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Original article

The beneficial prognostic value of hemoconcentration is negatively affected by hyponatremia in acute decompensated heart failure: Data from the Korean Heart Failure (KorHF) Registry☆

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ABSTRACT

Background: Hemoconcentration (HC) is associated with reduced mortality, whereas hyponatremia (HN) has been associated with an increased risk of adverse outcomes in patients with acute decompensated heart failure (ADHF). We sought to determine if the presence of HN influences the beneficial prognostic value of HC in ADHF patients.

Methods: We analyzed 2046 ADHF patients from the Korean Heart Failure Registry. We defined HC as an increased hemoglobin level from admission to discharge, and HN as sodium <135 mmol/L at admission. Our primary composite endpoint was all-cause mortality and/or HF re-hospitalization.

Results: Overall, HC occurred in 889 (43.5%) patients and HN was observed in 418 patients (20.4%). HC offered higher 2-year event-free survival in patients without HN (73.2% vs. 63.1% for no-HC, log-rank $p < 0.001$), but not in patients with HN (54.2% vs. 58.7% for no-HC, log-rank $p = 0.879$, p for interaction = 0.003). In a multiple Cox proportional hazard analysis, HC without HN conferred a significant event-free survival benefit (hazard ratio: 0.703, 95% confidence interval 0.542–0.912, $p = 0.008$) over no-HC with HN.

Conclusions: Only HC occurring in ADHF without HN was associated with improved clinical outcomes. These results provide further support for the importance of HN as a challenging therapeutic target in ADHF patients.

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Introduction

Heart failure (HF) is associated with high morbidity, mortality, and healthcare expenditures in developed countries. In the USA, almost one million hospitalizations for HF occur annually. Fluid overload is a main reason for re-hospitalizations in HF patients [1]. The effective and safe removal of congestion is an important therapeutic goal in hospitalized acute decompensated heart failure (ADHF) patients. Evidence-based data regarding the extent and duration of decongestion in ADHF have been limited. Hemoconcentration (HC), the relative increase in the cellular elements in blood, is a clinical parameter that predicts effective diuresis and is related to aggressive fluid removal. Several recent studies have shown that HC was related to improved clinical outcomes in patients with ADHF [2–6].

Hyponatremia (HN) is the most common electrolyte abnormality and is associated with adverse clinical outcomes in hospitalized patients with ADHF [7–11]. Therefore, it has been a component of the risk factors used in the prediction of prognosis in HF patients [12]. The pathophysiology of HN in ADHF is predominantly hypervolemic, accompanied by an excess of body water, which is a marker of congestion. However, the exaggerated sodium loss by a high dose of diuretics could lead to depletion of sodium, resulting in depletional HN during decongestion therapy, as it were treatment-induced hyponatremia. Therefore, we set out to determine if the presence of HN influences the beneficial prognostic value of HC in ADHF patients using data from a large nationwide registry in Korea. To our knowledge, there have been no studies conducted to evaluate the association between HC with or without HN and subsequent clinical outcomes in ADHF.

Methods

Study sample and design

The primary results of the Korean Heart Failure (KorHF) Registry have been previously reported [5,10,13,14]. Briefly, KorHF Registry was a nationwide, prospective, observational, multicenter, online registry that investigated the etiology, clinical characteristics, treatment modalities, morbidity, mortality, and the prognostic markers of hospitalized ADHF patients. A total of 3200 patients with the diagnosis of ADHF who were admitted within 24 h after symptom onset were enrolled from 24 hospitals in Korea. The ADHF diagnosis was based on specific symptoms in the patient's medical histories and signs on physical examination, according to the Framingham criteria. A confirmed diagnosis of HF was required also at discharge [13]. From the initial recruitment of 3200 patients, 357 patients without available echocardiographic data and 797 patients without other baseline and discharge laboratory data [e.g. hemoglobin (Hb), serum sodium, etc.] were excluded. Thus, the final analysis included 2046 patients. The primary composite endpoint of all-cause mortality and/or re-hospitalization due to HF exacerbation was collected by a review of the medical records and from telephone interviews conducted at the end of the study (1-year follow-up rate: 78.4%, 2-year follow-up rate: 65.5%). Research coordinators guided by documented definitions used standardized report forms to collect the follow-up events. Medical records were reviewed whenever patients required repeat hospitalization. In addition to patient telephone interviews, the referring physicians and institutions were contacted when necessary for additional information.

HC was defined as an increased Hb level from admission to discharge, i.e. Hb change (ΔHb) > 0 [5]. We used the widely accepted definition of HN as a serum sodium level $<$135 mmol/L at admission and discharge [10]. We calculated the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation: eGFR = 175 $\times$ [standardized serum creatinine (mg/dL)] $-$ 1.154 $\times$ age $-$ 0.203 $\times$ (0.742 if female) $\times$ (1.212 if black) [14].

Statistical analysis

Continuous variables were described using means and standard deviations (or median and interquartile range when it distributes non-normally), and categorical variables were described using numbers or percentages. We compared differences among groups using Student's *t*-test, Chi-square test, and ANOVA if necessary. Kaplan–Meier (K–M) survival analysis was used to estimate event-free survival, and log-rank tests were used to compare clinical outcomes in patients with HC and no-HC. Independent effects of variables and *p*-value for interaction on clinical events were calculated using Cox multivariable proportional hazards regression analysis and incorporating covariates with *p*-values less than 0.1 from unadjusted analyses. Hazard ratios (HRs) with 95% confidence intervals (CIs) demonstrated the risk of clinical events. Correlations between various laboratory value changes were examined by Pearson correlation analysis. Values of p less than 0.05 were considered statistically significant and all reported probability values were two-tailed. All analyses were conducted using SPSS version 21.0 software (SPSS/IBM Corp., Chicago, IL, USA).

Results

Baseline characteristics

The baseline characteristics and laboratory findings of ADHF patients (4 groups) are presented in Table 1 according to the presence of HC and HN. Overall, in ADHF patients, the mean Hb level was significantly decreased (12.4 $\pm$ 2.3 g/dL vs. 12.1 $\pm$ 2.1 g/dL, paired *t*-test $p < 0.001$), but the serum sodium level was not significantly changed (138.1 $\pm$ 5.2 mmol/L vs. 138.2 $\pm$ 4.6 mmol/L, paired *t*-test $p = 0.660$) from admission to discharge. No significant correlation was observed between Hb and serum sodium level changes between admission and discharge ($r = -0.039$, $p = 0.080$, $n = 1991$). Based on our definition of HC and HN, HC occurred in 889 (43.5%) patients and HN was observed in 418 (20.4%) patients. Patients who developed HC had significantly lower Hb, glucose, total cholesterol levels, and higher eGFR at admission compared to no-HC patients. Patients with HN had significantly lower Hb, total cholesterol, and sodium, while demonstrating higher glucose, blood urea nitrogen (BUN), and creatinine level compared to patients without HN. However, BUN/creatinine ratio, left ventricular ejection fraction, the prevalence of hypertension, diabetes mellitus, HF with reduced ejection fraction, and medication administration history were not significantly different among the four groups.

Associations with clinical outcomes

The primary endpoint of our study was the composite of all-cause mortality and/or re-hospitalization for HF aggravation. During median follow-up of 371 days (interquartile range, 85–872 days), 2-year events as a primary composite endpoint occurred in 34.6% ($n = 708$) of the patients, including in 16.6% ($n = 339$) of deaths. In K–M survival analysis, the HC group had a significantly higher 2-year event-free survival than the no-HC group (73.2% vs. 63.1%, respectively, log-rank $p < 0.001$; Fig. 1a). Based on the unadjusted Cox proportional hazards analysis, both HC (HR: 0.759, 95% CI: 0.658–0.875, $p < 0.001$) and HN (HR: 1.471, 95% CI: 1.251–1.729, $p < 0.001$) were prognostic predictors. However, based on the adjusted Cox regression model, only HC (HR: 0.743 95% CI: 0.632–0.874, $p < 0.001$), but not HN (HR: 1.088, 95% CI: 0.896–1.322,

Table 1
Baseline characteristics of four groups according to the presence of hemoconcentration (HC) or hyponatremia (HN).

	No-HC		HC	
	With HN (n = 252)	Without HN (n = 905)	With HN (n = 166)	Without HN (n = 723)
Clinical				
Male gender, n (%)	127 (50.4)	475 (52.5)	74 (44.6)	345 (47.7)
Age, years	70 ± 14[a]	68 ± 15	71 ± 14	67 ± 14
BMI, kg/m^2	22.2 ± 3.7[a]	23.7 ± 4.2	22.5 ± 3.4	23.3 ± 4.1
NYHA III/IV, n (%)	153 (60.7)	528 (58.3)	105 (63.3)	460 (63.6)
Ischemic origin of HF, n (%)	93 (36.9)[a]	384 (42.4)	66 (39.8)	241 (33.3)
HF adm history, n (%)	94 (37.3)[a]	221 (24.4)	58 (34.9)	186 (25.7)
Diabetes, n (%)	90 (35.7)[a]	268 (29.6)	62 (37.3)	208 (28.8)
Hypertension, n (%)	119 (47.2)	430 (47.5)	188 (53.0)	314 (43.4)
SBP, mmHg	127 ± 31[a]	135 ± 32	128 ± 28	132 ± 27
DBP, mmHg	76 ± 18[a]	81 ± 19	75 ± 16	79 ± 18
Heart rate/min	95 ± 26[a]	93 ± 26	93 ± 28	90 ± 26
Laboratory				
Hb adm, g/dL	12.5 ± 2.2[a]	13.2 ± 2.0	10.9 ± 2.1	11.8 ± 2.3
Hb dc, g/dL	11.1 ± 2.0[a]	11.9 ± 2.0	12.1 ± 2.0	12.9 ± 2.2
Glucose, mg/dL	183.9 ± 103.8[a]	165.1 ± 82.1	182.3 ± 93.2	147.2 ± 70.6
Cholesterol, mg/dL	161.4 ± 45.7[a]	172.1 ± 51.0	146.5 ± 40.2	158.7 ± 45.2
BUN, mg/dL	30.9 ± 20.8[a]	23.1 ± 13.7	30.3 ± 18.2	23.1 ± 14.1
Creatinine, mg/dL	1.72 ± 1.31[a]	1.37 ± 1.07	1.77 ± 1.52	1.38 ± 1.08
BUN/Cr	19.5 ± 9.1	18.5 ± 9.2	19.3 ± 8.0	18.5 ± 7.9
Sodium adm, mmol/L	130.7 ± 4.3[a]	139.9 ± 3.3	130.4 ± 4.7	140.2 ± 3.2
Sodium dc, mmol/L	135.4 ± 5.4[a]	139.0 ± 4.4	135.0 ± 4.8	138.8 ± 3.9
eGFR by MDRD, L/min/1.73 m^2	50.6 ± 30.0[a]	60.4 ± 38.9	50.8 ± 29.9	63.4 ± 38.5
Log NT-proBNP (n = 1409)	8.67 ± 1.30[a]	8.11 ± 1.53	8.98 ± 1.23	8.33 ± 1.38
Echocardiographic				
LVEF, %	38.6 ± 16.7	39.7 ± 15.5	37.7 ± 15.2	38.5 ± 15.8
HFrEF, n (%)	171 (67.9)	585 (64.6)	116 (69.9)	489 (67.6)
Discharge medications				
ACE inhibitors/ARBs, n (%)	150 (59.5)	597 (66.0)	105 (63.3)	459 (63.5)
Beta-blockers, n (%)	85 (33.7)	373 (41.2)	55 (33.1)	285 (39.4)
Spironolactone, n (%)	63 (25.0)	193 (21.3)	37 (22.3)	182 (25.2)

Values are the mean ± standard deviation or n (%). Hyponatremia is defined as serum sodium <135 mmol/L. BMI, body mass index; NYHA, New York Heart Association functional class; HF, heart failure; adm, admission; DBP, diastolic blood pressure; SBP, systolic blood pressure; Hb, hemoglobin; dc, discharge; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration ratio; MDRD, Modification of Diet in Renal Disease; NT-proBNP, N-terminal proB-type natriuretic peptide; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced LVEF (<45%); ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.
[a] Indicates p-value <0.05 by Chi-square test or ANOVA.

p = 0.393), was associated with significantly better event-free survival after adjustment for heart failure admission history, New York Heart Association III/IV status, diabetes mellitus, beta-blockers at discharge, age, body mass index, diastolic blood pressure, total cholesterol, BUN, and creatinine (Table 2) and these results were unchanged after further adjusting for known risk factors such as systolic blood pressure, and left ventricular ejection fraction.

The effect of hyponatremia on clinical outcomes in patients with HC or no-HC

To determine if the presence of HN influences the beneficial prognostic value of HC, we performed subgroup analyses (Fig. 2). First, we conducted a subgroup analysis according to the presence or absence of HN at admission. HC was a good prognostic marker in patients without HN (2-year event-free survival, 68.0% vs. 59.1% for no-HC, log-rank $p < 0.001$, n = 1628, Fig. 1b), but not in patients with HN (2-year event-free survival, 54.2% vs. 58.7% for non-HC, log-rank p = 0.879, n = 418, p for interaction = 0.003, Fig. 1c). In K–M survival analysis, HN was associated with a significantly lower 2-year event-free survival both in patients with HC (54.2% vs. 73.2% for without HN, log-rank $p < 0.001$, n = 889) and no-HC patients (58.7% vs. 63.1% for without HN, log-rank p = 0.037, n = 1157). In Cox proportional hazard analysis, HC was an independent predictor for primary composite endpoint (HR 0.723, 95% CI 0.601–0.871, p = 0.001) in patients without HN, but not in patients with HN at admission (HR 0.807, 95% CI 0.575–1.134, p = 0.217), consistently with the results of K–M analyses. And HC without HN was an independent and additive marker of good prognosis for the primary composite endpoint in the same adjusted Cox regression model (HR 0.703, 95% CI 0.542–0.912, p = 0.008, Table 3). We also had similar results for each component (e.g. all-cause mortality or HF re-hospitalization) of primary composite endpoint (data not shown).

Second, when we divided subgroups of patients based on the presence of HN at discharge, the beneficial prognostic value of HC was preserved in patients without HN at discharge (2-year event-free survival, 71.6% vs. 64.1% for no-HC, log-rank p = 0.001, n = 1639), but disappeared in patients with HN at discharge (2-year event-free survival, 59.5% vs. 53.8% for no-HC, log-rank p = 0.103, p for interaction = 0.037, n = 352), which is similar to the results from the analysis of data obtained at admission.

Third, we analyzed the relationship between HC and sodium level changes, and we analyzed only ADHF patients with HN (Na < 135 mmol/L) at admission. We categorized patients into two subgroups: improved HN (Na ≥ 135 mmol/L at discharge, n = 244) and persistent HN (Na < 135 mmol/L at discharge, n = 168). In patients with HC, no significant differences were observed in terms of 2-year event-free survival between the two groups (54.3% vs. 54.9% for persistent HN, log-rank p = 0.677, n = 165, Fig. 3a). However, for those with no-HC, patients with improved HN had a

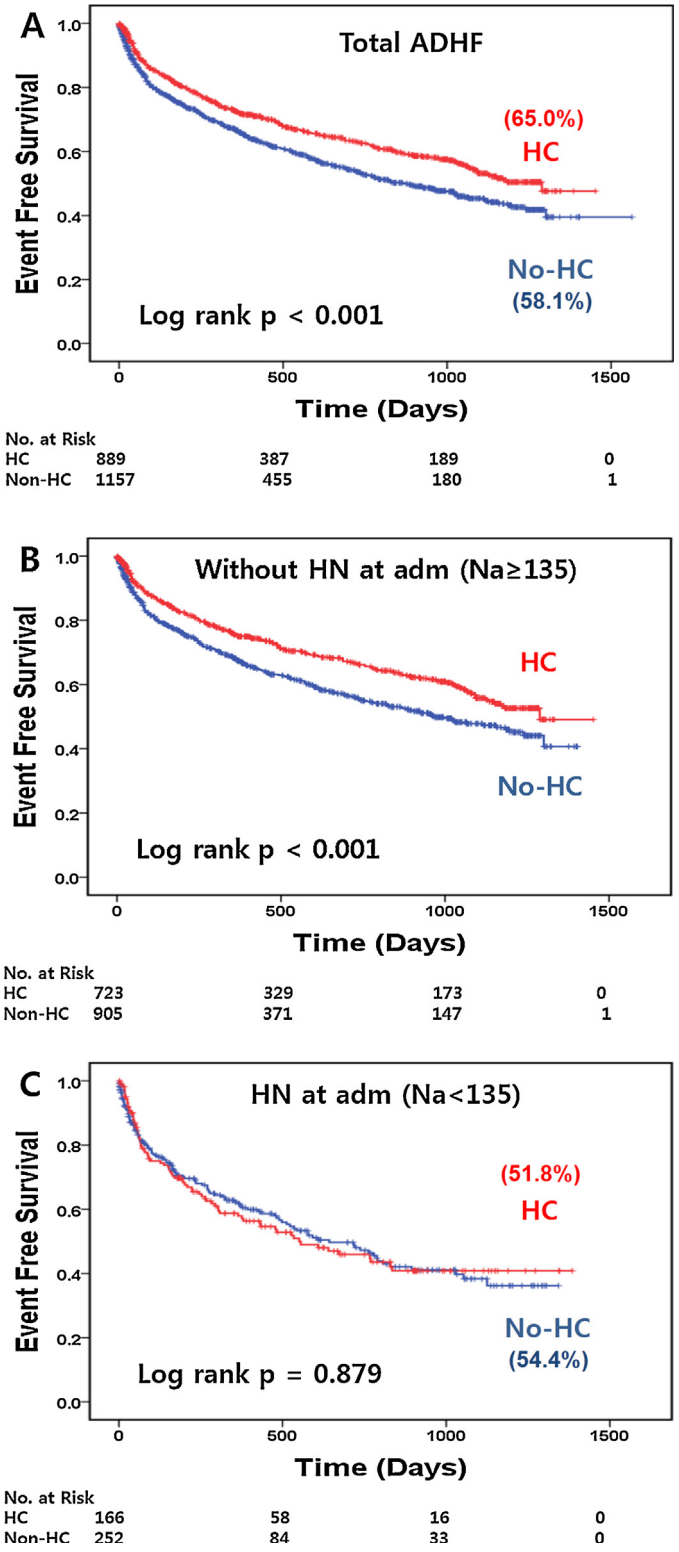

Fig. 1. The primary composite endpoint for hemoconcentration in all patients (Panel A), patients without hyponatremia (Panel B), and with hyponatremia at admission (Panel C). HC, hemoconcentration; Adm, admission; ADHF, acute decompensated heart failure.

significantly higher 2-year event-free survival compared to patients with persistent HN (63.3% vs. 50.5% for persistent HN, log-rank $p = 0.002$, $n = 247$, p for interaction = 0.881, Fig. 3b). Fig. 4 shows forest plots for adjusted Cox regression analysis for primary composite endpoint according to each subgroup.

Discussion

The principal finding of this study is that (1) HN at admission or discharge influences negatively the associated clinical outcomes of the patients with HC and that (2) HC without HN at admission is an independent and additive marker of good prognosis in ADHF.

HC is a clinical parameter that can predict effective diuresis and a good prognosis in patients with ADHF. HC has been defined as a measurement of non-plasma components of the intravascular space such as Hb, hematocrit, protein, and albumin [2–5,15,16]. Of these, the most widely used definition of HC is the change in Hb [3,5,15,16]. However, when we define HC as the change in Hb, we have to assume that the change in Hb is predominantly driven by changes in volume status rather than bleeding, bone marrow dysfunction, and subsequent transfusion [16]. Until now, there have been few reports describing the subgroup of patients in which HC is not related to good prognosis. In our study, HC was a good prognostic predictor, irrespective of anemia and renal dysfunction, which could be a widely used subgroup in an ADHF study (data not shown). However, there have been few reports describing the subgroup of patients in which HC is not related to good prognosis. A recently published study reported that only late HC (HC in the latter half of the hospitalization) was associated with improved survival compared to early HC [16]. In the present study, we found that HC was not a good predictor in ADHF patients with HN (at admission and discharge).

The pathophysiology of HN in ADHF is complex, generally considered as hypervolemic (dilutional) HN, and a problem of impaired water excretion rather than impaired sodium excretion. However, the combination of sodium-restricted diet and exaggerated sodium losses by a high dose of diuretic agents, especially in patients with severe hyperglycemia, might lead to severe depletion of sodium, resulting in depletional HN. So over-decongested patients by high dose of diuretics could be hyponatremia rather than decongestion-induced normonatremia or hypernatremia. But it is hard to distinguish whether HN comes from dilutional or depletional HN even though N-terminal pro B-type natriuretic peptide level was higher in patients with HN than those without HN, suggesting dilutional HN plays a role in HN development of our study. In addition, our results may imply that both HC and HN influence the prognosis of ADHF independently and the different pathophysiological mechanism may exist between HC and HN in ADHF and HN may result from other mechanisms beyond fluid overload. Therefore, we can speculate the beneficial prognostic value of HC might be influenced according to the situation of volume or sodium balance. As such, the clinical interpretations of HC in HN settings might be cautious, in particular with consideration to the balance between sodium and free water. Maybe, a different decongestion therapy may be needed beyond HC-guided therapy (e.g. ultrafiltration or a vasopressin antagonist) for patients with HN [17,18]. Further study is warranted to consider and distinguish the HN origin in ADHF.

In the clinical setting of ADHF, there have been some conflicting reports regarding whether improving HN during hospitalization is associated with a good or a detrimental prognosis. In most post hoc, retrospectively designed studies, improved HN and the correction of HN at discharge have not been found to be related to improved clinical outcomes in ADHF, even though HN at admission is related to increased short-term mortality [7,8,10]. In a randomized clinical trial, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST), tolvaptan improved only HF signs and symptoms, but had no effect on long-term mortality in patients hospitalized with HF [19–21]. However, in the recent post hoc analysis of EVEREST study, tolvaptan was found to be associated with improved long-term outcomes in patients with severe HN (Na < 130 mmol/L) [22,23].

Table 2
Cox proportional hazards regression analysis for the primary composite endpoint.

Variable	Unadjusted		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Heart failure admission history	1.858 (1.610–2.144)	<0.001	1.633 (1.378–1.934)	<0.001
NYHA III/IV	1.276 (1.102–1.477)	0.001	1.129 (0.953–1.336)	0.160
Diabetes mellitus	1.249 (1.079–1.446)	0.003	1.150 (0.969–1.366)	0.110
Beta-blockers at discharge	0.845 (0.731–0.977)	0.023	0.881 (0.747–1.041)	0.136
Age (year)	1.021 (1.016–1.027)	<0.001	1.020 (1.013–1.026)	<0.001
Body mass index (kg/m^2)	0.975 (0.956–0.994)	0.009	0.991 (0.970–1.013)	0.412
DBP (mmHg)	0.992 (0.988–0.996)	<0.001	0.994 (0.989–0.999)	0.013
Cholesterol (mg/dL)	0.997 (0.996–0.999)	0.001	0.999 (0.997–1.000)	0.126
BUN	1.017 (1.014–1.021)	<0.001	1.011 (1.006–1.017)	<0.001
Creatinine (mg/dL)	1.120 (1.074–1.168)	<0.001	1.031 (0.960–1.107)	0.401
Hemoconcentration	0.759 (0.658–0.875)	<0.001	0.743 (0.632–0.874)	<0.001
Hyponatremia	1.471 (1.251–1.729)	<0.001	1.088 (0.896–1.322)	0.393

HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association functional class; DBP, diastolic blood pressure; BUN, blood urea nitrogen.

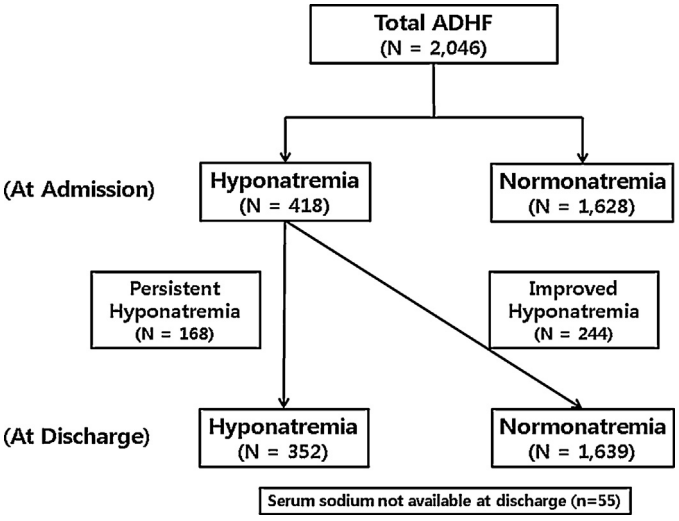

Fig. 2. Flowchart for subgroup analysis. ADHF, acute decompensated heart failure.

Table 3
Cox regression analysis for the primary composite endpoint based on hemoconcentration (HC) and hyponatremia (HN) at admission.

Variable	HR (95% CI)	*p*-value
No-HC with HN (*n* = 252)	Reference	
No-HC without HN (*n* = 905)	0.989 (0.773–1.266)	0.931
HC with HN (*n* = 166)	0.859 (0.616–1.199)	0.372
HC without HN (*n* = 723)	0.703 (0.542–0.912)	0.008

After adjusting for heart failure admission history, New York Heart Association III/IV status, diabetes mellitus, beta-blockers at discharge, age, body mass index, diastolic blood pressure, total cholesterol, blood urea nitrogen, and creatinine (using the same regression model as in Table 2 except hemoconcentration, hyponatremia).
HR, hazard ratio; CI, confidence interval.

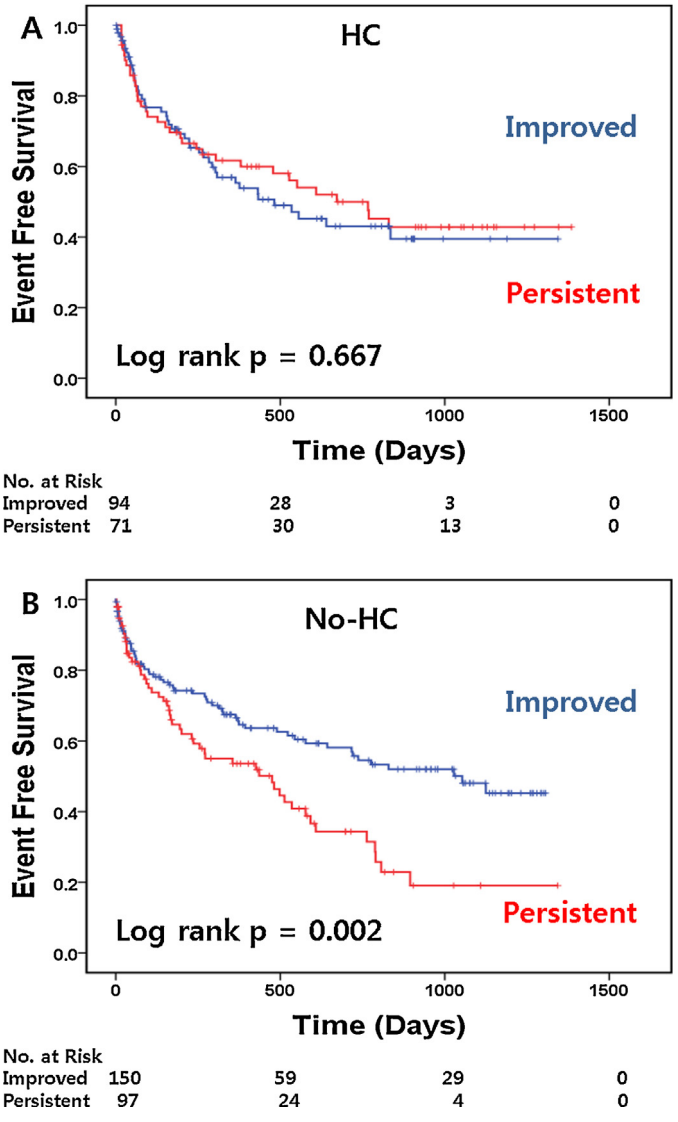

Fig. 3. The primary composite endpoint for improved HN vs. persistent HN in patients with hemoconcentration (Panel A) and in patients with no-hemoconcentration (Panel B). HC, hemoconcentration; HN, hyponatremia.

Most large-scale studies have shown that HC is an independent predictor after adjusting for various HF risk factors, such as sodium level at admission [2–5]. To date, there have been no studies analyzing the beneficial prognostic value of HC in the context of the changing sodium value between admission and discharge. Interestingly, in patients with HC, event-free survival was not affected by the sodium change pattern during hospitalization. However, improved HN in patients with no-HC had a significantly higher event-free survival compared to patients with persistent HN (Fig. 3b). One of the possible explanations for this difference in clinical outcomes between those with HC or no-HC might be the difference in their ability to tolerate diuresis rather than the

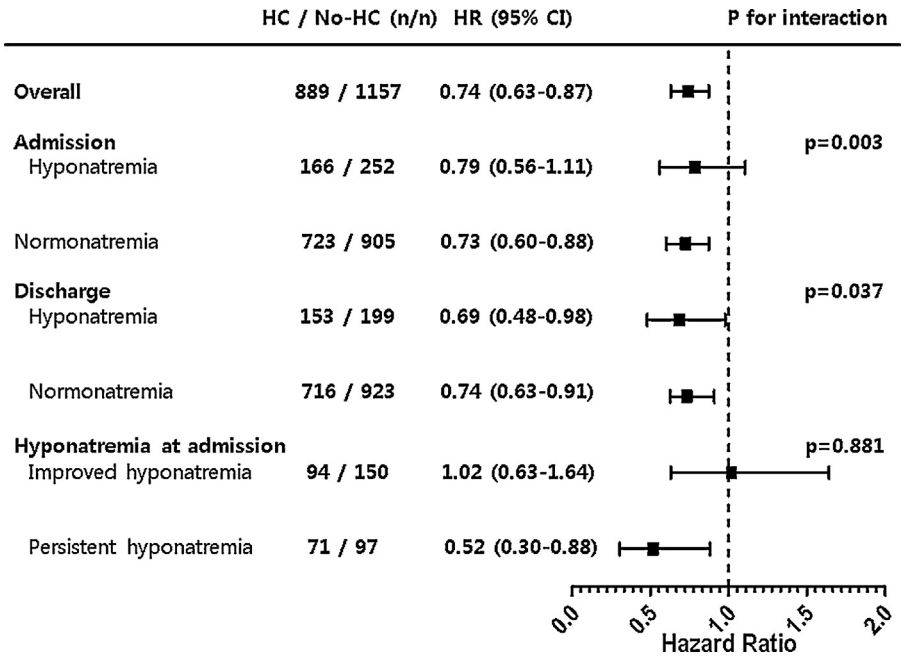

Fig. 4. Forest plots of hemoconcentration for adjusted Cox proportional hazard regression analysis for primary composite endpoint according to each subgroup. CI, confidence interval; HC, hemoconcentration; HR, hazard ratio.

diuresis itself, particularly in light of the recent suggestions that HC may be another surrogate marker for the severity of renal dysfunction in HF [16]. In this context, correction of HN might be beneficial in patients with no-HC or with severe HN.

Recently, HC-guided decongestive therapy has received attention as a novel approach toward personalized medicine in ADHF because it is a practical, non-invasive, and economically feasible strategy [24,25]. For example, the Hb level can serve as a guide to decongestion therapy, similar to the manner in which B-type natriuretic peptide is used [26,27]. Given the importance of decongestion in ADHF treatments, its subsequent effect of HC-guided decongestion therapy on clinical outcomes require additional research, supporting more reproducible clinical data in various ADHF settings.

Study limitations

Several limitations of our study must be considered when interpreting these results. First, due to some cases of incomplete records, we excluded some patients from the KorHF registry in our analysis of the fully adjusted multiple Cox regression model; this may introduce some selection bias. However, clinical characteristics such as all-cause mortality and HF re-hospitalization rate were comparable between our selected sample and the total registry during the follow-up period. Second, the absence of data regarding loop diuretics dose, creatinine change, cardiovascular mortality, frequency of blood draw during hospitalization, test variability of Hb levels, exclusion of in-hospital mortality cases, and longer follow-up duration in HC group may have weakened the clinical impact of this study. Unfortunately, we did not collect data for total protein, albumin, and hematocrit at registry enrollment. Therefore, we could not compare the prognostic power of other HC parameters based on these blood components [2]. Even though we excluded the patients who had history of blood transfusion for active bleeding, we could not totally distinguish hemodilution from unidentified bleeding or ineffective decongestion. It could be an important confounding factor in our analysis. Third, some results of the subgroup analysis may be coincidental findings, considering their non-significant *p*-value for studied interactions, although their *p*-value based on the log-rank test was significant. Considering the relatively lower administration rate of beta-blockers at discharge in Korea than western countries, there is a question as to whether our findings could be extrapolated to the population who have higher rate of beta-blockers use. Therefore, caution should be taken in interpreting and generalizing these results. Lastly, we did not have sufficient data to adjust for widely used biomarkers such as B-type natriuretic peptide in our regression models. Therefore, our findings should be considered as hypothesis generating and serve primarily to motivate further randomized clinical trials of decongestive strategies that can address causality.

Conclusions

The association between HC and clinical outcomes in ADHF is negatively influenced by HN at admission or discharge, with better clinical outcomes in HC patients without HN compared to those with HN or no-HC.

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Conflict of interest

None.

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