Relationship Between Serum Sodium Level and Length of Hospital Stay in Patients with Left Heart Disease-Associated Pulmonary Hypertension: Postprint

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Abstract

Background Pulmonary hypertension associated with left heart disease (PH-LHD) is the most common type of pulmonary hypertension (PH). Studies have shown that serum sodium levels are associated with severity and poor prognosis in Group 1 PH; however, their impact on PH-LHD has rarely been reported. Objective To investigate the relationship between serum sodium levels and N-terminal pro-brain natriuretic peptide (NT-proBNP) as well as echocardiographic parameters in PH-LHD patients, evaluate the impact of serum sodium levels on PH-LHD severity and hospitalization duration, and provide a theoretical basis for clinical management of PH-LHD patients and improvement of hospital turnover rates. Methods Clinical data from 360 PH-LHD patients hospitalized at the First Hospital of Shanxi Medical University between January 2020 and February 2022 were collected. Based on the median serum sodium level of 139 mmol/L (with serum sodium <135 mmol/L defined as hyponatremia), patients were divided into three groups: serum sodium <135 mmol/L group (50 cases), serum sodium 135–139 mmol/L group (136 cases), and serum sodium 140–145 mmol/L group (174 cases). Spearman rank correlation analysis was used to explore the correlation between serum sodium levels and hospitalization duration, NT-proBNP, and echocardiographic parameters; Kaplan-Meier survival curve analysis was employed to compare hospitalization duration among PH-LHD patients with different serum sodium levels; and binary logistic regression analysis was applied to investigate the effect of serum sodium levels on hospitalization duration in PH-LHD patients. Results Comparisons of age, hospitalization duration, NT-proBNP, left atrial anteroposterior diameter, right atrial area, left ventricular ejection fraction, and fractional shortening among the three PH-LHD patient groups showed statistically significant differences

(P<0.05); specifically, hospitalization duration and NT-proBNP in the serum sodium 140–145 mmol/L group were lower than those in the serum sodium <135 mmol/L group and the serum sodium 135–139 mmol/L group (P<0.05). Spearman rank correlation analysis revealed that serum sodium levels in PH-LHD patients were negatively correlated with hospitalization duration (r=-0.176), NT-proBNP (r=-0.135), right ventricular anteroposterior diameter (r=-0.110), and pulmonary artery systolic pressure (r=-0.105) (all P<0.05). Kaplan-Meier survival curve analysis showed that hospitalization duration differed significantly among PH-LHD patients in the three serum sodium level groups (2=12.469, P=0.002). After adjusting for control variables, binary logistic regression analysis showed that elevated serum sodium level was a protective factor against prolonged hospitalization duration in PH-LHD patients (OR=0.916, 95%CI=0.859-0.977, P=0.008); compared with patients with serum sodium 140–145 mmol/L, the risk of prolonged hospitalization duration increased in both the serum sodium <135 mmol/L group (OR=2.268, 95%CI=1.049-4.903, P=0.037) and the serum sodium 135–139 mmol/L group (OR=2.056, 95%CI=1.163-3.635, P=0.013). Conclusion Serum sodium levels are closely associated with PH-LHD severity, and decreased serum sodium level is an independent risk factor for hospitalization duration in PH-LHD patients, representing a potential therapeutic consideration that provides a new strategy for the diagnosis, treatment, and hospital turnover of PH-LHD.

Full Text

Relationship between Serum Sodium Levels and Length of Hospital Stay in Patients with Pulmonary Hypertension Associated with Left Heart Disease

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Abstract

Background: Pulmonary hypertension associated with left heart disease (PH-LHD) is the most common form of pulmonary hypertension (PH). While studies have shown that serum sodium is associated with severity and poor prognosis in group 1 PH, the effect of serum sodium on PH-LHD has been rarely reported.

Objective: To investigate the relationship between serum sodium levels and N-terminal pro-brain natriuretic peptide (NT-proBNP) as well as echocardiographic parameters in PH-LHD patients, and to evaluate the effect of serum sodium on PH-LHD severity and length of hospital stay, thereby providing a theoretical basis for clinical diagnosis and treatment of PH-LHD patients and improving hospital turnover. **Methods:** Clinical data were collected from 360 adult inpatients diagnosed with PH-LHD at the First Hospital of Shanxi Medical University between January 2020 and February 2022. Based on the median serum sodium level of 139 mmol/L (with serum sodium <135 mmol/L defined as hyponatremia), patients were divided into three groups: serum sodium <135 mmol/L group (n=50), 135-139 mmol/L group (n=136), and 140-145 mmol/L group (n=174). Spearman correlation analysis was used to examine the correlation between serum sodium level and length of hospital stay, NT-proBNP, and echocardiographic parameters. Kaplan-Meier survival curve analysis was used to compare hospital stay duration among PH-LHD patients with different serum sodium levels. Binary logistic regression analysis was used to investigate the effect of serum sodium levels on length of hospital stay in PH-LHD patients. **Results:** Significant differences were observed among the three groups in age, length of hospital stay, NT-proBNP, left atrial diameter, right atrial area, left ventricular ejection fraction, and fractional shortening (P<0.05). Patients in the serum sodium 140-145 mmol/L group had shorter hospital stays and lower NT-proBNP levels compared to both the serum sodium <135 mmol/L group and the serum sodium 135-139 mmol/L group (P<0.05). Spearman correlation analysis showed that serum sodium level was negatively correlated with length of hospital stay (r=-0.176), NT-proBNP (r=-0.135), right ventricular diameter (r=-0.110), and pulmonary artery systolic pressure (r=-0.105) in PH-LHD patients (P<0.05). Kaplan-Meier survival curve analysis revealed statistically significant differences in hospital stay duration among the three serum sodium groups (^{2}=12.469, P=0.002). Binary logistic regression analysis after adjusting for control variables showed that elevated serum sodium level was a protective factor against prolonged hospital stay in PH-LHD patients (OR=0.916, 95%CI=0.859-0.977, P=0.008). Compared with patients having serum sodium 140-145 mmol/L, those with serum sodium <135 mmol/L (OR=2.268, 95%CI=1.049-4.903, P=0.037) and those with serum sodium 135-139 mmol/L (OR=2.056, 95%CI=1.163-3.635, P=0.013) both had increased risks of prolonged hospitalization. **Conclusion:** Serum sodium level is closely associated with PH-LHD severity, and decreased serum sodium level is an independent risk factor for prolonged hospital stay in PH-LHD patients. This represents a potential therapeutic consideration and provides a new strategy for PH-LHD management and hospital turnover.

Keywords: Pulmonary arterial hypertension; Pulmonary hypertension associated with left heart disease; Serum sodium; Echocardiography; Length of stay; Logistic models

Introduction

Pulmonary hypertension associated with left heart disease (PH-LHD) is the most common form of pulmonary hypertension (PH), accounting for 65%–80% of PH cases. The pathophysiological mechanism of PH-LHD is currently understood as follows: left heart disease leads to elevated left atrial pressure, causing increased pulmonary circulation pressure and structural and functional changes in small pulmonary arteries, which results in pulmonary vascular remodeling and ultimately leads to right heart failure and even death. PH-LHD has an insidious onset with nonspecific symptoms, and its epidemiological data remain unclear. Treatment primarily focuses on alleviating the underlying disease, with limited data available on targeted therapies, resulting in poor prognosis and high mortality.

In the "Opinions on Strengthening the Performance Assessment of Tertiary Public Hospitals" issued by the General Office of the State Council, average length of hospital stay is a key performance indicator, representing the mean duration of hospitalization for discharged patients over a specified period. Length of hospital stay serves as a critical metric for measuring hospital healthcare quality, comprehensive management level, and operational efficiency, and is directly related to patients' medical economic burden as well as the utilization, quality, and sustainable development of healthcare resources. Abnormal serum sodium levels are a common issue among inpatients that can influence treatment decisions and represent a major factor prolonging hospital stay.

Studies have shown that hyponatremia is an important marker of left heart failure and a consequence of more severe right ventricular dysfunction and hemodynamic impairment in PH patients. Clinical records reveal that PH-LHD patients often present with abnormal serum sodium levels, yet the relationship between serum sodium and length of hospital stay remains unclear. Therefore, this retrospective case analysis investigates the association between serum sodium levels and hospital stay duration in PH-LHD patients to provide a theoretical basis for clinical diagnosis and treatment, with significant implications for improving patient outcomes, reducing hospitalization time, lowering medical costs, and enhancing hospital operational efficiency and rational allocation of medical resources.

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1. Subjects and Methods

1.1 Study Subjects

We collected clinical data from 2,583 patients who were hospitalized at the First Hospital of Shanxi Medical University between January 2020 and February 2022 and received a first-time diagnosis of PH. Based on inclusion and exclusion criteria, 360 patients with definitive evidence of left heart disease diagnosed with PH-LHD were ultimately included as study subjects. The screening flowchart

is shown in Figure 1 [Figure 1: see original paper].

Inclusion criteria: Patients had confirmed left heart disease and met the diagnostic criteria in the "Chinese Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension (2021 Edition)" issued by the Chinese Medical Association, with echocardiographic diagnosis showing pulmonary artery systolic pressure (PASP) $ $40mmHg(1mmHg = 0.133kPa).PASPwasestimatedusingthetricuspidregurgitationmethod : PASP = 4V^{2}$+right atrial pressure, where V represents tricuspid regurgitation velocity (TRV).

Exclusion criteria: (1) Patients aged <18 or >90 years; (2) Pregnant patients with PH; (3) Patients with pneumoconiosis or silicosis; (4) Patients with malignant tumors; (5) Patients with immunodeficiency or other acute/chronic organic diseases such as hepatic or renal insufficiency; (6) Patients without serum sodium measurements; (7) Patients with other types of PH. This study was approved by the Research Ethics Committee of the First Hospital of Shanxi Medical University (approval number: K-138), and informed consent was waived.

1.2 Data Collection

We collected relevant clinical data from patients, including: (1) demographic information: sex, age, BMI, length of hospital stay, smoking history, alcohol consumption history, diabetes history, and hypertension history; and (2) clinical data: etiology (heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, valvular heart disease, congenital or acquired cardiovascular disease), serum sodium, N-terminal pro-brain natriuretic peptide (NT-proBNP), and echocardiographic parameters (left atrial diameter, right ventricular diameter, right atrial area, left ventricular ejection fraction, fractional shortening, TRV, and PASP). All collected data represented the first test results obtained on the actual day of admission before any treatment was administered.

1.3 Definitions and Grouping

Smoking history was defined as current or past habitual smoking of at least one cigarette daily for $ $6 months. Alcohol consumption history was defined as current or past habitual drinking at least once weekly for $ $1 year. Diabetes history was defined as fasting plasma glucose $ $7.0 mmol/L, 2-hour post-oral glucose tolerance test (75 g) $ $11.1 mmol/L, or glycated hemoglobin $ $6.5% (48 mmol/mol). Hypertension history was defined as office blood pressure measured on three separate occasions showing systolic pressure $ $140 mmHg and/or diastolic pressure $ $90 mmHg without antihypertensive medication.

Heart failure with reduced ejection fraction was defined as LVEF<50%; heart failure with preserved ejection fraction was defined as LVEF$ $50%. The normal reference range for serum sodium was 135–145 mmol/L, with hyponatremia defined as serum sodium <135 mmol/L. The median serum sodium level in our study population was 139 mmol/L. Based on this, patients were divided

into three groups: serum sodium <135 mmol/L group (n=50), serum sodium 135-139 mmol/L group (n=136), and serum sodium 140-145 mmol/L group (n=174).

1.4 Statistical Methods

SPSS 25.0 statistical software was used for data processing and analysis. Non-normally distributed continuous variables were expressed as median (P25, P75), and between-group differences were compared using non-parametric rank-sum tests. Categorical data were expressed as proportions [n (%)], and between-group differences were compared using ^{2} tests. Spearman rank correlation analysis was used to examine the correlation between serum sodium levels and length of hospital stay, NT-proBNP, and echocardiographic parameters. Kaplan-Meier survival curve analysis was used to compare hospital stay duration among PH-LHD patients with different serum sodium levels. Binary logistic regression analysis was used to investigate the effect of serum sodium levels on length of hospital stay in PH-LHD patients. Statistical significance was set at $P<0.05$.

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2. Results

2.1 Basic Characteristics of PH-LHD Patients

The study cohort consisted of 360 PH-LHD patients, including 183 males (50.8%) and 177 females (49.2%). The median age was 70.0 (61.0, 78.8) years, and the median length of hospital stay was 11.0 (8.0, 16.0) days. Among them, 25 patients (6.9%) had PH-LHD associated with heart failure with reduced ejection fraction, 31 (8.6%) had PH-LHD associated with heart failure with preserved ejection fraction, 56 (15.6%) had PH-LHD associated with valvular heart disease, and 248 (68.9%) had PH-LHD associated with congenital or acquired cardiovascular disease. PH-LHD patients exhibited elevated NT-proBNP, TRV, and PASP levels. The basic characteristics of PH-LHD patients are presented in Table 1 .

2.2 Comparison of Characteristics Among Different Serum Sodium Groups

Comparisons among the three serum sodium groups revealed statistically significant differences in age, length of hospital stay, NT-proBNP, left atrial diameter, right atrial area, left ventricular ejection fraction, and fractional shortening ($P<0.05$). Specifically, patients in the serum sodium 140-145 mmol/L group had shorter hospital stays and lower NT-proBNP levels compared to both the serum sodium <135 mmol/L group and the serum sodium 135-139 mmol/L group ($P<0.05$). The left atrial diameter in the serum sodium 135-139 mmol/L group was greater than that in the serum sodium <135 mmol/L group, while left ventricular ejection fraction and fractional shortening were lower. The serum

sodium 140–145 mmol/L group had lower age, length of hospital stay, NT-proBNP, left ventricular ejection fraction, and fractional shortening compared to the serum sodium <135 mmol/L group. Additionally, the serum sodium 140–145 mmol/L group had shorter hospital stays, lower NT-proBNP, and smaller right atrial areas compared to the serum sodium 135–139 mmol/L group (P<0.05). No significant differences were observed in BMI, sex, smoking history, alcohol consumption history, diabetes history, hypertension history, etiology, right ventricular diameter, TRV, or PASP among the three groups (P>0.05). Detailed comparisons are shown in Table 2 .

2.3 Correlation Analysis of Serum Sodium Levels with Hospital Stay, NT-proBNP, and Echocardiographic Parameters

Spearman rank correlation analysis demonstrated that serum sodium levels were negatively correlated with length of hospital stay (r=-0.176), NT-proBNP (r=-0.135), right ventricular diameter (r=-0.110), and pulmonary artery systolic pressure (r=-0.105) in PH-LHD patients (P<0.05). Correlation details are presented in Table 3 .

2.4 Relationship Between Serum Sodium Levels and Hospital Stay

Kaplan-Meier survival curve analysis revealed statistically significant differences in hospital stay duration among the three serum sodium groups (^{2}=12.469, P=0.002). Patients with serum sodium <135 mmol/L and those with serum sodium 135–139 mmol/L had lower discharge rates compared to patients with serum sodium 140–145 mmol/L (^{2}=9.665 and 4.608, respectively, P<0.05), as shown in Figure 3 [Figure 3: see original paper].

2.5 Binary Logistic Regression Analysis of Serum Sodium Levels Affecting Hospital Stay

The average length of hospital stay for PH-LHD patients was 12.8 days. Using prolonged hospital stay as the dependent variable [assignment: yes ($ $12.8 days)=1, no (<12.8 days)=0] and serum sodium level (assignment: actual value) and its categories (assignment: serum sodium <135 mmol/L=1, 135–139 mmol/L=2, 140–145 mmol/L=3) as independent variables, binary logistic regression analysis was performed after adjusting for control variables including age, NT-proBNP, left atrial diameter, right ventricular diameter, right atrial area, left ventricular ejection fraction, fractional shortening, and PASP (all assigned as actual values). After adjustment, elevated serum sodium level was found to be a protective factor against prolonged hospital stay in PH-LHD patients (OR=0.916, 95%CI=0.859–0.977, P=0.008). Compared with patients having serum sodium 140–145 mmol/L, those with serum sodium <135 mmol/L (OR=2.268, 95%CI=1.049–4.903, P=0.037) and those with serum sodium 135–139 mmol/L (OR=2.056, 95%CI=1.163–3.635, P=0.013) both had increased risks of prolonged hospitalization. Detailed results are shown in Table 4 .

Discussion

PH-LHD has an insidious onset with nonspecific symptoms and is typically associated with right ventricular dysfunction caused by progressive pulmonary vascular disease. As the condition progresses, right heart insufficiency gradually develops, eventually leading to right heart failure and even death. The primary pathophysiological mechanism of hyponatremia in heart failure involves activation of the sympathetic nervous system and renin-angiotensin-aldosterone system when cardiac output decreases, causing increased arginine vasopressin release that leads to fluid retention, increased blood volume, edema, and hyponatremia. Hemodynamic disturbances, myocardial damage, and hypoxia triggered by PH can also cause neurohormonal and sympathetic nervous system changes that ultimately result in fluid retention and hyponatremia. Hyponatremia manifests right ventricular dysfunction and hemodynamic derangement and is associated with neurohormonal system activation and impaired hemodynamics. In summary, hyponatremia can exacerbate heart failure in PH-LHD patients, accelerate PH-LHD disease progression, and consequently prolong hospital stay.

As a clinical indicator, serum sodium can reflect the body' s metabolic capacity and thus disease severity, affecting patients'length of hospital stay. This provides a novel approach for the diagnosis and treatment of PH-LHD patients and for improving hospital turnover and resource utilization.

NT-proBNP is a sensitive and specific biomarker for identifying early cardiac dysfunction and an established biomarker for PH. Our results showed that PH-LHD patients with serum sodium 140–145 mmol/L had lower NT-proBNP levels compared to those with serum sodium <135 mmol/L and 135–139 mmol/L, and serum sodium level was negatively correlated with NT-proBNP. This indicates that hyponatremia can worsen cardiac insufficiency in PH-LHD patients, promote the progression of pulmonary hypertension, and prolong hospital stay.

Echocardiography is the most important clinical tool for evaluating PH, and myocardial remodeling is a key factor in the development and progression of heart failure. Studies have shown that PASP is significantly higher in severe PH-LHD patients compared to those with mild PH-LHD. Our results demonstrated that patients with serum sodium 140–145 mmol/L had smaller right atrial areas than those with serum sodium 135–139 mmol/L, and serum sodium level was negatively correlated with right ventricular diameter, PASP, and length of hospital stay. This suggests that hyponatremia may cause right heart structural changes leading to myocardial remodeling and influence PASP elevation, thereby exacerbating PH-LHD severity and prolonging hospital stay. These findings indicate that serum sodium is an important indicator for evaluating disease severity and progression in PH-LHD patients.

Interestingly, however, patients with serum sodium 140–145 mmol/L had lower left ventricular ejection fraction and fractional shortening compared to those

with serum sodium <135 mmol/L. Since the pathogenesis of PH-LHD remains unclear and the role of left ventricular ejection fraction and fractional shortening in the development of PH-LHD with abnormal sodium is not well understood, it is difficult to determine whether this phenomenon is characteristic of PH-LHD patients with more abnormal sodium levels or merely an incidental finding due to the small sample size and lack of representativeness in the serum sodium <135 mmol/L group. The effect of serum sodium levels on left ventricular ejection fraction and fractional shortening in PH-LHD patients warrants further investigation.

Kaplan-Meier survival curve analysis showed that PH-LHD patients with serum sodium <135 mmol/L and those with serum sodium 135–139 mmol/L had lower discharge rates compared to patients with serum sodium 140–145 mmol/L. As serum sodium levels decreased, hospital stay duration increased, with patients having serum sodium <135 mmol/L experiencing the longest hospitalizations. Binary logistic regression analysis after adjusting for relevant variables revealed that elevated serum sodium level was a protective factor against prolonged hospital stay. Compared with patients having serum sodium 140–145 mmol/L, those with serum sodium <135 mmol/L and 135–139 mmol/L both had increased risks of prolonged hospitalization, indicating that decreased serum sodium level is an independent risk factor for extended hospital stay in PH-LHD patients. These findings also demonstrate that even within the normal reference range, lower serum sodium levels are associated with increased risk of disease progression, prolonged hospital stay, and poor prognosis, consistent with the results of Thongprayoon et al. Fluctuations in serum sodium level serve as a surrogate marker for PH-LHD severity and a predictor of prolonged hospitalization. Therefore, in clinical practice, physicians should closely monitor the impact of serum sodium <135 mmol/L and lower-normal levels (135–139 mmol/L) on disease severity in PH-LHD patients, dynamically observe and regulate sodium levels, and maintain serum sodium at the higher end of the reference range as a potential new strategy to improve disease progression and shorten hospital stay.

This study is a retrospective single-center investigation focusing on PH-LHD patients, a population with the poorest prognosis compared to other PH types. Therefore, this study may be subject to bias from including a higher-risk patient population regardless of sodium levels and may not be generalizable to other PH populations. Future large-scale, prospective multicenter studies are needed to confirm the impact of serum sodium on PH.

Conclusion

In summary, serum sodium levels in PH-LHD patients were negatively correlated with length of hospital stay, NT-proBNP, right ventricular diameter, and PASP. Elevated serum sodium level was a protective factor against prolonged

hospital stay. These findings indicate that serum sodium level is closely associated with PH-LHD severity, and decreased serum sodium level is an independent risk factor for extended hospital stay in PH-LHD patients. This represents a potential therapeutic consideration and provides a new strategy for PH-LHD management and hospital turnover. Early and appropriate intervention to improve patient outcomes may serve as a novel approach for enhancing hospital resource utilization and healthcare management quality in the new era.

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Author Contributions

QIN Xiaojiang and SUN Lin conceived the overall research objectives and study design. SUN Lin performed data analysis and interpretation and drafted the manuscript. SUN Lin, GUO Yunting, ZHAO Xu, and DONG Lin were responsible for data collection, organization, and entry. SHI Yiwei, HOU Xiaomin,

and NIE Jisheng contributed to quality control and manuscript revision. QIN Xiaojiang supervised study implementation, quality control, and final approval of the manuscript and takes overall responsibility for the article.

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Note: Figure translations are in progress. See original paper for figures.