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Admission serum sodium and osmolarity are not associated with the occurrence or outcomes of acute respiratory distress syndrome in critically ill

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ABSTRACT

Background: Previous studies suggested that hypernatremia or hyperosmolarity may have protective effects in lung injury. We hypothesized that hypernatremia and/or hyperosmolarity would prevent ARDS.
Design: Retrospective cohort study of all admissions at medical, surgical, and multidisciplinary intensive care units in Mayo Clinic, Rochester from the year of 2009 to 2019. The occurrence of ARDS was identified using a validated computerized search strategy. The association between serum sodium/osmolarity and the occurrence of ARDS was analyzed using a multivariable logistic regression model. The relationship between serum sodium/osmolarity and outcomes of ARDS was analyzed using linear and logistic regression models.
Results: Among 50,498 patients, the serum sodium level on admission did not have a significant association with the occurrence of ARDS, with an adjusted odds ratio of 0.95 [95% CI (0.86, 1.05)]. There was no significant association between calculated serum osmolarity and the occurrence of ARDS, with an adjusted odds ratio of 1.03 [95% CI (1.00, 1.07)]. 1560 patients developed ARDS during the ICU stay. Their serum sodium level and osmolarity level did not have a significant association with their outcomes.
Conclusions: Admission serum sodium or serum osmolarity were not associated with the occurrence or outcomes of ARDS in ICU.

1. Introduction

Acute Respiratory Distress Syndrome (ARDS) is reported to occur in around 5–10% of critically ill patients and is associated with high mortality and morbidity [1,2]. The current treatment strategy is largely supportive, and very few therapeutic interventions have demonstrated outcome benefits. Meanwhile, a large body of literature has demonstrated that ARDS is a preventable condition by identifying the key elements of ARDS prevention, including lung-protective ventilation, early reassessment of non-invasive ventilation, standard aspiration precautions, adequate antimicrobial treatment and infection source control, optimal fluid management, and restrictive transfusion [3]. A scoring system of predisposing conditions and risk modifying factors of lung injury, the Lung Injury Prediction Score (LIPS), was derived from a multicenter observational cohort and demonstrated satisfactory validity in predicting lung injury risk in hospitalized population [4,5]. Therefore, recent research efforts on ARDS have been re-directed towards the prediction and prevention of this devastating complication of many critical illnesses [6].

The lung-protective effect of hypernatremia and hyperosmolarity has been hypothesized based on observational and experimental studies. Large cohort studies indicated that hypernatremia and

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; LIPS, Lung Injury Prediction Score; ICU, Intensive Care Unit; APACHE, Acute Physiology and Chronic Health Evaluation; PaO2, The partial pressure of oxygen in the arterial blood; FiO2, The fraction of inspired oxygen; PEEP, Positive end-expiratory pressure; IQR, Interquartile range; GEE, Generalized Estimating Equations; OR, Odds Ratio; CI, Confidence Interval; AECC, American-European Consensus Conference.

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hyperosmolarity during the first 24 h of intensive care unit (ICU) stay were associated with worse outcomes in the general critically ill population, however, the association was not seen in the subgroup with respiratory diagnoses [7-9]. These findings suggested that hypernatremia or hyperosmolarity may have lung-protective effects in the critically ill. On this basis, many animal studies were conducted and detected lung-protective effects of hypernatremia or hyperosmolarity. Bihari and colleagues reported induced hypernatremia, created by infusing hypertonic saline, mitigated lung injury in an animal model. Similarly, more preclinical data showed that hyperosmolar infusion attenuated lung injury in various lung injury animal models, created by hemorrhagic shock [10-12], aspiration [13], intratracheal acid [13], or infection [14]. The protective effect of induced hypernatremia in moderate-to-severe ARDS was also demonstrated in a prospective clinical trial [15].

The hypothesized lung-protective effect of hyperosmolarity remains unproven in large-scale clinical settings. Thus, we have designed this study to retrospectively investigate whether sodium level and calculated osmolarity level upon admission to the ICU are associated with the occurrence rate or outcomes of ARDS. We hypothesized that a higher serum sodium level or higher calculated serum osmolarity within 24 h after ICU admission would be associated with 1) a lower occurrence rate of ARDS in patients at risk of ARDS and 2) favorable outcomes in patients who developed ARDS.

2. Methods

The study was approved by Mayo Clinic Institutional Review Board (Approval No. 13–008906, Title: 'Does Serum Osmolarity Affect Outcomes of Patients with Acute Lung Injury?', Approved on 12/4/2013). All patients provided informed consent allowing their medical records reviewed for research purposes. All research activities were in accordance with the ethical standards of the Mayo Clinic ethics committee on human experimentation and with the Helsinki Declaration of 1975.

2.1. Study population

This is a retrospective cohort study of adult patients admitted to the medical, surgical, and multidisciplinary ICUs at two hospitals in the Mayo Clinic Health System from January 1, 2009, to January 1, 2019. Our inclusion criterion was adult patients with age ≥ 18 years old. The exclusion criterion was patients who did not provide authorization for use of their health records. Jail or prison detainees were also excluded according to Minnesota Research Authorization Regulations. Only the first ICU admission was included for review if a patient had more than one ICU admissions during one hospitalization.

2.2. Data collection

The diagnoses, key events in the clinical course, laboratory tests, respiratory parameters, the severity of illness (represented by The Acute Physiology and Chronic Health Evaluation, APACHE III score), and outcomes were collected from the EHR. The definitions of the collected data items are listed in Supplemental Table 1. The first available serum sodium value and the most extreme sodium value within 24 h after ICU admission were used for analysis. The most extreme sodium value was the value with the largest deviation from the laboratory normal range (135–145 mmol/L). All values documented in the EHR were considered true values and we did not exclude 'outliers'. The first available sodium, urea, and glucose values within 24 h after ICU admission were used for the calculation of serum osmolarity.

2.3. Computable phenotyping of ARDS

An EHR-based computable phenotyping strategy to identify ARDS has been previously published [16]. According to this rule-based search strategy, physicians' judgement, if available, are fully acknowledged. All patients who had a clinical diagnosis of ARDS after ICU admission were identified. A clinical diagnosis of ARDS was defined as ICD-9 code 518.52, or ICD-10 code J80, or having 'ARDS' or' acute respiratory distress syndrome' documented in the clinicians' notes. In addition, for patients who did not have a clinical diagnosis of ARDS during the ICU admission, automatic EHR searching was applied. ARDS was identified if all these criteria were met:

(1) PaO_2/FiO_2 ratio ≤300.
(2) PEEP ≥5 cm H_2O on invasive or noninvasive mechanical ventilation.
(3) Bilateral infiltrates on chest radiographs.
(4) The presence of at least one risk factor for ARDS (sepsis/septic shock, pneumonia, pancreatitis, trauma, aspiration, multiple transfusion, drug overdose, and shock) ≤7 days prior to the onset of 1), 2), and 3).

(1), (2), (3) must be met concurrently.

The following screening was conducted to further increase the specificity of identifying ARDS. ARDS risk factors (i.e., sepsis/septic shock, pneumonia, aspiration, pancreatitis, trauma, drug overdose, shock, and multiple transfusions) were searched for in the health records. Among cases without known ARDS risk factors, those with cardiogenic pulmonary edema, cardiogenic shock, or acute decompensated heart failure were excluded. According to previous ARDS cohort creation exercise, 28% of ARDS cases were documented by clinicians, when the computable phenotyping strategy based on the Berlin definition was used as gold standard [16].

2.4. Statistical analysis

Patient characteristics were summarized descriptively with median (Interquartile range, IQR) for continuous variables and frequency counts and percentages for categorical variables. In the first analysis, the relationship between sodium/osmolarity and the occurrence of ARDS was assessed using univariate and multivariable logistic regression. The multivariable models adjusted for admission ICU and lung injury prediction score (LIPS) using restricted cubic splines. The assumption of a linear function form was assessed by comparing model fit to a version using restricted cubic splines. The second analysis assessed the relationship between sodium/osmolarity and outcomes of interest, among patients who developed ARDS in the ICU, using univariate and multivariable linear regression models with generalized estimating equations (GEE). Outcomes of interest were ICU-free days, ventilation-free days, and mortality within 28 days of ARDS diagnosis. The multivariable models adjusted for admission ICU, APACHE score, and PaO_2/FiO_2 ratio. A similar analysis considered the primary explanatory variable of most extreme sodium in the first 24 h of ICU admission. Patients who developed ARDS prior to ICU admission were excluded from the first analysis because the endpoint of the analysis was the occurrence of ARDS. Patients who developed ARDS prior to ICU admission were also excluded from the second analysis because the variable time lapse between ARDS recognition and ICU admission (i.e. the time of sodium/osmolarity collection) introduced uncontrollable confounding factors. Sodium values were analyzed on a scale of 10 mmol/L for the convenience of calculation and display. For example, an Odds Ratio of 0.88 means the odds of an event reduces to 0.88 times when the sodium level increases by 10 mmol/L. Similarly, calculated osmolarity values were analyzed on a scale of 10 Osm/L.

In the first analysis, data were missing for sodium and calculated osmolarity. Multiple imputations were used to handle missing data for these variables assuming data were missing at random. Twenty-five imputed datasets were created, analyses run on each and results pooled across imputations to account for uncertainty in missingness. In the second analysis data were missing for sodium, calculated osmolarity,

Table 1
Patient demographics ($n = 50,498$).

Characteristic	Patients with a sodium value less than the median value[§] ($N = 19,195$)	Patients with a sodium level greater than or equal to the median value ($N = 27,061$)	First Sodium value missing ($N = 4242$)
Age, median (Q1, Q3)	65.0 (53.0, 75.0)	65.0 (52.0, 76.0)	61.0 (43.0, 75.0)
Gender, n (%)			
Female	8330 (43%)	12,149 (45%)	1888 (45%)
Male	10,865 (57%)	14,911 (55%)	2354 (55%)
Missing	0 (0%)	1 (0%)	0 (0%)
BMI, median (Q1, Q3)	27.8 (23.8, 33.0)	28.2 (24.1, 33.5)	27.6 (23.6, 32.7)
Type of ICU, n (%)			
Medical ICU	7249 (38%)	10,182 (38%)	1444 (34%)
Medical/Surgical/Transplant ICU	4882 (25%)	5440 (20%)	964 (23%)
Surgical/Trauma ICU	7064 (37%)	11,439 (42%)	1834 (43%)
Lung Injury Prediction Score, median (Q1, Q3)	4.5 (2.5, 7.0)	4.0 (2.0, 6.5)	2.5 (1.0, 4.0)

[§] Median sodium level: 134.5 mmol/L.

APACHE score, and PaO_2/FiO_2 ratio. Similar to the first analysis, multiple imputation was used and 25 imputed datasets were created. In all analyses two-tailed *p*-values of 0.05 or less were considered statistically significant. Data management and statistical analysis were performed in SAS Studio 3.8 (SAS Institute Inc., Cary, North Carolina).

3. Results

During the study period, 82,084 patients from medical, surgical and trauma ICUs met the screening criteria. 50,498 patients met the inclusion criteria (Table 1). Of these, 1560 patients developed ARDS during the ICU stay (Fig. 1). Patients with new-onset ARDS during ICU admission had a 28-day mortality of 34%. Their 28-day ICU-free duration was 18.0 (IQR, 0, 23.7) days, and their 28-day ventilator-free duration was 24.8 (IQR 21.3, 26.5) days.

The univariate analysis showed that serum sodium level upon ICU admission was associated with a decrease in the occurrence of ARDS [OR 0.88 (95% CI 0.80, 0.98; *p*-value = 0.016]. However, after adjustment, serum sodium level was not associated with a decrease in the occurrence of ARDS [aOR 0.95, 95% CI (0.86, 1.05); *p*-value = 0.310]. Similarly, the univariate analysis assessing the relationship between calculated serum osmolarity upon ICU admission and the occurrence of ARDS was significant [OR 1.10, 95% CI (1.06, 1.14); p-value<0.001], but after adjustment the association was no longer statistically significant [aOR 1.03, 95% (CI 1.00, 1.07); p-value = 0.085] (Table 2).

Among the patients who developed ARDS during the ICU stay, the first serum sodium level upon admission did not have a significant association with ICU-free days [adjusted estimated difference 0.08 days, 95% CI (−0.85, 1.02), $p = 0.859$], ventilator-free days [adjusted estimated difference − 0.02, 95% CI (−0.62, 0.58), $p = 0.950$], or 28-day mortality [aOR, 1.02, 95% CI (0.84, 1.24), $p = 0.810$]. The association remained insignificant when the most extreme sodium values during the first 24 h of ICU stay were used for analysis. In addition, there was no significant association between the calculated serum osmolarity and the outcomes of ARDS [adjusted estimated difference in ICU-free days −0.26, 95% CI (−0.63, 0.12), $p = 0.177$; adjusted estimated difference in ventilator-free days −0.05, 95% CI (−0.28, 0.19), $p = 0.705$; aOR of 28-day mortality 1.07, 95% CI (0.99, 1.15), $p = 0.112$] (Table 3).

4. Discussion

This retrospective cohort study suggested that the sodium level or calculated osmolarity level during the first 24 h of ICU admission did not have a significant association with the occurrence rate of ARDS during the following ICU stay. Among the patients who developed ARDS during ICU admission, hypernatremia or hyperosmolarity were not associated with a difference in their clinical outcomes.

Hypernatremia and hyperosmolarity are common in critically ill patients. There are a wide variety of causes, including poor oral intake, renal dysfunction, or iatrogenic factors such as the use of diuretics or sodium-containing medications [17]. Their effects on lung injury remain controversial. Preclinical studies show that hypertonic fluid may mitigate lung injury by affecting both the innate and adaptive immunity reduction in lung injury [18]. Hypertonic saline solution affects the release of cytokines [19,20], reduces neutrophil sequestration [11,14,21,22], and inhibits endothelial cell activation [23]. Another proposed lung-protective mechanism of hyperosmolarity is preventing an increase in permeability by reducing calcium influx through mechanosensitive calcium channel TRPV4 [24]. Other reported mechanisms include enhancing the lung capillary barrier [25], or lowering pulmonary vascular resistance therefore improving perfusion of ventilated regions of the lung [26]. On the contrary, Yagi and colleagues reported hyperosmolarity is a risk factor for increased extrapulmonary lung water [27] which could lead to worse respiratory outcomes [23].

In clinical settings, the hypothesized lung-protective effect of hypernatremia/hyperosmolarity has been tested in prospective clinical studies and remains controversial. A randomized trial comparing hypertonic to isotonic crystalloid fluid as prehospital resuscitation suggested that the hypertonic saline group had a lower incidence of respiratory distress syndrome, although statistically insignificant [28]. Another randomized trial studying the lung-protective effect of hypertonic saline in blunt trauma was stopped for futility after the second interim analysis and did not demonstrate a difference in ARDS-survival [29]. Empirically induced hypernatremia has suggested clinical improvement in patients with moderate-to-severe ARDS in a clinical trial [15], however, it is still unknown whether hypernatermia secondary to other reasons, such as care process or dehydration, has lung-protective effect. Considering that hypernatremia and hyperosmolarity were reported to be associated with worse outcomes in the general critically ill population [7-9], the absence of association between hypernatremia/hyperosmolarity and mortality in this study suggests that hypernatremia and hyperosmolarity may have protected the subgroup of ARDS patients from poor outcomes.

Our study has several strengths. First, this is the first large clinical cohort study that investigated the association between hypernatremia/hyperosmolarity and ARDS in the era of Berlin definition. Most of the previous studies on hyperosmolarity and lung injuries were conducted in trauma-induced organ injury models. In our cohort, we included patients from various types of ICUs, representing a comprehensive real-world critically ill population who were at risk of ARDS due to different predisposing conditions, such as sepsis, surgeries, transfusions, etc. Their ARDS risk was stratified by the lung injury prediction score, which enabled us to build regression models to assess the association between hypernatremia/hyperosmolarity and ARDS. Second, studying ARDS in observational cohorts is traditionally challenged by the well-known under-recognition of this syndrome in the extremely complex critical care setting. The clinical recognition rate remains low from 26.5% using AECC (American-European Consensus Conference) definition [30] as the gold standard to 28.4% using the Berlin definition as

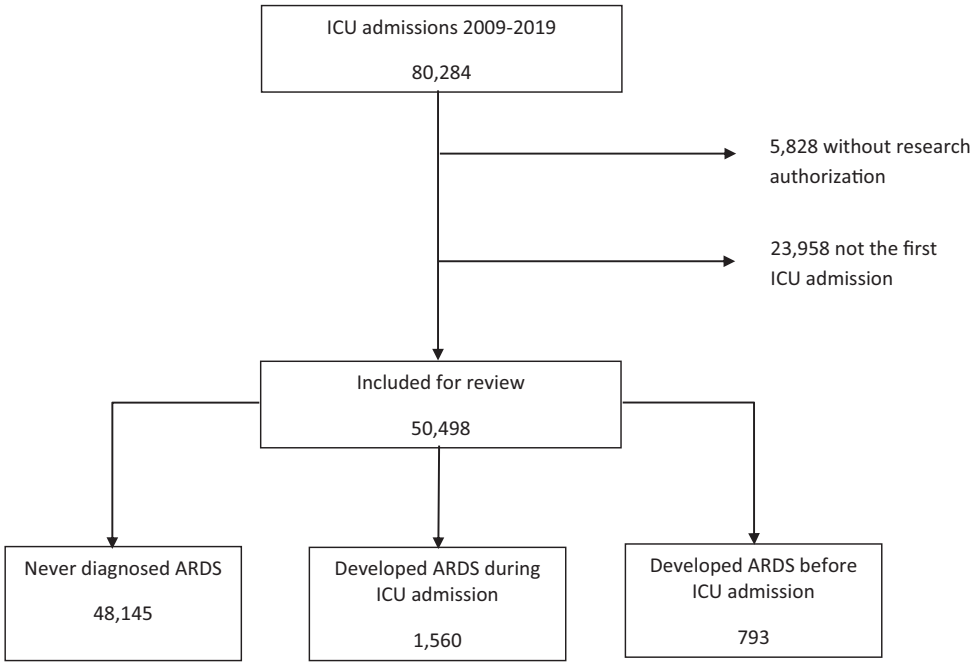

Fig. 1. Among 50,498 admissions that met the inclusion criteria, 1560 patients developed ARDS during the ICU stay.

Table 2
The association between sodium/ calculated osmolarity and the occurrence of ARDS during ICU admission.

Input variable of Logistic regression	Unadjusted			Adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
First ICU sodium value						
ARDS during ICU stay	0.88	(0.80, 0.98)	0.016	0.95	(0.86, 1.05)	0.310
Calculated osmorality						
ARDS during ICU stay	1.10	(1.06, 1.14)	<0.001	1.03	(1.00, 1.07)	0.085

The first ICU sodium value was analyzed on a scale of 10 mmol/L. For example, an Odds Ratio of 0.88 means the odds of the occurrence of ARDS reduces to 0.88 times when the sodium level increases by 10 mmol/L.
The calculated osmolality was analyzed on a scale of 10 Osm/L.

the gold standard [16]. The application of a computable phenotyping strategy allowed us to identify all ARDS cases and avoid underdiagnosis.

There are several limitations of the study. First, retrospective studies in the complex critical care setting are often affected by confounding factors. Thus, we adjusted the logistic regression models for admission reasons and lung injury risk to limit confounding biases. Similarly, the linear regression models were adjusted for admission reasons, APACHE score, and PO_2/FiO_2 ratio. Prospective trials are still needed to investigate whether manipulating osmolarity changes the outcomes of lung injury. Second, the single laboratory measurement we used for the analyses may not represent the dynamic trend of electrolytes that leads to fluid shift. As a supplement to the main analysis, the most extreme sodium values were entered into the model resulting in the same conclusion. Due to the retrospective nature of the study, we did not have the capacity to identify artifact values (or 'outliers'). Third, this report only reflects an experience prior to the COVID-19 era,

Table 3
The association between admission sodium/calculated osmolarity and the outcomes of ARDS during ICU admission.

Input variable of Regression models	Unadjusted			Adjusted		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value
First sodium ICU value[†]						
ICU-free days[*]	0.32	(−0.66, 1.31)	0.523	0.08	(−0.85, 1.02)	0.859
Ventilation-free days[‡]	−0.07	(−0.66, 0.51)	0.807	−0.02	(−0.62, 0.58)	0.950
28-day mortality[⁂]	0.95	(0.78, 1.16)	0.643	1.02	(0.84, 1.24)	0.810
Calculated osmolarity[‡]						
ICU-free days	−0.57	(−0.95, −0.19)	0.003	−0.26	(−0.63, 0.12)	0.177
Ventilation-free days	−0.04	(−0.27, 0.19)	0.754	−0.05	(−0.28, 0.19)	0.705
28-day mortality	1.12	(1.04, 1.22)	0.003	1.07	(0.99, 1.15)	0.112
Most extreme sodium value in first 24 hours[†]						
ICU-free days	1.26	(0.20, 2.32)	0.020	0.57	(−0.48, 1.61)	0.287
Ventilation-free days	0.12	(−0.51, 0.76)	0.698	0.17	(−0.48, 0.82)	0.604
28-day mortality	0.84	(0.68, 1.03)	0.096	0.98	(0.78, 1.21)	0.822

[*] The estimates for ICU-free days are the estimated difference in days alive and days spent out of the ICU within 28 days from admission; patients who die have zero ICU-free days.
[‡] The estimates for Ventilation-free days are the estimated difference in days alive and days off ventilation within 28 days from admission.
[⁂] The estimates for 28-day mortality are Odds Ratios.
[†] The first ICU sodium value and the most extreme sodium value in the first 24 h were analyzed on a scale of 10 mmol/L.
[‡] Calculated osmolarity was analyzed on a scale of 10 Osm/L.

while 'rapidly improving ARDS' [31] consisted of a significant portion of the ARDS patients. Thus, the observed mechanical ventilation duration is shorter than that during the COVID-19 pandemic. The authors also attributed the short mechanical ventilation duration to persistent compliance to evidence-based care, such as lung-protective ventilation, conservative fluid management, daily assessment for weaning, and offering palliative care.

Overall, our study is the first large-scale clinical cohort study that investigated the potential association between admission sodium/osmolarity levels and ARDS during ICU admission. The results did not support the manipulation of serum sodium/osmolarity as a lung-protective measure at the early stage of critical illnesses.

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Author contributions

Funding acquisition and project administration: HL;Conceptualization: HL, AB, OG; Data Curation: RK, TW, HL; Formal Analysis and methodology: TW, HL, AL; Writing-original draft: HL; Writing-review & editing: OG, SC, AL, AB.

Consent for publication

All the authors give their authorization to publish the article.

Availability of data and materials

The data used for this research are available from the corresponding author on reasonable request and subject to Institutional Review Board guidelines.

Ethical approval and consent to participate

This study was reviewed and approved by the Institutional Review Board at Mayo Clinic, Rochester (IRB 13-008906). All research activities were in accordance with the ethical standards of the Mayo Clinic ethics committee on human experimentation and with the Helsinki Declaration of 1975. Informed consent was waived for patients with Minnesota research authorization.

Declaration of Competing Interest

All authors have disclosed that they do not have any conflicts of interest related to this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154179.

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