [131–134]	<0.001
Serum potassium, mEq/L	4.1 [3.7–4.5]	3.9 [3.5–4.2]	0.02
BNP, pg/mL	749 [438–1151]	772 [454–1148]	0.83
Hemoglobin, g/dL	12.3 [10.9–13.7]	11.8 [10.5–13.3]	0.13
Hematocrit, %	38 [34–42]	36 [32–40]	0.02
Clinical signs at admission, %			
Pulmonary rales	82	92	0.02
Third heart sound	63	24	<0.001
Jugular venous distention	59	22	<0.001
Hepatomegaly	89	29	<0.001
Peripheral edema	85	45	<0.001
Risk factors, %			
Diabetes mellitus	32	30	0.85
Hypertension	39	29	0.15
Dyslipidemia	34	37	0.68
Smoke	23	22	0.87
CAD, %	40	39	0.90
Atrial fibrillation, %	50	48	0.81
CKD, %	40	56	0.008

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate.

42%, with the incidence of WRF at 21%. Median serum sodium at baseline was 138 [134–141] mEq/L. Other baseline characteristics are summarized in Table 1, stratified according to the presence of hyponatremia. When comparing patients with dilutional versus depletion hyponatremia, the former had a more advanced age (84 [70–91] vs. 82 [67–86] years) and were less frequently male (44 vs. 56%), but these data were not statistically significant. Patients with dilutional hyponatremia showed lower levels of discharge hemoglobin (10.5 [9.7–11.1] vs. 12.3 [10.8–13.5] g/dL) and discharge hematocrit (32 [29–34] vs. 38 [33–41] %) compared to patients with depletion hyponatremia. There was a significantly higher prevalence of NYHA class IV in the dilutional group with respect to the depletion group (74 vs. 41%; $p = 0.008$) No other statistically significant differences were found regarding EF, laboratory parameters at discharge, and risk factors (Table 2).

Renal Function and Hematocrit Levels at Discharge

When evaluating IV loop diuretic therapy during hospitalization, patients with dilutional versus depletion hyponatremia received higher daily IV furosemide doses (200 [150–250] vs. 150 [125–175] mg/day; $p = 0.002$) (Fig. 1) There were no differences between those two

Table 2. Differences in clinical and laboratory parameters in patients with dilutional hyponatremia and depletional hyponatremia

	Dilutional hyponatremia (n = 27)	Depletional hyponatremia (n = 41)	p value
Age, years	84 [70–91]	82 [67–86]	0.22
Males, %	44	56	0.34
EF, %	35 [25–40]	35 [20–45]	0.99
NYHA class III/IV, n	7/20	24/17	0.008
Laboratory data at admission			
Creatinine, mg/dL	1.50 [0.80–2.00]	1.50 [1.15–1.99]	0.61
eGFR, ml/min/1.73 m ²	44 [29–89]	44 [32–57]	0.70
BUN, mg/dL	70 [39–114]	73 [57–134]	0.37
Serum sodium, mEq/L	133 [130–134]	133 [131–134]	0.67
Serum potassium, mEq/L	3.7 [3.4–4.2]	4.0 [3.6–4.4]	0.10
BNP, pg/mL	769 [476–1429]	776 [446–1105]	0.76
Hemoglobin, g/dL	10.3 [9.4–11.0]	12.8 [12.0–13.7]	<0.001
Hematocrit, %	31 [29–33]	40 [36–42]	<0.001
Laboratory data at discharge			
Creatinine, mg/dL	1.60 [0.89–2.00]	1.40 [1.00–1.75]	0.96
eGFR, ml/min/1.73 m ²	42 [26–84]	46 [34–61]	0.74
BUN, mg/dL	68 [39–134]	78 [47–122]	0.79
Serum sodium, mEq/L	135 [133–138]	136 [132–138]	0.80
Serum potassium, mEq/L	4.0 [3.6–4.3]	3.8 [3.6–4.1]	0.27
BNP, pg/mL	395 [198–957]	476 [245–779]	0.92
Hemoglobin, g/dL	10.5 [9.7–11.1]	12.3 [10.8–13.5]	<0.001
Hematocrit, %	32 [29–34]	38 [33–41]	<0.001
Clinical signs at admission, %			
Pulmonary rales	85	80	0.62
Third heart sound	59	66	0.58
Jugular venous distention	67	54	0.29
Hepatomegaly	96	85	0.15
Peripheral edema	96	78	0.04
Risk factors, %			
Diabetes mellitus	33	29	0.72
Hypertension	22	36	0.21
Dyslipidemia	27	34	0.80
Smoke	33	14	0.07
CAD, %	41	39	0.89
Atrial fibrillation, %	51	43	0.88
CKD, %	55	53	0.87
WRF, %	22	24	0.83

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; WRF, worsening renal function.

groups in terms of WRF occurrence (Table 2). Among patients with dilutional compared to depletional hyponatremia, there was a higher rate of persistence of hyponatremia upon discharge (63 vs. 34%, respectively; $p = 0.02$; Fig. 2), while there was a lower percentage of patients with normal hematocrit levels at discharge (18 vs. 70%, respectively; $p < 0.001$). Moreover, there was a significantly higher rate of patients with persistence of congestion at

Fig. 1. Median IV in-hospital furosemide dosage in patients according to hyponatremia classification.

Fig. 2. Rate of persistence of hyponatremia in patients with dilutional and depletional hyponatremia.

discharge in the dilutional versus depletional group (81 vs. 58%, respectively; $p = 0.05$) (Fig. 3). Additional analysis regarding serum sodium levels at admission or at discharge is shown in online supplementary Figure 3.

Dividing our population according to the presence or not of hemoconcentration at discharge, we did not find any difference in terms of renal function, BNP, electrolytes, BNP, risk factors, and adverse events.

Clinical Outcomes

Adverse events at 60 days occurred in 61 patients (30 deaths and 31 rehospitalizations), whilst at 180 days there were 47 deaths and 79 rehospitalizations. At 60 days, the risk for death or rehospitalization was significantly higher if dilutional hyponatremia was present at baseline (univariate HR [95% CI] = 2.64 [1.40–4.99]; $p = 0.003$; Table 3). After adjustment for significant baseline characteristics, this relationship was maintained (HR 2.17 [1.08–4.37]; $p = 0.03$; Table 3). In contrast, depletional hyponatremia did not show any significant relation with 60 days' adverse events occurrence both in the univariate and in the multivariable model (HR 1.39 [0.72–2.68], $p = 0.32$, and HR 1.31 [0.66–2.59], $p = 0.43$, respectively; Table 3). At 180 days, both dilutional hyponatremia (HR 2.17 [1.32–3.55]; $p = 0.002$) and depletional hyponatremia (HR 1.71 [1.11–2.62]; $p = 0.01$) were significantly associated with death or

Fig. 3. Persistence of congestion at discharge rate according to hyponatremia classification.

Table 3. Univariate and multivariable Cox regression analysis for death or rehospitalization at 60 days

Parameter	Death or rehospitalization (60 days)			
	univariate		multivariable ^a	
	HR (95% CI of HR)	p value	HR ^a (95% CI of HR)	p value
Dilutional hyponatremia	2.64 [1.40–4.99]	0.003	2.17 [1.08–4.37]	0.03
Depletional hyponatremia	1.39 [0.72–2.68]	0.32	1.31 [0.66–2.59]	0.43
Normonatremia	Ref		Ref	
BNP decrease $\geq 30\%$	0.79 [0.47–1.32]	0.37	0.93 [0.53–1.63]	0.80
WRF	1.77 [1.02–3.08]	0.04	1.64 [0.91–2.96]	0.10
Persistence of congestion ^b	1.50 [0.88–2.54]	0.13	1.33 [0.76–2.33]	0.32

BNP, B-type natriuretic peptide; WRF, worsening renal function. ^a Adjusted for age, gender, chronic kidney disease, atrial fibrillation, and cardiovascular risk factors (hypertension, dyslipidemia, diabetes, ischemic heart disease, smoking). ^b At discharge.

rehospitalization on univariate analysis, which was maintained after adjustment (HR 1.88 [1.10–3.21], $p = 0.02$, and HR 1.64 [1.05–2.57], $p = 0.03$, respectively; Table 4). Both depletional and dilutional hyponatremia demonstrated a stronger prognostic impact compared to incident WRF, BNP changes, and persistent congestion (Tables 3, 4). Kaplan-Meier curves confirmed these findings, showing the highest risk for adverse outcome with dilutional hyponatremia over time, with the risk for depletional hyponatremia situated in-between (Fig. 4).

Analysis of the whole population dividing patients into normonatremic and hyponatremic ($n = 68$) showed that lower levels of serum sodium (under the median 133 [131–134] mEq/L) were related to increased risk of adverse events at 180 days (HR: 1.74 [1.18–6.35]; $p = 0.02$); Kaplan-Meier curves confirmed these findings ($p = 0.008$) (online suppl. Fig. 4).

Discussion

Hyponatremia is commonly defined as serum sodium levels <135 mEq/L, and is the most common electrolyte abnormality found in hospitalized patients with heart failure [11]. Its prevalence in AHF ranges from 15 to 25% [17–19]. Different studies have evaluated the rela-

Fig. 4. Kaplan-Meier 180-day survival curves in patients divided into dilutional hyponatremia, depletional hyponatremia, and normonatremia groups.

Table 4. Univariate and multivariable Cox regression analysis for death or rehospitalization at 180 days

Parameter	Death or rehospitalization (180 days)			
	univariate		multivariable ^a	
	HR (95% CI of HR)	p value	HR ^a (95% CI of HR)	p value
Dilutional hyponatremia	2.17 [1.32–3.55]	0.002	1.88 [1.10–3.21]	0.02
Depletional hyponatremia	1.71 [1.11–2.62]	0.01	1.64 [1.05–2.57]	0.03
Normonatremia	Ref	Ref		
BNP decrease ≥30%	0.88 [0.61–1.27]	0.52	0.95 [0.64–1.41]	0.79
WRF	1.30 [0.86–1.97]	0.21	1.28 [0.82–2.00]	0.26
Persistence of congestion ^b	1.48 [1.03–2.13]	0.03	1.37 [0.93–2.00]	0.11

BNP, B-type natriuretic peptide; WRF, worsening renal function. ^a Adjusted for age, gender, chronic kidney disease, atrial fibrillation, and cardiovascular risk factors (hypertension, dyslipidemia, diabetes, ischemic heart disease, smoking). ^b At discharge.

relationship between lower serum sodium levels and prognosis in AHF. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry among others, hyponatremia represented a main predictor of postdischarge mortality rate [20, 21]. In AHF patients, different mechanisms may contribute to the development of hyponatremia. Upregulation of neurohumoral systems reduce free water clearance and promote dilution of plasma. On the other hand, because of the ubiquitous use of diuretics in AHF, hyponatremia may be related to sodium depletion [7]. Interestingly, hematocrit is emerging as a potential marker for plasma dilution in AHF [14, 22–24]. In this study, hyponatremia was subdivided into dilutional cases with hematocrit values <35% versus depletional cases with hematocrit values ≥35%.

Patients with dilutional versus depletional hyponatremia seemed to characterize a sicker population at higher risk for adverse outcomes, as was demonstrated by their significantly higher loop diuretic in-hospital dosage and higher congestion persistence rate at discharge.

Moreover, dilutional hyponatremia less often resolved upon discharge when compared to depletional hyponatremia. Follow-up analysis showed a strong relationship between dilutional hyponatremia and poor prognosis both at 2 and 6 months. Depletional hyponatremia on the other hand was only related to long-term adverse events at 6 months. These results could be explained by different clinical profiles of hyponatremic patients in AHF. Firstly, hyponatremic patients showed a worse clinical status when compared to normonatremic patients. The former had higher serum creatinine levels, lower EF, lower serum potassium levels, and lower hematocrit. Moreover, patients with hyponatremia were treated with higher furosemide maintenance doses. Importantly, patients with hyponatremia could be subdivided according to their hematocrit levels into dilutional and depletional groups. Dilutional patients received higher IV furosemide doses in hospital. Despite higher diuretic dosage, such patients did not demonstrate efficient decongestion, and they showed higher rates of hyponatremia persistence and less often normal hematocrit levels at discharge. Regarding renal function, patients with dilutional versus depletional hyponatremia did not show a different incidence of WRF. While WRF on univariate analysis was significantly associated with clinical outcome after 60 days, this was no longer the case when including hyponatremic status. Interestingly, our multi-variable model did not show any relation between persistence of congestion and poor prognosis. Results from the EVEREST trial showed that minimal resting signs of congestion were related to high mortality and readmission rate [25]. The lack of any relationship between persistence of congestion and outcome could be due to the different patient phenotypes and discharge modality, which is mainly based on chest X-ray findings and dyspnea relief. This is a procedure commonly applied in clinical practice: often patients with peripheral edema reduction and dyspnea relief are judged ready for discharge; this is not verified by LV filling, pulmonary wedge, and right atrial pressure estimation. Indeed, congestion evaluation by clinical score has got several limitations because of poor concordance with pulmonary pressure and its modest accuracy in comparison with total fluid status retention [16, 26].

Considering our results, it is possible to classify the AHF population into three groups: (1) patients with normonatremia who have the best prognosis; (2) patients with depletional hyponatremia who seem well decongested upon discharge and have a somewhat poorer long-term outcome; and (3) patients with dilutional hyponatremia with worse functional status, persistent congestion at discharge, and poor short- and long-term outcome. The last group could represent patients with severe left ventricular dysfunction, higher congestion status and neurohormonal activation (RAAS and SNS). The major value of the current study lies in its extensive description of the clinical characteristics of hyponatremia patients. The higher furosemide dosage with less complete decongestion in patients with dilutional hyponatremia suggests a poor diuretic response, which might be because of lower sodium concentrations in the renal interstitium around the loop of Henle. The consequence is a reduced natriuresis since pre-urine sodium levels are decreased. This mechanism could eventually lead to increased hemodynamic congestion and reduced peripheral congestion. In these patients, the manner to improve outcome should be sustained decongestion together with hemoconcentration [14, 21–24]. Unfortunately, in our sample we did not find any difference in terms of outcome in patients experiencing hemoconcentration during hospitalization. This is probably due to the smaller sample size with respect to the above-cited study and shorter follow-up period.

For all these reasons, many studies focused on timing of hyponatremia and its relationship with prognosis. A recent subanalysis of the ESCAPE and DOSE trials showed that persistent hyponatremia had a significantly increased risk of death and rehospitalization when compared to patients without hyponatremia [6]. Similarly, Donzé et al. [27] demonstrated that severe discharge persistent hyponatremia was related to death at 30 days or rehospitalization. Thus, it would be necessary to promote free water excretion. Tolvaptan and acetazolamide appear to be the most useful drugs to improve symptoms and outcome in dilu-

tional patients [28, 29]. In our analysis, the dilutional group, which experienced the worse outcome, represented the product of poor diuretic response, lack of hemoconcentration, and persistence of hyponatremia.

Limitations

Our study should be interpreted in the light of some limitations. Firstly, our sample size was small with the possibility that some results are underpowered. We did not directly measure plasma volume, which would be the gold standard to determine dilution versus depletion. Therefore anemia might have confounded the results; indeed we did not measure red blood cell volume which could define true anemia in heart failure patients [30]. We adopted 35% as the cut-off for normal hematocrit levels according to our laboratory normal range and the correlation with plasma osmolarity in our sample. The proposed formula has been validated in 20 patients having both glycemic and albumin measurement; a wider application is probably mandatory to confirm our results. We did not collect spot urine to evaluate sodium levels, which are probably able to determine dilution and outcome [31]. We did not consider cases of hyponatremia that were induced by treatment. Our treatment was not standardized, and physicians were probably not blinded to serum sodium levels, which might have led to bias. Congestion evaluation by clinical score has several limitations because of poor concordance with pulmonary pressure and its modest accuracy in comparison with total fluid status retention. However, the clinical judgement based on the sum of congestion signs, still remains the most comprehensive and applicable method in multicenter trials [32]. Finally, our study did not include any quality of life questionnaire which could better characterize our patients regarding symptoms and clinical status.

Conclusions

Low hematocrit levels in AHF patients with hyponatremia reveal a population more difficult to decongest (i.e., dilutional hyponatremia) and with poor clinical outcome. In contrast, patients with hyponatremia but normal hematocrit level are better decongested, and they experience an intermediate outcome between patients with dilutional hyponatremia and no hyponatremia. Our evaluation could afford a better stratification in hyponatremic patients with AHF according to hematocrit levels, and our findings should be confirmed in a larger population.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

G.R. has given substantive intellectual contribution to this study; he has given substantial contributions to its conception and design; he has given final approval of the version to be published. F.H.V. has given substantive intellectual contributions to this study; he has given final approval of the version to be published. R.N. has been involved in revising the manuscript critically for important intellectual content. A.P. has extensively revised the manuscript and provided additional input on the final version of the paper.

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