

Could dysnatremias play a role as independent factors to predict mortality in surgical critically ill patients?

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Abstract

Several studies have demonstrated the impact of dysnatremias on mortality of intensive care unit (ICU) patients. The objective of this study was to assess whether dysnatremia is an independent factor to predict mortality in surgical critically ill patients admitted to ICU in postoperative phase.

One thousand five hundred and ninety-nine surgical patients (58.8% males; mean age of 60.6 ± 14.4 years) admitted to the ICU in the postoperative period were retrospectively studied. The patients were classified according to their serum sodium levels (mmol/L) at admission as normonatremia (135–145), hyponatremia (<135), and hypernatremia (>145). APACHE II, SAPS III, and SOFA were recorded. The capability of each index to predict mortality of ICU and hospital mortality of patients was analyzed by multiple logistic regression.

Hyponatremia did not have an influence on mortality in the ICU with a relative risk (RR) = 0.95 (0.43–2.05) and hospital mortality of RR = 1.40 (0.75–2.59). However, this association was greater in patients with hypernatremia mortality in the ICU (RR = 3.33 [95% confidence interval, CI 1.58–7.0]) and also in hospital mortality (RR = 2.9 [95% CI = 1.51–5.55]). The pairwise comparison of ROC curves among the different prognostic indexes (APACHE II, SAPS III, SOFA) did not show statistical significance. The comparison of these indexes with serum sodium levels for general population, hyponatremia, and normonatremia was statistically significant ($P < .001$). For hypernatremia, the AUC and 95% CI for APACHE II, SAPS III, SOFA, and serum sodium level were 0.815 (0.713–0.892), 0.805 (0.702–0.885), 0.885 (0.794–0.945), and 0.663 (0.549–0.764), respectively. The comparison among the prognostic indexes was not statistically significant. Only SOFA score had a statistic difference compared with hypernatremia ($P < .02$).

The serum sodium levels at admission, especially hypernatremia, may be used as an independent predictor of outcome in the surgical critically ill patients.

Abbreviations: APACHE II = acute physiology and chronic health evaluation II, AUC = area under the ROC curve, CI = confidence interval, ICUs = intensive care units, ROC = receiver-operating characteristics, RR = relative risk, SAPS III = simplified acute physiology score, SOFA = sequential organ failure assessment.

Keywords: APACHE, hypernatremia, hyponatremia, intensive care, SAPS III

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1. Introduction

The dysnatremias are the most frequent electrolytic disorders found in hospitalized patients and in patients admitted to the intensive care units (ICUs).^[1–4] Sodium is an extracellular ion and its concentration and osmolarity determine the shift of water between intracellular and extracellular fluids. There is a balance between ingestion and excretion of water and salt. Changes in sodium concentration and osmotic pressure could result in activation of the neuroendocrine system and homeostatic processes controlled by the hypophysis and hypothalamus. Systemic inflammatory response may occur in some situations, such as polytrauma, acute diseases and side effects of drugs, leading to an imbalance in the mechanism of osmoregulation and hormonal action, for example, arginine vasopressin. These changes may be the cause or consequence of organ dysfunctions in critically ill patients and can be associated with increased morbidity and mortality.^[5] Hyponatremia is defined as the serum sodium level <135 mmol/L and hypernatremia as serum sodium level >145 mmol/L. The prevalence of hyponatremia ranges from 13.7% to 15%, depending on the normal value plasma sodium

reference, whereas the hypernatremia is found in 2% to 9% of cases.^[1–4,6–7] The hypernatremia can decrease cardiac contractility, increase peripheral resistance to insulin, cause difficulty in hepatic lactate clearance, and lead to changes in cell tonicity. Depending on the concentration and time of installation, hypernatremia may cause several neuromuscular manifestations.^[7–11] Similarly, the low serum sodium level can have a profound effect in neurologic function.^[10,11]

Several studies^[1–4,6] have demonstrated the impact of dysnatremias on mortality of ICU patients. However, the data have been presented for patients in case-mix ICUs, with few data related specifically to patients in postoperative period. The main goal of this retrospective study was to assess whether dysnatremias are independent factors to predict mortality in surgical critically ill patients admitted to ICU in postoperative period.

2. Methods

This retrospective study was conducted in a 20-bed adult ICU of Sao Francisco Hospital, Ribeirao Preto, São Paulo, Brazil. This tertiary ICU admits adult patients in critical condition such as clinical cases or surgical patients in early postoperative period. The study protocol was approved by the Research Ethics Committee of Clinics Hospital of Ribeirão Preto Medical School, University of São Paulo (Protocol 7076/2010). Surgical patients admitted to ICU between 2011 and 2013 were analyzed. Data concerning the diagnosis upon ICU arrival, comorbidities, demographic profile, and prognostic indexes such as Acute Physiology Chronic Evaluation II (APACHE II), Simplified Acute Physiology Score (SAPS III), and Sequential Organ Failure Assessment (SOFA) were recorded.^[12–15] Data for calculation of the prognostic indexes and serum sodium level were collected during the first 24 hours after patient admission. Normal serum sodium was defined a serum sodium level between 135 and 145 mmol/L.

2.1. Statistical analysis

Statistical analysis was performed using Stata[®] version 6.0 software (College Station, TX). Initially, we performed univariate analyses by χ^2 test for dichotomous variables, and test of

Wilcoxon/Mann–Whitney test for continuous variables. Patients with hyponatremia or hypernatremia were analyzed against the normonatremia in relation to death during ICU stay and death during hospitalization. Then, the data were submitted to 4 logistic regression models to evaluate separately the impact of hyponatremia and hypernatremia on the proposed outcomes, and its effect on potential confounding variables. It was included in the models, the demographic and clinical variables that exhibited statistically significant association ($P < .05$) with outcomes through univariate analysis.

The capability of each prognostic index (APACHE II, SAPS III, SOFA) and the serum sodium level at different situations (general population, normonatremia, hyponatremia and hypernatremia) to predict mortality of patients were analyzed by receiver-operating characteristics (ROC) curves. The area under de curve (AUC) and the respective confidence interval (CI) were recorded to measure the overall index accuracy. Comparison among these curves was tested as proposed by DeLong et al.^[16] The level of significance was set at $P < 0.05$. ROC curves analyses were performed using the software MedCalc version 12 (Ostend, Belgium).

3. Results

This retrospective study included 1599 patients (58.8% males and 41.2% females, mean age of 60.6 ± 14.4 years). The predominant surgeries were cardiac (505/31.6%), such as myocardial revascularization, prosthetic heart valves and aorta surgery, followed by digestive surgery (344/21.5%), neurosurgery (271/16.9%), vascular surgery (255/15.9%), and others (224/14.1%). Demographic, clinical, and mean prognostic indexes values are described in Table 1.

To assess the relationship of dysnatremias with mortality, a univariate analysis was initially realized. Patients with hyponatremia and hypernatremia were compared to normonatremia. Hyponatremia had an influence on mortality in the ICU (relative risk [RR]=1.91 [95% CI=1.13–3.17]) and hospital mortality (RR=2.059 [95% CI=1.38–3.05]). However, this association was greater in patients with hypernatremia mortality in the ICU (RR=5.45 [95% CI=3.65–8.1]) and also in hospital mortality (RR=4.54 [95% CI=3.25–6.35]). In the evaluation of the independent variables that could be associated with mortality, it

Table 1

Demographic and clinical characteristics of the surgical patients admitted to ICU.

	Patients n=1599	Hyponatremia n=155	Normonatremia n=1363	Hypernatremia n=81
Sex (M) n/%	927/58.8	92/5.7	806/50.4	29/1.8
Age, y	60.6 ± 14.4	63.7 ± 13.9	59.9 ± 14.3	64.5/15
APACHE II	13.96 ± 7.9	15.53 ± 6	13.46 ± 4.5	19.28 ± 7.2
SAPS III	39.6 ± 10.9	44.7 ± 12.92	38.36 ± 10.1	51.44 ± 14.7
SOFA	4.8 ± 2.5	5.09 ± 2.67	4.63 ± 2.4	7 ± 3.5
Mechanical ventilation, n/(%)	824/51.5	63/40.6	704/51.6	57/70.4
ICU mortality, n/(%)	114/7.12	16/10.3	74/5.4	24/29.6
Hospital mortality, n/ (%)	167/10.4	26/16.8	111/8.1	30/37
ICU length of stay, days	2.94 ± 2.1	3.68 ± 3.2	2.77 ± 1.9	4.37 ± 3
Hospital length of stay, days	11.8 ± 9.13	18.98 ± 17.53	10.9 ± 8	13.8 ± 9.2
Sepsis n (%)	152/9.5	22/14.2	110/8	20/24.7
Dialysis-requiring AKI, n (%)	50/3.1	12/3.2	34/24.9	4/7.7
Vasopressors, n (%)	744/46.5	59/38	639/46.9	46/56.8
Blood transfusions, n (%)	397/24.8	48/30.9	321/23.5	28/34.5
Emergency surgeries, n (%)	372/23.2	49/31.6	292/21.4	31/38.3

AKI=acute kidney failure, APACHE II=acute physiology and chronic health evaluation II, ICU=intensive care unit, SAPS III=simplified acute physiology score, SOFA=sequential organ failure assessment. Values are expressed as mean ± standard deviation or number (%), when required.

Table 2

Multivariate analysis of the outcome and their relationship in patients with hyponatremia.

	ICU mortality		Hospital mortality	
	Relative risk	CI 95%	Relative risk	CI 95%
Age, y	1.016	0.99–1.03	1.029	1.01–1.04
SAPS III	1.088	1.06–1.11	1.056	1.03–1.07
Vasopressors	5.061	2.35–10.8	1.410	0.82–2.42
Dialysis-requiring AKI	2.981	1.27–6.99	2.035	0.91–4.50
Blood transfusions	2.474	1.43–4.2	2.678	1.72–4.16
Mechanical ventilation			4.967	2.51–9.79
Sepsis	2.624	1.34–5.10	2.582	1.46–4.55
Emergency surgery	0.660	0.32–1.36	0.727	0.40–1.30
Elective surgery	0.491	0.44–1.61	0.445	0.25–0.77
Hyponatremia	0.950	0.43–2.05	1.402	0.75–2.59

AKI=acute kidney failure, CI=confidence interval, SAPS III=simplified acute physiology score.

was employed a multivariate analysis and outcome of patients and its correlation with hyponatremia. It was observed that the need for vasopressors, blood transfusions, dialysis-requiring acute kidney injury (AKI), mechanical ventilation, and cases of severe sepsis and septic shock were independent factors associated with mortality. Hyponatremia was only associated to the hospital mortality. The variables emergency or elective surgeries did not show correlation with mortality (Table 2). The same statistical model was designed for the analysis of hypernatremia and it was observed that the variables such as age, SAPS III, blood transfusions, mechanical ventilation, sepsis, and hypernatremia were independent factors associated with mortality (Table 3). To confirm the association of hypernatremia with mortality, we conducted a multivariate model with prognostic indexes as variables (APACHE II, SAPS III, SOFA) and hypernatremia as an independent factor associated with mortality (Table 4).

In the general population of the study (n=1599), the AUC and 95% CI for APACHE II, SAPS III, SOFA, and serum sodium levels were 0.907 (0.892–0.921), 0.893 (0.877–0.908), 0.894 (0.878–0.909), and 0.606 (0.582–0.630), respectively. The pairwise comparison of ROC curves among the different prognostic indexes (APACHE II, SAPS III, SOFA) did not show

Table 3

Multivariate analysis of the outcome and their relationship in patients with hypernatremia.

	ICU		Hospital	
	Relative risk	CI	Relative risk	CI
Age, y	1.015	0.99–1.03	1.025	1.01–1.04
SAPS III	1.076	1.05–1.10	1.059	1.04–1.08
Vasopressors	10.10	4.24–24.1	1.787	1.01–3.14
Dialysis-requiring AKI	1.862	0.73–4.69	1.502	0.63–3.54
Blood transfusions	2.605	1.48–4.58	2.857	1.80–4.53
Mechanical ventilation			3.317	1.66–6.60
Sepsis	4.616	2.4–8.87	4.020	2.28–7.0
Emergency surgery	0.803	0.38–1.66	0.802	0.44–1.44
Elective surgery	0.812	0.42–1.57	0.478	0.27–0.84
Hypernatremia	3.333	1.58–7.00	2.901	1.51–5.55

AKI=acute kidney failure, CI=confidence interval, ICU=intensive care unit, SAPS III=simplified acute physiology score.

Table 4

Multivariate analysis of outcome, considering the hypernatremia, prognostic indexes, and organ dysfunction.

	ICU mortality		Hospital mortality	
	Relative risk	CI	Relative risk	CI
Sex	0.98	0.56–1.72	1.14	0.73–1.79
Age, y	1.01	0.99–1.03	1.01	1.00–1.03
APACHE II	1.08	1.02–1.15	1.07	1.02–1.13
SAPS III	1.03	1.00–1.05	1.04	1.02–1.06
SOFA	1.36	1.21–1.53	1.19	1.08–1.30
Hypernatremia	2.37	1.09–5.12	2.62	1.34–5.12

APACHE II=acute physiology and chronic health evaluation II, CI=confidence interval, ICU=intensive care unit, SAPS III=simplified acute physiology score, SOFA=sequential organ failure assessment.

statistical significance. The comparison of these indexes with sodium was statistically significant ($P < 0.001$). The same approach described above was used for patients with hyponatremia (n=155, 9.7%), normonatremia (n=1363, 85.2%), and hypernatremia (n=81, 5.1%). The comparison among the ROC curves for APACHE II, SAPS III, and SOFA showed similar statistic results for hyponatremia and normonatremia ($P < 0.001$). In the case of hypernatremia, the AUC and 95% CI for APACHE II, SAPS III, SOFA, and serum sodium levels were 0.815 (0.713–0.892), 0.805 (0.702–0.885), 0.885 (0.794–0.945), and 0.663 (0.549–0.764), respectively. The pairwise comparison among the prognostic indexes and hypernatremia was not statistically significant. However, only SOFA score had a statistic difference compared with hypernatremia ($P < 0.02$). The ROC curves for the prognostic indexes and serum sodium levels for general population, hyponatremia, normonatremia, and hypernatremia are depicted in Figure 1.

4. Discussion

The fate of dysnatremias in the prognosis of critically ill patients is already known.^[1–4,6–7] Indeed, Darmon et al^[2] demonstrated that hyponatremia (serum sodium level ≥ 125 and < 130 mmol/L), adjusted to comorbidities and severity of illness, is not only independently associated with a worse outcome of patients but these authors also pointed out the relevance to consider borderline serum sodium level consequences. Padhi et al^[17] have found in their study that patients with hyponatremia presented a higher length of stay in the ICU ($P = 0.02$) and days of mechanical ventilation ($P < 0.05$), with consequent increase in rates of mortality ($P = 0.01$), compared to patients with normal serum sodium level. Similarly, Leung et al^[18] evaluated a total of 75,423 patients with preoperative hyponatremia (serum sodium < 135 mmol/L) and compared with 888,840 patients with normal sodium levels (135–144 mmol/L). These authors observed that the preoperative hyponatremia was related to an enhanced risk of postoperative mortality (5.2% vs. 1.3%; odds ratio [OR]=1.44; 95% CI=1.38–1.50). It was identified in this study that hyponatremia was a predictor of mortality of surgical patients. A study developed in ICU in a University Hospital of Morocco in 2188 patients found an incidence of hyponatremia of 13.7%. Hospital mortality was 37.7%.^[19] It was considered that 5 variables were significantly associated with mortality in a multivariate analysis: hyponatremia (serum sodium level < 125 mmol/L), with an RR of 2.10 (95% CI=1.43–3.08), coma Glasgow scale < 9 (RR=2.66; 95% CI=1.25–5.66), coma Glasgow scale between 9 and 13 (RR=1.94; 95% CI=

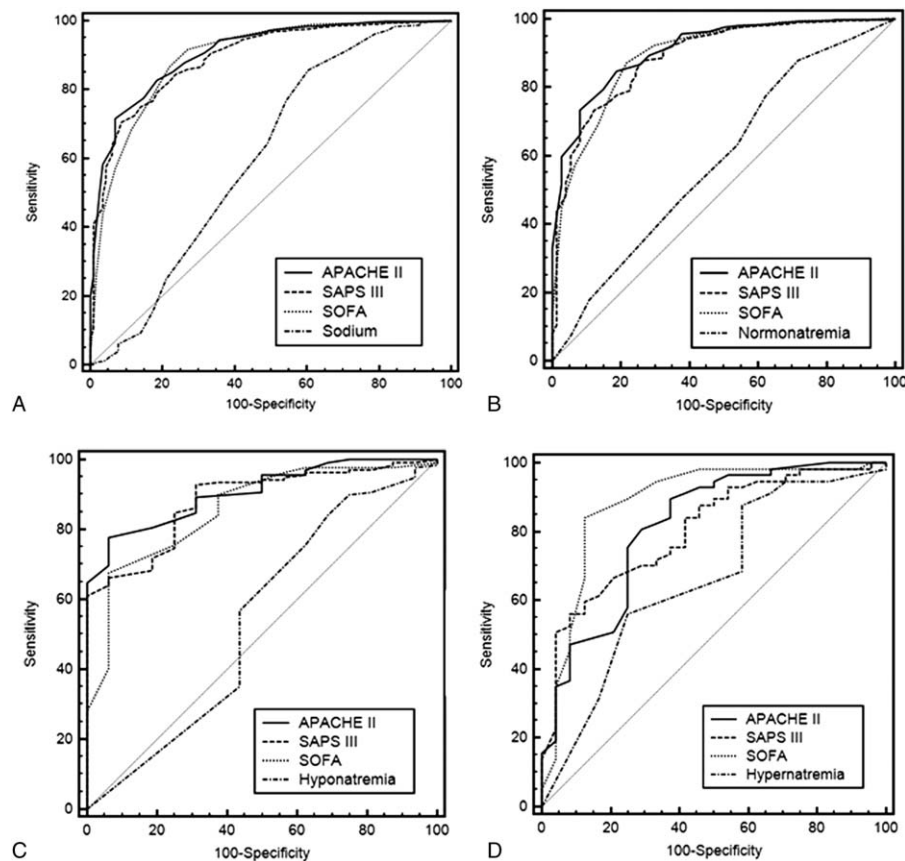


Figure 1. Comparison of receiver-operating characteristic (ROC) curves of Acute Physiology Chronic Evaluation II (APACHE II), Simplified Acute Physiology Score (SAPS III) and Sequential Organ Failure Assessment (SOFA) and serum sodium levels in the general population (A), patients with normonatremia (B), hyponatremia (C), and hypernatremia (D).

1.31–2.88), circulatory shock (RR=1.80; 95% CI=1.10–3.05), and uremia >10 mmol/L (RR=1.59; 95% CI=1.08–2.34). In this study, hyponatremia was an independent risk factor associated with mortality. In a previous study conducted by our research group, Basile-Filho et al^[20] have investigated retrospectively 195 surgical critically ill patients in the postoperative period and it was evaluated whether serum sodium values could be used as predictors of mortality. It was observed an AUC for APACHE II of 0.841 (95% CI=0.78–0.89; sensitivity=79.3; specificity=77.8). The sodium at admission the AUC was 0.721 (95% CI=0.65–0.78; sensitivity=64.7; specificity=71.1). The Sodium-48i_{1/2}h showed an AUC of 0.754 (95% CI=0.69–0.81; sensitivity=68.7; specificity=77.8). We concluded that the persistence of hypernatremia throughout the ICU stay could play an independent role in prediction of mortality.

A study developed in 2 ICUs of Dutch University Hospitals evaluated 80,571 patients over a 2 decades period.^[21] A total of 913,272 serum sodium measurements were performed. The authors showed that incidence of severe hypernatremia (sodium >155 mmol/L) has been increased dramatically over the years. This incidence was 0.7% in the period of 1992 to 1996, compared with 6.3% in the period of 2009 to 2012. The severe dysnatremias were associated with a significantly higher mortality during the entire period of study ($P<0.001$). The hypernatremia in this investigation was correlated with

mortality. Other studies^[22,23] had indicated high rates of mortality in hypernatremic patients, especially those in ICU, ranging from 15% to 50%, depending on the severity of illness. Waite et al^[24] demonstrated, in 207,702 critical patients, that hypernatremia acted as an independent risk factor for mortality with an RR of 1.34 and 95% CI=1.4–1.45. Lenz et al^[24] investigated 436,209 patients in ICU and they observed that patients with hypernatremia (sodium ≥ 160 mmol/L) showed a greater probability of death, with OR=4.2 (95% CI=3.6–4.9). Furthermore, Lenz et al^[25] investigated 436,209 patients admitted to ICU. The authors observed that patients with hypernatremia (sodium ≥ 160 mmol/L) showed a increased risk of death, with 4.2 OR (95% CI=3.6–4.9). A study developed in 519 neurologic critically ill patients^[26] identified 106 patients admitted to ICU with hyponatremia (20.4%) and 177 (34.1%) with hypernatremia (69/13.29% on admission and 108/20.81% throughout the ICU stay). The hypernatremia in admission or in the ICU stay could not differentiate between survivors and non-survivors. However, only the hypernatremia in ICU stay was an independent risk factor for mortality with high sensitivity ($P=0.001$). Additionally, a retrospective study performed in ICU of a general hospital of Istanbul^[27] for a period of 6 years has shown that only SAPS II was associated with increased mortality (OR 1.05 [95% CI=1.02–1.09]). The OR for

dysnatremias (sodium <125 mmol/L and >150 mmol/L) to predict mortality was 4.37 (95% CI=2.29–8.36) in patients with organ dysfunction.

This study has some limitations, first this is a retrospective study, second it was not evaluated the dysnatremias' etiology as well as the follow-up about this electrolyte during the length at ICU.

The data of the present study were able to detect that hypernatremia in the ICU admission might be an effective predictor of mortality in surgical critically patients. It is worthwhile to emphasize, nevertheless, the importance that dysnatremias are related to lack of free water or sodium ion, multiple comorbidities, and drug treatments, which alter the concentration, absorption, and filtration of sodium and water, independently of prescription. Moreover, the neuroendocrine and inflammatory metabolic response induced by surgical trauma and other acute injuries could intensify the dysnatremias, and influence the response of organs and systems to fluid administration. These data also suggest that the impact of hypernatremia on mortality of surgical patients should not be underestimated, and therefore has an extreme importance in the maintenance of normal serum levels of this electrolyte. Thus, these evidences should be taken into account by physicians, such as intensivists, anesthesiologists, nephrologists, and surgeons for the intrinsic factors of the patient and the treatment of the dysnatremias, especially hypernatremia. These professionals must be aware that the prevention and correction of these disturbances in patients' ICU arrival improve survival. In conclusion, according to our data, hypernatremia was an independent factor associated with mortality in surgical patients admitted to ICU, and hyponatremia was neither associated with ICU nor with hospital mortality.

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