Predictive Role of Hypernatremia for Acute Kidney Injury in Patients with Sepsis

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Abstract

Introduction Septic acute kidney injury (AKI), identified when both sepsis and AKI present, is a syndrome of acute function impairment and organ damage, accounting for ~50% AKI in ICU (Intensive Care Unit)

Method This study retrospectively reviewed 591 patients who were diagnosed of sepsis and admitted to the ICU of Beijing Friendship Hospital from January 2009 to December 2014. According to the concentration of serum sodium, the 591 patients were further divided into three groups: normal group, hyponatremia group and hypernatremia group.

Result $PaCO_2$ (P=0.014), concentration of Na^+ (P<0.001) and Cl^- (P<0.001), BUN (P<0.001), APACHE score (P<0.001), SOFA score (P<0.001) and Glasgow score (P<0.001) showed significant differences. CK (P=0.012; OR=1.000), BUN (P=0.002; OR=1.047), Cl^- (P<0.001;OR=1.255), lactic acid (P=0.001;OR=1.244), and HCO_3^- (P<0.001;OR=1.180) may be risk factors for hypernatremia in patients with sepsis. APACHE score (P=0.028;OR=1.222) and CK (P=0.014;or=1.003) may be risk factors for AKI in patients with hypernatremia. Na^+ suggested a good predictive ability for AKI (P<0.001; AUC: 0.586) but not for death (P=0.104)

Conclusion Hypernatremia is independently associated with an increased risk and has a predictive ability of AKI in patients with sepsis.

Introduction

Sepsis is a systemic and deleterious host response, which leads to severe sepsis and septic shock, with mortality of more than 25%[1, 2]. The progress of this disease could further deteriorate when subsequent acute organ dysfunction or combination with hypotension not reversed with fluid resuscitation happens[3, 4]. Among critically ill patients, sepsis is thought to be the most common cause of severe AKI[5, 6]. Septic acute kidney injury (AKI), identified when both sepsis and AKI present, is a syndrome of acute function impairment and organ damage, accounting for ~ 50% AKI in ICU (Intensive Care Unit)[7, 8]. The hospital mortality is 47% and 1-year survival is only 77% for patients with stage 2–3 AKI lack of resolution within 7 days[8]. Although advances have been made in modern diagnostic methods, limitations in specificity and sensitivity still get in the way between research purpose and clinical application.

Hypernatremia, defined as the concentration of Na^+ > 145 mmol/L, is one of the most common electrolyte disorder among patients who are critically ill[9]. In clinical practice, hypernatremia is a frequent condition of life-threatening potential and found to occur in 9% ICU patients[10, 11]. Hypernatremia can cause peripheral insulin resistance, hepatic gluconeogenesis impairment, neuropsychiatric impairment, cardiac contractility dysfunction, etc[11]. However, only a limited number of studies have focused on hypernatremia. Rather than just an alternative marker of disease severity, hypernatremia may be a prognostic risk factor for happening of AKI. Therefore, we evaluated the predictive and prognostic role of hypernatremia for AKI in patients with sepsis.

Materials And Methods

Population

This study retrospectively reviewed 591 patients who were diagnosed of sepsis and admitted to the intensive care unit (ICU) of Beijing Friendship Hospital from January 2009 to December 2014. Patients who were hospitalized in ICU for less than 24 h, pregnant, and suffering from diseases causing elevated serum sodium were excluded. According to the concentration of serum sodium, the 591 patients were further divided into three groups: normal group, hyponatremia group and hypernatremia group (Figure 1).

Data collection

Clinical data of patients were collected, including age, gender, BMI (Body Mass Index), body temperature, respiratory rate, heart rate, SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), pH, PaO_2 (Arterial partial pressure of oxygen), $PaCO_2$ (Arterial partial pressure of carbon dioxide), concentration of HCO_3^-, K^+, Na^+, Cl^-, Ca^{2+}, ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), D-BIL (Direct bilirubin), T-BIL (Total bilirubin), albumin, hemoglobin, D-Dimer, lactic acid, CK (Creatine Kinase), CK-MB, UA (Uric Acid), UpH (Uric pH), BUN (Blood Urea Nitrogen), Creatinine , APACHE score, SOFA score and Glasgow score.

Previous history of nephropathy, diabetes, hyperlipidemia, hypertension, coronary heart disease, chronic heart failure, COPD (Chronic Obstructive Pulmonary Disease), cirrhosis, tumor, smoking and drinking were recorded. Infection site was also recorded, including lung, biliary tract, urinary system, skin and soft tissue, abdominal and pelvic cavity.

Organ dysfunctions including respiratory system dysfunction, circulatory system dysfunction, liver dysfunction, kidney dysfunction, and coagulation system dysfunction were recorded as well.

Definitions

Normal serum Na^+ ranged from 135 to 145 mmol/L. Hypernatremia was defined as the concentration of Na^+ more than 145 mmol/L. Hyponatremia was defined as the concentration of Na^+ less than 135 mmol/L.

Definition of sepsis was according to "Surviving Sepsis Campaign (2012)" as the presence of infection together with systemic manifestations[1].

Definition of AKI was referred to the diagnostic criteria of AKIN (Acute Kidney Injury Network) and KDGIO (the Kidney Disease Improving Global Outcomes)[12, 13].

Statistical Analysis

Continuous variables were expressed as mean ± SD. Date with abnormal distribution were expressed as median (interquartile range). Chi-square test were used for comparison. Univariate analysis was performed first, followed by multivariate analysis for hypernatremia, AKI and death. The ROC (receiver operating characteristic) curve was used in analyzing predictive ability of Na^+ for AKI and death. P<0.05 was regarded as significant difference.

Results

First, we compared the basic characteristics of patients with sepsis grouped by the level of serum sodium concentration. 155 patients were hypernatremia and 96 patients were hyponatremia. At the same time, 340 patients had the Na^+ within normal range (Figure 1). As shown in Table 1, $PaCO_2$ (P=0.014), concentration of Na^+ (P<0.001) and Cl^- (P<0.001), BUN (P<0.001), APACHE score (P<0.001), SOFA score (P<0.001) and Glasgow score (P<0.001) showed significant differences. T-BIL (P=0.049) and creatinine (P=0.049) might have a difference among three groups. While there were no differences found in age (P=0.270), gender (P=0.442), BMI (P=0.198), body temperature (P=0.197), respiratory rate (P=0.51), heart rate (P=0.359), SBP (P=0.925), DBP (P=0.106), pH (P=0.344), PaO_2 (P=0.359), concentration of HCO_3^- (P=0.086), K^+ (P=0.392), Ca^{2+} (P=0.626), ALT (P=0.682), AST (P=0.562), T-BIL (P=0.950), albumin (P=0.270), hemoglobin (P=0.431), D-Dimer (P=0.222), lactic acid (P=0.057), CK (P=0.894), CK-MB (P=0.503), UA (P=0.298), and UpH (P=0.627).

Then, the clinical features of patients with sepsis among three groups were further evaluated (Table 2). The AKI showed obvious difference (P=0.008), and patients with AKI had a much higher percentage of hypernatremia. Although the difference in death was not significant (P=0.078), the mortality of hypernatremia group (38.1%) was a little higher than hyponatremia (31.3%) and normal group (27.9%). The severity of sepsis seemed not to be different among three groups with quite similar incidence rate (P=0.164). As for infection site, urinary infection (P=0.016), and abdominal and pelvic infection (P=0.010) showed significant differences. Moreover, the number of organ dysfunction was different statistically (P=0.009), and hypernatremia group (88.4%) tended to have multiple organ dysfunctions (2 or 3) in comparison with hyponatremia (70.8%) and normal group (75.3%). Specifically, the difference in circulatory system dysfunction was statistic (P=0.048). By analysis of previous history, most diseases showed no difference except COPD (P=0.017) and cirrhosis (P=0.005).

To find potential risk factors, multivariate analysis for hypernatremia in patients with sepsis was performed (Table 3). No significant differences were found in APACHE score (P=0.768), SOFA score (P=0.678), Glasgow score (P=0.176), DBP (P=0.596), urinary infection (P=0.813), lung infection (P=0.183), history of COPD (P=0.097), and History of chronic heart failure (P=0.067). CK (P=0.012; OR=1.000), BUN (P=0.002; OR=1.047), Cl^- (P<0.001;OR=1.255), lactic acid (P=0.001;OR=1.244), and HCO_3^- (P<0.001;OR=1.180) may be risk factors.

Furthermore, the multivariate analysis for AKI in patients with hypernatremia was carried out. As shown in Table 4, APACHE score (P=0.028; OR=1.222) and CK (P=0.014; OR=1.003) may be risk factors. Whereas, SOFA score, Glasgow score, respiratory rate, BUN, lactic acid, HCO_3^-, and $PaCO_2$ did not show differences.

By multivariate analysis for death in patients with hypernatremia, it could be observed that AKI (P<0.001; OR=6.850) and respiratory system dysfunction (P=0.013; OR=29.872) suggested significantly higher risk for death. HCO3- (P=0.016; OR=1.107) was also a risk factor for death.

Finally, the predictive ability of Na^+ for AKI and death was studied (Table 6 and Figure 2). Na^+ suggested a good predictive ability for AKI (P<0.001; AUC: 0.586) but not for death (P=0.104).

Discussion

From our results, the factors indicating kidney function such as BUN and creatinine were significantly different among the three groups, especially higher in hypernatremia group. Besides, urinary infection further indicated a close relationship between AKI and sepsis. There are multiple factors involved in the occurrence of AKI, and the mechanism of increased mortality and morbidity risks associated with AKI remains to be elucidated. It was concluded by Bagshaw et al. that patients with septic AKI had an increased risk for death and longer duration of hospitalization[14]. Many researchers regarded sepsis as a leading precipitant of AKI, while someone reminded not to ignore the sepsis developing after AKI[6, 14, 15]. Mehta et al. looked at the relationship between AKI and sepsis using a multicenter and observational study, and found that sepsis frequently develops after AKI and predicts a poor prognosis, with high mortality rates and relatively long duration of hospitalization[15]. Recently, Gomez et al. reported the metabolic reprogramming and tolerance in coordinating adaptive strategies during sepsis-induced AKI[16]. As addressed by Honore et al., the relationship is more complicated than a simple question of chicken and egg, in need of a future well-informed clinical trial[17].

The major cause of hypernatremia is water depletion, resulting from either reduced intake or excessive loss[10]. Thus, hypernatremia is usually regarded as a hypovolemic electrolyte disorder. From the experience of clinical practice, urinary loss is the most common reason. Notably, this circumstance is more prominent in the recovery after AKI, and hypervolemic hypernatremia has been studied in this process[10, 18]. Besides, it has also been pointed out that severe sepsis patients receiving 0.9% saline fluid resuscitation may acquire hypernatremia in an early process[19].

Corticosteroids is commonly used for treating sepsis[20, 21]. The results of previous studies showed a mild increase in sodium level and increased the risk of hypernatremia with high-certainty evidence[20–23]. It is suggested that administration of corticosteroids is associated with reduced 28-day mortality compared with placebo use or standard supportive care[22]. Another large RCT named Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial showed that hydrocortisone plus fludrocortisone of low doses reduced 90-day mortality among patients with septic shock[24]. However, Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial showed a

significantly different result that the mortality was not decreased[25]. Whether the subsequent hypernatremia in turn influences the effect of corticosteroids remains to be further studied.

It has been noticed that the concentration of Cl⁻ was also different among three groups and showed a similar trend as Na⁺. Moreover, Cl⁻ together with HCO_3^- and lactic acid were risk factors for hypernatremia. As suggested in a prospective study by Levy et al., the muscle Na + K + ATPase activity may raise lactate concentrations in septic shock[26]. We think the electrolyte disorder inside body may account for the predictive ability of Na⁺ for AKI. Mendes et al. regarded predialysis hypernatremia as a prognostic marker in AKI in need of renal replacement therapy[27]. Wu et al. reported serum sodium as a reliable and validated predictor for mortality in enteric fistula patients complicated with sepsis[28]. However, in consistent with their conclusion, Na⁺ did not indicate a meaningful predictive ability for death in patients with sepsis combined with AKI. The metabolic disturbances, including hypernatremia, hypercapnia and elevated lactates, caused by AKI in sepsis was associated with encephalopathy as well[29].

The limitation for this study is retrospective of data from a single center. We mainly focus on the risk factors for AKI in patients with sepsis, but have not compared the treatment yet. For a in-depth study, the evaluation of biomarkers will be involved in our future study.

Conclusion

Hypernatremia is independently associated with an increased risk and has a predictive ability of AKI in patients with sepsis. Multi-center clinical trials are needed to be performed to further confirm this result.

Declarations

Ethics approval and consent to participate

This study was approved by Beijing Friendship Hospital , Capital Medical University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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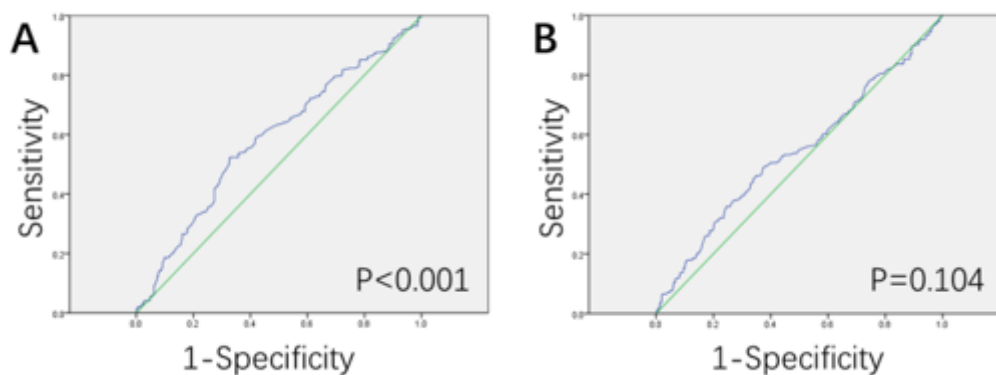
Tables

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Figures
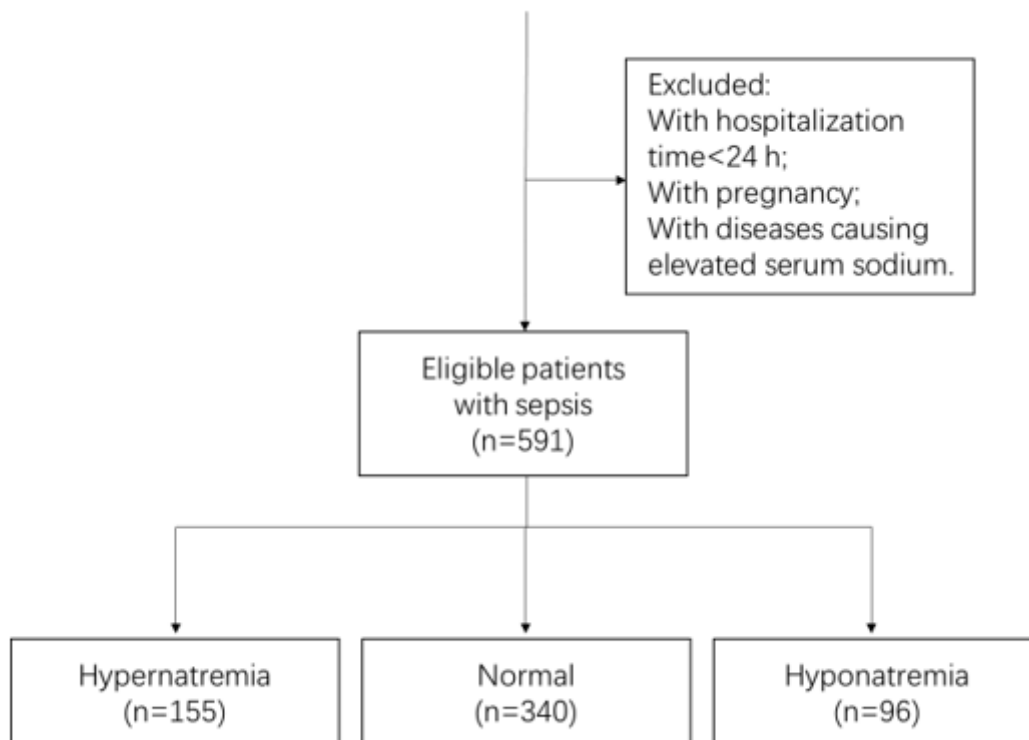
Figure 1

Flow chart of patients involved in this study

Figure 2

ROC curves of Na+ for AKI (A) and death (B) in patients with sepsis.

Supplementary Files

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