The Association Between Serum Sodium Variation During Pediatric Intensive Care Unit Admission and the Risk of Clinical Outcomes in Critically Ill Children: A Retrospective Cohort Study

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Introduction. Dysnatremia at Pediatric Intensive Care Unit (PICU) has been associated with adverse outcomes; however, the impact of sodium variation during PICU stay remains underexplored. We aimed to assess the association between dysnatremia and sodium fluctuations during PICU admission and the probability of prolonged PICU stay (≥7days) and mortality.
Methods. This retrospective cohort study included 966 critically ill children (2019–2022) with at least two serum sodium measurements during PICU admission. Patients were classified as normonatremic, hyponatremic, hypernatremic, or mixed dysnatremic based on all sodium values. Sodium fluctuation was defined as the difference between the highest and lowest sodium levels during admission and categorized into quartiles. Associations of dysnatremia categories and sodium fluctuation with prolonged PICU stay and PICU mortality were evaluated using multivariable logistic regression.
Results. During the PICU admission, 542 patients developed dysnatremia. The PICU-acquired dysnatremia was independently associated with higher odds of prolonged PICU stay after adjusting for major confounders. The PICU-acquired hypernatremia (OR:5.23;95%CI:1.72-15.92) and mixed dysnatremia (OR:2.89;95%CI:1.14-7.29) had significantly higher odds for PICU mortality. Even mild sodium fluctuations (4-8mmoL/L) during PICU admission were significantly associated with higher odds of prolonged PICU stay. The highest (≥15mmol/L) fluctuations in serum sodium levels during PICU admission were also significantly associated with higher odds of PICU mortality (OR:2.74;95%CI:1.11-6.79).
Conclusion. Our findings underscore the importance of careful monitoring of serum sodium levels during PICU admission to improve clinical outcomes. These results should be interpreted in light of the retrospective design and the unavailability of standardized illness-severity scores (e.g., PRISM or PIM) in the dataset.

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INTRODUCTION

Sodium serves as a vital extracellular cation within the body, and its serum concentrations are rigorously regulated by a variety of homeostatic biological mechanisms.[1] Despite considerable changes in salt and water intake, the body adeptly maintains serum sodium levels between 135 and 145 mEq/L, and deviations from this range are referred to as dysnatremia.[2] Dysnatremia is the most common electrolyte disorder in critically ill pediatric patients, primarily presents as an imbalance of body water homeostasis, which depends on salt and water consumption, insensible losses, and urinary concentration or dilution (predominantly regulated by vasopressin in most cases).[2-4] Dysnatremia consists of two main classifications, namely hyponatremia (serum sodium concentration < 135 meq/L) and hypernatremia (serum sodium concentration > 145 meq/L).[2] Furthermore, in recent years, multiple studies have also demonstrated co-occurrence of hyponatremia and hypernatremia in the same patient over a short period; this phenomenon is defined as mixed dysnatremia.[5] Approximately one-third of critically ill patients present with dysnatremia upon intensive care unit (ICU) admission, while another third may develop this condition during their stay in the ICU.[6] In this framework, previous studies demonstrated that dysnatremia during ICU admission was independently linked to poor prognosis.[7-9] In addition, recent literature highlights that even mild dysnatremia during ICU admission can substantially impact clinical outcomes in critically ill patients, correlating with a markedly increased risk of prolong ICU stay and mortality.[10] Therefore, it is crucial to accurately identify critically ill patients with dysnatremia for effective management.

In this framework, few studies have investigated the relationship between fluctuations in serum sodium levels and clinical outcomes among critically ill pediatric populations.[11,12] Topjian *et al.* reported that greater sodium variability in children with externalized ventriculostomy drains was associated with a 59% increase in the risk of in-hospital mortality, although hyponatremia itself was not independently linked to seizures or mortality.[11] Similarly, Gupta *et al.*, in a prospective cohort of pediatric patients with non-traumatic coma, found no significant association between dysnatremia during PICU admission and mortality.[12] These limited and heterogeneous findings underscore the need for larger studies to clarify the prognostic implications of sodium fluctuations in critically ill children.

Although previous studies have contributed valuable insights, further research is required to clarify the relationship between serum sodium level variations during PICU admission and clinical outcomes in critically ill children. The limited sample sizes, focus on sodium fluctuations primarily at admission, and restriction to specific subgroups reduce the generalizability of their findings. In order to address this gap in the existing body of research, our study aimed to elucidate the association between changes in sodium levels during PICU admission and the risk of prolonged PICU stay (≥ seven days) and mortality.

MATERIAL AND METHODS

This retrospective cohort study included critically ill patients aged 1 month to 18 years old who were admitted to the Mofid Children's Hospital PICU in Tehran, Iran, from April 2019 to May 2022. This study was carried out in accordance with the principles established in the Declaration of Helsinki guidelines. The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Approval No.: IR.SBMU.RICH.REC.1401.050), and the requirement for written informed consent from parents/guardians and patients was obtain. Eligible participants were critically ill children aged 1 month to 18 years who were admitted to the PICU of Mofid Children's Hospital between April 2019 and May 2022. Inclusion criteria were: (1) PICU length of stay ≥24 hours and (2) availability of at least two serum sodium measurements during the PICU admission. The exclusion criteria were as follows: (1) patients who were admitted to the PICU for less than 24 hours, (2) patients who without recorded baseline demographic, anthropometric, and related biochemical measurements (3), patients lacking at least two documented serum sodium levels during admission. Demographic information was collected upon the patient's PICU admission and recorded in the unit's database in accordance with the standard procedure for admitting and discharging patients. The research team systematically performed comprehensive evaluations of the unit's

database. The weight of immobile infants under the age of two years was assessed according to a standard protocol. For children and adolescents over two years of age capable of standing, parents or nurses assisted in measuring their weight. Height measurements were obtained using a non-elastic measuring tape when the patient was in a supine position with the head in a neutral alignment and the lower limbs (knee and ankle) thoroughly stretched. The Glasgow Coma Scale (GCS) was evaluated upon the PICU admission.[13] The GCS score possesses a range extending from three (indicative of profound unconsciousness) to 15 (indicative of complete consciousness) in an individual. The GCS score was classified as mild (GCS > 13), moderate (8 < GCS < 13), and severe (GCS < 8).[14,15] The nutritional status at PICU admission was evaluated through the calculation of the BMI-for-age z-score values utilizing the World Health Organization growth charts[16,17] as well as the AnthroPlus program.[17] According to the nutritional status, the patients were classified as follows: (1) underweight (BMI-for-age z-score < -2), (2) normal weight (-2 ≤ BMI-for-age z-score ≤ +1), and (3) overweight/obese (BMI-for-age z-score > +1).[16,17] Malnutrition was defined as being either underweight or overweight/obese.[18,19] Hyponatremia at PICU admission was defined as serum sodium levels below 135 mmol/L and hypernatremia was defined as having a sodium level that exceeds 145 mmol/L. Patients were categorized according to all sodium values recorded during their PICU stay, leading to the identification of four distinct dysnatremia groups: normonatremia (all values 135–145 mmol/L), hyponatremia (≥1 value < 135 mmol/L and no values > 145 mmol/L), hypernatremia (≥1 value > 145 mmol/L and no values < 135 mmol/L), and mixed dysnatremia (≥1 value < 135 mmol/L and ≥1 value > 145 mmol/L at any time during admission). Sodium fluctuation was defined as the difference between the highest and lowest sodium concentrations during PICU admission and was categorized into our data-derived quartiles (Q1 ≤4 mmol/L, Q2: 4–8 mmol/L, Q3: 8–15 mmol/L, Q4 ≥15 mmol/L), with higher quartiles indicating greater fluctuation severity. The estimated glomerular filtration rate (GFR) was calculated utilizing the Schwartz formula.[20] Blood samples were obtained daily during PICU admission to evaluate the serum concentrations of biochemical variables. The concentration of serum sodium was determined using an ion-selective electrode (ISE) assay conducted with the Caretium XI-921 device (made in China). The creatinine measurement was performed using a Jaffe colorimetric-kinetic assay with the BioLis 24i analyzer (manufactured in Japan).

Statistical analysis

Statistical analysis was performed employing the Statistical Package software for Social Sciences (SPSS, Version 26; Chicago, IL, USA). The normality of the variables was assessed through the utilization of histogram charts and the Kolmogorov–Smirnov goodness of fit analysis. Continuous variables with a normal distribution, non-normally distributed variables, and categorical variables are represented as means and standard deviations (SD), medians and interquartile ranges (IQR), and proportions, along with their corresponding percentages. The Independent samples t-test and analysis of variance (ANOVA) were utilized to compare the mean values of variables that exhibit a normal distribution. In contrast, the Mann–Whitney U test and the Kruskal–Wallis test were applied to assess variables that do not follow a normal distribution. The Chi-square test was utilized to assess the differences in categorical variables between patients with normonatremia and those with dysnatremia. Logistic regression analysis was utilized to compute both the unadjusted and adjusted odds ratios (OR) along with their respective 95% confidence intervals (95% CI) regarding our clinical outcomes. This analysis included groups with dysnatremia, with normonatremia serving as the reference group, as well as quartiles of sodium level fluctuations, using the lowest quartile as the reference. The multivariate logistic regression model was adjusted for age, gender, diagnosis category, admission type, GCS score status, baseline serum sodium, eGFR, and nutritional status. Sensitivity analysis was also conducted after excluding participants with hypo- or hypernatremia at PICU admission. All *P*-values are evaluated as two-sided, and a *P*-value under 0.05 was considered a statistically significant level.

RESULTS

During the study period, a total of 1,126 patients were recorded. One hundred and two patients

were excluded for being admitted to the PICU for less than 24 hours; an additional 58 patients were excluded due to inadequate anthropometric and biochemical data. Finally, 966 patients enrolled into the study, including 423 girls and 543 boys.

Table 1 summarizes the baseline characteristics of all patients and by natremia status. Among the participants, 424 patients (43.9%) maintained normonatremia, whereas 542 (56.1%) developed dysnatremia during their PICU stay. The mean age was 53.9 ± 54.6 months and the mean BMI was 15.8 ± 7.4 kg/m². Most admissions were medical; the three most common diagnostic categories were neuromuscular disorders (25.5%), gastrointestinal diseases (12.9%), and cardiorespiratory conditions (12.7%). The majority of patients had mild GCS score status and were in a state of malnutrition. Compared to normonatremic patients, those who developed dysnatremia had lower baseline sodium levels, higher serum creatinine, and longer PICU stays. The rates of prolonged PICU stay and mortality were also significantly higher in the dysnatremic group.

No significant differences were observed among natremia status categories with respect to gender, age, weight, height, BMI, nutritional status, and

Table 1. The characteristics of participants across natremia status during PICU admission.

	Total sample (N = 966)	Normonatremia (N = 424)	Dysnatremia (N = 542)	*P**
Boys (%)	543 (56.2)	231 (54.5)	312 (57.6)	.34
Age (month)	53.9 ± 54.6	50.8 ± 54.1	56.4 ± 54.9	.11
Height (cm)	97.5 ± 32.9	96.3 ± 33.5	98.4 ± 32.5	.33
Weight (kg)	17.2 ± 14.9	17.2 ± 15.4	17.1 ± 14.5	.98
Body mass index (kg/m^2)	15.8 ± 7.4	15.9 ± 6.8	15.7 ± 7.8	.74
Admission type				
Elective surgery (%)	181 (18.7)	116 (27.4)	65 (12.2)	
Emergency surgery (%)	57 (5.9)	34 (8.0)	23 (4.2)	< .01
Medical (%)	728 (75.4)	274 (64.6)	454 (83.8)	
Diagnosis category				
Cardiorespiratory (%)	123 (12.7)	45 (10.6)	78 (14.4)	
Neuromuscular (%)	246 (25.5)	126 (29.7)	120 (22.1)	
Infectious disease (%)	73 (7.6)	10 (2.4)	63 (11.6)	
Hematology/oncology (%)	64 (6.6)	18 (4.2)	46 (8.5)	
Gastrointestinal (%)	125 (12.9)	36 (8.5)	89 (16.4)	< .01
Renal, endocrine (%)	97 (10.0)	39 (9.2)	58 (10.7)	
Surgical (%)	181 (18.7)	116 (27.4)	65 (12.0)	
Emergency (%)	57 (5.9)	34 (8.0)	23 (4.2)	
Glasgow Coma Score Status				
Mild (%)	634 (65.6)	309 (72.9)	325 (60.0)	
Moderate (%)	122 (12.6)	64 (15.1)	58 (10.7)	< .01
Severe (%)	210 (21.7)	51 (12.0)	159 (29.3)	
Nutritional status				
Normal weight (%)	441 (45.7)	200 (47.2)	241 (44.5)	
Underweight (%)	330 (34.2)	135 (31.8)	195 (36.0)	.40
Overweight or obese (%)	195 (20.1)	89 (21.0)	106 (19.6)	
Serum sodium level (mmol/L)	136.6 ± 5.1	138.0 ± 2.5	135.6 ± 6.3	< .01
Serum creatinine level (mg/dl)	0.66 ± 0.46	0.62 ± 0.32	0.70 ± 0.55	< .01
estimated glomerular filtration rate	86.9 ± 40.5	86.9 ± 38.1	86.8 ± 42.4	.97
Acute kidney injury (%)	59 (6.1)	12 (2.8)	47 (8.7)	< .01
PICU length of stay (days)	6.0 ± 17.5	2.8 ± 4.5	8.5 ± 22.7	< .01
Prolonged PICU stay† (%)	207 (21.4)	34 (8.0)	173 (31.9)	< .01
PICU mortality (%)	63 (6.5)	11 (2.6)	52 (9.6)	< .01

Data represented as mean ± standard deviation, or median (interquartile) for continuous variables and number and percent for categorical variables.
*Chi-square or Fisher's exact, and analysis of variance or Kruskal-Wallis tests were used to test the categorical and continuous variables across nutritional status categories.
†Prolonged PICU stay was defined as a length of stay of ≥7 days.

estimated GFR.

Supplementary table 1 shows the patient's characteristics according to natremia status categories. Hyponatremia was the most frequent abnormality (37.2%), followed by mixed dysnatremia (13.1%) and hypernatremia (5.9%). Neuromuscular disorders predominated among normonatremic, hyponatremic, and mixed dysnatremic patients, whereas gastrointestinal conditions were the main cause of admission in the hypernatremic group. In the majority of cases, the patients exhibited a mild GCS score and normal nutritional status across all categories of natremia. The incidence rates of prolonged PICU stay and PICU mortality were 8.0% and 2.6% for normonatremic patients, 23.6% and 6.1% for hyponatremic patients, 40.4% and 17.5% for hypernatremic patients, and 52.0% and 16.0% for mixed dysnatremic patients.

Table 2 provides the OR and corresponding 95% CI for odds of clinical outcomes across natremia status. Patients who developed PICU-acquired hyponatremia had significantly higher extended PICU stay and mortality odds compared to patients who maintained normonatremic status during their PICU admission in both unadjusted as well as age and gender-adjusted models. In the fully adjusted model, no significant association was found between PICU-acquired hyponatremia and the mortality in the PICU odds (OR: 1.33; 95% CI: 0.55-3.20). However, patients with PICU-acquired hyponatremia had a significantly higher likelihood of experiencing a longer stay in the PICU (OR: 3.62; 95% CI: 2.18-6.00) compared to patients who maintained a normonatremic status during their PICU admission. Patients with PICU-acquired hypernatremia had significantly higher all clinical outcomes odds in both crude and adjusted models compared to patients who maintained a normonatremic status during their PICU admission. In the fully adjusted model, the clinical outcomes odds for individuals with PICU-acquired hypernatremia were as follows: prolonged PICU stay (OR: 7.05; 95% CI: 3.21-15.48) and mortality (OR: 5.23; 95% CI: 1.72-15.92). The findings indicate that patients who experienced dysnatremia during their admission to the PICU had a significantly higher likelihood of an extended PICU stay compared to those who maintained a normonatremic status during their PICU admission. The ORs and the corresponding 95%CI were as follows: prolonged PICU stay odds (OR: 8.13; 95% CI:4.57-14.44) and PICU mortality odds (OR: 2.89; 95% CI:1.14-7.29).

Table 3 represents the association between fluctuations in serum sodium levels during PICU admission and clinical outcomes odds. Participants with the highest fluctuations in serum sodium levels, compared to patients with the lowest fluctuations, had significantly higher experiencing all clinical outcomes odds in both crude and adjusted models. In the full adjusted model, the ORs and the corresponding 95%CI were as follows: prolonged PICU stay odds ratio (OR: 9.93; 95% CI:5.27-18.71) and PICU mortality odds ratio (OR: 2.74; 95% CI:1.11-6.79).

Supplementary Tables 2 and 3 present a sensitivity analysis examining the relationship between sodium variation and the odds of clinical outcomes after excluding participants with dysnatermia at PICU admission. Findings showed

Table 2. The association between natremia status during PICU admission and risk of clinical outcomes.

	Normonatremia (N = 424)	Hyponatremia (N = 360)	Hypernatremia (N = 57)	Mixed dysnatremia (N = 125)
Prolonged PICU stay*				
Crude	1.00 (Reference)	3.54 (2.31-5.43)	7.76 (4.11-14.63)	12.42 (7.57-20.40)
Model 1	1.00 (Reference)	3.61 (2.35-5.55)	7.99 (4.19-15.25)	12.17 (7.40-20.00)
Model 2	1.00 (Reference)	3.62 (2.18-6.00)	7.05 (3.21-15.48)	8.13 (4.57-14.44)
PICU mortality				
Crude	1.00 (Reference)	2.44 (1.16-5.11)	7.99 (3.22-19.80)	7.15 (3.32-15.39)
Model 1	1.00 (Reference)	2.47 (1.75-5.18)	8.28 (3.26-21.02)	6.64 (3.05-14.44)
Model 2	1.00 (Reference)	1.33 (0.55-3.20)	5.23 (1.72-15.92)	2.89 (1.14-7.29)

Abbreviations: PICU: Pediatric Intensive Care Unit.
Model 1: adjusted for age and gender.
Model 2: additionally adjusted for admission type, diagnosis category, Glasgow Coma Scale score status, baseline serum sodium, eGFR, and nutritional status.
*Prolonged PICU stay was defined as a length of stay of ≥7 days.

Table 3. The association between fluctuations in serum sodium level during PICU admission and the risk of clinical outcomes.

	1st quartile (≤4 mmol/L)	2nd quartile (4-8 mmoL/L)	3rd quartile (8-15 mmol/L)	4th quartile (≥15 mmol/L)	*P*-value for trend
Prolonged PICU stay*					
Cases/number of patients	14/254	23/209	55/257	115/246	
Crude	1.00 (Reference)	2.12 (1.06-4.23)	4.67 (2.52-8.64)	15.05 (8.30-27.26)	< .001
Model 1	1.00 (Reference)	2.17 (1.08-4.33)	4.75 (2.56-8.16)	15.05 (8.30-27.28)	< .001
Model 2	1.00 (Reference)	1.98 (0.97-4.05)	3.86 (2.02-7.36)	9.93 (5.27-18.71)	< .001
PICU mortality					
Cases/number of patients	7/254	6/209	16/257	34/246	
Crude	1.00 (Reference)	1.04 (0.34-3.15)	2.34 (0.95-5.79)	5.66 (2.46-13.03)	< .001
Model 1	1.00 (Reference)	1.14 (0.37-3.45)	2.50 (1.00-6.22)	5.64 (2.44-13.04)	< .001
Model 2	1.00 (Reference)	1.02 (0.32-3.23)	1.69 (0.65-4.42)	2.74 (1.11-6.79)	.01

Abbreviations: PICU: Pediatric Intensive Care Unit.
Model 1: adjusted for age and gender.
Model 2: additionally adjusted for admission type, diagnosis category, Glasgow Coma Scale score status, baseline serum sodium, eGFR, and nutritional status.
†Prolonged PICU stay was defined as a length of stay of ≥7 days.

that patients who developed dysnatremia had significantly higher prolonged PICU stay odds. In addition, patients who developed hypernatremia during PICU admission had significantly higher PICU mortality odds (OR: 6.01; 95% CI:1.92 -18.85). However, no significant association was found between developing hyponatremia and mixed dysnatremia and the odds of PICU mortality. Furthermore, greater fluctuations in serum sodium levels were significantly associated with odds of clinical outcomes.

DISCUSSION

This retrospective cohort study is the first to evaluate the relationship between serum sodium level variations during PICU admission and clinical outcomes among critically ill pediatric patients in Iran. Our findings demonstrated that the development of PICU-acquired dysnatremia was independently associated with an increased risk of prolonged PICU stay, while hypernatremia and mixed dysnatremia were significant predictors of mortality. Moreover, both mild and marked fluctuations in serum sodium levels were linked to adverse outcomes, including extended hospitalization and higher mortality rates. Taken together, these results highlight the prognostic value of monitoring sodium trends during PICU admission. They suggest that sodium disturbances and fluctuations are not merely incidental findings but may serve as important clinical markers of disease severity and treatment complexity. Early recognition of these abnormalities may enable more precise risk stratification, closer clinical surveillance, and timely therapeutic interventions aimed at mitigating complications and improving outcomes in critically ill children. These data possess significant importance due to a variety of compelling reasons. First, our study evaluated dysnatremia developed during PICU admission, while previous works focused on dysnatremia at PICU admission or a single disturbance. This information can assist clinicians in carefully evaluating the implications of medical management decisions during PICU admission and remaining attentive on PICU-acquired dysnatremia. Second, recognizing that fluctuations in sodium levels are independent risk factor for extended stays in the PICU and associated mortality, researchers should further investigate the physiological causes and pathophysiological impact. This exploration may assist clinicians in identifying at-risk patients earlier in order to potentially improve clinical outcomes.

Dysnatremia is a common electrolyte disturbance in critically ill pediatric populations and has been increasingly recognized as an important prognostic factor.[2] Previous studies have predominantly focused on sodium abnormalities present at PICU admission, examining their relationship with length of stay and mortality.[2,21-26] However, limited studies have examined the association between PICU-acquired dysnatremia and the risk of worse outcomes, which may better reflect evolving physiological and therapeutic processes during critical illness.

Consistent with our findings, a prospective case–

control study reported that children who developed hyponatremia during their PICU stay experienced significantly longer admissions compared to those who maintained normonatremia, although mortality rates were similar between the groups.[27] Similarly, Luu *et al.* found that hyponatremia developing within the first two hours of PICU admission among children with bronchiolitis was associated with higher mortality, prolonged length of stay, and increased need for noninvasive ventilatory support.[22] In adult ICU cohorts, dysnatremia has also been linked to adverse outcomes. For example, Darmon *et al.* showed that ICU-acquired hypernatremia was associated with a higher risk of 28-day mortality, whereas hyponatremia did not show a similar effect.[28] Other large retrospective studies have demonstrated that hypernatremia and mixed dysnatremia are consistently associated with increased ICU length of stay and mortality, whereas the impact of hyponatremia is less uniform.[29,30] Our findings align with this broader literature, showing that hypernatremia and mixed dysnatremia are strongly associated with PICU mortality, whereas hyponatremia is more closely related to prolonged PICU stay but not mortality. The lack of a significant mortality associated with hyponatremia and mixed dysnatremia in our cohort may partly reflect their lower incidence and potentially different underlying pathophysiological mechanisms. In line with prior evidence, the relationship between dysnatremia and mortality appears complex, likely involving a combination of causal physiological effects, underlying comorbidities, and factors related to the severity and nature of the primary illness.[5,6,28,30] Several biological and clinical mechanisms may explain these associations. Sodium disturbances often reflect the underlying severity of illness—conditions such as severe sepsis, shock, or neurological injury can disrupt fluid and electrolyte homeostasis through neuroendocrine and inflammatory pathways.[31] Dysnatremia may also result from iatrogenic factors, including fluid administration strategies, diuretic use, osmotic therapies, and delayed correction.[32] Hypernatremia can exacerbate cellular dehydration, compromise cerebral perfusion, and worsen hemodynamic stability, thereby increasing mortality risk.[33] In contrast, hyponatremia may result from non-osmotic antidiuretic hormone secretion or fluid overload, leading to prolonged recovery but not necessarily increased short-term mortality.[33] Mixed dysnatremia may indicate greater physiological instability and repeated shifts in fluid balance, reflecting both disease severity and complex management.[2] Taken together, these mechanisms highlight that sodium disturbances are not merely incidental findings but may act as both markers and mediators of disease severity, thereby influencing clinical outcomes. Future large, prospective studies are needed to clarify these mechanistic pathways and determine whether early identification and targeted interventions for dysnatremia can improve outcomes in critically ill children.

Not only developing dynatremia during PICU admission but also the fluctuations in the serum sodium levels during PICU admission may substantially influence the clinical outcomes.[34] Our study findings indicated that even mild fluctuations in serum sodium levels during PICU admission and fluctuations exceeding 15 mmol/L are significantly correlated with an elevated risk of prolonged PICU stay and mortality, respectively. Interestingly, our data also showed that the incidence of prolonged PICU stay and mortality (represented in Table 3) as well as baseline severe GCS and malnutrition (data not shown), increased with increased quartile of sodium level fluctuations. In this particular framework, Topjian *et al.* demonstrated that substantial fluctuations in daily serum sodium levels during the management of externalized ventricular drains were correlated with heightened odds of in-hospital mortality in critically ill children with externalized ventriculostomy drains during PICU admission.[11] Moreover, a retrospective case-control study in critically ill children who were admitted to PICU showed that patients who were at the third and highest quartiles of sodium variability during PICU admission were significantly associated with higher odds of in-hospital mortality.[35] In the framework of the prospective study, it was shown that fluctuations in serum sodium levels from baseline up to 72 hours were similar between non-survivors and survivors among pediatric nontraumatic patients with coma admitted to PICU.[12] Another retrospective cohort study showed that adult patients who had the highest fluctuations in serum sodium levels compared to those with the lowest ones had a significantly higher risk of in-hospital death.[36] The explanations for the differences

in the results mentioned above include the study design, age group, sample sizes, place of admission (ward or ICU), differences in the study population, and the cut-off levels to define the fluctuations in serum sodium levels. However, although there is a strong rationale for the link between the highest fluctuations during ICUs admission and the risk of mortality, there is a lack of data on the risk associated with small sodium level fluctuations, and the mechanism leading to higher mortality remains unclear. The fluctuations of sodium levels could potentially serve as a crucial marker for assessing the severity of an underlying disease. This has the potential to offer valuable insights into disease progression and treatment strategies. Interestingly, a prospective cohort study showed that correcting dysnatremia is independently associated with survival, with the effect being greater with faster correction rates of up to 12 mmol/L per day.[28] However, our study was not designed to elucidate a possible causal relationship between fluctuations in sodium levels and the clinical outcomes risks. Due to the retrospective and observational nature of the study, we can only observe an association between exposures and outcomes and speculate on potential mechanisms.

Strength and limitation

The findings of our study have uncovered numerous strengths that significantly enhance the quality of our work. This study is one of the largest retrospective cohort studies evaluating the relationship between sodium variability during PICU admission and clinical outcomes in critically ill pediatrics. Our study is the first to examine PICU-acquired dysnatremia and fluctuations in sodium levels, focusing on their impact on the risk of extended PICU stays and mortality in patients admitted to the PICU. However, it is important to recognize that there are certain limitations that need to be taken into account. First, this study is limited by its retrospective observational design, as it evaluates previously collected information, which prevents the evaluation of causes of dysnatremia. Second, we had no data on several factors affecting sodium variations, including the nature of dysnatremia (acute, chronic, symptomatic, or asymptomatic), history of chronic health diseases, fluid management, diuretic therapy, nutritional management (enteral and parenteral), and medications (e.g., osmotic therapy). Furthermore, the retrospective nature of the study resulted in inconsistent availability of data on other electrolytes, including potassium, calcium, and chloride, so preventing their inclusion in the analysis and potentially leading to residual confounding. Third, our efforts included an endeavor to appraise the severity of illness by considering descriptive and biochemical variables, encompassing diagnosis category, nutritional status, GCS status, and baseline eGFR. Nevertheless, it is advisable to gauge the severity of illness by utilizing established markers such as the Pediatric Index of Mortality and the Pediatric Risk of Mortality. Despite our efforts to control for major confounders in our analyses, we must acknowledge that the possibility of residual or unmeasured confounders cannot be completely ruled out.

CONCLUSION

In conclusion, our research indicates that dysnatremia developed during PICU admission is linked to a higher risk of extended PICU stays. PICU-acquired hypernatremia was significantly associated with an increased risk of mortality. Even mild fluctuations in sodium levels during PICU admission, particularly those exceeding 15 mmol/L, are significantly correlated with an increased risk of prolonged PICU stay and mortality. This highlights the crucial need to carefully monitor serum sodium levels during a patient's PICU stay to improve clinical outcomes.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Approval No.: IR.SBMU.RICH.REC.1401.050). The requirement for written informed consent was waived due to the retrospective nature of the study and the use of de-identified data.

AVAILABILITY OF SUPPORTING DATA

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHORS' CONTRIBUTIONS

ZP and GA conceived and designed the research. MB, MH, and AB performed the procedure. AN analyzed data. ZP, AN, and GA wrote the manuscript. All authors read and approved the manuscript.

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