ICU Mortality is Increased in Septic Shock Patients Accompanied with Hypo- or Hyper- Serum Osmolarity: A Retrospective Study

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ICU mortality is increased in septic shock patients accompanied with hypo- or hyper- serum osmolarity: A retrospective study

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Take-home message: Serum osmolarity is an easy and reliable factor to predict ICU mortality of septic shock patients. Correction of hyper-osmolarity could lead to a reduction in the mortality.
Abstract

Purpose: While many factors that are associated with increased mortality in septic shock patients have been identified, the effect of serum osmolarity to altering patient outcomes among ICU patients with septic shock has not been studied. This study was designed to examine the association of serum osmolarity with ICU 28-day mortality in that population.

Methods: The MIMIC-IV database was employed to identify patients diagnosed with septic shock. The serum osmolarity was calculated according to the serum concentration of Na⁺, K⁺, glucose and urea nitrogen synchronously. The statistical approaches used included multivariate logistic regression, propensity score analysis, inverse probability-weighting and causal mediation analysis.

Results: In this study, significant difference of 28-day mortality was observed in septic shock patients accompanied with hypo-osmolarity, hyper-osmolarity and normal osmolarity (30.8%, 35.0% and 23.0%, P<0.001) which was detected at ICU admission. We also found that transforming the hyper-osmolarity into normal osmolarity by fluid therapy in day 2 and day 3 would decrease this mortality.

Conclusion: Serum abnormality is significantly associated with increased 28-day mortality in septic shock patients.

Key words: Serum osmolarity, Septic shock, ICU mortality
Introduction

Sepsis is a complex disorder in intensive care unit (ICU) and has severe health and economic burden on the patient and healthcare systems worldwide [1, 2]. According to the latest definition (Sepsis-3), septic shock is defined as a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are profound enough to substantially increase the risk of mortality [2, 3]. As concluded by Jean-Louis V et.al, the frequency of septic shock was estimated at 10.4% in studies reporting values for patients diagnosed at ICU admission and the mean ICU mortality of septic shock patients was 37.3% [3].

Over the past decades, a substantial amount of risk factors have been identified to predict the ICU mortality of septic shock patients, including serum albumin level, central venous pressure measurement, sequential organ failure assessment (SOFA) score, acute physiology and chronic health evaluation II(APACHE II) score and simplified acute physiology score II (SAPS II) [4-8]. However, the role of admission serum osmolarity which reflects the distribution of extracellular and intracellular water distribution, has not been studied in septic shock patients.

Serum osmolarity mainly depends on the concentration of Na⁺, K⁺, glucose and urea nitrogen, and is strongly associated with various body fluid balance [9]. The relativity of serum osmolarity and disease severity or hospital mortality has already been studied in several patient populations like those with stroke, intracranial hemorrhage, acute coronary syndrome, pulmonary disease and those admitted in the ICU [10-15]. Despite
the consistency of clinical results indicating that serum osmolarity abnormalities are associated with increased hospital mortality, these conclusions are still not applicable to septic shock patients.

In this study, we conducted a retrospective study investigating the relationship between admission serum osmolarity and ICU mortality in patients with septic shock, collected in the MIMIC-IV database. Moreover, we studied whether the correction of serum osmolarity abnormality after admission could have a positive effect on the outcome of these patients.

**Methods**

**Study population**

This study is a retrospective study collected data from the Medical Information Mart for Intensive Care IV (MIMIC-IV version 0.4) database [16]. The author Gang H acquired the access of this database (Certification number 39516115). Firstly, 13604 patients diagnosed with sepsis were collected from this database. Then, we excluded patients who were not admitted into the ICU for the first time and those younger than 18 years old. Also, we excluded sepsis patients without septic shock and 5055 patients were preliminarily included in this study. Afterwards, according to the latest sepsis-3 criteria, 69 patients with sofa score lower than 2 points, and 279 patients with ICU stay shorter than 24 hours were excluded. Therefore, 4707 septic shock patients met the criteria and included in the final study.
In our study, the patients’ age, gender, weight, comorbidities, type of ICU admission, mean arterial pressure (MAP), heart rate, temperature, respiratory rate, oxygen saturation (SpO2), white blood cell (WBC), hemoglobin, platelet, sodium ($\text{Na}^+$), potassium ($\text{K}^+$), glucose, urea nitrogen, creatinine, albumin and lactate detected at the ICU admission were included.

**Calculation of serum osmolarity**

Serum osmolarity was calculated using the equation $(\text{Na}^+ + \text{K}^+) \times 2 + (\text{glucose}/18) + (\text{urea}/2.8)$. Only values of each element measured at the same time were used in this study. In this study, 290-309 mmol/L was used as the normal range and reference group. Hyperosmolarity (> 309 mmol/L) was categorized into two groups (310-319 mmol/L and > 319 mmol/L) in order to further examine the effect of hyperosmolarity in septic shock patients.

**Primary and secondary outcomes**

The primary outcome of this study is the ICU 28-day mortality. The secondary outcomes included the hospital mortality, length of ICU stay, volume of fluids administration, volume of crystalloids administration, volume of urine output, colloids intake, blood products intake, albumin intake, vasopressors-free days, ventilation-free days and AKI incidence.
Statistical analysis

Continuous variables are presented as mean and standard error (SE) or median and interquartile range (IQR). Categorical variables are presented as numbers and percentages. Comparisons between groups are made using Student’s t test or analysis of variance or Kruskal-Wallis test for continuous variables and X² test for categorical variables.

Multivariate regression was selected to characterize the relationship between serum osmolarity and ICU mortality. Baseline characteristics such as age, gender, weight, sofa score, MAP, heart rate, hypertension, respiratory rate, temperature, SpO₂, wbc, plt, hemoglobin, bun, creatinine, lactate, serum osmolarity group, use of albumin, use of colloids, use of blood products were selected to enter the multivariate logistic regression model (stepwise backward elimination method). In this study, the loss of variables was replaced by the mean value if the proportion of lost values was less than 10%, or replaced by values within adjacent 2 days firstly if this proportion ranged from 10% to 20%. The value would be abandoned if the percentage of loss was larger than 20%.

Except for multivariate logistic regression, propensity score matching (PSM) and propensity score based inverse probability of treatment weighing (IPTW) were used to adjust the covariates to ensure the robustness of our finding. 1:1 nearest neighbor matching with a caliper width of 0.05 was applied, and the IPTW model was created using the estimated propensity scores as weights. Afterwards, the logistic regression
was performed on the matched and weighted cohort separately, while the outcome was generated from the matched cohort.

Causal mediation analysis (CMA) produces an average causal mediation effect (ACME), average direct effect (ADE) and total effect on the outcome mediating through a mediator. In this study, we explored whether the effect of serum osmolarity on ICU mortality was proportionally mediated by the SpO2 and serum lactate.

Results

Baseline characteristics

In this study, a total of 4707 patients diagnosed with septic shock were enrolled, and the flow diagram of cohort selection was shown in Fig. 1. The baseline characteristics of survivors and non-survivors were presented in Table 1. The non-survivors had significantly higher sofa score (11.5 vs 8.5) and lactate (5.5 vs 3.7). Also, the serum osmolarity was statistically higher (307.3 vs 304.7) in non-survivor group, compared with that in survivor group.

Primary and secondary outcomes

Serum osmolarity was categorized into 4 groups and outcomes were compared within these groups using chi-square test or Kruskal-Wallis test. As shown in table 2, the ICU 28-day mortality was significantly lower in normal serum osmolarity group (290-309
mmol/L) than hypo-osmolartity (< 290 mmol/L) and hyper-osmolarity (310-319 mmol/L and > 319 mmol/L) (23.0% vs 30.8%, 33.9% and 36.0%, P<0.001). This difference was still observed in hospital mortality of septic shock patients. However, the difference of ICU length of stay (LOS) was not significant in 4 groups (P = 0.249).

In this study, we also compared albumin intake, fluid intake (crystalloids intake, colloids intake and colloids intake), urine output, vasopressor-free days, ventilation-free days and acute kidney injure (AKI) incidence in these groups and the detailed results were presented in the Table 2. Compared with hyper-osmolarity group, less fluid was administrated in hypo and normal osmolarity patients (day 1 and day 2, P<0.01), while more urine was produced (day 1, 2 and 3, P<0.01). Besides, the proportion of patients who achieved albumin, colloids and blood products infusion was statistically higher in hypo-osmolarity group (P<0.01), while the AKI incidence within first 24 hours was significantly higher in hyper-osmolarity group.

**Sensitivity analysis**

The multivariate logistic regression was used to identify the relationship between serum osmolarity and ICU mortality, and the result showed that both hypo-osmolarity and hyper-osmolarity were significantly associated with ICU mortality (OR 1.48, p=0.002 and OR 1.28 p=0.009). Except for multivariate logistic regression, the propensity score matching model (PSM) and inverse probability of treatment weighing (IPTW) were also used to verify this relationship, and the same trend of association was observed.
Causal mediation analysis (CMA) showed that the SpO2 mediated 4.90% (95% CI 1.99%-7.85%; P=0.002) of the effect of serum osmolarity in ICU mortality, and the level of lactate at admission mediated 5.41% (95% CI 2.40%-8.22%; P=0.002) of this effect (Fig. 2).

**Correction of abnormal serum osmolarity decrease the ICU mortality**

In this study, we also presented the dynamics of mortality and serum osmolarity within 3 days after ICU admission (Fig. 3). As shown in figure 3A, those patients with hypo-osmolarity at admission transformed to normal osmolarity in day 2 and day 3 after treatment did not show significant decrease of mortality, compared with those remained in hypo-osmolarity. However, this trend did not exist in normal and hyper-osmolarity group. In normal osmolarity group, the ICU mortality was statistically lower in patients maintaining normal osmolarity or transforming to hypo-osmolarity, compared with those transformed to hyper-osmolarity in day 2 and day 3 (P<0.001) (Fig. 3B). Obviously, in the hyper-osmolarity group, patients who achieved the normal osmolarity in day 2 and day 3 had a statistically lower ICU mortality (P<0.001 and P<0.01) than those patients remaining hyper-osmolarity (Fig. 3C).
Discussion

Although many previous studies have studied the association between serum osmolarity and mortality in critically ill patients, emergency medical patients and patients with stroke, intracranial hemorrhage and acute coronary syndrome, there was limited study identifying the relationship between serum osmolarity and ICU mortality of septic shock patients. In this study, we demonstrated that abnormal serum osmolarity was associated with significantly higher ICU 28-day mortality than normal serum osmolarity for the first time, as well as higher hospital mortality. We also verified that correction of serum osmolarity into the normal range would decrease this mortality.

Fluid balance of the body is of vital importance for septic shock patients, and serum osmolarity plays a significant role in the distribution of intracellular and extracellular fluid distribution [11, 17]. As reported, perturbation of serum osmolarity is common in patients who are admitted into the ICU, which leads to the disturbance of body’s internal environment, potentially resulting in adverse outcomes [18]. Hyper-osmolarity could lead to the mobilization of fluid from venous capacitance vessels to the circulatory volume, thereby aggravating the hypoxia of organs or tissues [19, 20]. Besides, hyper-osmolarity is always accompanied by hypernatraemia or hyperglycaemia, which have been reported as separate risk factors for cardiac mortality [21, 22]. In previous study, hypo-osmolarity on admission were also significantly associated with increased mortality in critically ill and emergency patients [18]. However, the exact pathophysiological mechanism of hypo-osmolarity on increased mortality was still unknown.
For septic shock patients, hemodynamic instability is widely recognized as a risk factor for mortality, and many approaches have been practiced to detect and then reverse that instability [23, 24]. Blood pressure, mean arterial pressure and lactate concentration are three major factors indicating the fluid balance or tissue perfusion of the body, and plenty of studies have focused on them [25-27]. However, except for these factors, serum osmolarity is also an effective one to identify the instability of fluid balance. The serum osmolarity could simply reflect substantial organ dysfunction or derangement of overall homeostatic mechanisms for salt, glucose and urea in particular, thereby it is a very easy score to calculate, based on the data that are generally available for most hospital admissions. Besides, we have identified the treatment or correction of the hyper-osmolarity detected on admission could lead to a reduction in mortality among septic shock patients, indicating that serum osmolarity could serve as a credible method to predict ICU mortality of these patients.

Although this study is the first one to investigate the relationship between serum osmolarity and ICU mortality of patients diagnosed as septic shock, and it is also firstly study the effect that correction of serum osmolarity abnormality have on ICU mortality, it still have several limitations. First, this is a retrospective study which could not strictly balance the baseline characteristics of patients with different serum osmolarity categories. Second, the serum osmolarity in the present study was calculated rather than being measured directly, which could result in deviation from actual serum osmolarity values despite the optimal calculation equation and simultaneous values of components were considered. Therefore, to further explore the relationship between serum
osmolarity and ICU mortality of septic shock patients, a larger and prospective study should be performed.

**Conclusion**

In conclusion, through the analysis of a large clinical database, our study indicates that both hypo-osmolarity and hyper-osmolarity at ICU admission were associated with increased mortality in patients with septic shock. Moreover, correction of hyper-osmolarity into the normal level would decreased this mortality.

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Author contribution

Jianxin Zhang, Tao Fu and Weidong Jin designed the study. Gang Heng and Jiasi Zhang performed the research and wrote the article. Benqi Huang, Yanbing Shen, Zhonghu Li, Jiankun Jia and Chengcheng Zhang analysed the data and conducted primary statistical analysis.

Competing interests

The authors declare that they have no competing interests.

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Availability of supporting data

The datasets presented in the current study are available in the MIMIC-IV database (https://physionet.org/content/mimiciv/0.4/)

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston,
MA), and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

Consent for publication

Not applicable

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### Table 1: Comparison of baseline characteristics between survivors and non-survivors

| Variables          | Total (n=4707) | Survivors (n=3392) | Non-survivors (n=1315) | P value |
|--------------------|----------------|--------------------|------------------------|---------|
| Age (years)        | 67±0.2        | 66±0.3             | 70±0.4                 | <0.001  |
| Male (n (%))       | 2602 (55.3%)  | 1894 (55.8%)       | 708 (53.8%)            | 0.259   |
| Weight (kg)        | 83.6±0.4      | 83.9±0.4           | 82.8±0.9               | 0.338   |
| SOFA score         | 9.4±0.1       | 8.5±0.1            | 11.5±0.1               | <0.001  |
| Comorbidities      |               |                    |                        |         |
| COPD (n (%))       | 495 (10.5%)   | 371 (10.9%)        | 124 (9.4%)             | 0.130   |
| CAD (n (%))        | 1041 (22.1%)  | 769 (22.7%)        | 272 (20.7%)            | 0.141   |
| Hypertension (n (%)) | 1705 (36.2%) | 1283 (37.8%)       | 422 (32.1%)            | <0.001  |
| Type of ICU        |               |                    |                        | <0.001  |
| Medical (n (%))    | 2787 (59.2%)  | 2009 (59.2%)       | 778 (59.2%)            |         |
| Surgical (n (%))   | 519 (11.0%)   | 388 (11.4%)        | 131 (10.0%)            |         |
| Coronary (n (%))   | 512 (10.9%)   | 332 (9.8%)         | 180 (13.7%)            |         |
| Cardiac (n (%))    | 338 (7.2%)    | 268 (7.9%)         | 70 (5.3%)              |         |
| Trauma (n (%))     | 473 (10.0%)   | 341 (10.1%)        | 132 (10.0%)            |         |
| Vital signs        |               |                    |                        |         |
| MAP (mmHg)         | 51±0.2        | 52±0.2             | 48±0.4                 | <0.001  |
| Heart rate         | 90±0.3        | 89±0.3             | 93±0.5                 | <0.001  |
| Respiratory rate   | 21±0.1        | 20±0.1             | 22±0.1                 | <0.001  |
| Temperature (℃)    | 36.9±0.0      | 37±0.0             | 36.7±0.0               | <0.001  |
| SpO2               | 96.6±0.0      | 96.9±0.0           | 96.0±0.1               | <0.001  |
| Laboratory tests   |               |                    |                        |         |
| WBC                | 15±0.2        | 14±0.2             | 16.5±0.4               | <0.001  |
| Hemoglobin         | 10±0.0        | 10.5±0.0           | 10.2±0.1               | <0.001  |
| Platelet           | 198.6±1.7     | 201.7±2.0          | 190.7±3.3              | 0.005   |
| BUN                | 36.7±0.4      | 34.7±0.5           | 42.1±0.8               | <0.001  |
| Creatinine         | 1.9±0.0       | 1.8±0.0            | 2.2±0.0                | <0.001  |
| Glucose            | 162.1±1.5     | 162.0±1.8          | 162.7±2.8              | 0.822   |
| Lactate            | 4.2±0.5       | 3.7±0.0            | 5.5±0.1                | <0.001  |
| Albumin            | 3.0±0.0       | 3.1±0.0            | 2.8±0.0                | <0.001  |
| Osmolarity         | 305.4±0.3     | 304.7±0.3          | 307.4±0.6              | <0.001  |
Table 2: Characteristics and outcomes by serum osmolarity categories

| Outcomes                     | Serum osmolarity categories (mmol/L) | <290 (n=633) | 290-309 (n=2536) | 310-319 (n=826) | >319 (n=712) | P value |
|-----------------------------|--------------------------------------|--------------|------------------|------------------|--------------|---------|
| ICU mortality (n (%))       |                                       | 195 (30.8%)  | 593 (23.0%)      | 282 (33.9%)      | 256 (36.0%)  | <0.001  |
| Hospital mortality (n (%))  |                                       | 205 (32.4%)  | 629 (24.8%)      | 292 (35.4%)      | 268 (37.6%)  | <0.001  |
| ICU LOS (median (IQR))      |                                       | 9.3 (4.9-17.9)| 9.9 (5.7-18.0)  | 10.1 (5.4-18.5) | 9.8 (4.8-17.3)| 0.249   |
| Albumin intake within 3 days (n (%)) |     | 213 (33.6%)  | 626 (24.7%)      | 170 (20.6%)      | 137 (19.2%)  | <0.001  |
| Fluid intake in day 1 (ml)  |                                       | 9664.4 ± 349.0| 10128.4 ± 201.8 | 10384.7 ± 350.2 | 13690.2 ± 1128.8 | 0.249   |
| Fluid intake in day 2 (ml)  |                                       | 5375.3 ± 228.3| 5113.4 ± 98.5   | 5443.7 ± 170.3  | 5741.8 ± 191.4 | 0.007   |
| Fluid intake in day 3 (ml)  |                                       | 4789.8 ± 214.1| 4448.9 ± 95.2   | 4866.8 ± 188.3  | 4519.2 ± 177.1 | 0.337   |
| Urine output in day 1 (ml)  |                                       | 1766.5 ± 58.6 | 1758.7 ± 34.4   | 1450.8 ± 51.2   | 1404.8 ± 62.3 | <0.001  |
| Urine output in day 2 (ml)  |                                       | 1553.8 ± 62.4 | 1603.5 ± 39.7   | 1440.3 ± 68.4   | 1360.8 ± 55.9 | <0.001  |
| Urine output in day 3 (ml)  |                                       | 1653.1 ± 67.2 | 1761.0 ± 38.3   | 1637.0 ± 69.1   | 1550.0 ± 64.2 | 0.006   |
| Crystalloids intake in day 1 (ml) |     | 9077.0 ± 328.1| 9639.4 ± 187.4  | 9892.0 ± 331.5  | 13116.9 ± 1073.5 | <0.001  |
| Crystalloids intake in day 2 (ml) |     | 5123.5 ± 221.7| 4893.1 ± 94.0   | 5238.8 ± 161.8  | 5547.7 ± 184.4 | 0.003   |
| Crystalloids intake in day 3 (ml) |     | 4601.7 ± 206.0| 4282.3 ± 91.7   | 4700.4 ± 171.8  | 4366.5 ± 171.8 | 0.295   |
| Colloids intake within 3 days (n (%)) |     | 354 (55.9%)  | 1216 (47.9%)    | 332 (40.2%)     | 276 (38.8%)  | <0.001  |
| Blood products within 3 days (n (%)) |     | 296 (82.6%)  | 1438 (56.7%)    | 445 (53.9%)     | 380 (53.4%)  | 0.002   |
| Vasopressor-free in 28 days |                                       | 19.8 ± 0.4   | 20.5 ± 0.2      | 20.4 ± 0.3      | 21.0 ± 0.3   | 0.006   |
| Ventilation-free in 28 days |                                       | 21.4 ± 0.4   | 22.2 ± 0.2      | 23.3 ± 0.2      | 23.6 ± 0.2   | 0.003   |
| AKI within 24 hours (n (%))  |                                       | 343 (54.2%)  | 1464 (57.7%)    | 542 (65.6%)     | 443 (62.2%)  | <0.001  |

Table 3: Primary outcomes analysis with different models

| Model                        | Variables | Odds ratio | 95% CI | P value |
|------------------------------|-----------|------------|--------|---------|
| Multivariable logistic regression | Hypo-osmolarity (<290) | 1.71 | 1.38-2.13 | <0.001 |
|                              | Hyper-osmolarity (>309) | 1.28 | 1.09-1.50 | 0.002  |
| IPTW                         | Hypo-osmolarity (<290) | 1.83 | 1.52-2.21 | <0.001 |
|                              | Hyper-osmolarity (>309) | 1.25 | 1.08-1.45 | 0.005  |
| PSM                          | Hypo-osmolarity (<290) | 2.02 | 1.43-2.86 | <0.001 |
|                              | Hyper-osmolarity (>309) | 1.37 | 1.11-1.68 | 0.003  |
Fig. 1: Study flow diagram of the present study.
Fig. 2: Casual mediation analysis of SpO2 and lactate at admission. (A) The effect of SpO2 mediated of the serum osmolarity in ICU mortality. (B) The effect of lactate mediated of the serum osmolarity in ICU mortality. The solid line represents the normal osmolarity group, and the dashed line represents the abnormal osmolarity group.
Fig. 3: The dynamics of mortality and serum osmolarity within 3 days after ICU admission. (A) The dynamical ICU mortality of these patients with hypo-osmolarity at admission transformed to normal osmolarity in day 2 and day 3. (B) The dynamical ICU mortality of these patients with normal osmolarity at admission transformed to hypo-, normal or hyper-osmolarity in day 2 and day 3. (C) The dynamical ICU mortality of these patients with hyper-osmolarity at admission transformed to normal osmolarity in day 2 and day 3. The mortality changes of patients who transformed to hyper-osmolarity in hypo-osmolarity group and who transformed to hypo-osmolarity in hyper-osmolarity group were not presented as the number is in single digit, which could result in statistical bias.