Trimatch comparison of the prognosis of hypochloremia, normolchloremia and hyperchloremia in patients with septic shock

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Abstract

Background

Septic shock is a lethal disease, and identifying high-risk patients through noninvasive and widely available biomarkers can help improve global outcomes. While the clinical impact of chloride levels on critically ill patients remains unclear, this study aims to investigate the association between hypochloremia and mortality following ICU admission among septic shock patients.

Methods

This is an analysis of data stored in the databases of Medical Information Mart for Intensive Care IV (MIMIC-IV). The initial chloride levels were classified as hypochloremia, normal chloraemia, and hyperchloraemia. A multivariate logistic regression model was applied, adjusting for age, lactate, pH, PO$_2$, urine volume, RDW, creatinine, and liver disease, to assess the association between the three categories of chloride levels and mortality.

Results

Of 3726 patients included in the study, 470 patients (12.6%) had hypochloremia on ICU admission. During the follow-up period, 1120 (33.5%) patients died. Hypochloremia was significantly associated with increased mortality and the incidence of AKI after adjusting for several variables.

Conclusions

Hypochloremia is independently associated with higher hospital mortality, AKI incidence among septic shock patients. However, further high-quality research is necessary to establish the precise relationship between hypochloremia and septic shock prognosis.

Introduction

Sepsis and septic shock pose a major threat to public health, causing significant morbidity and mortality[1]. The average mortality rate for septic shock patients within 30 days is reported at 34.7%, with a 38.5% mortality rate at 90 days [2]. Early recognition of patients at high risk for death remains pivotal in the proper management of sepsis [3]. Therefore, discovering effective and convenient biomarkers for the timely diagnosis and prognosis of sepsis is of paramount importance.

While chloride is one of the earliest measurable electrolytes, its significance has long been overshadowed by other major serum electrolytes, notably sodium. Several studies have investigated the epidemiology of sodium disturbances and their possible impact on adverse outcomes in critically ill patients[3, 4]. The incidence of dysnatremia in ICU patients ranges from 25% and 45%. Even mild hyponatremia and hypernatremia are associated with significantly higher mortality[5]. Although hypochloremia is very common in critical situations, it has not received appropriate attention.
Chloride is the most principal anion in plasma and interstitial fluid, it constitutes approximately one third of the extracellular fluid tonicity [4]. Its importance lies in its vital contribution to various physiological processes within the body, including electrolyte and acid-base balance regulation, muscular activity, osmotic pressure control, fluid compartmentalization, and immunomodulation [5]. Deviations from chloride's normal range values, either higher or lower, can increase the risk of adverse patient outcomes [6–8].

However, the effect of chloride on septic shock remains controversial, as studies have shown conflicting results. For instance, Neyra et al. investigated the association between hyperchloremia and hospital mortality in adult ICU patients with severe sepsis or septic shock [9]. They divided patients into two subgroups based on Cl- levels at the time of ICU admission: hyperchloremia and non-hyperchloremia, the results are show that the critically ill septic patients with hyperchloremia represent an overall sicker population and are associated with all-cause hospital mortality [9]. However, they ignored the effect of hypochloremia on their results, and patients with hypochloremia should be excluded from the non-hyperchloremia group for comparison.[10]. As well as Suetrong et al [11]. Although Lee et al has divided the patients into three groups: hyperchloremia, hypochloremia and normal chloride, the baseline characteristics were significantly different between the three groups [7]. Further, the findings are mixed with some indicating no differences [12], and others finding hyperchloremia is a risk factor for the prognosis of patients with septic shock [11].

To gain a clearer understanding of the prognostic significance of chloride levels in septic shock patients, we categorized them into three groups: hypochloremia, normal chloraemia, and hyperchloraemia. This investigation utilizing modern statistical techniques to balance the three groups simultaneously for any confounding factors [13]. Subsequently, we assessed the link between hypochloremia or hyperchloremia, and the prognosis of septic shock patients.

**Methods**

**Database**

This study is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement [14]. We extracted data from Medical Information Mart for Intensive Care (MIMIC)-IV v1.0 [15], which is a public database containing hospitalisation information. It is a relational database containing real hospital stays for patients admitted to a tertiary academic medical centre in the United States. It included 76,540 ICU admissions for 53,150 patients from 2008 to 2019.

**Ethical considerations**

This study was in accordance with the ethical standards of the Declaration of Helsinki and was approved by the institutional review boards of MIT and Beth Israel. Author Yu completed the required courses for the use of this database and obtained the corresponding certificate (Record ID 28806891).

**Study cohort**

We used the Angus’s methods to identify critically ill patients with septic shock [16]. We only included ICU admission data of the first admission and of adult patients (age > 16 years) who had been in the ICU for at least 1 day. Patients without chloridion were excluded. Thus, patients were divided into three groups according to serum chloride, and the outcomes were further compared among those three groups: Normal group, Low group, and High group (Fig. 1).
Covariates

Data were extracted from the database using structured query language (SQL). The following demographic parameters were collected: race (white, black, others), gender, age, weight, Sequential Organ Failure Assessment (SOFA), charlson index (peripheral vascular disease, chronic pulmonary and renal disease), urine, vital signs (heart rate (HR), mean artery pressure (MAP)) and laboratory values (lactate, PO$_2$, pH, Hb, PLT, Red blood Cell distribution width (RDW), potassium, sodium, albumin(ALB). In addition, significant interventions (renal replace therapy (RRT), crystalloid bolus and vasoactive agents were also collected as variables.

Outcomes

The primary outcome of the study was hospital mortality. The secondary outcome was icu mortality and the incidence of hospital acquired AKI.

Management of Missing Data

To avoid bias introduced by missing data, we used the K-nearest neighbor (KNN) to impute missing data [17]. The detail of the missing value is shown in Additional file Figure.S2.

Statistical methods

All available covariates were included as a priori risk factors in the models [7, 8, 18]. Logistics LASSO regression was employed for variable selection [19]. We utilized the “glmnet” package to fit the logistic LASSO regression. Then, To control potential confounding factors effectively, we applied doubly robust estimation methodology [20] (TriMatch analysis and multivariable regression[21]).

Propensity score matching (PSM) is widely used to adjust for inter group variations and eliminate biases in non randomized trials of two treatment regimens. In this study, the optimal matching algorithm was adopted for 1:1:1 matching, and a caliper width equal to 0.25 of the standard deviation of the logit of the PS using TriMatch package. In this study, consider two groups (hyperchloremia group and hypochloremia group) and a control (normal group). We estimate propensity scores with three separate logistic regression models where model one predicts hyperchloremia group with normal group, model two predicts hypochloremia group with normal group, and model three predicts hyperchloremia group with hypochloremia group. Since each unit has a propensity score (PS) in two of the three models, their scores are connected. Those persons who do not have any match are removed from the sample. Only the unique triplets with the smallest total PS distance are finally retained in the matched sample.

In the matched cohort, continuous variables were reported as the median ± standard deviation. Proportions were calculated for categorical variables. ANOVA was used to analyze continuous variables. Pearson’s chi-square test was used to analyze categorical variables.

Univariate logistic regression and multivariable logistic regression were performed to estimate the comparative risks of primary and secondary outcomes.

Statistical significance was considered to be indicated by two-sided p < 0.05. All analyses were performed with R version 4.1.3.

Sensitivity analysis
We conducted several sensitivity analyses, which are concisely summarized in Table 3. We conducted a series of sensitivity analyses with the cohort with missing data, the cohort after imputation and the cohort after TriMatch to assess the outcomes. Further, we also evaluated the effect of changes in chloride on the outcome on day 2.

Results

Basic Information

Upon reviewing 76,540 admissions from MIMIC-IV, we identified 3,726 patients with septic shock, after screening out those who did not meet our inclusion criteria, such as readmission, age < 16 years, ICU stay < 1 day, and missing chloride levels. The incidence of hyperchloremia in septic shock patients was 25.9%, and hypochloremia was 12.6% [see Additional file Table.S1]. In comparison to non-hypochloremic patients, those with hypochloremia on ICU admission were more likely to be male, had a higher incidence of acute renal injury and mortality risk, a higher SOFA score, and more comorbidities. Conversely, patients with hyperchloremia had the lowest ICU and Hospital mortality rates, higher urine volume, and lower SOFA scores. There were significant differences between the three groups in several of the baseline characteristics before PSM. With the use of 1:1:1 PSM via the TriMatch package, 404 patients with hypochloremia were matched with 404 patients with hyperchloremia and 404 patients with normal chloride (Table 1).

Primary outcome and sensitivity studies

We used LASSO for variable selection. Finally, age, race, lactate, pH, PO\textsubscript{2}, RDW, creatinine, combined liver disease, and 24h urine volume were selected. Further analysis of Trimath, all covariates were considered balanced in the Matched cohort. Thus, logistic regression was performed. The adjusted OR showed an adverse effect between the hypochloremia group and Hospital mortality [OR 1.58, 95% CI 1.16–2.17, P = 0.004] (Table 2). However, we did not find evidence of a relationship between hyperchloremia and hospital mortality [OR 1.07, 95% CI 0.77–1.47, P = 0.7] (Table 2). For the sensitivity analysis, as summarized in Table 3, all estimation models led to the same conclusion: patients with hypochloremia group had higher Hospital mortality. Hyperchloremia group was not related to death in Hospital mortality.

In addition, we also found that the normal group increased with $\Delta$Cl$^-$ (Cl$^-$ ($0$ - Cl$^-$ $24$)) (the Cl$^-$ decreased on the second day) the Hospital mortality was higher (Table 4), while changes in chloride levels within the hypochloremia or hyperchloremia group were not found to have significant associations with hospital mortality.

Secondary outcomes studies with propensity score matching

We also found that hypochloremia group was associated with ICU mortality and Hospital acquired AKI, while hyperchloremia group was not associated with ICU mortality and Hospital acquired AKI (Table 2).

Discussion

The main result of this study is initial serum chloride abnormalities is common and significantly associated with in-hospital mortality in septic shock patients. Given the preciseness and accessibility of LASSO regression, we performed the LASSO regression analysis to screen covariates. Further, in order to minimize the effect of these confounders, a doubly robust approach [20], in which propensity score methods are used in combination with regression adjustment. propensity score methods, particularly in combination with a traditional regression-based
adjustment, are a viable alternative when an RCT is not feasible. By the TriMatch analysis [21], we were able to create three groups homogeneous for age, race, lactate, pH, PO$_2$, RDW, Creatinine, combined liver disease and 24h urine volume. Finally, for all matched cases, patients are at the same starting line to compare the impact of initial serum chloride on prognosis.

Our results are similar to the results of Lee et al study, indicating that low chlorine is a risk factor for septic shock patients. Although the mechanism of increased mortality caused by hypochloremia is unclear, a possible reason for these outcomes could be that Chloride is vital for maintenance of serum electroneutrality, acid-base balance, fluid homeostasis, osmotic pressure [22]. But Lee et al study showed that 19.3% had hypochloremia and 3.0% had hyperchloremia. And our study showed that there were more patients with hyperchloremia than with hypochloremia. This may be because our data is from Beth Israel Deaconess Medical Center, one of the best hospitals in the United States. Some septic shock patients have been resuscitated with chlorine-rich crystalloid in the emergency room or ward before being admitted to the ICU. Septic shock patients are frequently exposed to normal saline to restore the effective circulatory volume in resuscitation stage[1]. But normal saline is a non-neutral and one of the most widely used chloride-rich crystalloid infusion solution[23]. Therefore, hyperchloremia in septic shock patients most often results from iatrogenic chloride overload[24, 25].

Hypochloremia, a condition often observed in critically ill patients, can result from various factors such as diuretic therapy, significant gastric drainage, vomiting, chronic respiratory acidosis, heart failure, syndrome of inappropriate antidiuretic hormone secretion, and excess infusion of hypotonic solutions [26]. Hypochloremia could be a sign of illness severity as a result of dysregulated homeostasis. Based on our results, paying attention to initial serum levels may help physicians detect severe patients early and intervene to improve prognosis in patients with septic shock.

The specific mechanism by which hypochloremia increases mortality rates is yet to be understood; however, metabolic alkalosis may be a contributing factor. According to Stewarts physicochemical theory, serum chloride plays a significant role in regulating acid-base homeostasis[16]. Strong ion difference (SID) determines the acid-base state based on the theory, and the disparity between sodium and chloride ion levels determines the SID. If a large amount of normal saline is infused to increase blood volume, it can elevate chloride levels, thus reducing SID and increasing the concentration of H$^+$ to cause acidosis. Addressing acidosis with sodium bicarbonate can increase Na$^+$ concentration and normalize SID to alleviate the acidosis. However, the relationship between metabolic alkalosis and mortality in critically ill patients is not clear. Given that patients with hypochloremia manifest metabolic alkalosis, it is challenging to identify the primary factor leading to poor prognosis.

Huang et al found that patients with hypochloremia and coronary artery disease with congestive heart failure were associated with short-term and long-term mortality[27]. Hypochloremia can be considered as a sign of clinical complexity, and the same hypochloremia could be a sign of the severity of illness as a result of dysregulated homeostasis[27]. Low concentrations of Cl$^-$ may upregulate the expression of proinflammatory cytokines, thereby accelerating the inflammatory response[28]. In addition, Cl$^-$ plays a key role in the core regulatory pathway of physiological stability. For example, low levels of chloride are associated with high anion gap and elevated levels of renin[29, 30].

Host immunity is a crucial component in the manifestation of critical illness including septic shock. Chloride plays an important role in neutrophil function. Phagosomes of neutrophils require the continuous passage of chloride ions through various chloride channels and cotransporters, providing substrates for myeloperoxidase to produce
hypochloric acid[31–34]. Low extracellular chloride concentrations were associated with decreased neutrophil function[34], which could explain why patients with hypochloremia had poorer prognosis.

In comparison, hyperchloremia was not related to the incidence of AKI and mortality in this study. Our findings are consistent with several negative retrospective cohorts assessing the role of hyperchloremia [12].

But our results differ from those of Neyra et al[9]. Different from previous studies, in order to avoid the influence of the hypochloremia group on the results, we divided them into three groups. Theoretically, the three matched groups will not be affected by age, lactate, pH, PO_{2}, urine volume, RDW, creatinine, liver disease and other variables. Hypochloremia, as well as pH and disease severity, could impact the results, leading to varying outcomes. Nevertheless, we need further studies with more expansive populations from multiple centers to establish a relationship between hyperchloremia and the prognosis of septic shock.

Despite several limitations, our study is notable for its large cohort that assessed the association of hypohloremia and ICU mortality in septic shock patients. Additionally, we utilized advanced statistical techniques to balance out three groups simultaneously for confounding factors. Nonetheless, our study’s retrospective nature poses a risk of selection bias, and we failed to account for the effect of serum chloride ion's increase in reducing the mortality of patients with hypochloremia. Moreover, our research considered only Cl\(^{-}\) measurements obtained within the first 24 hours of sepsis, without studying the prognostic effects of all measurements taken during ICU stay and variations in serum Cl\(^{-}\) levels.

**Conclusions**

In ICU patients with septic shock, derangements in serum chloride levels are prevalent, with hyperchloreaemia occurring more frequently than hypochloremia. Hypochloremia is independently associated with higher hospital mortality, AKI incidence among septic shock patients. Further studies are required to identify the specific role of hypochloreaemia on the outcome of septic shock patients.

**Abbreviations**

ICU: Intensive Care Unit

AKI: Acute kidney injury

OR: Odds ratio

RRT: Renal replacement therapy

SOFA: Sequential Organ Failure Assessment

RDW: Red blood Cell distribution width

SID: Strong ion difference

**Declarations**

Ethics approval and consent to participate
The study was an analysis of anonymized publicly available databases with preexisting institutional review board approval.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the MIMIC-IV (https://mimic-iv.mit.edu) databases.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Xueshu Yu: Designed the study, performed data collection, wrote the first draft, coordinated the input of all authors, supervised the study.

Xiangyuan Ruan: Performed data collection and assessment, wrote the first draft, coordinated the input of all authors.

Yifan Gao: Contributed to data interpretation, revised the manuscript for important intellectual content.

Xiaojuan Lai: Performed all statistical analyses, revised the manuscript for important intellectual content.

Baoxin Wang: Contributed to data interpretation, revised the manuscript for important intellectual content.

Jinmei Wu: Contributed to data interpretation, revised the manuscript for important intellectual content.

All authors approved the final version of the manuscript.

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References


Tables

Table 1 Baseline characteristics of the patient between the KNN cohort and the Match cohort.
<table>
<thead>
<tr>
<th>Variables</th>
<th>KNN cohort</th>
<th>Match cohort</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal group</td>
<td>Low group</td>
<td>High group</td>
</tr>
<tr>
<td></td>
<td>N = 2289</td>
<td>N = 470</td>
<td>N = 967</td>
</tr>
<tr>
<td>Age (%)</td>
<td></td>
<td>&lt; 0.001</td>
<td>0.616</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>1387 (60.60)</td>
<td>222 (47.23)</td>
<td>599 (61.94)</td>
</tr>
<tr>
<td>&lt;=60</td>
<td>902 (39.40)</td>
<td>248 (52.77)</td>
<td>368 (38.06)</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td>0.44</td>
<td>0.42</td>
</tr>
<tr>
<td>White</td>
<td>1526 (66.7)</td>
<td>299 (63.6)</td>
<td>635 (65.7)</td>
</tr>
<tr>
<td>Black</td>
<td>184 (8.0)</td>
<td>46 (9.8)</td>
<td>93 (9.6)</td>
</tr>
<tr>
<td>Other</td>
<td>579 (25.3)</td>
<td>125 (26.6)</td>
<td>239 (24.7)</td>
</tr>
<tr>
<td>Lactate (mean (SD))</td>
<td>2.61 (1.33)</td>
<td>2.62 (1.28)</td>
<td>2.67 (1.38)</td>
</tr>
<tr>
<td>pH (mean (SD))</td>
<td>7.33 (0.11)</td>
<td>7.34 (0.12)</td>
<td>7.30 (0.11)</td>
</tr>
<tr>
<td>PO&lt;sub&gt;2&lt;/sub&gt; (mean (SD))</td>
<td>56.76 (19.33)</td>
<td>54.87 (19.24)</td>
<td>58.55 (19.64)</td>
</tr>
<tr>
<td>RDW (mean (SD))</td>
<td>15.86 (2.62)</td>
<td>16.51 (2.83)</td>
<td>15.65 (2.52)</td>
</tr>
<tr>
<td>Creatinine (mean (SD))</td>
<td>1.49 (0.82)</td>
<td>1.79 (0.87)</td>
<td>1.44 (0.80)</td>
</tr>
<tr>
<td>Liver disease (%)</td>
<td>&lt; 0.001</td>
<td>0.636</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>521 (22.8)</td>
<td>182 (38.7)</td>
<td>173 (17.9)</td>
</tr>
<tr>
<td>No</td>
<td>1768 (77.2)</td>
<td>288 (61.3)</td>
<td>794 (82.1)</td>
</tr>
<tr>
<td>Urine (%)</td>
<td>&lt; 0.001</td>
<td>0.075</td>
<td></td>
</tr>
<tr>
<td>Anuria</td>
<td>86 (3.8)</td>
<td>44 (9.4)</td>
<td>28 (2.9)</td>
</tr>
<tr>
<td>Variables</td>
<td>KNN cohort</td>
<td>Match cohort</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
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<td>-------------------------------</td>
<td></td>
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<tr>
<td></td>
<td>Normal group</td>
<td>Low group</td>
<td>High group</td>
</tr>
<tr>
<td></td>
<td>N = 2289</td>
<td>N = 470</td>
<td>N = 967</td>
</tr>
<tr>
<td>Oliguria</td>
<td>238 (10.4)</td>
<td>69 (14.7)</td>
<td>113 (11.7)</td>
</tr>
<tr>
<td>others</td>
<td>1965 (85.8)</td>
<td>357 (76.0)</td>
<td>826 (85.4)</td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td>731 (31.9)</td>
<td>199 (42.3)</td>
<td>281 (29.1)</td>
</tr>
<tr>
<td>ICU mortality (%)</td>
<td>500 (21.8)</td>
<td>145 (30.9)</td>
<td>207 (21.4)</td>
</tr>
<tr>
<td>AKI (%)</td>
<td>1820 (79.5)</td>
<td>421 (89.6)</td>
<td>743 (76.8)</td>
</tr>
</tbody>
</table>

For all continuous covariates, the mean values and standard deviations are reported. Urine: Anuria: <100 ml/d, oliguria: >=100 ml/d and < 400 ml/d, Others: >=400 ml/d, RDW: RBC Distribution Width, AKI: Acute Kidney Injury.

Table 2 The primary outcomes and secondary outcomes.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>OR (95%CI)</th>
<th>P value</th>
<th>Adjust OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal group</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Low group</td>
<td>1.56 (1.17–2.09)</td>
<td>0.003</td>
<td>1.58 (1.16–2.17)</td>
<td>0.004</td>
</tr>
<tr>
<td>High group</td>
<td>1.01 (0.75–1.36)</td>
<td>0.94</td>
<td>1.07 (0.77–1.47)</td>
<td>0.7</td>
</tr>
<tr>
<td>ICU mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal group</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Low group</td>
<td>1.75 (1.26–2.44)</td>
<td>0.001</td>
<td>1.72 (1.21–2.46)</td>
<td>0.003</td>
</tr>
<tr>
<td>High group</td>
<td>1.17 (0.83–1.65)</td>
<td>0.38</td>
<td>1.24 (0.85–1.80)</td>
<td>0.25</td>
</tr>
<tr>
<td>Hospital-acquired AKI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal group</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Low group</td>
<td>2.01 (1.35–3.02)</td>
<td>0.001</td>
<td>2.01 (1.32–3.10)</td>
<td>0.001</td>
</tr>
<tr>
<td>High group</td>
<td>0.70 (0.5–0.97)</td>
<td>0.04</td>
<td>0.70 (0.49–1.01)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 3 Sensitivity analysis results.
### Table 4 The effect of changes in chloride on the outcome on day 2.

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Adjust OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal group</td>
<td>1.10 (1.04–1.17)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low group</td>
<td>1.03 (0.99–1.07)</td>
<td>0.19</td>
</tr>
<tr>
<td>High group</td>
<td>1.05 (1.00–1.10)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Figures**
Figure 1
Legend not included with this version.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile.docx