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The association between sodium fluctuations and mortality in surgical patients requiring intensive care☆,☆☆

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A R T I C L E I N F O

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A B S T R A C T

Purpose: Serum sodium derangement is the most common electrolyte disturbance among patients admitted to intensive care. This study aims to validate the association between dysnatremia and serum sodium fluctuation with mortality in surgical intensive care patients.
Method: We performed a retrospective analysis of the Medical Information Mart for Intensive Care II database. Dysnatremia was defined as a sodium concentration outside physiologic range (135-145 mmol/L) and subjects were categorized by severity of dysnatremia and sodium fluctuation. Univariate and multivariable logistic regressions were used to test for associations between sodium fluctuations and mortality.
Results: We identified 8600 subjects, 39% of whom were female, with a median age of 66 years for analysis. Subjects with dysnatremia were more likely to be dead at 28 days (17% vs 7%; $P < .001$).
There was a significant association between sodium fluctuation and mortality at 28 days (adjusted odds ratio per 1 mmol/L change, 1.10 [95% confidence interval, 1.08-1.12; $P < .001$]), even in patients who remained normotremic during their intensive care unit stay (1.12 [95% confidence interval, 1.09-1.16; $P < .001$])
Conclusions: This observational study validates previous findings of an association between serum sodium fluctuations and mortality in surgical intensive care patients. This association was also present in subjects who remained normonatremic throughout their intensive care unit admission.

1. Introduction

Sodium plays an important role as the predominant extracellular cation found in the body and its concentrations are tightly regulated by a number of homeostatic biological mechanisms [1]. Despite great variations in salt and water intake, the body finely maintains serum sodium between 135 and 145 mmol/L and readings outside this range (hyponatremias or hypernatremias) are termed *dysnatremias*.

Serum sodium abnormalities are a common finding within the intensive care setting [2-4]. Dysnatremia can affect a number of physiological functions [5,6] and has been shown to negatively impact upon prognosis for patients in intensive care [2-4,7]. Both dysnatremia at admission and that acquired in the intensive care unit (ICU) have been shown to have a direct influence on prognosis [8]. Current studies have mostly been conducted in unselected general hospital populations and mixed ICU populations of both medical and surgical patients. There has been a single study investigating the link between dysnatremia and mortality specifically in ICU surgical patients [9].

Studies have also found that rapid correction of serum sodium levels in hypernatremic patients has a deleterious effect on survival [10,11]. In cardiac surgical patients, it was found that those with the greatest rate of change of serum sodium concentration were more likely to die [12]. Investigations into serum sodium fluctuations and mortality in intensive care patients are lacking. A recent study by Sakr and colleagues

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[9] found an independent association between sodium fluctuations and mortality, even in patients who remained within the reference range throughout their ICU stay. The association of sodium fluctuations and mortality has been validated in only one other study, in a subgroup of a pediatric population requiring externalized ventricular drains [13].

Our objective was to validate previous findings of an association between dysnatremia and both absolute sodium and sodium fluctuations with outcome in an external population of surgical patients requiring intensive care. Our primary hypothesis is that the presence of dysnatremia and fluctuations in serum sodium in both dysnatremic and normotremic patients is related to outcome in surgical ICU patients. To test this hypothesis, we performed a retrospective observational cohort study with the use of an open-source clinical database of critically ill patients.

2. Methods

2.1. Data source and study population

Data used to conduct the observational study were obtained from the Medical Information Mart for Intensive Care (MIMIC II) clinical database. This dataset was developed by a partnership between the Massachusetts Institute of Technology, Philips Healthcare, and Beth Israel Deaconess Medical Centre (BIDMC) [14], and is compiled from information relating to patients who were hospitalized between January 2001 and December 2008. This includes all physiological data recorded in the ICU, clinical variables, investigation results (including laboratory tests), and survival outcome data. Survival outcome data were collected from social security death records after discharge.

The institutional review boards at BIDMC and the Massachusetts Institute of Technology granted ethical approval for the use of the MIMIC II database for research. A waiver for the informed consent requirement was also included in the institutional review board approval because the database does not contain protected health information.

We included consecutive surgical patients who met the inclusion criteria of age greater than 17 years and entry in the database between January 2001 and December 2008. Patients who were missing baseline sodium measurements or covariate data were excluded from the analysis.

The fluid management strategy used at the BIDMC broadly follows that outlined in the surviving sepsis campaign [15]. Typically, 30 mL/kg of crystalloid is used for hypotension or lactatemia fluid resuscitation.

2.2. Exposure and outcome

Our primary exposure of interest was serum sodium fluctuation during ICU admission. The highest and lowest measured serum sodium readings were used to compute a maximum fluctuation value during admission. Patients were then categorized as those whose serum sodium went outside the reference range and those who remained within that range throughout their stay.

A secondary exposure of interest was an absolute serum sodium concentration measured to be either greater than 145 mmol/L or less than 135 mmol/L on ICU admission. Patients were categorized by severity of dysnatremia as follows: normal (135-145 mmol/L), mild hyponatremia (130-134 mmol/L), severe hyponatremia (<130 mmol/L), mild hypernatremia (146-150 mmol/L), and severe hypernatremia (>150 mmol/L; Fig. 1).

The primary outcome was 28-day mortality. Secondary outcomes were 1-year mortality, ICU mortality, and hospital mortality.

2.3. Statistical analysis and modeling strategy

Data for continuous variables are presented as medians with interquartile ranges (IQRs) and categorical variables are reported as frequencies with percentages. We assessed graphically the assumption of a normal distribution for the primary exposure variable groups using histograms. Univariate and multivariable logistic regressions were used to assess the association between the exposure variable and outcomes. For univariate analysis, the exposure was entered into the model alone and we report odds ratios (ORs) with 95% confidence intervals (CIs). In an attempt to account for confounding from other parameters, we constructed multivariable logistic models. We initially included in the multivariable model all variables with a statistically significant univariate association with outcome to control for potentially clinically relevant confounding. Variables that were not associated with the outcome in the multivariable model were manually removed from the model to achieve model parsimony. Variables included in the multivariate analysis included age, sex, care unit, Simplified Acute Physiology Score II, and Sequential Organ Failure Assessment (SOFA) scores at admission, sepsis, congestive heart failure, liver disease, diabetes mellitus, and categorized creatinine value.

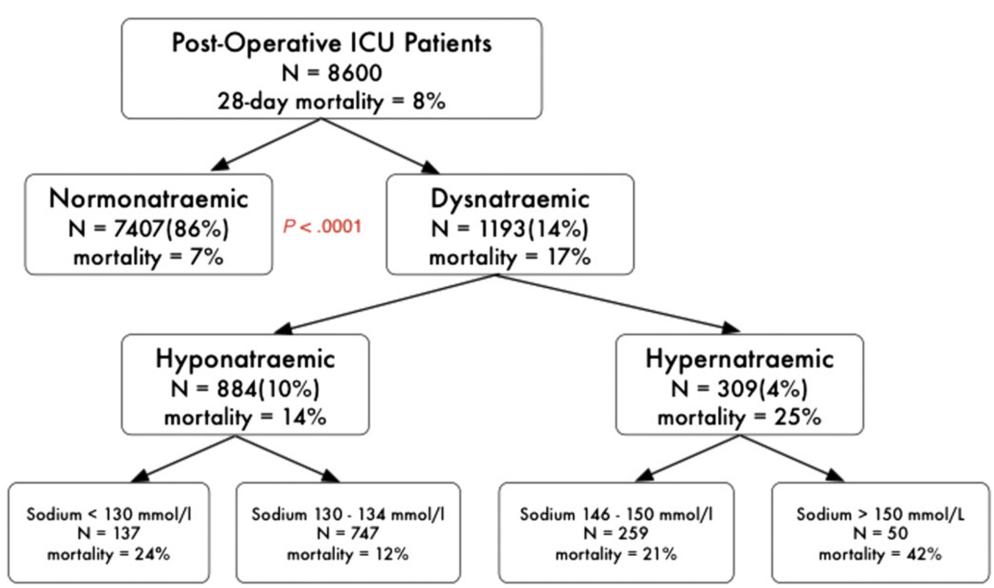

Fig. 1. Schematic representation of the 28-day mortality of postoperative ICU patients according to serum sodium levels on ICU admission. χ^2 Test for the difference between normotremic and dysnatremic patients.

2.4. Subset analysis

We performed a subgroup analysis to assess the effect of the development of dysnatremia among patients with a normal serum sodium on ICU admission. For this analysis, we identified patients who had first measured serum sodium level between 135 and 145 mmol/L and computed the maximum absolute change in serum sodium level during the ICU stay. We computed the number of patients who developed dysnatremia during the ICU stay. We used multivariable logistic regression to assess the association between the maximum change from normal baseline and 28-day mortality.

3. Results

3.1. Cohort characteristics

A total of 8600 surgical intensive care patients were included in the final analysis. Table 1 displays the descriptive statistics of the study group that have been categorized on the basis of baseline sodium values: normotremia (135-145 mmol/L), hyponatremia (<135 mmol/L), and hypernatremia (>145 mmol/L). A total of 7407 patients (86%) were normotremic at baseline, and 884 (10%) and 309 (4%) were hyponatremic and hypernatremic, respectively. In the subgroup of patients who presented to the ICU with normal sodium values (n = 7410), a total of 973 patients (13%) developed dysnatremia during the ICU stay.

There were significant differences in age, sex, and comorbidity status between normotremic and dysnatremic patients (Table 1). Patients with a dysnatremia were found to be older and more likely to be female. Hypernatremic patients had a higher SOFA score; patients with hyponatremia were more likely to be administered a vasopressor or be on ventilation. The data also show significantly higher rates of congestive heart failure and liver failure in all dysnatremic patient groups, a higher incidence of diabetes and renal failure in patients with hyponatremia, and a higher incidence of hypertension among patients with hypernatremia.

Table 1
Characteristics of study cohort according to baseline serum sodium data

Demographic	Normotremia, n = 7407 (86%)	Hyponatremia, n = 884 (10%)	Hypernatremia, n = 309 (4%)
Age (y)	65 (53-77)	67 (55-78)*	69 (51-80)*
Female, n (%)	2778 (38)	390 (44)**	151 (49)**
Admission type, n (%)			
Elective	2144 (29)	154 (18)	49 (16)
Emergency	5023 (68)	682 (77)	252 (82)
Urgent	243 (3)	48 (5)	8 (3)
Baseline observations			
GCS (IQR)	9 (3-15)	11 (3-15)	7 (3-15)
Systolic BP, mm Hg (IQR)	121 (107-137)	120 (104-136)*	121 (107-137)
Baseline severity			
SOFA (IQR)	7 (3-9)	7 (3-9)	8 (5-11)**
Vasopressor, n (%)	3380 (46)	359 (41)*	130 (42)
Ventilator, n (%)	4968 (67)	487 (55)*	212 (68)
Comorbidities, n (%)			
Congestive heart failure	1005 (14)	173 (20)**	68 (22)**
Hypertension	2459 (33)	310 (35)	85 (28)*
Chronic pulmonary disease	1082 (15)	161 (18)	54 (17)
Diabetes	1842 (25)	634 (28)*	70 (23)
Hypothyroid	79 (9)	584 (8)	28 (9)
Renal failure	219 (3)	40 (5)**	8 (3)
Liver failure	273 (4)	79 (9)**	29 (9)**
Sepsis	1074 (15)	213 (24)	118 (38)
Outcomes, n (%)			
ICU mortality			408 (5)
Hospital mortality			635 (7)
28-d mortality			706 (8)
1-y mortality			1286 (15)

* $P < .05$.
** $P < .001$.

3.2. Dysnatremia and mortality

Overall 28-day mortality rate was 8% for all surgical patients in the ICU setting. Compared with patients with normonatremia, patients who presented with a dysnatremia had higher 28-day mortality (17% vs 7%; $P < .0001$; Fig. 1).

Patients with hyponatremia represented 10% of the total cohort and had a 28-day mortality rate of 14%. Patients with a serum sodium on admission between 130 and 134 mmol/L (n = 747) had a 28-day mortality rate of 12% and those with a level lower than 130 mmol/L (n = 137) had a 28-day mortality rate of 24%. Those with hypernatremia represented 4% of the total cohort and had the highest 28-day mortality rate of 25%. Those with a serum sodium of 146 to 150 mmol/L (n = 259) had a 28-day mortality rate of 21% and those with a level higher than 150 mmol/L (n = 50) had a rate of 42%.

There was a statistically significant association between dysnatremia and 28-day mortality in unadjusted analysis. This association remained after multivariate adjustment for demographics, severity of illness, and comorbidities. Odds ratios corresponding to 28-day and 1-year mortality increase with severity of dysnatremia and are presented in Fig. 2.

3.3. Sodium fluctuations

The median fluctuation in serum sodium concentration during ICU stay (mmol/L) was 2 (IQR, 0-5; range, 0-40). Degree of serum sodium fluctuation during the ICU stay was found to be significantly associated with both 28-day and ICU mortality ($P < .0001$, Mantel-Haenszel test; Fig. 3). For each 1-mmol variation in sodium, there was a significant association with 28-day mortality (unadjusted OR, 1.15 [95% CI, 1.13-1.18; $P < .001$]). After application of the multivariate model, we found an independent association between sodium fluctuation and 28-day mortality (adjusted OR, 1.10 [95% CI, 1.08-1.12; $P < .001$]; Fig. 3).

3.4. Sodium variation in normonatremic patients

The association of sodium fluctuation and mortality was also found in patients who remained normonatremic throughout the entire length of the ICU stay ($P < .0001$, Mantel-Haenszel test; Fig. 4). For each 1-mmol variation in sodium, there was a significant association with 28-day mortality (unadjusted OR, 1.18 [95% CI, 1.15-1.21; $P < .001$]). Using the multivariate model, we found an independent association between each 1-mmol sodium fluctuation and 28-day mortality (1.12 [95% CI, 1.09-1.16; $P < .001$]).

4. Discussion

In this large observational study of adult surgical patients requiring ICU care, we found that dysnatremia is common in critically ill patients and an independent risk factor for ICU mortality. This study adds to the growing body of evidence suggesting that sodium fluctuation is an independent risk factor for ICU mortality. It validates a previous finding by Sakr and colleagues of an independent association between sodium fluctuations and mortality in patients who did not have a sodium dysregulation at any point in their ICU admission.

Sodium homeostasis is the appropriate regulation of sodium in the extracellular fluid and is crucial for the functioning of a vast number of biochemical and electrical processes within the body. Hyponatremia can result from a number of conditions including chronic heart, renal or liver dysfunction, syndrome of inappropriate antidiuretic hormone secretion, and Addison disease and hypothyroidism [6,16]. Hypernatremia is caused by a lack of thirst or access to free water, making the elderly and the critically ill high-risk groups [7,17].

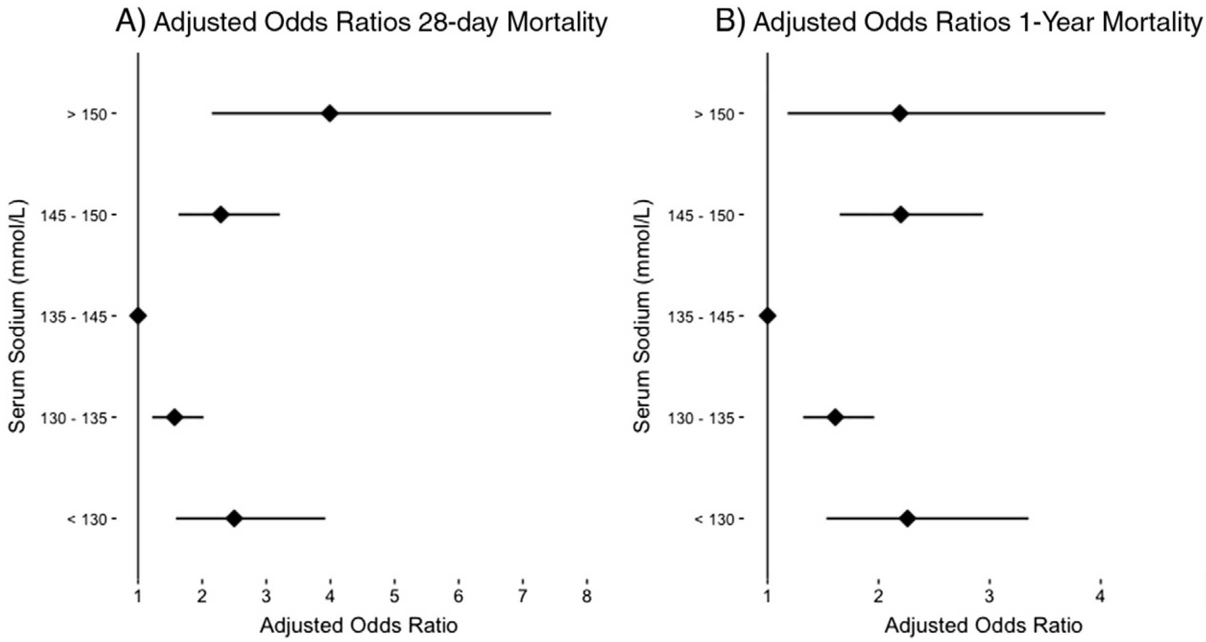

Fig. 2. Adjusted ORs of 28-day and 1-year mortality of patients with different severities of dysnatremia. An increased risk of both 28-day and 1-year mortality in patients with dysnatremia is shown when compared with reference patients with serum sodium levels of 135 to 145 mmol/L. When looking at 28-day and 1-year mortality, there is a stepwise increase in risk of mortality with increasing severity of serum sodium dysregulation.

Previous studies have reported a range of different values for the prevalence of dysnatremia on admission to ICU [2,4,7,18]. This variation may be due to heterogeneity of individuals included in the cohorts and the different cutoffs used to define dysnatremia. Past studies have reported a higher prevalence of dysnatremia in medical and mixed ICU patients which may be a reflection of an increased severity of illness [3,7,18,19]. Within our cohort, 14% of patients presented to ICU with a dysnatremia and another 13% developed one during their stay.

This study is consistent with previous studies by demonstrating a close association between sodium dysregulation and mortality of the critically ill patient. [2,3,7,20]. Although we can establish association, the nature of our study does not allow determine causation. Profound hyponatremia can lead to severe neurologic complications such as cerebral oedema and herniation [21,22]. Hypernatremia presents as a range of clinical manifestations including peripheral insulin resistance, impaired hepatic gluconeogenesis and lactate clearance, various neuromuscular manifestations, and decreased ventricular contractility [5,17,23-25]. Many studies now highlight the importance of taking into account serum sodium levels when assessing the risk of surgical ICU patients [2-4,9,12,19,26,27]. The severity of illness scoring systems Acute Physiology and Chronic Health Evaluation II [26] and Simplified Acute Physiology Score II [27] both include baseline serum sodium.

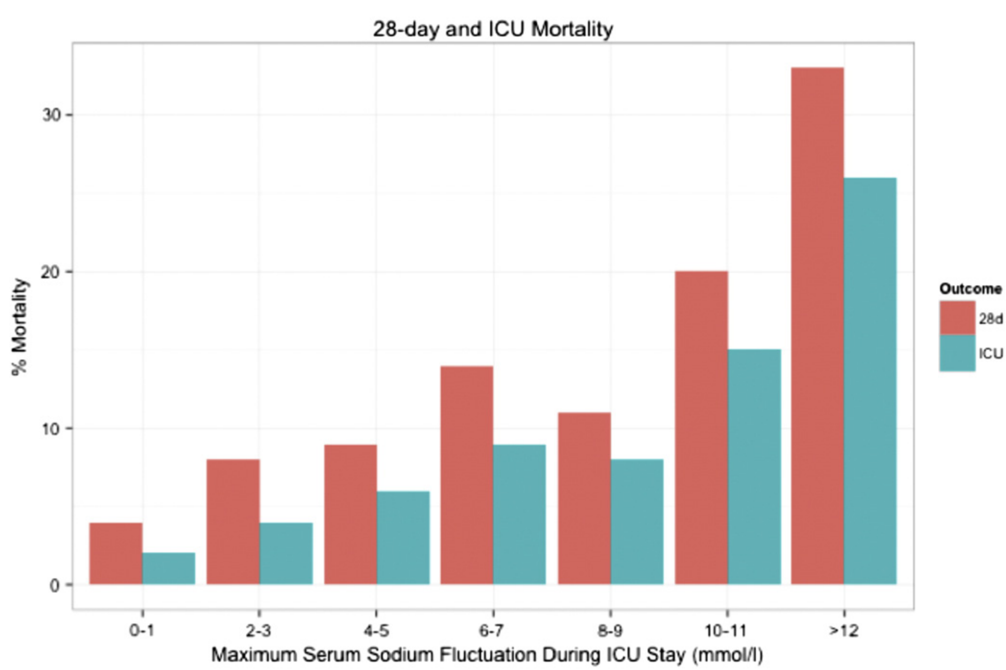

Fig. 3. Bar chart representing maximum serum sodium fluctuations (mmol/L) and mortality (%) in patients admitted to surgical ICU ($P < .0001$; Mantel-Haenszel test).

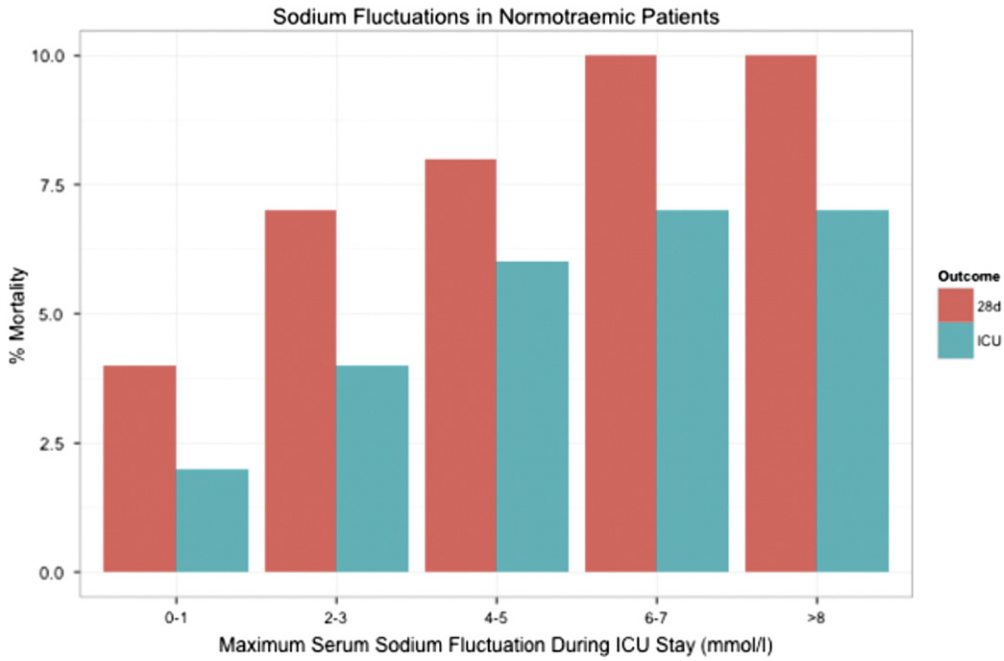

Fig. 4. Bar chart representing maximum sodium fluctuations (mmol/L) and mortality (%) in patients who were normonatremic on admission to surgical ICU ($P < .0001$; Mantel-Haenszel test).

The link between sodium fluctuations and mortality in critically ill patients is poorly characterized. The association of sodium fluctuations and mortality has been shown in a large cohort of adult surgical ICU patients [9] and in pediatric ICU patients who require externalized ventriculostomy drains [13]. Our study validates the findings of an independent association between sodium fluctuations and mortality, and also the association between degree of sodium fluctuation and an increased odds of in-hospital mortality. Sakr and colleagues [9] have been the first to describe the influence of sodium fluctuation on mortality in patients who do not have a sodium dysregulation at any point during their ICU stay. Our study is the first to validate the finding of an independent association between sodium fluctuations and mortality in postsurgical ICU patients.

Current management strategies for sodium imbalance depend on the onset of the dysnatremia, volume status, and the severity of patients' symptoms. Acute hyponatremia that is eliciting moderate to severe symptoms is treated with hypertonic saline to correct serum sodium and reduce the risk of cerebral oedema. Chronic hyponatremia causing only mild symptoms is treated by the cessation of supplementary fluids and medications that may be contributing, and investigations into the cause of the dysnatremia should be pursued [6,16]. Hypernatremia can be corrected by the replacement of water deficits [16,17]. Evidence suggests that treatment should be directed by the frequent monitoring of serum sodium levels and not by the use of sodium change prediction formulae [28,29].

The strengths of our study include a large cohort size using all surgical patients providing increased generalizability. We acknowledge a number of limitations that must be considered when interpreting these results. Although we have attempted to control for comorbid conditions and severity of illness, the possibility of unmeasured confounding remains due to the observational design of this study. For instance, dysnatremia may be secondary to aggressive diuretic use in the intensive care setting and may reflect comorbidities such as cardiac failure or hypertension. In addition, this study fails to include length of ICU stay in the analysis. Patients who spend a short amount of time in ICU could influence results by being exposed to a smaller risk of mortality and degree of sodium fluctuation. The MIMIC II database captures a huge range of clinical variables and patient information and allows for multivariable modeling. The data are from a single center, and all associations reported are dependent on variables that were measured in the ICU and included in the database. Finally, patients who were sicker may have had additional blood tests resulting in more apparent sodium fluctuations.

5. Conclusions

In this observational study of postoperative patients, dysnatremia is common and is associated with increased risk of mortality in postoperative patients requiring intensive care. We found that fluctuations in serum sodium were associated with an increase in 28-day mortality, even in those patients with normal serum sodium measurements during the course of the ICU stay. These data highlight the importance of dysnatremia prevention and strict control of sodium in postoperative patients.

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