original article

The combined impact of hyponatremia and hematocrit on the risk for 90-day readmission and death in patients with heart failure: dilutional hyponatremia versus depletional hyponatremia

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BACKGROUND: Hyponatremia is common in hospitalized patients with heart failure (HF) and predicts a poor prognosis after discharge. In general, hyponatremia can be divided into two types: dilutional or depletional.

OBJECTIVE: Assess the impact of hyponatremia type on short-term outcomes.

DESIGN: Retrospective cohort

SETTINGS: Single center in China

PATIENTS AND METHODS: We sorted patients by hyponatremia into two types: dilutional hyponatremia (DiH, with hematocrit <35%) and depletional hyponatremia (DeH, with hematocrit ≥35%). The Kaplan-Meier method and Cox regression analysis were used to identify the impact of hyponatremia types on the risk for 90-day readmission and death.

MAIN OUTCOME MEASURES: 90-day readmission and death combined.

SAMPLE SIZE: 1770 patients.

RESULTS: Hyponatremia was present in 324/1770 patients with 182 cases classified as DiH versus 142 as DeH. Kaplan-Meier analyses showed a higher incidence of poor short-term outcomes in hyponatremia compared with normonatremia (log-rank *P*<.001), and the risk was higher in DiH than DeH although the difference was not statistically significant (log-rank *P*=.656). Multivariate Cox regression analyses showed that only DiH was independently associated with short-term outcomes (HR=1.34, 95%CI: 1.02-1.77, *P*=.038), but not DeH (HR=1.32, 95%CI: 0.97-1.80, *P*=.081). Analysis of the secondary endpoints showed that DiH increased the risk of readmission but not death (HR=1.36, *P*=.035 for readmission; HR=1.13, *P*=.831 for all-cause death).

CONCLUSIONS: Low hematocrit, rather than high hematocrit, with hyponatremia was associated with a risk of 90-day readmission in patients with HF.

LIMITATIONS: Single center, nonrandomized.

CONFLICT OF INTEREST: None.

Hyponatremia is present in about 15%-30% of hospitalized patients with heart failure (HF).[1-3] Prior studies have established that hyponatremia in patients with is independently associated with adverse clinical outcomes of readmission or death, regardless of HF types.[4-7] In general, hyponatremia can be divided into two types: dilutional or depletional. The former is caused by excess water retention rather than sodium deficiency, while the latter is due to increased sodium excretion and often accompanied by potassium/magnesium losses.[8,9] Appropriate differentiation between hyponatremia types requires comprehensive history taking, clinical examination, and correct interpretation of laboratory results.[9] As a simplified indicator, hematocrit has been proposed as a suitable surrogate for volume status measurement and can be used to distinguish plasma dilution in HF.[10-14]

So far, the joint impact of hyponatremia and hematocrit on the prognosis of HF has not been investigated. Therefore, we performed this retrospective cohort study and hypothesized that hyponatremia types defined by hematocrit had different effects on clinical outcomes. The aim of this study was to investigate the association between hyponatremia types and the prognosis in patients with HF within 90 days after discharge.

PATIENTS AND METHODS

The current study used data from a HF database established by a retrospective cohort study in Sichuan, China.[15] From 2016 to 2019, information on 2008 patients with HF was collected by integrating electronic healthcare records and follow-up outcome data. A total of 166 attributes were collected, including demographic data, baseline clinical characteristics, comorbidities, laboratory findings, drugs and outcomes. The study was approved by the ethics committee of hospital (Approval Number: 2020-010) and complied with the Declaration of Helsinki. Informed consent was waived due to the retrospective design of the study. The dataset is available at PhysioNet (https://doi.org/10.13026/8a9e-w734).[16]

All types of HF were included in this study (n=2008). First, we excluded 44 patients with missing values for height (n=4), weight (n=4), blood pressure (n=3), sodium (n=11) and hematocrit (n=28). Second, subjects who had connective tissue diseases (n=4), malignant lymphoma (n=1), solid tumor (n=39), liver disease or ALT >120 U/L (n=150) and AIDS (n=4) were not included in the analysis. Finally, a total of 1770 patients who completed a 90-day follow-up were selected (**Figure 1**).

Diagnosis and dilutional and depletional hyponatremia definition

Heart failure was defined by the European Society of Cardiology (ESC) criteria.[17] Hyponatremia was defined as serum sodium <135 mmol/L at admission. Obesity was defined as body mass index (BMI) ≥28 kg/m^2 according to the expert consensus in China.[18] Concomitant diseases were defined as having a corresponding medical history.

We defined hyponatremia types based on hematocrit level as dilutional hyponatremia (DiH) and depletional hyponatremia (DeH). According to the previous study,[10] a cut-off value ≥35% showed a good sensitivity and specificity (80%) to assess HF patients with normal or low plasma osmolarity. Therefore, patients with sodium <135 mmol/L and hematocrit <35% were classified as DiH (n=182), and those with sodium <135 mmol/L and hematocrit ≥ 35% were classified as DeH (n=142).

Endpoints and covariates

The primary endpoint was the short-term outcome readmission with all-cause death within 90 days after hospital discharge. The secondary endpoint was readmission within 90 days or all-cause death, separately. All participants were followed up for 90 days to obtain the admission and death information. Potential confounders were selected based on prior knowledge and the correlation with the primary endpoint tested by univariate models. Variables with statistical significance (P<.001) were entered into a multivariate Cox regression analysis as covariates.

Statistical analysis

Continuous variables are presented as mean (standard deviation) for normal distributions or median (interquartile range) for skewed distributions, while discrete variables are presented as counts with percentages (%). The independent samples *t* test, Mann-Whitney U test or chi-square test were used as appropriate to compare the baseline characteristics between DiH and DeH groups. Kaplan-Meier curves were constructed for the endpoint and compared using log-rank tests among patients with normonatremia, DiH and DeH. After adjusting for the covariates, the relationship between hyponatremia types and the short-term outcome was analyzed by Cox proportional hazard regression in the overall population and several subgroups Data analyses were conducted using R software version 4.1.2 (https://www.R-project.org/) and the packages 'survival' and 'forestplot'.

RESULTS

Of the 1770 participants with HF in our analysis, 324 patients (18.3%) were diagnosed as having hyponatremia on admission, including 182 cases of DiH and 142 cases of DeH. Compared with normonatremia, HF patients with hyponatremia had a higher prevalence of diabetes and chronic kidney disease (CKD), lower body mass index (BMI), blood pressure, albumin, and HDL-C, and higher uric acid, potassium, fibrinogen, and intravenous diuretic use (**Table 1**). DiH were older, a higher prevalence of CKD, had a higher SBP, creatinine, and BNP, while DeH had higher pulse rates, hemoglobin, albumin, ALT, TC, HDL-C and LDL-C (**Table 2**).

The incidence of the primary endpoint was 344 (23.8%) for normonatremia, 67 (36.8%) for DiH and 49 (34.5%) in DeH, respectively. Kaplan-Meier curves showed a significant difference in the incidence of the primary endpoint among the three groups (log-rank test: *P*<.001, **Figure 2**). The risk in DiH seemed to be higher than DeH, but the statistical test of the comparison was not significant(log-rank *P*=.656).

We first performed univariate analysis to identify covariates that might have influenced the outcomes. CKD, SBP, DBP, creatinine, uric acid, potassium and intravenous diuretic use were statistically significant and included in the multivariate analysis (**Table 3**). After controlling these covariates, the multivariate Cox regression analysis showed that compared with normonatremia, DiH had an increased risk of the primary endpoint (HR=1.34, 95%CI: 1.02-1.77, *P*=.038), but not DeH (HR=1.32, 95%CI: 0.97-1.80, *P*=.081). The results were similar for the risk of readmission, but neither type of hyponatremia was associated with 90-day all-cause mortality (**Table 4**).

Several subgroups were divided to reanalyze the association between hyponatremia types and the primary endpoint (**Figure 3**). DiH significantly increased the risk of the primary endpoint in female patients with diabetes or hypertension, and those without COPD, whereas DeH had a worse prognosis in older patients, patients with diabetes, COPD, or obesity.

DISCUSSION

Using a retrospective cohort of HF, we have demonstrated the combined impact of hyponatremia and hematocrit on the risk of 90-day readmission and death combined. Despite the overwhelming evidence regarding the prognostic value of hyponatremia for patients with HF, few studies have focused on hyponatremia types for the prediction of short-term outcomes. We used hematocrit as the criterion to distinguish different types of hyponatremia and found that DiH independently increased the risk of short-term outcomes, but not DeH. The observations from this study provide new insights into the role of hematocrit and arouse our interest in discussing the pathophysiological difference between hyponatremia types in patients with HF. Several studies have shown that hyponatremia is associated with readmission or death in patients with HF.[4-7] In a post hoc analysis from the Heart Failure Registry of Taipei Veterans General Hospital (HARVEST) study, Lu et al[19] found that hyponatremia combined with de-

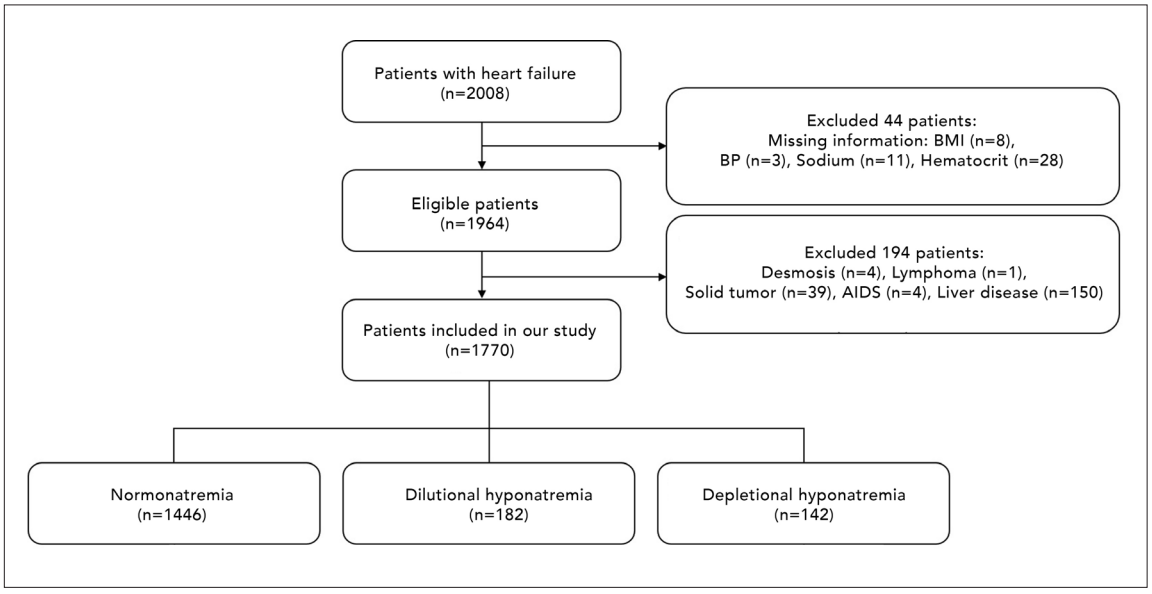

Figure 1. Study flowchart.

Table 1. Demographic and clinical characteristics of heart failure patients in the study.

	Normonatremia (n=1446)	Hyponatremia (n=324)	*P* value
Male	592 (40.9)	127 (39.2)	.607
Age >70 years	1077 (74.5)	233 (71.9)	.378
Diabetes	308 (21.3)	100 (30.9)	**<.001**
Chronic kidney disease	313 (21.6)	97 (30.0)	**.002**
Chronic obstructive pulmonary diseases	170 (11.8)	37 (11.4)	.940
Pulse (beats/min)	84.8 (20.8)	85.2 (23.0)	.738
Body mass index (kg/m^2)	21.5 (3.9)	20.7 (3.6)	**.002**
Systolic blood pressure (mmHg)	134.1 (23.5)	122.2 (23.3)	**<.001**
Diastolic blood pressure (mmHg)	78.0 (13.9)	71.5 (13.1)	**<.001**
Left ventricular ejection fractions (%)	52 (42, 61)	50 (40, 60)	.638
Hemoglobin (g/dL)	11.5 (2.4)	11.4 (2.8)	.585
Alanine aminotransferase (U/L)	20 (13, 31)	19 (13, 31)	.719
Albumin (g/L)	36.8 (4.8)	36.0 (5.6)	**.012**
Creatinine (mg/dL)	1.18 (0.88)	1.40 (0.98)	**<.001**
Uric acid (mg/dL)	7.78 (2.56)	8.69 (3.38)	**<.001**
Potassium (mmol/L)	3.88 (0.61)	4.31 (0.91)	**<.001**
Triglyceride (mmol/L)	0.96 (0.71, 1.31)	0.96 (0.70, 1.30)	.752
Total cholesterol (mmol/L)	3.74 (1.06)	3.65 (1.15)	.171
High density lipoprotein cholesterol (mmol/L)	1.13 (0.34)	1.06 (0.39)	**.002**
Low density lipoprotein cholesterol(mmol/L)	1.86 (0.75)	1.80 (0.74)	.230
Fibrinogen (g/L)	3.18 (0.96)	3.52 (1.26)	**<.001**
B-type natriuretic peptide (pg/mL)	729 (304, 1605)	668 (251, 1662)	.442
Angiotensin converting enzyme inhibitors	567 (39.2)	112 (34.6)	.136
Intravenous diuretic use	1221 (84.4)	289 (89.2)	**.036**

Data are n (%), mean (standard deviation) or median (interquartile range).

creased serum sodium during hospitalization led to a better risk assessment in patients with HF. To the contrary, correction of hyponatremia during hospitalization can reduce the odds of 30-day unplanned readmission or death by about 50%.[3] Consistent with the results of previous studies, the present study also showed a higher incidence of short-term outcomes in patients with hyponatremia during follow-up compared to those with normonatremia.

Hyponatremia is a common electrolyte disorder in the course of HF. DiH is more common than DeH in the pathophysiology of hyponatremia in HF.[20] Excess renal retention of water is the most common cause of DiH in patients with HF, which means total body wa-

Table 2. Basic characteristics in patients by state of hyponatremia.

	Dilutional Hyponatremia (n=182)	Depletional Hyponatremia (n=142)	*P* value
Male	58 (31.9)	69 (48.6)	**.003**
Age >70 years	144 (79.1)	89 (62.7)	**.002**
Diabetes	61 (33.5)	39 (27.5)	.294
Chronic kidney disease	68 (37.4)	29 (20.6)	**.002**
Chronic obstructive pulmonary diseases	19 (10.4)	18 (12.7)	.651
Pulse (beats/min)	82.6 (23.3)	88.5 (22.3)	**.022**
Body mass index (kg/m^2)	20.6 (3.5)	21.0 (3.8)	.332
Systolic blood pressure (mmHg)	125.1 (23.8)	118.5 (22.1)	**.012**
Diastolic blood pressure (mmHg)	71.4 (13.7)	71.5 (12.4)	.957
Left ventricular ejection fractions (%)	52 (41-62)	49 (38-60)	.744
Hemoglobin (g/dL)	9.6 (2.0)	13.8 (1.6)	**<.001**
Alanine aminotransferase (U/L)	17 (12-28)	21 (15-36)	**.005**
Albumin (g/L)	34.5 (5.6)	38.0 (4.9)	**<.001**
Creatinine (mg/dL)	1.59 (1.12)	1.16 (0.68)	**<.001**
Uric acid (mg/dL)	8.94 (3.54)	8.37 (3.15)	.133
Potassium (mmol/L)	4.36 (1.01)	4.25 (0.77)	.300
Triglyceride (mmol/L)	0.92 (0.68-1.24)	1.00 (0.74-1.34)	.186
Total cholesterol (mmol/L)	3.36 (1.07)	4.02 (1.14)	**<.001**
High density lipoprotein cholesterol (mmol/L)	1.00 (0.37)	1.13 (0.41)	**.005**
Low density lipoprotein cholesterol(mmol/L)	1.59 (0.65)	2.09 (0.77)	**<.001**
Fibrinogen (g/L)	3.46 (1.20)	3.58 (1.32)	.408
B-type natriuretic peptide (pg/mL)	695 (334-1902)	593 (163-1514)	**.032**
Angiotensin converting enzyme inhibitors	58 (31.9)	54 (38.0)	.299
Intravenous diuretic use	161 (88.5)	128 (90.1)	.762

Data are n (%), mean (standard deviation) or median (interquartile range)

ter is in excess relative to existing sodium stores, resulting in edema.[21] In addition, the activation of the renin-angiotensin-aldosterone or the sympathetic nervous system and/or arginine vasopressin (AVP) release are involved in the occurrence of DiH.[20,22] In contrast, DeH is characterized by an absolute shortage of total sodium reserves, which is relatively common in HF patients using diuretics.[23] Other factors contributing to a negative sodium balance include osmotic diuresis (e.g., hyperglycemia), gastrointestinal losses and third-space losses, especially if patients adhere scrupulously to the salt-restricted diets.[24, 25]

Before our study, little was known about the role of hemotocrit level in short-term outcomes in hospitalized HF patients with hyponatremia. Ruocco et al[10] distinguished DiH and DeH by hematocrit (35%) and

concluded that DiH is characterized by a population with more difficult decongestion in HF and poor clinical outcome, while DeH is characterized by less congestion and better short-term outcomes. Hematocrit has been proposed as a suitable surrogate for volume status as it is readily available and less costly.[26] Studies have shown that optimizing hematocrit levels before discharge contributes to reducing rehospitalization and improving survival in HF patients.[27,28] Therefore, we used the optimal cut-off point of hematocrit (35%) to distinguish DiH and DeH as prior studies did. Our analysis revealed that only DiH, but not DeH, was independently associated with short-term outcomes, which is consistent with previous studies. However, the Kaplan-Meier curves did not show a statistical significance between DiH and DeH in the impact on short-term outcomes. Potential explanations include insufficient follow-up for the outcomes. The Kaplan-Meier curve showed a higher incidence of short-term outcomes in DiH compared with DeH, but the log-rank test was not significant. Long-term follow-up is required to clarify this issue. Another possible explanation is that hematocrit may not be a perfect marker for distinguishing hyponatremia types. In this term, a more powerful and easily accessible surrogate is needed to predict the short-term outcomes in different types of hyponatremia. Comprehensive consideration of medical history, clinical examination, and laboratory results is of great importance in the diagnosis of DiH and DeH. Serum sodium <135 mmol/L and plasma osmolality <285 mOsm/L is an essential precondition for hypotonic hyponatremia, which also excluded pseudohyponatremia.[29] DiH often presents as hypervolemia, and inadequately suppressed urinary osmolality (≥100 mOsm/L). To the contrary, DeH presents as hypovolemia, adequately suppressed urinary osmolality (<100 mOsm/L) and depleted urinary sodium (<50 mmol/L).[9] Proper differentiation between DiH and DeH is crucial in clinical practice as it guides the subsequent treatment. Limiting water intake and promoting free water excretion are the two essential components of therapy of DiH. Caution should be observed in supplementation with hypertonic saline as it may worsen the status of water-sodium retention, and should be combined with loop diuretics if necessary.[30-32] For the treatment of DeH, administration of isotonic or hypertonic saline would effectively correct the status of sodium deficiency.[33] Importantly, replenishment of potassium and magnesium stores contributes to the correction of both DiH and DeH.[34,35]

There are several limitations in this study. First, the distinction between DiH and DeH could be defined more comprehensively using other factors such as blood volume, plasma osmolality and urinary osmolality. Hematocrit alone is not a standard means of distinguishing different types of hyponatremia. Although a prior study demonstrated that hematocrit levels have a good correlation with plasma osmolarity and can be used to distinguish different types of hyponatremia to some extent,[10] more extensive research is needed to confirm our results. Second, we only col-

Table 3. Univariate Cox regression analysis for 90-day readmission and death.

Variables	Hazard ratio (95% CI)	*P* value
Male	1.08 (0.89-1.29)	.440
Age >70 years	1.23 (0.99-1.54)	**.058**
Diabetes	1.34 (1.09-1.64)	**.005**
Chronic kidney disease	1.54 (1.26-1.88)	<.001
Chronic obstructive pulmonary diseases	1.12 (0.86-1.48)	.401
Pulse (beats/min)	1.00 (0.96-1.04)	.936
Body mass index (kg/m^2)	0.98 (0.95-1.00)	**.050**
Systolic blood pressure (mmHg)	0.90 (0.86-0.93)	**<.001**
Diastolic blood pressure (mmHg)	0.88 (0.83-0.95)	**<.001**
Left ventricular ejection fractions (%)	1.00 (0.98-1.01)	.586
Hemoglobin (g/dL)	1.00 (0.99-1.00)	**.020**
Alanine aminotransferase (U/L)	0.99 (0.99-1.00)	**.049**
Albumin (g/L)	1.00 (0.98-1.02)	.743
Creatinine (mg/dL)	1.22 (1.13-1.31)	**<.001**
Uric acid (mg/dL)	1.11 (1.07-1.14)	**<.001**
Potassium (mmol/L)	1.25 (1.12-1.40)	**<.001**
Triglyceride (mmol/L)	0.98 (0.90-1.08)	.713
Total cholesterol (mmol/L)	0.94 (0.83-1.06)	.298
High density lipoprotein cholesterol (mmol/L)	0.88 (0.80-0.97)	**.009**
Low density lipoprotein cholesterol(mmol/L)	0.82 (0.61-1.09)	.167
Fibrinogen (g/L)	0.87 (0.76-0.99)	**.040**
B-type natriuretic peptide (pg/mL)	1.01 (1.00-1.02)	**.003**
Angiotensin converting enzyme inhibitors	0.85 (0.70-1.03)	.096
Intravenous diuretic use	1.83 (1.33-2.52)	**<.001**

lected information on the use of intravenous diuretics, but ignored the type and dose of diuretics used. Despite multivariable analysis, the results may not be robust enough due to unknown factors. Third, we only obtained data at admission. Although previous studies have shown that serum sodium concentration at admission is a strong predictor of long-term mortality in patients with heart failure,[5] it is still necessary to combine data at discharge to improve the prognostic value in future studies. Finally, the present study was a retrospective single-center cohort design, and only short-term outcomes were included in the analysis. Therefore, multi-center, larger samples and longer-term follow-up are needed in future research.

In conclusion, DiH defined by low hematocrit independently increased the risk of 90-day readmission in patients with HF. In contrast, DeH failed to predict the short-term outcomes. Further studies are needed to evaluate the impact of hematocrit in hyponatremic patients on the long-term prognosis of heart failure.

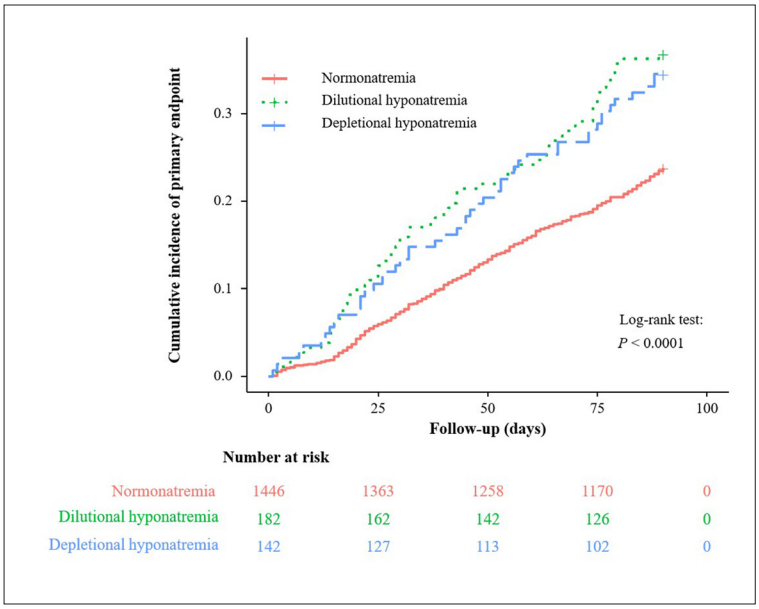

Figure 2. Kaplan–Meier curve for 90-day readmission and death combined (*P*<.0001 combined; DiH vs DeH log-rank *P*=.656).

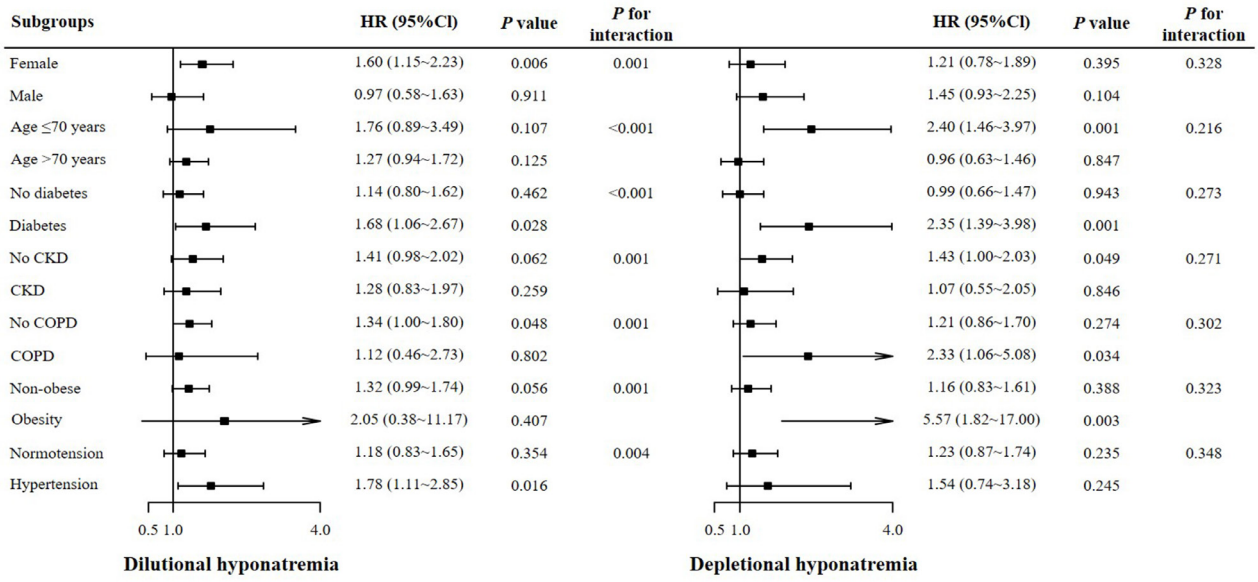

Figure 3. Subgroup analysis for the risk of 90-day readmission and death with dilutional or depletional hyponatremia.

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