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ABOUT COVER

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AIMS AND SCOPE

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ORIGINAL ARTICLE

Retrospective Study

Prognostic impact of hypernatremia for septic shock patients in the intensive care unit

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Abstract

BACKGROUND

Hypernatremia represents a significant electrolyte imbalance associated with numerous adverse outcomes, particularly in cases of intensive care unit (ICU)-acquired hypernatremia (IAH). Nevertheless, its relevance in patients with septic shock remains uncertain.

AIM

To identify independent risk factors and their predictive efficacy for IAH to improve outcomes in patients with septic shock.

METHODS

In the present retrospective single-center study, a cohort of 157 septic shock patients with concurrent hypernatremia in the ICU at The First Affiliated Hospital of Soochow University, between August 1, 2018, and May 31, 2023, were analyzed. Patients were categorized based on the timing of hypernatremia occurrence into the IAH group (n = 62), the non-IAH group (n = 41), and the normonatremia group (n = 54).

RESULTS

In the present study, there was a significant association between the high serum

sodium concentrations, excessive persistent inflammation, immunosuppression and catabolism syndrome and chronic critical illness, while rapid recovery had an apparent association with normonatremia. Moreover, multivariable analyses revealed the following independent risk factors for IAH: Total urinary output over the preceding three days [odds ratio (OR) = 1.09; 95%CI: 1.02–1.17; P = 0.014], enteral nutrition (EN) sodium content of 500 mg (OR = 2.93; 95%CI: 1.13–7.60; P = 0.027), and EN sodium content of 670 mg (OR = 6.19; 95%CI: 1.75–21.98; P = 0.005) were positively correlated with the development of IAH. Notably, the area under the curve for total urinary output over the preceding three days was 0.800 (95%CI: 0.678–0.922, P = 0.001). Furthermore, maximum serum sodium levels, the duration of hypernatremia, and varying sodium correction rates were significantly associated with 28-day in-hospital mortality in septic shock patients (P < 0.05).

CONCLUSION

The present findings illustrate that elevated serum sodium level was significantly associated with a poor prognosis in septic shock patients in the ICU. It is highly recommended that hypernatremia be considered a potentially important prognostic indicator for the outcome of septic shock.

Key Words: Hypernatremia; Hypernatremia acquired in the intensive care unit; Septic shock; Persistent inflammation; Immunosuppression; Catabolism syndrome; Chronic critical illness; Prognosis

Core Tip: The aim of the present observational study was to improve outcomes in patients with septic shock by identifying independent risk factors and their predictive efficacy for intensive care unit-acquired hypernatremia. Additionally, the present findings indicate a significant association between the prognosis of septic shock patients and variables such as peak serum sodium levels, duration of hypernatremia, and differing rates of sodium correction. As such, the present authors propose that hypernatremia may serve as a critical predictive marker for the prognosis of septic shock.

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INTRODUCTION

Sepsis is defined as an inflammatory body response to infection, with severe sepsis and septic shock being more severe forms[1]. Globally, the incidence of sepsis is estimated at 48.9 million cases, with 11 million sepsis-related deaths reported, accounting for 19.7% of all deaths worldwide[2]. Septic shock, in particular, is associated with significantly higher 30- and 90-day mortality rates, both exceeding 30%[3]. Septic shock has a significant negative impact on health outcomes in intensive care unit (ICU) patients, facing three clinical outcomes in addition to high costs and longer hospital stays: (1) Early death within 14 days; (2) Rapid recovery (RR); and (3) Chronic critical illness (CCI)[4]. Previous research has demonstrated that patients with CCI often develop persistent inflammation, immunosuppression, and catabolism syndrome (PICS), which contributes to the poor clinical outcomes observed in this group[5,6]. Specifically, following the activation of both pro-inflammatory and anti-inflammatory responses, survivors either experience RR or progress into a state of persistent catabolism and organ dysfunction, leading to CCI. Unfortunately, approximately one-third of survivors develop CCI, characterized by a poor quality of life and infrequent recovery[7].

Hypernatremia (serum sodium concentration > 145 mmol/L) is a common electrolyte disturbance[8]. Approximately 7% of patients presented with hypernatremia upon admission, and this prevalence increased to as much as 9% during their ICU stay, with 77.1% of critically ill patients with sepsis being affected[9,10]. Notably, compared to non ICU-acquired hypernatremia (IAH), IAH is associated with increased morbidity and mortality[11,12]. In septic shock, chronic catabolism driven by inflammation can lead to the development of hypernatremia[13]. Conversely, hypernatremia can exacerbate protein catabolism and systemic inflammation, contributing to the progression of PICS[14]. Thus, intense inflammation can lead to an increase in serum sodium concentration, while elevated serum sodium levels may also act as a significant promoter of the inflammatory response. Recently, questions have been raised regarding whether serum sodium levels directly influence the severity and prognosis of patients with septic shock[13]. In response, the specific relationship between hypernatremia and clinical trajectories of septic shock patients has become a primary focus both domestically and internationally. In order to improve the clinical prognosis of septic shock patients, it is also particularly important to identify the independent risk factors with high predictive value for hypernatremia.

As a result, a single-center retrospective study was conducted to analyze the correlation between hypernatremia and PICS, as well as its association with clinical outcomes such as CCI and RR. Furthermore, independent risk factors for IAH were identified, and their predictive efficacy was evaluated to improve the prognosis of septic shock patients. Finally, the

relationship between serum sodium levels and the prognosis of septic shock patients was examined by analyzing the correlation between IAH and non-IAH, the duration of hypernatremia, blood sodium levels, sodium correction rates, and 28-day in-hospital mortality.

MATERIALS AND METHODS

Setting and participants

The present single-center retrospective study included adult patients with septic shock admitted to the ICU at The First Affiliated Hospital of Soochow University between August 1, 2018, and May 31, 2023. The inclusion criteria for the study were: (1) Adults aged ≥ 18 years; (2) Serum sodium concentration greater than 135 mmol/L during or prior to ICU admission; and (3) A diagnosis of septic shock. Exclusion criteria were: (1) Patients with missing serum sodium concentration data; (2) Patients with brain death; (3) Patients with a high likelihood of death within 48 hours; (4) Patients with hyponatremia; and (5) Pregnant patients. The patient screening flowchart is presented in Figure 1.

Variables and outcomes data

Data were collected from patients' medical records, encompassing various parameters. Demographic data included age and gender. Comorbidities recorded included hypertension, diabetes mellitus, coronary heart disease, cerebral infarction, and sepsis-associated encephalopathy (SAE). Laboratory parameters collected included albumin, C-reactive protein (CRP), the serum urea to serum creatinine ratio (BUN/SCr), serum prealbumin, myoglobin (Myo), and maximum body temperature, among others. Interventions such as mechanical ventilation and continuous renal replacement therapy (CRRT) were also noted. Clinical scores recorded included the Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE II), quick Sequential Organ Failure Assessment (qSOFA), and SOFA. Additionally, information on pathogenic bacteria, including Gram-positive (G+), Gram-negative (G−) bacteria, and fungi, was documented. The primary clinical outcomes included length of stay (LOS) in the ICU, LOS outside the ICU, early death within 14 days and 28-day in-hospital mortality.

Main definition

CCI was defined for patients with an ICU stay of ≥ 14 days, accompanied by evidence of persistent organ dysfunction, as determined by components of the SOFA score[15]. RR patients were defined as those who were discharged from the ICU within 14 days with complete resolution of organ dysfunction[14]. PICS was defined by the presence of specific laboratory markers suggested in the literature. These included an ICU stay of at least 10 days, evidence of inflammation (CRP > 50 mg/L for ≥ 2 days), immunosuppression (lymphocyte count < 0.8×10^9/L for ≥ 2 days), and catabolism (weight loss > 10%, body mass index < 18, or albumin < 30 g/L during hospitalization)[16]. An overview of other definitions used in the present study is given in Supplementary Table 1.

Statistical analysis

Categorical variables were presented as percentages of the total number of cases and compared using the Pearson χ^2 test or Fisher's Exact test. Quantitative variables with a normal distribution were expressed as mean ± SD, with differences evaluated using one-way analysis of variance. Continuous variables with a non-normal distribution were analyzed using the Kruskal-Wallis test and reported as median and interquartile range. Univariate logistic regression analysis was performed to identify risk factors for IAH, and variables found to be significant were further analyzed using multivariate logistic regression. Receiver-operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was calculated to assess the predictive value of independent risk factors for IAH. Kaplan-Meier analysis was used to assess the impact of IAH, maximum serum sodium levels, duration of hypernatremia, and sodium correction rate on 28-day in-hospital mortality. A P value of < 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 25.0, with ROC and Kaplan-Meier analyses performed using GraphPad Prism version 8.0.2.

RESULTS

Characteristics of patients

Among the 9345 patients admitted to the ICU, 157 patients fulfilled the inclusion criteria. The baseline characteristics of patients are shown in Table 1. Patients were divided into three groups: IAH (n = 62, 39.49%), non-IAH (n = 41, 26.11%), and normonatremia (n = 54, 34.39%). The mean age of all 157 patients was 65.85 ± 15.64 years old, and 31.85% of patients were female.

As shown in Table 1, the indicators of significant differences were as follows: SAE (P = 0.002), the concentration of Cl^- (P = 0.019), BUN/SCr (p = 0.001), serum prealbumin (P = 0.042), Myo (P = 0.008), maximum body temperature (P = 0.017), need for mechanical ventilation (MV, P = 0.002), APACHE II score (P = 0.001), infection with G^- bacteria (P = 0.003) and ICU-LOS (P < 0.001).

Association between hypernatremia and PICS, CCI and RR

As shown in Figure 2, only 16.28% of PICS patients had normal sodium levels, similar to those in CCI groups (15.00%).

Table 1 Baseline clinical characteristics, *n* (%)/mean ± SD/median (25th-75th percentiles)

Variable	IAH (*n* = 62)	Non-IAH (*n* = 41)	Normonatremia (*n* = 54)	*P* value
Age, years	66.20 ± 15.40	66.10 ± 16.90	65.30 ± 15.10	0.956
Sex (Female)	22 (35.48)	10 (24.39)	18 (33.33)	0.476
Comorbidities				
Hypertension	31 (50.00)	23 (56.10)	24 (44.44)	0.530
Diabetes mellitus	16 (25.81)	9 (21.95)	10 (18.52)	0.611
CHD	4 (6.45)	1(2.44)	4 (7.41)	0.626
Cerebral infarction	10 (16.13)	6 (14.63)	3 (5.56)	0.186
SAE	20 (32.23)	24 (58.54)	13 (24.07)	0.002
Laboratory parameters				
K^+, mmol/L	3.89 ± 0.62	3.92 ± 0.83	4.17 ± 0.74	0.078
Ca^{2+}, mmol/L	1.08 (1.04, 1.17)	1.08 (1.02, 1.20)	1.09 (1.06, 1.12)	0.895
Cl^-, mmol/L	102.85 (98.03, 106.03)	103.20 (98.50, 112.05)	100.30 (96.63, 104.03)	0.019
SCr, μmol/L	148.50 (91.30, 214.73)	116.80 (73.85, 190.10)	113.55 (72.00, 297.38)	0.524
BUN/SCr	216.23 (149.83, 264.87)	267.56 (194.18, 371.69)	185.06 (133.73, 250.25)	0.001
BUN, mmol/L	18.90 (11.15, 25.88)	20.81 (13.20, 29.55)	15.00 (11.43, 24.14)	0.185
ALB, g/L	26.23 ± 5.55	27.55 ± 3.71	27.52 ± 5.40	0.290
Serum prealbumin, mg/L	68.35 (50.55, 100.45)	63.40 (38.45, 86.55)	81.20 (63.68, 118.38)	0.042
PCT, ng/mL	11.29 (3.40, 50.00)	9.87 (3.18, 31.61)	14.58 (2.40, 34.00)	0.964
WBC, 10^9/L	19.12 ± 11.12	18.47 ± 9.41	21.31 ± 11.34	0.387
CRP, mg/L	191.49 ± 92.02	206.49 ± 86.19	166.42 ± 84.56	0.083
Lym, 10^9/L	0.34 (0.20, 0.53)	0.35 (0.20, 0.62)	0.40 (0.21, 0.63)	0.765
NT-proBNP, ng/L	2673 (806, 8020)	4221 (635, 14221)	3220 (912, 10625)	0.720
Myo, ng/mL	329 (146, 575)	706 (316, 1952)	259 (120, 630)	0.008
Body temperature max, °C	38.15 (37.40, 38.60)	37.80 (37.50, 38.40)	37.50 (37.20, 38.10)	0.017
Delirium	12 (19.35)	9 (21.95)	8 (14.81)	0.657
Interventions				
MV	45 (72.58)	34 (82.93)	27 (50.00)	0.002
CRRT	24 (38.71)	18 (43.90)	18 (33.33)	0.573
Clinical scores				
GCS score	6.00 (5.00, 10.00)	5.00 (3.00, 6.00)	6.50 (3.00, 9.75)	0.109
APACHE II score	17.49 ± 5.52	21.72 ± 6.40	16.38 ± 8.30	0.001
qSOFA score	1 (1, 2)	2 (1, 2)	2 (1, 2)	0.239
SOFA score	10.31 ± 3.98	10.64 ± 4.08	9.48 ± 5.41	0.444
SIRS	56 (90.32)	36 (87.80)	50 (92.59)	0.498
Pathogenic				
G^+ bacteria	7 (11.29)	2 (4.88)	10 (18.52)	0.126
G^- bacteria	31 (50.00)	29 (70.73)	19 (35.19)	0.003
Fungi	5 (8.06)	3 (7.32)	8 (14.81)	0.380
G^+ and G^- bacteria, *n* (%)	4 (6.45)	1 (2.44)	2 (3.70)	0.594
G^+ bacteria and fungi, *n* (%)	1 (1.61)	0 (0.00)	1 (1.85)	0.695

G⁻ bacteria and fungi	3 (4.84)	1 (2.44)	2 (3.70)	0.823
Time				
ICU LOS, days	16.50 (8.75, 26.75)	12.00 (5.00, 25.50)	5.00 (2.00, 12.00)	< 0.001
LOS outside the ICU, days	0.00 (0.00, 9.00)	0.00 (0.00, 7.00)	2.00 (0.00, 11.25)	0.155
Died within 14 days	22 (35.48)	22 (53.66)	20 (37.04)	0.146

IAH: ICU-acquired hypernatremia; ICU: Intensive care unit; CHD: Coronary heart disease; SAE: Sepsis-associated encephalopathy; SCr: Serum creatinine; BUN/SCr: Urea-to-creatinine ratio; BUN: Blood urea nitrogen; ALB: Serum albumin; PCT: Procalcitonin; WBC: White blood cell counts; CRP: C-reactive protein; Lym: Lymphocytes; NT-proBNP: N-terminal pro-B-type natriuretic peptide; Myo: Myoglobin; MV: Mechanical ventilation; CRRT: Continuous renal replacement therapy; GCS: Glasgow coma scale; APACHE II: Acute physiology and chronic health evaluation II; qSOFA: Quick sequential organ failure assessment; SOFA: Sequential organ failure assessment; SIRS: Systemic inflammatory response syndrome; LOS: Length of stay.

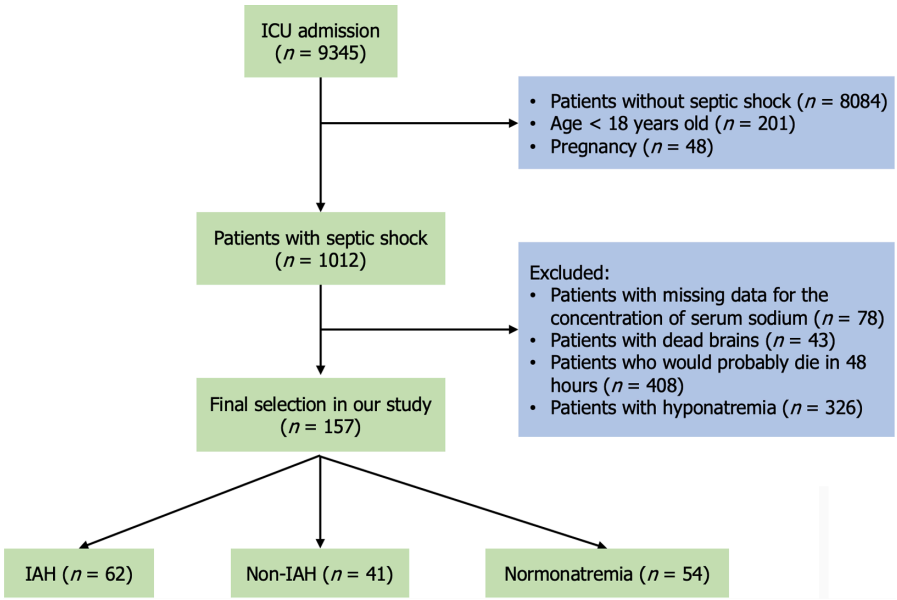

Figure 1 Flow chart of patients involved in this study. ICU: Intensive care unit; IAH: Intensive care unit-acquired hypernatremia.

However, in RR patients, the ratio was as high as 64.29%. In addition, the proportion of IAH varied among the different groups, with 55.81% in PICS, 55.00% in CCI and only 26.19% in RR (Figure 2A and B). The bar chart showed that 53.23% of patients with IAH developed CCI and only 17.74% of patients with RR. The reverse was true for patients with normonatremia (CCI: 16.67% *vs* RR: 50.00%). The data for patients with non-IAH were very similar to those of patients with IAH, with no statistically significant difference between the two groups. However, the statistical significance in both groups was greater than that observed in the normonatremia group (Figure 2B). Additionally, an analysis based on PICS criteria revealed a trend consistent with that seen in CCI (Figure 2A and B). These findings suggest a significant association between elevated serum sodium levels and both PICS and CCI, particularly in patients with IAH, whereas RR was significantly associated with normonatremia. Hence, the state of elevated sodium can predict poor clinical trajectories with septic shock patients.

Risk factors for IAH in patients with septic shock

The univariate logistic regression analysis demonstrated that IAH had an apparent association with kidney insufficiency [odds ratio (OR) = 0.22; 95%CI: 0.06-0.86; P = 0.029], the total urine volume in the preceding three days (OR = 1.10; 95%CI: 1.04-1.17; P = 0.002), the sodium content of enteral nutrition (EN) = 500mg (OR = 3.18; 95%CI: 1.36-7.45; P = 0.008), the sodium content of EN = 670mg (OR = 5.52; 95%CI: 1.74-17.49; P = 0.004), and diuretic (OR = 2.44; 95%CI: 1.14-5.21; P = 0.021) (Table 2). These significant characteristics in the univariate analyses were entered into multivariate models. The results showed that total urine volume in the preceding three days (OR = 1.09; 95%CI: 1.02-1.17; P = 0.014), the sodium content of EN = 500mg (OR = 2.93; 95%CI: 1.13-7.60; P = 0.027) and the sodium content of EN = 670mg (OR = 6.19; 95%CI: 1.75-21.98; P = 0.005) were positively correlated independent risk factors for the development of IAH (Table 3).

Prediction for the occurrence of IAH

After identifying the independent risk factors, ROC analysis was used to calculate the AUC for each factor to better predict the occurrence of IAH. As shown in Figure 3 and Table 4, the urine output on the first day (AUC = 0.75, 95%CI: 0.60–0.90, P = 0.008), second day (AUC = 0.77, 95%CI: 0.63–0.91, P = 0.004), and third day (AUC = 0.78, 95%CI: 0.65–0.91,

Table 2 Univariate analysis for risk factors of intensive care unit-acquired hypernatremia in septic shock patients, *n* (%)/mean ± SD

	IAH	Normonatremia	Univariate	*P* value
	(*n* = 62)	(*n* = 54)	OR (95%CI)	
Diabetes mellitus	17 (27.42)	10 (18.52)	1.66 (0.69-4.03)	0.26
Kidney insufficiency	3 (4.84)	10 (18.52)	0.22 (0.06-0.86)	0.029
Body temperature max, °C	38.15 (37.40-38.60)	37.50 (37.20-38.10)	1.17 (0.85-1.60)	0.348
Urine volume, ml				
1^{st} + 2^{nd} + 3^{rd}	5775.00 (2908.75-7512.50)	3730.00 (257.50, 5732.50)	1.10 (1.04-1.17)	0.002
The sodium content of EN				
315 mg	13 (20.97)	7 (12.96)	1.78 (0.65-4.85)	0.259
500 mg	26 (41.94)	10 (18.52)	3.18 (1.36-7.45)	0.008
670 mg	19 (30.65)	4 (7.41)	5.52 (1.74-17.49)	0.004
Diuretic	43 (69.35)	26 (48.15)	2.44 (1.14-5.21)	0.021
Mannitol	8 (12.90)	4 (7.41)	1.85 (0.53-6.53)	0.338
Glucocorticoids	37 (59.68)	27 (50.00)	1.48 (0.71-3.09)	0.296
Blood glucose max, mmol/L	10.86 ± 3.62	9.73 ± 3.51	1.09 (0.98-1.22)	0.095
CRP, mg/L	191.49 ± 92.02	166.42 ± 84.56	1.00 (1.00-1.01)	0.135
Lym, 10^9/L	0.34 (0.20, 0.53)	0.39 (0.21, 0.62)	0.71 (0.31-1.62)	0.419
Serum prealbumin, mg/L	68.35 (50.55, 100.45)	81.20 (63.68, 118.38)	0.99 (0.98-1.00)	0.073
ALB, g/L	26.23 ± 5.55	27.52 ± 5.40	0.96 (0.89-1.03)	0.209
BUN, mmol/L	18.90 (11.15, 25.88)	15.00 (11.43, 24.14)	1.00 (0.98-1.03)	0.833
BUN/SCr	227.44 ± 117.94	198.05 ± 90.72	1.00 (1.00-1.01)	0.144
APACHE II score	17.49 ± 5.52	16.38 ± 8.30	1.02 (0.97-1.08)	0.402
SOFA score	10.31 ± 3.98	9.48 ± 5.41	1.04 (0.96-1.13)	0.356
SIRS, *n* (%)	58 (93.55)	52 (96.30)	0.56 (0.10-3.17)	0.51

IAH: ICU-acquired hypernatremia; ICU: Intensive care unit; OR: Odd ratio; EN: Enteral nutrition; CRP: C-reactive protein; Lym: Lymphocytes; ALB: Serum albumin; BUN: Blood urea nitrogen; BUN/SCr: Urea-to-creatinine ratio; APACHE II: Acute physiology and chronic health evaluation II; SOFA: Sequential organ failure assessment; SIRS: Systemic inflammatory response syndrome.

Table 3 Multivariate analysis for independent risk factors of intensive care unit-acquired hypernatremia in septic shock patients, *n* (%)

	IAH	Normonatremia	Multivariate	*P* value
	(*n* = 62)	(*n* = 54)	OR (95%CI)	
Kidney insufficiency	3 (4.84)	10 (18.52)	0.37 (0.08-1.67)	0.197
Urine volume, ml				
1^{st} + 2^{nd} + 3^{rd}	5775 (2908.75, 7512.5)	3730 (257.5, 5732.5)	1.09 (1.02-1.17)	0.014
The sodium content of EN				
500 mg	26 (41.94)	10 (18.52)	2.93 (1.13-7.60)	0.027
670 mg	19 (30.65)	4 (7.41)	6.19 (1.75-21.98)	0.005
Diuretics-	43 (69.35)	26 (48.15)	1.87 (0.78-4.47)	0.159

IAH: ICU-acquired hypernatremia; ICU: Intensive care unit; OR: Odd ratio; EN: Enteral nutrition.

Table 4 Areas under the receiver operator curves presented of predicting intensive care unit-acquired hypernatremia

Variable	AUC	95%CI	*P* value
Urine volume 1st + 2nd + 3rd	0.80	0.68-0.92	0.001
Urine volume 1st	0.75	0.60-0.90	0.008
Urine volume 2nd	0.77	0.63-0.91	0.004
Urine volume 3rd	0.78	0.65-0.91	0.003
The sodium content of EN	0.60	0.43-0.78	0.274

AUC: Areas under the curve; ROC: Receiver operator curves; EN: Enteral nutrition.

P = 0.003) demonstrated good predictive potential for IAH. Notably, the total urine output over the first three days achieved an AUC of 0.80 (95%CI: 0.68–0.92, *P* = 0.001), indicating that the combined analysis of these three variables provided a stronger prediction for the occurrence of IAH compared to any single variable alone. However, the AUC for EN was less than 0.7 (AUC = 0.60, 95%CI: 0.43–0.78, *P* = 0.274), indicating lower predictive potential.

28-day in-hospital mortality with septic shock patients

The correlation between the 28-day in-hospital mortality of septic shock patients and serum sodium condition was expressed using Kaplan–Meier curve analysis (Figure 4). There was no significant statistical difference in 28-day in-hospital mortality among the IAH, non-IAH and normonatremia groups (*P* = 0.255) (Figure 4A). Nevertheless, the different maximum serum sodium levels were significantly associated with 28-day mortality in patients (*P* = 0.035). Notably, the group with the lowest serum sodium concentration (145-150 mmol/L) exhibited a higher risk of death compared to other groups (Figure 4B). The duration of hypernatremia also showed a statistically significant effect on patient outcomes (*P* = 0.018), with patients experiencing hypernatremia for more than 20 days demonstrating the highest survival rate (Figure 4C). Further, the sodium correction rates had a significant impact on 28-day mortality (*P* = 0.030), with correction rates of 9-11 mmol/L per 24 hours associated with the best 28-day survival rate (Figure 4D). Subgroup analysis revealed that 28-day mortality was significantly higher in patients receiving CRRT for hypernatremia compared to those not treated with CRRT (Supplementary Figure 1). Supplementary Table 2 presented the 7-, 14-, and 28-day in-hospital mortality rates for patients with septic shock.

DISCUSSION

In the present study, three significant data analyses were performed on hypernatremia in septic shock patients. Firstly, it was observed that elevated serum sodium status was highly correlated with poor clinical trajectory, especially IAH. Hence, independent risk factors for IAH were identified through multifactorial analysis, and their predictive utility was determined. Finally, the initial state, duration and correction rate of serum sodium can affect the short-term prognosis of septic shock patients.

Hypernatremia, especially IAH, was a significant factor leading to adverse clinical trajectory. A hypersaline state can lead to inappropriate activation of the immune system, driving macrophages to polarize into a pro-inflammatory phenotype[17]. Meanwhile, severe infection can disrupt the activity of the hypothalamic-pituitary-adrenal axis, increasing the body's demand for free water. This heightened need can result in significant free water deficiency, ultimately leading to hypernatremia[18]. This suggests that inflammation and elevated sodium levels have a bidirectional, cause-and-effect relationship. The present findings confirm a significant association between excessive sodium and PICS, which appears to form a self-sustaining vicious cycle. Among patients with PICS, 83.72% (36/43) exhibited hypernatremia, and 55.81% (24/43) had IAH (Figure 2A). Similarly, the incidence of PICS was higher in patients with hypernatremia (whether ICU-acquired or present at admission) compared to those with normonatremia (38.71% *vs* 29.27% *vs* 12.96%). This association mirrors the relationship between elevated serum sodium levels and CCI but is inversely related to the RR group (Figure 2B and C). Therefore, the interaction between hypernatremia, PICS, and CCI underscores the importance of monitoring and managing elevated serum sodium concentrations in septic shock patients.

In the ICU, the most common cause of hypernatremia is the loss of net water and the increase in sodium intake[19]. Both of these reasons are reflected in the present results. The total urine volume in the preceding three days and the sodium content of EN were identified as independent risk factors for IAH. In the ICU, most patients are supported by EN. Na^+ is a key component of osmotic pressure in EN preparations, with osmolarity typically ranging from 490 to 790 mOsm/kg[20]. Research has shown that the higher the osmotic pressure difference between the gastrointestinal secretion and EN solution, the stronger the inhibition of the gastrointestinal tract on EN solution, which is manifested as excessive intake of sodium and insufficient intake of water[21,22]. At the same time, high osmotic pressure can also cause osmotic diarrhea, further causing high concentrated hypernatremia[23]. Based on the present data, when the sodium content of EN = 500mg, the risk of IAH increased 2.93 times (*P* = 0.027), and 6.19 times when it reached 670 mg (*P* = 0.005). Further, in patients with poor renal function or osmotic diseases, such as diabetes insipidus and osmotic diuresis, the balance of sodium and water is disrupted[24,25]. Na is reabsorbed by the renal tubules into the interstitial fluid, while the ascending

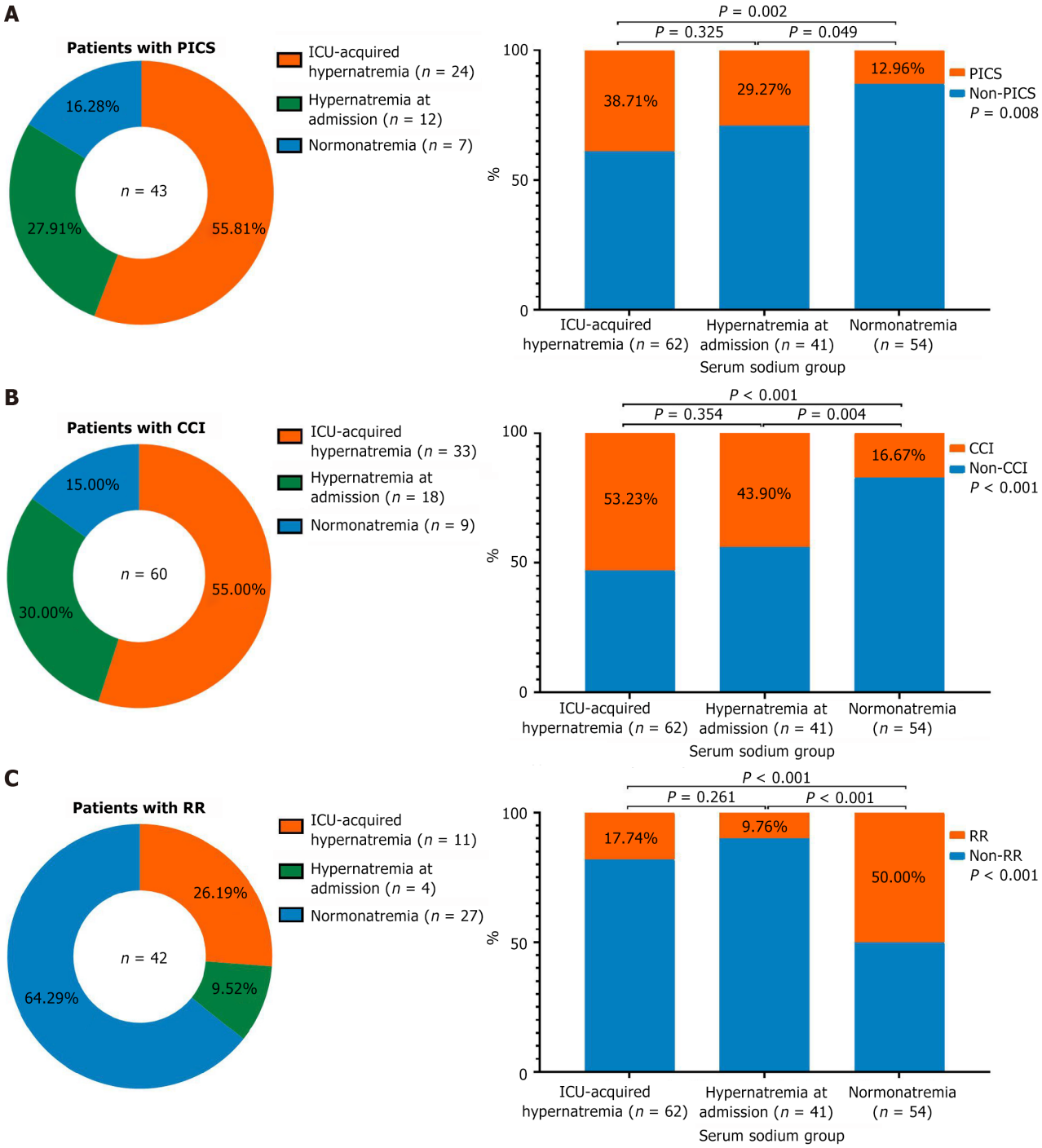

Figure 2 The relationship of persistent inflammation, chronic critical illness and rapid recovery for patients with septic shock between intensive care unit-acquired hypernatremia group, hypernatremia at admission group and normonatremia group. A: Patients with persistent inflammation; B: Patients with chronic critical illness; C: Patients with rapid recovery. ICU: Intensive care unit; PICS: Persistent inflammation, immunosuppression and catabolism syndrome; CCI: Chronic critical illness; RR: Rapid recovery.

limb of the loop of Henle actively secretes sodium into the interstitial space, which is impermeable to water[26]. As a result, Na is continuously pumped out resulting in an elevated blood sodium level[11]. Consequently, in patients with septic shock in ICU, it is recommended to choose EN formulations with low sodium content and to implement strict monitoring and control of total urine output during the first 3 days to help reduce the incidence of IAH.

Although previous studies have identified an optimal serum sodium cut-off value of 147.55 mmol/L in patients with critical nervous system conditions[27], the ideal serum sodium peak for patients with septic shock remains unclear. Notably, in the present study, septic shock patients exhibited the highest 28-day mortality (57.89%) when serum sodium levels ranged between 145 and 150 mmol/L, whereas the lowest 28-day mortality (12.50%) was observed when sodium levels were between 160 and 165 mmol/L. Based on these findings, maintaining serum sodium levels between 160 and 165 mmol/L during septic shock may offer a more favorable short-term prognosis compared to mild or severe sodium elevations. From a pathophysiological perspective, this differs from patients with sepsis or nervous system dysfunction.

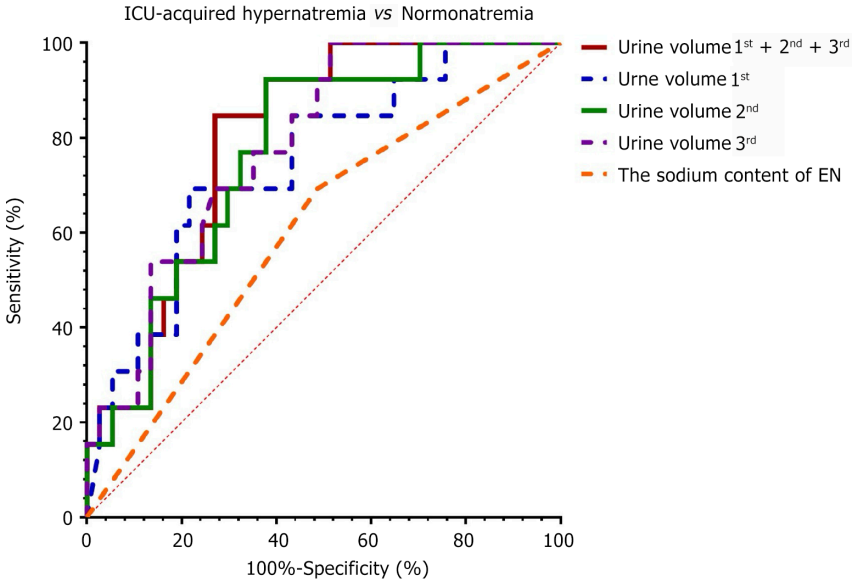

Figure 3 The receiver-operating characteristic analysis of independent risk factors for intensive care unit-acquired hypernatremia. ROC: Receiver-operating characteristic. EN: Enteral nutrition.

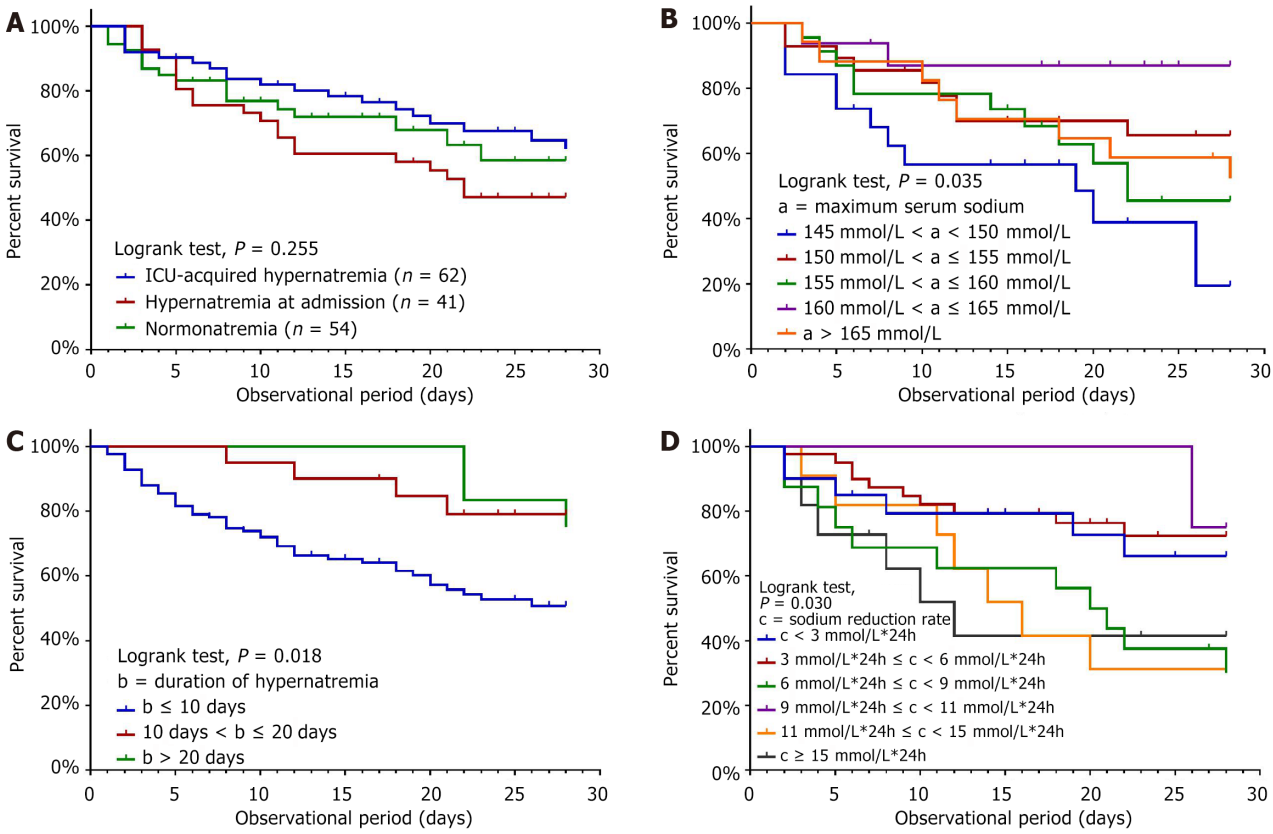

Figure 4 Kaplan-Meier survival curves stratified by serum sodium for septic shock patients. A: Patients stratified by different types of serum sodium; B: Patients stratified by maximum serum sodium; C: Patients stratified by duration of hypernatremia; D: Patients stratified by sodium reduction rate.

In septic shock, a moderate increase in serum sodium can raise the osmotic pressure and tension of extracellular fluid, which may help reduce diffuse cerebral edema caused by septic encephalopathy. Additionally, it could mitigate hypovolemic shock due to extensive plasma leakage[28–31]. Moreover, clinical recommendations suggest that in patients with rapid hypernatremia, a correction rate of 1 mEq/L/h is considered safe, while patients with chronic hypernatremia should be corrected at a rate of 0.5 mEq/L/h, with a maximum change of 8 to 10 mEq/L/24h[19]. The present study is consistent with this result. The rate of sodium reduction at 9 to 11 mmol/L/24 hours was associated with the lowest 28-day in-hospital mortality, especially compared with the rapid correction group (11 to 15 mmol/L and ≥ 15 mmol/L/24 hours). In summary, the present authors speculate that moderately persistent high serum sodium status may mitigate the

progression of histiocytic edema and hypovolemia resulting from septic shock, thereby improving patient outcomes.

While the present study yielded encouraging results, there are potential limitations to consider. First, it was a single-center study with a relatively small sample size. Second, the complexity of septic shock introduces multiple factors that may confound the association between hypernatremia and mortality. Despite these limitations, the findings present valuable insights into the relationship between hypernatremia, PICS, as well as the clinical trajectories of CCI and RR in septic shock patients. Further, the data suggest that the initial sodium levels, duration of hypernatremia, and sodium correction rates can significantly influence the short-term prognosis of septic shock patients. Given the rarity and high mortality rate of this life-threatening condition, conducting large-scale clinical studies can be difficult. Therefore, a larger multi-center study with a higher number of cases is warranted to confirm these results.

CONCLUSION

In summary, elevated serum sodium, particularly IAH, was identified as one of the most important factors influencing CCI and PICS in septic shock patients. The urine volume over the previous three days and the sodium content in EN were found to be independent risk factors for IAH, with total urine volume in the prior three days being a strong predictor. Additionally, the prognosis of septic shock patients was significantly associated with maximum serum sodium levels, the duration of hypernatremia, and the rate of sodium correction. At present, there are no globally accepted guidelines for the management of hypernatremia in septic shock. These findings suggest that hypernatremia may serve as a critical predictive indicator for patient outcomes in septic shock, underscoring the need for careful monitoring and management of sodium levels in these patients.

FOOTNOTES

Author contributions: Shi MQ, Wang X contributed to data curation, formal analysis, visualization; Wang Y, Ji FH contributed to conceptualization; Zhou H, Peng K, Wang J contributed to writing-original draft; Chen J, Fan CL writing-review and editing.

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REFERENCES

1 **Fernando SM**, Rochwerg B, Seely AJE. Clinical implications of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *CMAJ* 2018; **190**: E1058-E1059 [PMID: 30201611 DOI: 10.1503/cmaj.170149]

2 **Rudd KE**, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJL, Naghavi M. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; **395**: 200-211 [PMID: 31954465 DOI: 10.1016/S0140-6736(19)32989-7]

3 **Bauer M**, Groesdonk HV, Preissing F, Dickmann P, Vogelmann T, Gerlach H. [Mortality in sepsis and septic shock in Germany. Results of a

systematic review and meta-analysis]. *Anaesthesist* 2021; **70**: 673-680 [PMID: 33559687 DOI: 10.1007/s00101-021-00917-8]
4 **Rosenthal MD**, Vanzant EL, Moore FA. Chronic Critical Illness and PICS Nutritional Strategies. *J Clin Med* 2021; **10** [PMID: 34070395 DOI: 10.3390/jcm10112294]
5 **Davoudi A**, Corbett DB, Ozrazgat-Baslanti T, Bihorac A, Brakenridge SC, Manini TM, Rashidi P. Activity and Circadian Rhythm of Sepsis Patients in the Intensive Care Unit. *IEEE EMBS Int Conf Biomed Health Inform* 2018; **2018**: 17-20 [PMID: 30411088 DOI: 10.1109/BHI.2018.8333359]
6 **Hesselink L**, Hoepelman RJ, Spijkerman R, de Groot MCH, van Wessem KJP, Koenderman L, Leenen LPH, Hietbrink F. Persistent Inflammation, Immunosuppression and Catabolism Syndrome (PICS) after Polytrauma: A Rare Syndrome with Major Consequences. *J Clin Med* 2020; **9** [PMID: 31936748 DOI: 10.3390/jcm9010191]
7 **Rosenthal MD**, Kamel AY, Rosenthal CM, Brakenridge S, Croft CA, Moore FA. Chronic Critical Illness: Application of What We Know. *Nutr Clin Pract* 2018; **33**: 39-45 [PMID: 29323761 DOI: 10.1002/ncp.10024]
8 **Liamis G**, Filippatos TD, Elisaf MS. Evaluation and treatment of hypernatremia: a practical guide for physicians. *Postgrad Med* 2016; **128**: 299-306 [PMID: 26813151 DOI: 10.1080/00325481.2016.1147322]
9 **Olsen MH**, Møller M, Romano S, Andersson J, Mlodzinski E, Raines NH, Sherak R, Jeppesen AN. Association Between ICU-Acquired Hypernatremia and In-Hospital Mortality: Data From the Medical Information Mart for Intensive Care III and the Electronic ICU Collaborative Research Database. *Crit Care Explor* 2020; **2**: e0304 [PMID: 33354677 DOI: 10.1097/CCE.0000000000000304]
10 **De Freitas G**, Gudur A, Vela-Ortiz M, Jodelka J, Livert D, Krishnamurthy M. Where there is sodium there may be sepsis. *J Community Hosp Intern Med Perspect* 2019; **9**: 296-299 [PMID: 31528275 DOI: 10.1080/20009666.2019.1634407]
11 **Lindner G**, Funk GC, Schwarz C, Kneidinger N, Kaider A, Schneeweiss B, Kramer L, Druml W. Hypernatremia in the critically ill is an independent risk factor for mortality. *Am J Kidney Dis* 2007; **50**: 952-957 [PMID: 18037096 DOI: 10.1053/j.ajkd.2007.08.016]
12 **Waite MD**, Fuhrman SA, Badawi O, Zuckerman IH, Franey CS. Intensive care unit-acquired hypernatremia is an independent predictor of increased mortality and length of stay. *J Crit Care* 2013; **28**: 405-412 [PMID: 23369520 DOI: 10.1016/j.jcrc.2012.11.013]
13 **Quinn JW**, Sewell K, Simmons DE. Recommendations for active correction of hypernatremia in volume-resuscitated shock or sepsis patients should be taken with a grain of salt: A systematic review. *SAGE Open Med* 2018; **6**: 2050312118762043 [PMID: 29593868 DOI: 10.1177/2050312118762043]
14 **Rugg C**, Ströhle M, Treml B, Bachler M, Schmid S, Kreutziger J. ICU-Acquired Hypernatremia Is Associated with Persistent Inflammation, Immunosuppression and Catabolism Syndrome. *J Clin Med* 2020; **9** [PMID: 32962124 DOI: 10.3390/jcm9093017]
15 **Cox MC**, Brakenridge SC, Stortz JA, Hawkins RB, Darden DB, Ghita GL, Mohr AM, Moldawer LL, Efron PA, Moore FA. Abdominal sepsis patients have a high incidence of chronic critical illness with dismal long-term outcomes. *Am J Surg* 2020; **220**: 1467-1474 [PMID: 32807383 DOI: 10.1016/j.amjsurg.2020.07.016]
16 **Gentile LF**, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, Moldawer LL, Moore FA. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. *J Trauma Acute Care Surg* 2012; **72**: 1491-1501 [PMID: 22695412 DOI: 10.1097/TA.0b013e318256e000]
17 **Wenstedt EF**, Verberk SG, Kroon J, Neele AE, Baardman J, Claessen N, Pasaoglu ÖT, Rademaker E, Schrooten EM, Wouda RD, de Winther MP, Aten J, Vogt L, Van den Bossche J. Salt increases monocyte CCR2 expression and inflammatory responses in humans. *JCI Insight* 2019; **4** [PMID: 31672939 DOI: 10.1172/jci.insight.130508]
18 **Flierl MA**, Rittirsch D, Weckbach S, Huber-Lang M, Ipaktchi K, Ward PA, Stahel PF. Disturbances of the hypothalamic-pituitary-adrenal axis and plasma electrolytes during experimental sepsis. *Ann Intensive Care* 2011; **1**: 53 [PMID: 22208725 DOI: 10.1186/2110-5820-1-53]
19 **Braun MM**, Barstow CH, Pyzocha NJ. Diagnosis and management of sodium disorders: hyponatremia and hypernatremia. *Am Fam Physician* 2015; **91**: 299-307 [PMID: 25822386]
20 **Barrett JS**, Shepherd SJ, Gibson PR. Strategies to manage gastrointestinal symptoms complicating enteral feeding. *JPEN J Parenter Enteral Nutr* 2009; **33**: 21-26 [PMID: 19028933 DOI: 10.1177/0148607108325073]
21 **Wesselink E**, Koekkoek KWAC, Looijen M, van Blokland DA, Witkamp RF, van Zanten ARH. Associations of hyperosmolar medications administered *via* nasogastric or nasoduodenal tubes and feeding adequacy, food intolerance and gastrointestinal complications amongst critically ill patients: A retrospective study. *Clin Nutr ESPEN* 2018; **25**: 78-86 [PMID: 29779822 DOI: 10.1016/j.clnesp.2018.04.001]
22 **Tatsumi H**. Enteral tolerance in critically ill patients. *J Intensive Care* 2019; **7**: 30 [PMID: 31086671 DOI: 10.1186/s40560-019-0378-0]
23 **Xin Y**, Tian M, Deng S, Li J, Yang M, Gao J, Pei X, Wang Y, Tan J, Zhao F, Gao Y, Gong Y. The Key Drivers of Brain Injury by Systemic Inflammatory Responses after Sepsis: Microglia and Neuroinflammation. *Mol Neurobiol* 2023; **60**: 1369-1390 [PMID: 36445634 DOI: 10.1007/s12035-022-03148-z]
24 **Natochin YV**, Golosova DV. Vasopressin receptor subtypes and renal sodium transport. *Vitam Horm* 2020; **113**: 239-258 [PMID: 32138950 DOI: 10.1016/bs.vh.2019.08.013]
25 **Halmos EP**, Muir JG, Barrett JS, Deng M, Shepherd SJ, Gibson PR. Diarrhoea during enteral nutrition is predicted by the poorly absorbed short-chain carbohydrate (FODMAP) content of the formula. *Aliment Pharmacol Ther* 2010; **32**: 925-933 [PMID: 20670219 DOI: 10.1111/j.1365-2036.2010.04416.x]
26 **Bernal A**, Zafra MA, Simón MJ, Mahía J. Sodium Homeostasis, a Balance Necessary for Life. *Nutrients* 2023; **15** [PMID: 36678265 DOI: 10.3390/nu15020395]
27 **Hu B**, Han Q, Mengke N, He K, Zhang Y, Nie Z, Zeng H. Prognostic value of ICU-acquired hypernatremia in patients with neurological dysfunction. *Medicine (Baltimore)* 2016; **95**: e3840 [PMID: 27583842 DOI: 10.1097/MD.0000000000003840]
28 **Broll M**, John S. [Hypernatremia]. *Med Klin Intensivmed Notfmed* 2020; **115**: 263-274 [PMID: 32179951 DOI: 10.1007/s00063-020-00667-2]
29 **Sakamoto A**, Hoshino T, Boku K, Hiraya D, Inoue Y. Fatal acute hypernatremia resulting from a massive intake of seasoning soy sauce. *Acute Med Surg* 2020; **7**: e555 [PMID: 32832094 DOI: 10.1002/ams2.555]
30 **Hahn RG**, Patel V, Dull RO. Human glycocalyx shedding: Systematic review and critical appraisal. *Acta Anaesthesiol Scand* 2021; **65**: 590-606 [PMID: 33595101 DOI: 10.1111/aas.13797]
31 **Mutter CM**, Smith T, Menze O, Zakharia M, Nguyen H. Diabetes Insipidus: Pathogenesis, Diagnosis, and Clinical Management. *Cureus* 2021; **13**: e13523 [PMID: 33786230 DOI: 10.7759/cureus.13523]

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