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Using Machine Learning to Explore the Impact of Borderline Hyponatremia on Adverse Outcomes in Heart Failure Patients: A Data Mining Approach

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ABSTRACT

An association between slightly low serum sodium levels within the normal range and increased mortality risk in heart failure patients has been observed. However, the precise borderline level of serum sodium in heart failure patients remains undetermined, and the impact of borderline hyponatremia on heart failure outcomes remains unclear. This study aims to identify the threshold for borderline hyponatremia and assess the relationship between borderline hyponatremia and adverse outcomes in hospitalized heart failure patients. The adverse events, encompassing all-cause deaths and cardiac transplantation. This retrospective cohort study included 1,249 heart failure patients treated at the Heart Failure Center of Fuwai Hospital, Beijing, China, between 2009 and 2013, of which the incidence of adverse events was 23.1%. The optimal threshold for borderline hyponatremia were identified using Youden index and machine learning. Furthermore, we used Cox proportional risk analysis, smooth curve fitting, and Kaplan-Meier survival curve to assess the relationship between sodium levels and the incidence of adverse outcomes in patients with heart failure while considering potential confounding factors such as age and gender. We created three different models using univariate and multivariate Cox proportional-hazard regression models, including an unadjusted model, a minimally adjusted model, and a fully adjusted model. For patients with borderline hyponatremia, the HRs and 95%CIs for their unadjusted, minimally adjusted, and fully adjusted models were 1.90 (1.46, 2.48), P=<0.0001, 1.86 (1.43, 2.44), P<0.0001, and 1.37 (1.03, 1.81), P=0.0280. There was a significant association between borderline hyponatremia and adverse outcome.

KEYWORDS

Hyponatremia; Heart failure; Threshold, Machine learning

1. INTRODUCTION

As a global epidemic that affects approximately 26 million people worldwide [1], heart failure is a disease that consumes a high amount of healthcare resources and expenditure, with hospitalization being the main expenditure for heart failure patients [2]. Hospitalization rates for heart failure patients are high [3], imposing a heavy economic burden on both society, families, and individuals. Because of aging of population, the impact of heart failure will increase markedly [4]. While hyponatremia, a common electrolyte disorder in hospitalized patients , affects about 5% of adults and up to 15% to 38% of hospitalized patients [5]. One-third of critically ill patients in the ICU have moderate to severe hyponatremia [6]. As a relatively common manifestation in hospitalized heart failure patients , hyponatremia is associated with longer hospital stays and higher in-hospital and early post-discharge mortality [7]. Increasing evidence indicates that serum sodium levels are related to adverse outcomes in heart failure patients [8].

Plasma sodium concentration is essentially determined by plasma water intake and loss (in urine, feces, and sweat) and the water content of the plasma is finely regulated by a system including sensory organs (e.g. the carotid receptor and hypothalamus), vasopressin and the kidney. Sodium is the main factor determining plasma osmolality. Even small variations of plasma sodium concentration leading to the movement of water between intracellular and extracellular spaces, with a potential clinical impact [9]. Previous studies have shown a U-shaped relationship between serum sodium levels and mortality [10]. Both hyponatremia and hypernatremia upon admission to the ICU are independent risk factors for poor prognosis , and both hyponatremia and hypernatremia indicate a poorer prognosis in heart failure [11]. Low serum sodium concentration is an essential determinant of long-term mortality in heart failure patients [12], and hyponatremia is typically defined as serum sodium concentration ≤ 135mmol/L [13]. Low serum sodium levels within the normal range are associated with an increased risk of mortality in patients with heart failure [14] with serum sodium thought to have the lowest mortality in the range of 138 to 142 mmol/L [15]. In practice, however, reference ranges for sodium levels are usually between 135 and 145 mmol/L. Previous studies have often overlooked the associated risk of death in patients with heart failure at low serum sodium levels within the normal range Although largely preventable, the impact of deviations from this reference range is often underestimated [16].

There is a study defines the range of borderline hyponatremia as 133-137 mmol/L [17] However, one study defines the range of borderline hyponatremia as 130-135 mmol/L [9]. These standards are not consistent. (More granular determination is needed to determine whether patients with heart failure who are at increased risk of adverse outcomes within the currently accepted range of normal serum sodium concentrations. Our study contributes to a more comprehensive understanding of the relationship between serum sodium levels and the prognosis of patients with heart failure, thereby providing a basis for more accurate clinical management.)

In order to enhance the evaluation of the correlation between borderline hyponatremia and unfavorable outcomes, we employed machine learning techniques in our study to determine the threshold. Machine learning makes it possible to analyze complex data in an automated manner, and various machine learning methods have been successfully applied to cardiovascular diseases to automate interpretation, accurately perform measurements, and, in some cases, predict novel diagnoses from less invasive tests [18].

This study aims to determine the threshold for borderline hyponatremia in heart failure patients through multiple methods and evaluate the association between borderline hyponatremia and the adverse outcomes.

2. MATERIALS AND METHODS

2.1. Study Population

This study is a secondary analysis of data from previously published research [19], the data pertaining to heart failure patients admitted to the Heart Failure Center of Fuwai Hospital in Beijing, China. These data were subjected to secondary analysis. The study enrolled a total of 1,528 hospitalized patients diagnosed with heart failure, consecutively, between March 2009 and April 2013. The primary outcomes of interest in this investigation encompassed adverse events, encompassing all-cause deaths and cardiac transplantation. Of the 1528 patients, 325 experienced adverse events (300 patients died, 25 patients underwent cardiac transplantation) during a median of 19.1 months follow up. Adverse events were ascertained every three months by electronic hospital records follow-up or conversations with patients or patients' families by telephone conducted by trained clinicians or cardiology nurses. Ethical approval was not required as a study using pre-existing research data for the retrospective analysis.

2.2. Inclusion and Exclusion Criteria

The study has included patients who met the following criteria: ages over 18 years, and serum sodium levels are below 142 mmol/L from a total of 1,528 hospitalized patients diagnosed with heart failure at the Heart Failure Center of Fuwai Hospital in Beijing, China. Patients under 18 years old or with serum sodium levels above 142 mmol/L were excluded from this study. In total, 1,249 heart failure patients were included in this study.

2.3. The Threshold for Borderline Hyponatremia

The author has combined study data, Youden index, and machine learning to determine the threshold for borderline hyponatremia. We identified the optimal critical value by maximizing the Youden index (Youden index = sensitivity + specificity - 1).

Logistic Regression (LR) is computationally simple and is easy to understand [20]. Classification and Regression Trees (CART) is a non-parametric method that can handle highly skewed or multimodal, ordinal, and categorical predictor variables, making them well-suited for clinical decision-making [21]. Extreme Gradient Boosting (XGBoost) is a high-performance machine learning algorithm with great interpretability potential due to its decision system based on recursive trees [22]. Random Forest (RF) is one of the most popular tree-based supervised learning algorithms, known for its flexibility and ease of use [23].

The author used follow-up data to develop models for predicting the occurrence of adverse outcomes using four methods: Logistic Regression (LR) , Classification and Regression Trees (CART) , Extreme Gradient Boosting (XGBoost) , and Random Forest (RF) . The author then estimated and compared the area under the curve (AUC) to evaluate the performance of the models and find the best model. The Dataset was randomly divided into a training set and a testing set with a sample size ratio of 7:3. The training set was used to train the machine learning models, the testing set was used for validation. Finally, the dependence plot of Shapley Additive exPlanations (SHAP) [24] was used to calculate the threshold for borderline hyponatremia.

The Random Forest (RF) machine learning model achieved the best performance among the four machine learning models and has an AUC of 0.80, XGBoost has an AUC of 0.79, CART has an AUC of 0.72, LR has an AUC of 0.78 (Figure 1A).

The dependence plot of the Random Forest (RF) model revealed a threshold of 136.4 mmol/L for serum sodium levels (Figure 1B). Furthermore, the Youden index method indicated a threshold of 137.65 mmol/L for serum sodium levels. Additionally (Table 1 and Table 2), based on existing study data, the threshold for borderline hyponatremia is reportedly 138 mmol/L [6].

Combining the results from the two methods and considering the available study data, take the average of the three values, we can infer that the threshold for borderline hyponatremia is between 137-138 mmol/L (Table 3).

Table 1. Calculate the threshold.

Method	Threshold	Average Threshold
Machine Learning	136.4	137.4
Youden Index	137.7	
References	138.0	

2.4. Study Population and Definitions

The author referenced the standards of laboratory departments in most hospitals in China, defining normal serum sodium concentration as levels between 135-142 mmol/L and hyponatremia as serum sodium levels ≤135 mmol/L [12]. Based on the borderline hyponatremia threshold, the author defined borderline hyponatremia as serum sodium levels between 135-138 mmol/L. This is because 135 mmol/L is the lower limit of the normal range. Once the serum sodium level falls below this value, a number of clinical symptoms or complications associated with hyponatremia may occur, and is therefore defined here as the lower limit of borderline hyponatremia. In practice, the definition needs to be simplified for easier understanding and application by physicians and other healthcare professionals, and it may be more practical and convenient to choose an integer value as the threshold. For the sake of clinical practice, we chose 138 mmol/L as the upper limit of borderline hyponatremia, rather than the mean value of 137.4 mmol/L that we calculated.

2.5. Statistical Analysis

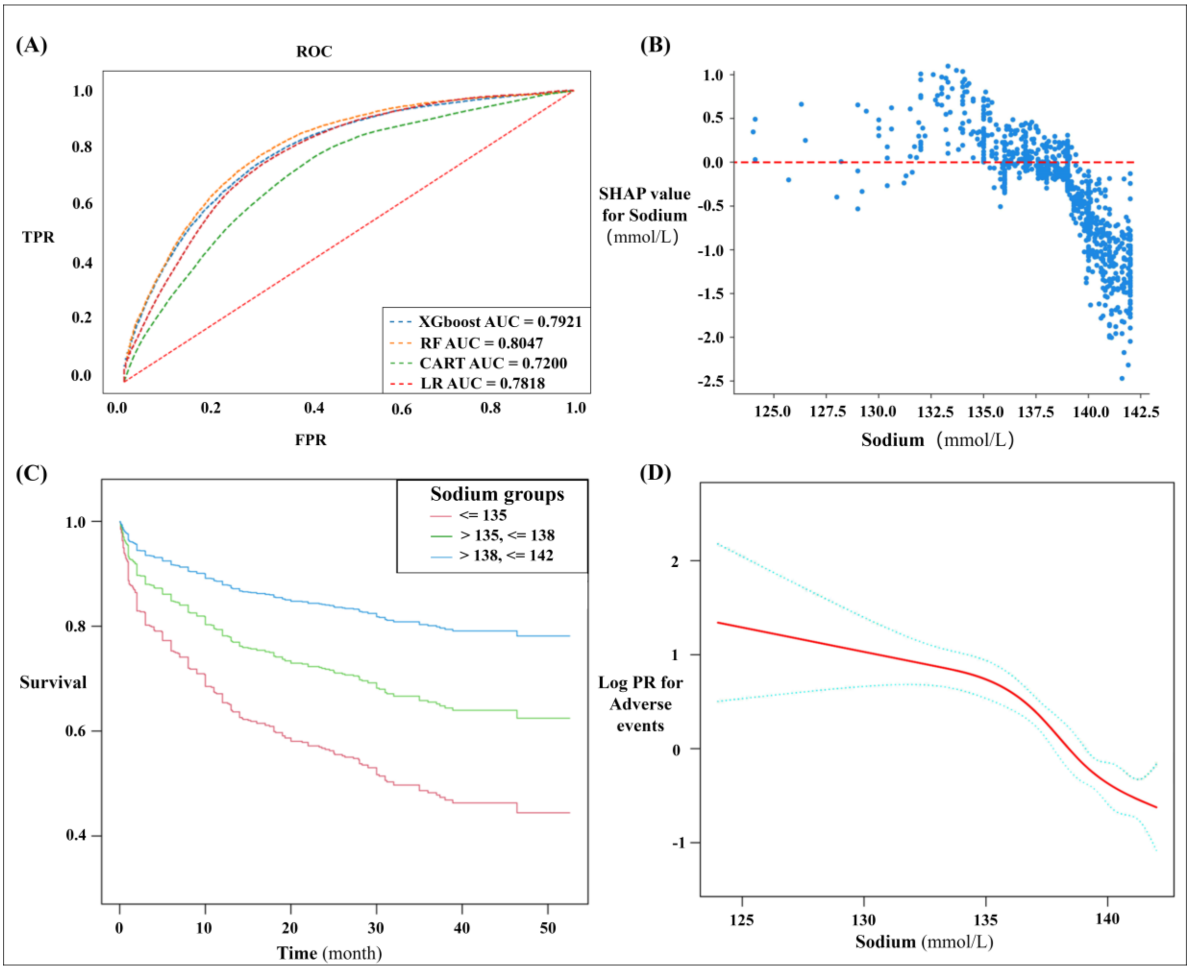


Figure 1. (A) Comparison of AUC values of the four models. (B) SHAP dependence plot. (C) Kaplan–Meier survival curves demonstrating differences in overall survival (month). (D) Association between serum sodium levels and adverse events (Adjusted for Sex; Age; NYHA; Ischemic heart disease; Hypertension; Diabetes mellitus; Valvular heart disease; LVEF; Blood urea nitrogen; Albumin; Creatinine; β-blockers).

Categorical variables were presented as frequencies and percentages. In contrast, continuous variables with a normal distribution were expressed as mean ± standard deviation, and non-normally distributed data were presented as median and interquartile range (IQR). We divided serum sodium levels into three intervals based on the normal reference range: one interval containing patients with a serum sodium below 135 mmol/L, one with a serum sodium from 135 to 138 mmol/L, and one with a serum sodium from 138 to 142 mmol/L, which was considered the reference range. We used Pearson's χ2 test to assess differences in categorical variables , and the Kruskal-Wallis rank sum test was used to assess differences in non-normally distributed continuous variables [25]. Serum sodium was treated in three ways: a continuous variable, a dichotomous variable, and a trichotomous variable. We created three different models using univariate and multivariate Cox proportional-hazard regression models, including an unadjusted model (unadjusted covariates), a minimally adjusted model (age and sex were the only covariates considered), and a fully adjusted model (adjusted for Sex; Age; NYHA; Ischemic heart disease; Hypertension; Diabetes mellitus; Valvular heart disease; LVEF; Blood urea nitrogen; Albumin; Creatinine; β-blockers) to examine the relationship between serum sodium concentration and the adverse outcomes. A Cox proportional hazards regression model using a cubic spline function and smooth curve fitting resolved non-linearity between serum sodium levels and adverse outcomes. The author evaluated the differences in adverse outcomes among patient groups with different serum sodium levels using Kaplan-Meier curves [26]. Additionally, a p-value < 0.05 was considered statistically significant.

Statistical analysis was conducted using EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) and R version 4.0.5 (http://www.R-project.org, The R Foundation). We implemented machine learning techniques in Python (version 3.10.6) using the Python Scikit-learn package.

Table 2. ROC analysis for continuous predictor.

Test	Sodium (mmol/L)
1	289
0	960
ROC area (AUC)	0.6535
95%CI low	0.6196
95%CI upp	0.6879
Best threshold	137.65
Specificity	0.7302
Sensitivity	0.5363

Table 3. Best threshold analysis.

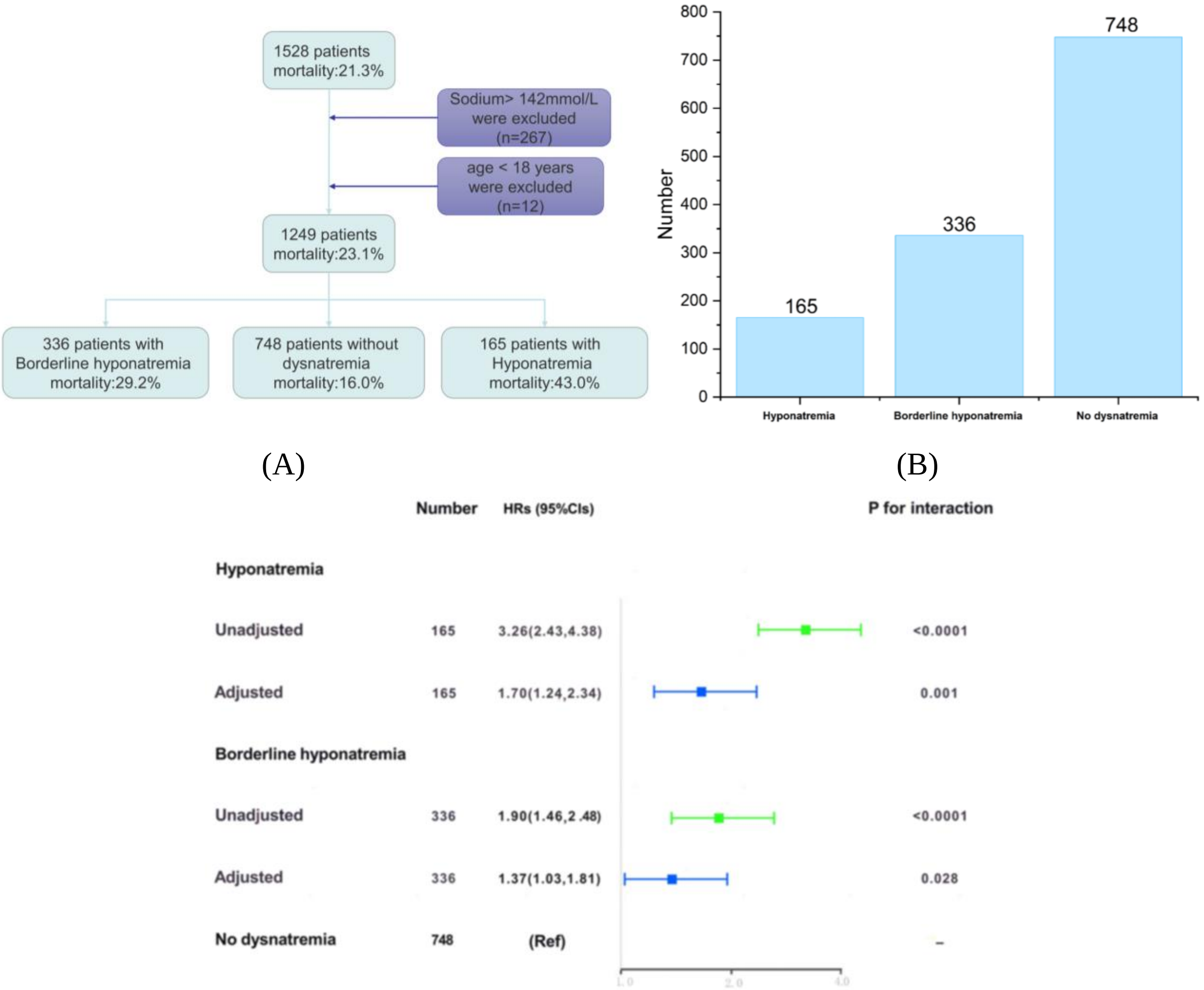
Test	Sodium (mmol/L)
Best threshold	137.65
Specificity	0.7302
Sensitivity	0.5363
Accuracy	0.6853
Positive-LR	1.9879
Negative-LR	0.635
Diagnose-OR	3.1307
N-for-diagnose	3.7518
Postive-pv	0.3744
Negative-pv	0.8395
a	155
b	259
c	701

3. RESULTS

3.1. Characteristics of Patients

Among the 1,528 heart failure inpatients included in the study, 267 patients (17.5%) were excluded due to serum sodium concentrations greater than 142 mmol/L, and 12 patients (0.8%) were excluded because they were under 18 years old (Figure 2A). A total of 1,249 patients were included in this study, with approximately 336 cases (26.9%) having borderline hyponatremia during hospitalization, 748 cases (59.9%) having normal serum sodium levels during hospitalization, and 165 cases (13.2%) having hyponatremia during hospitalization (Figure 2B).

A total of 1,528 heart failure inpatients were included in this study. The incidence of adverse outcomes in these patients was 23.1%. Heart failure patients with NYHA functional class IV symptoms accounted for 29.0% (362/1528) of the study population. The mean LVEF of the patients was 42.4%. Patients with hyponatremia were predominantly male, with an average age of 57.6 years at admission. The patients had an average BMI level of 24.1kg/m^2. Additionally, patients with hyponatremia had a higher prevalence of underlying chronic diseases (Table 4).



(A)

(B)

(C)

Figure 2. (A) Flowchart of patient selection. (B) The histogram of the number of patients and the serum sodium levels. (C) Relationship between sodium concentrations and adverse events. Hazard ratios (HRs) and 95% confidence intervals (95% CIs).

Table 4. Participant's baseline characteristics.

	Hyponatremia Na<=135 N=165	Borderline hyponatremia 135<Na<=138 N=336	No dysnatremia 138<Na<=142 N=748	P-value
Age, years	57.1 ± 16.2	57.8 ± 15.9	57.7 ± 14.6	0.865
Male	111 (67.3%)	263 (78.3%)	509 (68.0%)	0.002
History				
Hypertension	104 (63.0%)	189 (56.2%)	383 (51.2%)	0.015
Diabetes mellitus	128 (77.6%)	244 (72.6%)	563 (75.3%)	0.447
Ischemic heart disease	101 (61.2%)	176 (52.4%)	378 (50.5%)	0.046
Nonischemic cardiomyopathy	109 (66.1%)	236 (70.2%)	538 (71.9%)	0.318
Valvular heart disease	126 (76.4%)	279 (83.0%)	641 (85.7%)	0.012
Congenital heart disease	158 (95.8%)	328 (97.6%)	721 (96.4%)	0.465
Physical examination				
Heart rate, beats/min	80.1 ± 17.5	80.2 ± 18.7	76.9 ± 15.6	0.003
BMI, kg/m2	23.6 ± 4.9	23.6 ± 3.9	24.5 ± 4.2	0.002
NYHA				<0.001
II	25 (15.2%)	93 (27.7%)	253 (33.8%)	
III	58 (35.2%)	133 (39.6%)	325 (43.4%)	
IV	82 (49.7%)	110 (32.7%)	170 (22.7%)	
LVEF, n (%)	36.0 (28.0-53.0)	40.0 (30.0-56.0)	41.0 (30.0-55.0)	0.137
Hypertension, mmHg	110.5 ± 17.8	115.8 ± 19.4	120.8 ± 20.1	<0.001
Medication on presentation				
Loop diuretics	47 (28.5%)	109 (32.4%)	268 (35.8%)	0.156
ACEI/ARB	90 (54.5%)	171 (50.9%)	337 (45.1%)	0.038
β-blockers	40 (24.2%)	87 (25.9%)	156 (20.9%)	0.163
Aldosterone antagonists	58 (35.2%)	126 (37.5%)	284 (38.0%)	0.795
Digoxin	69 (41.8%)	171 (50.9%)	399 (53.3%)	0.027
Laboratory results				
White blood cell count	8.1 (6.1-9.9)	7.2 (6.0-8.9)	6.9 (5.7-8.5)	<0.001
Red blood cell	4.3 (3.8-4.9)	4.4 (4.0-5.0)	4.4 (4.0-4.9)	0.220
Hemoglobin, g/dL	129.9 ± 25.8	133.9 ± 24.0	134.8 ± 21.3	0.045
Total Protein, g/L	66.8 ± 8.6	68.1 ± 7.2	67.3 ± 7.0	0.109
Albumin, g/L	37.2 (33.0-40.4)	39.3 (36.0-42.8)	40.1 (37.5-43.1)	<0.001
Total bilirubin, umol/L	26.6 (18.0-45.0)	19.7 (13.7-32.0)	18.6 (13.4-27.0)	<0.001
Sodium, mmol/L	133.0 ± 2.3	136.9 ± 0.9	140.2 ± 1.1	<0.001
Creatinine, umol/L	94.3 (75.8-121.4)	92.8 (76.6-117.4)	85.3 (71.8-103.6)	<0.001
Blood urea nitrogen, mg/dL	9.6 (6.4-13.0)	8.0 (6.1-10.5)	7.1 (5.6-9.0)	<0.001
Uric acid, g/dL	452.0 (336.9-574.1)	421.0 (315.0-534.2)	405.7 (316.8-497.6)	0.002
Total cholesterol, mmol/L	4.1 (3.2-4.9)	4.1 (3.4-5.0)	4.2 (3.6-5.0)	0.254
High density cholesterol, mmol/L	0.9 (0.7-1.1)	0.9 (0.8-1.2)	1.0 (0.8-1.2)	<0.001
soluble ST2, ng/mL	61.3 (36.1-106.3)	41.5 (26.9-64.8)	33.5 (24.1-45.7)	<0.001
NT-proBNP, pg/mL	2375.8 (1132.0-4825.5)	1741.5 (846.7-3956.6)	1372.0 (742.8-2778.7)	<0.001
C-reactive Protein, mg/L	10.6 (3.8-23.9)	5.9 (2.9-16.5)	4.0 (2.3-8.3)	<0.001

Data are mean ± SD, median [Q1, Q3], or *N* (%).BMI, Body Mass Index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro–B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

3.2. Outcomes of Patients With Different Serum Sodium Levels

The incidence of adverse outcomes accounted for 23.1% of the total population. The incidence of adverse outcomes in patients with borderline hyponatremia at admission, the incidence of adverse outcomes was 29.2%. For patients with hyponatremia at admission, the incidence of adverse outcomes was 43%. Patients without hyponatremia at admission had an incidence of adverse outcomes of 16.0% (Figure 2A).

The HR and 95%CI for patients with normal serum sodium (>138 mmol/L) were 0.43 (0.34, 0.55), P<0.0001. For patients with borderline hyponatremia (>135 and <=138 mmol/L), the HR and 95%CI were 1.41 (1.11, 1.80), P=0.0055. For patients with hyponatremia (<=135 mmol/L), the HR and 95%CI were 2.57 (1.96, 3.36), P<0.0001. The factors (demographic data, vital signs, laboratory parameters, and comorbidities) remained independently associated with adverse outcomes (Table 5).

Table 5. Factors independently associated with adverse events.

	HRs	95% CIs	P value
Hyponatremia	2.57	(1.96, 3.36)	<0.0001
Borderline hyponatremia	1.41	(1.11, 1.80)	0.0055
No dysnatremia	0.43	(0.34, 0.55)	<0.0001
Digoxin	1.53	(1.21, 1.94)	0.0003
Female	0.87	(0.67, 1.13)	0.2931
Age, years	1.01	(1.00, 1.02)	0.0209
Hypertension	0.73	(0.58, 0.93)	0.0099
Ischemic heart disease	0.71	(0.56, 0.90)	0.0043
Nonischemic cardiomyopathy	1.53	(1.21, 1.95)	0.0005
Heart rate, beats/min	1.01	(1.00, 1.02)	0.0010
Hypertension	0.97	(0.96, 0.98)	<0.0001
LVEF, n(%)	0.97	(0.97, 0.98)	<0.0001
Hemoglobin, g/dL	0.99	(0.99, 1.00)	0.0009
Total Protein, g/L	0.97	(0.96, 0.99)	0.0008
Albumin, g/L	0.91	(0.89, 0.92)	<0.0001
Total bilirubin, umol/L	1.01	(1.01, 1.02)	<0.0001
Sodium, mmol/L	0.86	(0.83, 0.89)	<0.0001
Creatinine, umol/L	1.01	(1.01, 1.01)	<0.0001
Blood urea nitrogen, mg/dL	1.10	(1.08, 1.12)	<0.0001
Uric acid, g/dL	1.00	(1.00, 1.00)	<0.0001
Total cholesterol, mmol/L	0.70	(0.62, 0.78)	<0.0001
High density cholesterol, mmol/L	0.34	(0.22, 0.51)	<0.0001
soluble ST2, ng/mL	1.00	(1.00, 1.00)	<0.0001
NT-proBNP, pg/mL	1.00	(1.00, 1.00)	<0.0001
C-reactive protein, mg/L	1.01	(1.00, 1.01)	<0.0001
Loop diuretics	1.64	(1.26, 2.13)	0.0003
ACEI/ARB	0.59	(0.47, 0.75)	<0.0001
β-blockers	0.73	(0.56, 0.95)	0.0203
Aldosterone antagonists	1.28	(1.00, 1.63)	0.0501

(Hazard ratios (HRs) and 95% confidence intervals (95% CIs)). ACEI, angiotension-converting enzyme inhibitor; ARB, angiotensin receptor blocker.BMI, Body Mass Index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

Compared to those high in the normal range serum sodium levels (>138 mmol/L), low in the normal range serum sodium levels (≤138 mmol/L) were associated with a higher risk of adverse outcomes. The HRs and 95%CIs for their unadjusted, minimally adjusted, and fully adjusted models were 2.61 (2.07, 3.29), 2.57 (2.04, 3.25), and 1.72 (1.35, 2.21) (Table 6).

When considering serum sodium as a continuous variable, the unadjusted Cox proportional hazards regression model showed the HR and 95%CI for the incidence of adverse outcomes as 0.86 (0.83, 0.89). The minimally adjusted and fully adjusted models showed the HRs and 95%CIs of 0.86 (0.83, 0.89) and 0.92 (0.89, 0.95).

When dividing serum sodium levels into three intervals, using normal serum sodium (>138 mmol/L, ≤142 mmol/L) as the reference, the unadjusted Cox proportional hazards regression model showed the HRs and 95%CIs for the incidence of adverse outcomes in borderline hyponatremia (>135, ≤138 mmol/L) and hyponatremia (≤135 mmol/L) as 1.90 (1.46, 2.48) and 3.26 (2.43, 4.38), respectively. The adjusted Cox proportional hazards regression model showed the HRs and 95%CIs for the incidence of adverse outcomes in borderline hyponatremia (>135, ≤138 mmol/L) and hyponatremia (≤135 mmol/L) as 1.37 (1.03, 1.81) and 1.70 (1.24, 2.34), respectively (Table 6, Figure 2C). Patients with borderline hyponatremia (>135, ≤138 mmol/L) and hyponatremia (≤135 mmol/L) had a higher risk of adverse outcomes compared to patients with normal serum sodium level (>138 mmol/L, ≤142 mmol/L).

The Kaplan-Meier plot of hospitalized patients with heart failure showed no crossover between the curves, and survival decreased with decreasing serum sodium levels (Figure 1C). The curves do not intersect, and the survival rate of patients decreases with decreasing serum sodium levels. The non-linear relationship between serum sodium concentration and the incidence of adverse outcomes can be seen in Figure 1D.

Table 6. Association of sodium with mortality.

Variable	Crude model HRs (95%Cls) P-value	Model I HRs (95%Cls) P-value	Model II HRs (95%Cls) P-value
Sodium(mmol/L)	0.86 (0.83, 0.89) <0.0001	0.86 (0.83, 0.89) <0.0001	0.92 (0.89, 0.95) <0.0001
Sodium level category >= 138 mmol/L	1.0	1.0	1.0
Variable	Crude model HRs (95%Cls) P-value	Model I HRs (95%Cls) P-value	Model II HRs (95%Cls) P-value
<138 mmol/L	2.61 (2.07, 3.29) <0.0001	2.57 (2.04, 3.25) <0.0001	1.72 (1.35, 2.21) <0.0001
No dysnatremia	1.0	1.0	1.0
Borderline hyponatremia	1.90 (1.46, 2.48) <0.0001	1.86 (1.43, 2.44) <0.0001	1.37 (1.03, 1.81) 0.0280
Hyponatremia	3.26 (2.43, 4.38) <0.0001	3.26 (2.43, 4.38) <0.0001	1.70 (1.24, 2.34) 0.0010

(Hazard ratios (HRs) and 95% confidence intervals (95% CIs)). The sodium represents the reference interval. Model I is adjusted for age and sex. Model II is adjusted for sex; Age; NYHA; Ischemic heart disease; Hypertension; Diabetes mellitus; Valvular heart disease; LVEF; Blood urea nitrogen; Albumin; Creatinine; β-blockers.

4. DISCUSSION

This study, focusing specifically on hyponatremia in patients with heart failure at admission, demonstrates that hyponatremia and borderline hyponatremia were associated with adverse outcomes in hospitalized heart failure patients. Furthermore, our study used machine learning and other methods to infer that the threshold range for borderline hyponatremia at admission in heart failure patients was 137-138 mmol/L.

Consistent with previous studies [6, 9], our studies have shown that hyponatremia is closely related to adverse outcomes. This study revealed that the incidence of adverse outcomes in patients with hyponatremia at admission is 43%, indicating the worst prognosis among those with normal to low serum sodium levels, similar to the findings of another study [27]. Hyponatremia is a common electrolyte abnormality that may lead to life-threatening complications, which may occur at admission or develop due to the treatment or various comorbidities during hospitalization [28]. Studies have shown that elevated arginine vasopressin (AVP) levels mainly cause hyponatremia in patients with heart failure [29]. Heart failure reduces cardiac output , which can activate the sympathetic nervous system (SNS) [30]. Increased SNS activity stimulates the renin-angiotensin-aldosterone system (RAAS), resulting in sodium increases and water retention [29]. RAAS activation increases angiotensin II levels, leading to thirst and worsening of hyponatremia in HF patients [31]. The high mortality of hospitalized patients with hyponatremia may reflect the severity of the underlying diseases that cause hyponatremia rather than the effect of electrolyte disturbance itself [32]. However, this study was not designed to evaluate the association between these factors and does not establish causation from these associations.

As in other studies, we identified a statistically significant association between dysnatremia and adverse outcomes, even for small variations. At the same time, we have scientifically redefined the threshold for borderline hyponatremia. This study suggests that borderline hyponatremia (defined as serum sodium concentration between 135-138 mmol/L) is associated with adverse outcomes , similar to a previous study [33]. The research called into question the current understanding of the "normal" range of serum sodium levels (135-145 mmol/L) within the context of perioperative care, which is considered "normal" in the general population, may not be applicable in patients undergoing elective noncardiac surgery [33]. Another study showed that borderline hyponatremia or hypernatremia at admission is associated with increased in-hospital mortality regardless of the admission diagnosis [34]. Therefore, determining the threshold for borderline hyponatremia is of significance. A previous study indicated that serum sodium is usually used with a reference range of 135 to 145 mmol/L. However, the mortality increased as the serum sodium level decreased to less than 138 mmol/L or increased to more than 142 mmol/L; in addition, even serum sodium, usually classified as normal or slightly lower than normal, is independently associated with mortality, which is consistent with our results [35]. Previous research demonstrated that borderline hyponatremia at admission is independently associated with a higher risk of in-hospital mortality, and even minor changes in sodium concentration are associated with adverse outcomes [36]. Finally, within the normal and low serum sodium level ranges, the incidence of adverse outcomes increases significantly with decreasing serum sodium levels. This trend suggests we should pay attention to normal serum sodium levels.

Our study chose the Random Forest (RF) with the best performance after comparing the four machine learning models. The dependence plot based on the Random Forest (RF) model showed a threshold for serum sodium levels at 136.4 mmol/L. The Youden index indicated that the threshold of serum sodium levels was 137.65 mmol/L. Based on the above results and previous study, we comprehensively considered and inferred that the threshold range of borderline hyponatremia is 137-138mmol/L, which falls between the thresholds reported in the previous two studies [13, 37].

In addition to the Youden index and machine learning, there were other methods. When dealing with highly skewed datasets, Precision-Recall (PR) curves give a more informative picture of an algorithm's performance [38]. However, in the case of unbalanced category distribution, there may be some bias in the evaluation of model performance. One study explored how to perform cost-sensitive learning on unbalanced data. It proposed a method to determine thresholds using cost matrice to achieve cost-sensitive predictions by adjusting them during training [39]. Determining the cost matrix itself can be challenging, as different tasks and applications may assign different costs to the type of error. Due to the inadequacy of the above two methods, we did not take either one.

This study has some limitations. First, common to most retrospective database studies, this study cannot completely control for all confounding variables, the possible existence of unmeasurable confounders, or residual confounding, which may partially affect the observed results. Moreover, the author did not assess the impact of borderline hypernatremia or hypernatremia on the adverse outcomes. Although our study showed an independent correlation between borderline hyponatremia and adverse outcomes, the number of patients with high serum sodium levels was relatively small, which makes it challenging to evaluate the impact of borderline hypernatremia or hypernatremia on the incidence of adverse outcomes. Studies have shown that although patients with a higher degree of hypernatremia may have an increased risk of death, their prognosis may depend on the underlying severity of the disease rather than the hypernatremia itself [40], therefore, we did not include the hypernatremia patients. Additionally, while adverse outcomes are associated with borderline hyponatremia, we cannot prove that borderline hyponatremia directly influences the incidence of adverse outcomes. Therefore, further research is needed to explore the factors leading to this association and provide treatment recommendations based on these factors.

5. CONCLUSIONS

Our study indicates a close association between borderline hyponatremia and adverse outcomes in hospitalized heart failure patients. We inferred that the threshold range for borderline hyponatremia upon admission in heart failure patients is 138 mmol/L. The definition of the threshold for borderline hyponatremia is worthy of further research.

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