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Association of Hyperchloremia With Hospital Mortality in Critically Ill Septic Patients

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Objectives: Hyperchloremia is frequently observed in critically ill patients in the ICU. Our study aimed to examine the association of serum chloride (Cl) levels with hospital mortality in septic ICU patients.

Design: Retrospective cohort study.

Setting: Urban academic medical center ICU.

Patients: ICU adult patients with severe sepsis or septic shock who had Cl measured on ICU admission were included. Those with baseline estimated glomerular filtration rate less than 15 mL/min/1.73 m^2 or chronic dialysis were excluded.

Interventions: None.

Measurements and Main Results: Of 1,940 patients included in the study, 615 patients (31.7%) had hyperchloremia (Cl ≥ 110 mEq/L) on ICU admission. All-cause hospital mortality was the dependent variable. Cl on ICU admission (Cl_0), Cl at 72 hours (Cl_{72}), and delta Cl ($\Delta Cl = Cl_{72} - Cl_0$) were the independent variables. Those with Cl_0 greater than or equal to 110 mEq/L were older and had higher cumulative fluid balance, base deficit, and Sequential Organ Failure Assessment scores. Multivariate analysis showed that higher Cl_{72} but not Cl_0 was independently associated with hospital mortality in the subgroup of patients with hyperchloremia on ICU admission (adjusted odds ratio for Cl_{72} per 5 mEq/L increase = 1.27; 95% CI, 1.02–1.59; $p = 0.03$). For those who were hyperchloremic on ICU admission, every within-subject 5 mEq/L increment in Cl_{72} was independently associated with hospital mortality (adjusted odds ratio for ΔCl 5 mEq/L = 1.37; 95% CI, 1.11–1.69; $p = 0.003$).

Conclusions: In critically ill septic patients manifesting hyperchloremia (Cl ≥ 110 mEq/L) on ICU admission, higher Cl levels and within-subject worsening hyperchloremia at 72 hours of ICU stay were associated with all-cause hospital mortality. These associations were independent of base deficit, cumulative fluid balance, acute kidney injury, and other critical illness parameters. (*Crit Care Med* 2015; 43:1938–1944)

Key Words: chloride; hospital mortality; hyperchloremia; ICUs; sepsis

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Chloride is the most abundant anion in the extracellular fluid and constitutes approximately one third of the extracellular fluid tonicity (1). Chloride plays a pivotal role in many body functions including acid-base balance, muscular activity, osmosis, and immunomodulation (2). Despite its physiologic importance, chloride has captured little attention by the scientific community until recently (3) when chloride-rich solutions were associated with hyperchloremic metabolic acidosis (4, 5) and short-term mortality after noncardiac surgery (6, 7). The precise mechanisms of hyperchloremic metabolic acidosis are somewhat controversial: 1) HCO_3^- dilution (8), 2) chloride as a key contributor to the decrease in

strong ion difference influencing the dissociation of water with H^+ generation (Stewart approach) (9), and 3) the unbalanced dilution of the buffer system (HCO_3^- but not CO_2) (10).

The most common chloride-rich solution used in clinical practice is 0.9% saline (11), particularly in critical illness and perioperatively, and 0.9% saline is in reality a non-neutral solution (12) and has a supraphysiologic amount of chloride when compared with plasma (154 vs ~100 mEq/L, respectively) (13, 14). The consequent hyperchloremic metabolic acidosis derived from the liberal use of chloride-rich solutions has been described as a common but poorly recognized disorder in critically ill patients (15, 16), with numerous detrimental consequences (17, 18), particularly in those with severe sepsis and septic shock (19).

Critically ill septic patients are commonly exposed to 0.9% saline during the salvage phase of shock and therefore are susceptible to hyperchloremia in the postresuscitation phase. However, observational studies evaluating the association of hyperchloremia with hospital mortality have shown conflicting results and included only a small number of septic patients in the ICU (20–22).

The purpose of our study was to determine whether there was an independent association of serum chloride (Cl) levels at two different time points of ICU stay with hospital mortality in critically ill septic patients. The two evaluated Cl time points were ICU admission (Cl_0) and 72 hours of ICU stay (Cl_{72}). We hypothesized that higher Cl_{72} would be independently associated with hospital mortality, particularly in those patients who were hyperchloremic at the time of ICU admission.

MATERIALS AND METHODS

Study Design and Participants

We conducted a single-center observational retrospective cohort study using a population-based ICU database of patients with severe sepsis or septic shock admitted to an urban tertiary care hospital from May 2007 through April 2012. Severe sepsis or septic shock was defined by Angus criteria (23), using the *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) codes (24) for a bacterial or fungal infection and a diagnosis of acute organ dysfunction excluding gastrointestinal failure. We included all adult patients admitted to the ICU with a diagnosis of severe sepsis or septic shock who had at least one serum creatinine (SCr) measurement that was documented in the medical records within 3 months prior to ICU admission and one Cl measured at Cl_0. We excluded patients with baseline estimated glomerular filtration rate (eGFR) less than 15 mL/min/1.73 m^2 using the four-variable Modification of Diet in Renal Disease study equation (25), those undergoing any form of chronic dialysis, and those with absent recorded daily fluid balance within the first 72 hours of ICU stay. The protocol was approved by the hospital's institutional review board (#7044).

Study Variables

Serum chloride was measured by indirect potentiometry (SYNCHRON Systems; Beckman Coulter, Brea, CA). The delta chloride (ΔCl) was defined as the difference between Cl_{72} and Cl_0. The Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were calculated after integration of clinical and laboratory data within the first day of ICU admission. Cumulative fluid balance (CFB) was calculated based on total fluid input minus output within the first 72 hours of ICU stay. These data did not include pre-ICU fluid administration. Base deficit was calculated by subtracting the serum HCO_3^- measurement on ICU admission from the normal serum HCO_3^- value of 24 mEq/L. Subject-specific variables were obtained from electronic medical records (EMRs). Acute kidney injury (AKI) was adjudicated based on Kidney Disease Improving Global Outcomes consensus SCr-based criteria by comparing the highest SCr measured within the first 72 hours of admission and the reference SCr within 3 months before admission (26). Comorbidities (e.g., diabetes, hypertension, and heart failure) were identified using ICD-9-CM codes, except for anemia that was defined as admission hematocrit less than 39% for men and less than 36% for women. Data pertaining to drug exposure, red blood cell transfusion, and mechanical ventilation were based on hospital billing codes for the indexed admission within the time frame of the study. All collected data were validated through comprehensive individual review of 10% of EMRs by data management personnel blinded to the study.

Study Outcomes

The observation period lasted from ICU admission until the time of hospital discharge or death. The primary outcome measure was all-cause hospital mortality and was adjudicated based on EMR review by data management personnel blinded to the study.

Statistical Analysis

The study sample was analyzed as a single group and divided in two subgroups based on Cl levels at the time of ICU admission: hyperchloremia ($Cl_0 \geq 110$ mEq/L) and no hyperchloremia ($Cl_0 < 110$ mEq/L). Categorical data were reported as percentages and continuous data as means ± SD or median (interquartile range). The comparisons between groups for categorical variables were made using the chi-square test. For normally distributed continuous variables, a two-sided *t* test was used. The Wilcoxon signed rank test was used for nonparametric data.

The associations between hospital mortality (dependent variable) and 1) Cl at the time of ICU admission (Cl_0), 2) Cl at 72 hours of ICU stay (Cl_{72}), 3) ΔCl ($\Delta Cl = Cl_{72} - Cl_0$), and 4) their interaction with hyperchloremia at the time of ICU admission ($Cl_0 \geq 110$ mEq/L) were examined using logistic regression analysis. The associations between hospital mortality and the independent variables of interest (Cl_0, Cl_{72}, and ΔCl) were further examined in all patients and separately in both subgroups (hyperchloremia vs no hyperchloremia at the time of ICU admission) in multivariate logistic regression models that adjusted for confounders known to be associated with hospital mortality. The multivariate logistic regression model adjusted for candidate variables that had a *p* value less than

0.10 in the univariate models. Candidate variables included demographic data (age, gender, and race), comorbidity (baseline eGFR, diabetes, hypertension, heart failure, and anemia), indicators of critical illness (AKI, oliguria, APACHE II, SOFA, CFB, base deficit, mechanical ventilation, blood transfusion, and length of ICU stay), and drug exposure (diuretic, statin, aminoglycoside, and IV or intra-arterial iodine contrast). Only one of the two variables was included in the event of collinearity between variables. Covariate adjustment was also assessed with propensity score analysis (sensitivity analysis) using quintiles of the propensity scores in the logistic regression model for hospital mortality. The 95% CIs reported for the logistic regression odds ratios (ORs) were calculated by the Wald estimation. Two-sided *p* values less than 0.05 indicated statistical significance. Spreadsheet software and SAS 9.3 (SAS Institute, Cary, NC) were used in data acquisition and analysis.

RESULTS

Of 6,490 patients examined for eligibility, 1,940 satisfied inclusion and exclusion criteria (**Fig. 1**). Of these, 615 patients (31.7%) had hyperchloremia ($Cl_0 \geq 110$ mEq/L) on ICU admission. The median Cl_0 was 113 mEq/L (111–116 mEq/L) in the hyperchloremic subgroup and 104 mEq/L (100–107 mEq/L) in the nonhyperchloremic subgroup. During the observation period, from ICU admission until hospital discharge or death, 431 patients (22.2%) died: 147 (23.9%) in the subgroup with and 284 (21.4%) in the subgroup without hyperchloremia at admission. Baseline demographics and clinical characteristics of these two subgroups are provided in **Table 1**. The patients with hyperchloremia on ICU admission were older; more frequently African-Americans; and had higher CFB, base deficit, and APACHE II and SOFA scores. Furthermore, these patients required more blood transfusions, vasoactive drugs, and mechanical ventilation and were more frequently oliguric when compared with those without hyperchloremia at the time of ICU admission ($Cl_0 < 110$ mEq/L) (Table 1). Cl_{72} was available in 353 patients with and 726 without hyperchloremia at the time of ICU admission.

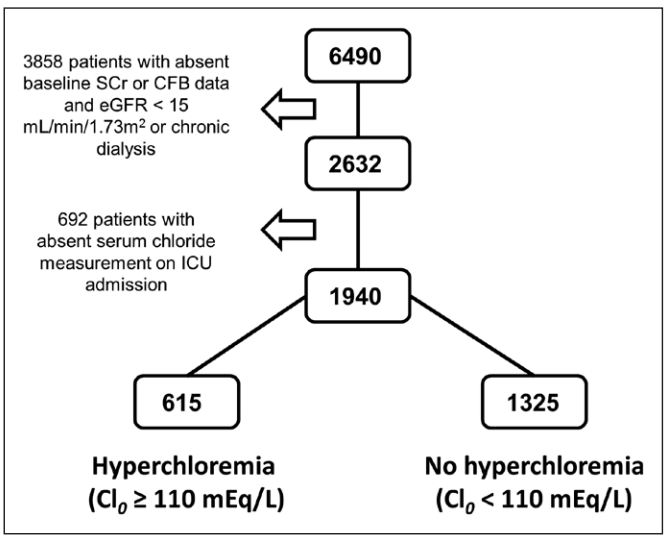

Figure 1. Cohort derivation and study scheme. CFB = cumulative fluid balance, Cl_0 = serum chloride at the time of ICU admission, eGFR = estimated glomerular filtration rate, SCr = serum creatinine.

Cl_0 was not associated with all-cause hospital mortality (OR_{Cl0} per 5 mEq/L increase = 1.04; 95% CI, 0.97–1.12; $p = 0.25$). Furthermore, no difference was found in the effect of Cl_0 on hospital mortality when stratified by the presence or absence of hyperchloremia ($Cl_0 \geq 110$ vs < 110 mEq/L) (**Table 2**).

Cl_{72} was associated with increased odds for hospital mortality in all patients. Each 5 mEq/L increase in Cl_{72} was associated with a 12% increase in odds for hospital mortality (OR_{Cl72} per 5 mEq/L increase = 1.12; 95% CI, 1.01–1.24; $p = 0.03$) (Table 2). There was statistical interaction between Cl_{72} and the presence or absence of hyperchloremia on ICU admission ($p = 0.02$). The increased odds for hospital mortality was detected only in those with hyperchloremia on ICU admission ($Cl_0 \geq 110$ mEq/L) (OR_{Cl72} per 5 mEq/L increase = 1.38; 95% CI, 1.13–1.68; $p = 0.002$) but not in those with Cl_0 less than 110 mEq/L on presentation (OR_{Cl72} per 5 mEq/L increase = 1.05; 95% CI, 0.92–1.20; $p = 0.46$) (Table 2).

In a multivariate model of the subgroup of patients with hyperchloremia at the time of ICU admission ($Cl_0 \geq 110$ mEq/L), Cl_{72} retained its significant association with hospital mortality (adjusted OR_{Cl72} per 5 mEq/L increase = 1.27; 95% CI, 1.02–1.59; $p = 0.03$) (**Table 3**).

Within-subject increase in Cl from ICU admission to 72 hours ($\Delta Cl = Cl_{72} - Cl_0$) was also associated with hospital mortality. Among all study subjects, each within-subject 5 mEq/L increase in Cl was associated with a 15% increase in the odds for hospital mortality (OR = 1.15; 95% CI, 1.05–1.29; $p = 0.003$) (Table 2). However, the increase in hospital mortality was solely driven by subjects with hyperchloremia on ICU admission. The odds for hospital mortality increased by 35% for each within-subject 5 mEq/L increment ($\Delta Cl = 5$ mEq/L) in those with hyperchloremia on ICU admission (Table 2). This association persisted in a multivariate model that adjusted for confounders (adjusted OR for ΔCl 5 mEq/L = 1.37; 95% CI, 1.11–1.69; $p = 0.003$) (Table 3).

As part of a sensitivity analysis, the propensity score–adjusted estimates for Cl_{72} and ΔCl 5 mEq/L yielded results similar to the multivariate models in Table 3 (among hyperchloremic patients at the time of ICU admission): adjusted OR_{Cl72} per 5 mEq/L increase = 1.29; 95% CI, 1.04–1.59; $p = 0.02$ and adjusted OR for ΔCl 5 mEq/L = 2.84; 95% CI, 1.32–6.13; $p = 0.008$.

DISCUSSION

In our study, we found an independent association between higher Cl_{72} and all-cause hospital mortality in critically ill septic patients who were hyperchloremic ($Cl_0 \geq 110$ mEq/L) at the time of ICU admission. Interestingly, the association of hyperchloremia and hospital mortality persisted after adjustment for several confounders including CFB (effect of fluid therapy, particularly 0.9% saline), base deficit (effect of metabolic

TABLE 1. Clinical Characteristics Stratified by Serum Chloride at the Time of ICU Admission

Variable	$Cl_0 \geq 110$ mEq/L ($n = 615$)	$Cl_0 < 110$ mEq/L ($n = 1,325$)	p
Demographics			
Age, yr, mean ± SD	67.8 ± 15.9	65.1 ± 15.8	< 0.001[a]
Male, %	48.3	54.2	0.02[a]
African-American, %	47.6	35.3	< 0.001[a]
Chronic conditions			
Baseline serum creatinine, mg/dL, median (IQR)	1.2 (0.9–1.6)	1.2 (0.9–1.6)	0.07
Baseline eGFR, mL/min/1.73 m^2, median (IQR)	61.9 (42.7–82.8)	62.9 (44.8–88.2)	0.09
Diabetes, %	21.5	21.9	0.83
Hypertension, %	43.6	42.9	0.79
Heart failure, %	2.9	3.0	0.91
Anemia, %	90.3	83.8	< 0.001[a]
Drug exposure at 72 hr			
Diuretic, %	37.2	42.4	0.045[a]
Statin, %	26.2	30.3	0.07
Iodine contrast, %	23.1	29.1	0.005[a]
Aminoglycoside, %	8.0	5.3	0.02[a]
Critical indicators on ICU admission			
Base deficit, mEq/L, mean ± SD	6.1 ± 6.2	2.0 ± 7.3	< 0.001[a]
Acute Physiology and Chronic Health Evaluation II score, mean ± SD	16.5 ± 7.3	13.2 ± 6.1	< 0.001[a]
Sequential Organ Failure Assessment score, mean ± SD	6.6 ± 4.0	5.3 ± 3.8	< 0.001[a]
Critical indicators at 72 hr			
Oliguria, %	15.0	10.0	0.003[a]
Cumulative fluid balance 72 hr, L, mean ± SD	5.4 ± 7.0	3.3 ± 6.4	< 0.001[a]
Vasopressor or inotrope, %	41.6	32.8	0.001[a]
Mechanical ventilation, %	49.4	38.9	< 0.001[a]
Red blood cell transfusion, %	5.0	2.3	0.002[a]
AKI, %	61.1	57.0	0.09
Length of hospital stay, d, median (IQR)	11.0 (6–20)	12.0 (7–20)	0.51

Cl_0 = serum chloride at the time of ICU admission, IQR = interquartile range, eGFR = estimated glomerular filtration rate based on Modification of Diet in Renal Disease study equation (20); iodine contrast only if IV or intra-arterial; oliguria defined as urine output < 500 mL in 24 hr, AKI = acute kidney injury based on Kidney Disease Improving Global Outcomes consensus serum creatinine–based criteria.

[a]Statistically significant, $p < 0.05$.

acidosis), AKI (effect of renal handling of chloride), and SOFA score (effect of severity of critical illness). Most importantly, every 5 mEq/L within-subject increment in Cl_{72} was independently associated with a 37% increase in the odds for hospital mortality in those patients who were already hyperchloremic on ICU admission.

Our study adds to the growing body of evidence showing that elevated Cl levels may be harmful in certain inpatient populations. Three observational studies have evaluated the association of hyperchloremia with hospital mortality in critically ill patients with systemic inflammatory response syndrome (SIRS) (20–22). These studies showed conflicting results and

TABLE 2. Univariate Association of Hospital Mortality With 1) Serum Chloride at the Time of ICU Admission, 2) Serum Chloride at 72 Hours of ICU Stay, and 3) Within-Subject Time-Related Change in Serum Chloride From ICU Admission to 72 Hours (ΔCl) in All Patients and Stratified by the Presence of Hyperchloremia at the Time of ICU Admission

	All Patients		No Hyperchloremia on Admission ($Cl_0 < 110$)		Hyperchloremia on Admission ($Cl_0 \geq 110$)	
Variable	Odds Ratio	p	Odds Ratio	p	Odds Ratio	p
Cl_0 (per 5 mEq/L)	1.04 (0.97–1.12)	0.25	0.95 (0.84–1.08)	0.43	1.18 (0.99–1.40)	0.07
Cl_{72} (per 5 mEq/L)	1.12 (1.01–1.24)	0.03[a]	1.05 (0.92–1.20)	0.46	1.38 (1.13–1.68)	0.002[a]
ΔCl (per 5 mEq/L)	1.15 (1.05–1.29)	0.003[a]	1.13 (0.99–1.28)	0.07	1.35 (1.11–1.64)	0.003[a]

Cl_0 = serum chloride at the time of ICU admission, Cl_{72} = serum chloride at 72 hr of ICU stay, $\Delta Cl = Cl_{72} - Cl_0$.
[a]Statistically significant, $p < 0.05$.

included only a small number of patients with severe sepsis or septic shock. One study in 488 critically ill patients did not show an association between Cl and mortality (21). Notably, the hospital mortality rate in this study was only 3%, precluding the ability to establish a firm conclusion. The other two studies revealed an association between Cl and hospital mortality. The first study was a prospective cohort of 175 critically ill patients in the ICU, 48% of whom had sepsis (20). The second study was a large retrospective cohort study of patients with SIRS, with only 6.8% reported to have sepsis (22). Both studies tested the univariate association between Cl levels and hospital mortality and neither adjusted for any potential confounders.

Critically ill septic patients are frequently exposed to chloride-rich solutions during resuscitation. The potential adverse effects of excessive chloride-rich crystalloid infusions have been suggested in two large retrospective cohort studies. Raghunathan et al (27) found a reduction in hospital mortality associated with the use of balanced IV fluids, and Shaw et al (22) demonstrated an association between higher IV chloride loads and hospital mortality.

The excessive administration of chloride-rich solutions may have detrimental consequences in the kidney. Small experimental studies in animals and humans have shown reductions in renal blood flow, glomerular filtration rate, and renal cortical tissue perfusion when exposed to high IV chloride loads (28, 29). A large prospective study, using a quasiexperimental design, reported a lower incidence of AKI when a chloride-restrictive fluid strategy was implemented in the ICU (30). Interestingly, we found that patients with hyperchloremia on ICU admission were more commonly oliguric when compared with those without hyperchloremia (Table 1).

Furthermore, evidence has shown that chloride-rich solutions may alter coagulation parameters and predispose to bleeding after major surgery (31, 32). In our cohort, we found that patients who were hyperchloremic on ICU admission had more commonly anemia and required more blood transfusions when compared with their nonhyperchloremic counterparts (Table 1).

The pathophysiologic mechanisms underlying the association between hyperchloremia and hospital mortality in sepsis

TABLE 3. Multivariate Analysis of Hospital Mortality as the Dependent Variable Among Hyperchloremic Patients at the Time of ICU Admission ($Cl_0 \geq 110$ mEq/L) for 1) Serum Chloride at the Time of ICU Admission, 2) Serum Chloride at 72 Hours of ICU Stay, and 3) Within-Subject Time-Related Change in Serum Chloride From ICU Admission to 72 Hours (ΔCl)

	Multivariate Model for Cl_0		Multivariate Model for Cl_{72}		Multivariate Model for ΔCl	
Variable	Odds Ratio Hospital Mortality	p	Odds Ratio Hospital Mortality	p	Odds Ratio Hospital Mortality	p
Cl_0 (per 5 mEq/L)	0.84 (0.65–1.07)	0.16	–	–	–	–
Cl_{72} (per 5 mEq/L)	–	–	1.27 (1.02–1.59)	0.03[a]	–	–
ΔCl (per 5 mEq/L)	–	–	–	–	1.37 (1.11–1.69)	0.003[a]

Cl_0 = serum chloride at the time of ICU admission, Cl_{72} = serum chloride at 72 hr of ICU stay, $\Delta Cl = Cl_{72} - Cl_0$.
[a]Statistically significant, $p < 0.05$.
Multivariate models adjusted for age, gender, hypertension, acute kidney injury (Kidney Disease Improving Global Outcomes serum creatinine–based criteria), oliguria, cumulative fluid balance, vasopressor or inotrope requirements, mechanical ventilation, Sequential Organ Failure Assessment (SOFA) score, and base deficit. Multivariate models included all variables associated with hospital mortality on univariate analysis at $p < 0.10$. Acute Physiology and Chronic Health Evaluation II was not included in the multivariate model because of collinearity with the SOFA score.

remain to be determined. Host immunity is a key component in the manifestation of critical illness including sepsis. In vitro cell models have demonstrated an augmented proinflammatory response to hyperchloremic metabolic acidosis mediated by nitric oxide and higher interleukin (IL)-6 to IL-10 ratio when compared with lactic acidosis (33). These observations were reproduced in murine septic models whereby hyperchloremic metabolic acidosis increased circulating levels of IL-6, IL-10, and tumor necrosis factor (34). Similarly, increased nitric oxide production was observed in hydrochloric acid–induced experimental acidosis (35, 36). Therefore, hyperchloremic metabolic acidosis may be a proinflammatory modulator in sepsis.

Chloride also plays an important role in neutrophil function. Neutrophil phagosomes require a continuous influx of chloride through different chloride channels and cotransporters (37, 38) in order to provide substrate for hypochloric acid generation by myeloperoxidase (39). Low or absent extracellular chloride concentration has been associated with decreased neutrophil function (40, 41). It is not known whether high extracellular chloride generates an augmented neutrophil response, which could further contribute to the proinflammatory imbalance observed in sepsis and hyperchloremic acidosis.

Our results should be interpreted with caution. The observational nature of our investigation is susceptible to bias and confounding. Selection bias may be possible given the rigorous inclusion and exclusion criteria. However, selection bias due to missing values is unlikely because data were not missing in a systematic differential manner between the two subgroups. Similar to any other observational study, information on comorbidities is dependent on EMR documentation, which may increase the risk of information bias. However, there is no reason to believe that there would be a systematic differential information bias between the two subgroups. Furthermore, data were electronically extracted from EMRs by data management personnel blinded to the study. The accuracy of data collection was further validated by individual EMR review of 10% of data. Although we adjusted for confounding by rigorous multivariate regression analyses including covariate adjustment using propensity scores, residual confounding by unmeasured covariates may not have been completely eliminated. Finally, given the observation period and objectives of our study, data pertaining to the amount of fluid administered before ICU admission or the type of fluid (chloride load) were not available.

The strengths of our study are its large sample size, the careful selection of a representative sample of patients with severe sepsis or septic shock admitted to the ICU, and the multivariate adjustment for clinical confounders directly linked to hyperchloremia and hospital mortality such as base deficit, CFB, AKI, and comprehensive critical illness severity scores. None of the studies that have previously revealed the association between Cl levels and hospital mortality accounted for confounding. Our study is unique in the multivariate design and patient population.

CONCLUSIONS

Critically ill septic patients with hyperchloremia at the time of ICU admission represent an overall sicker population. In patients manifesting hyperchloremia (Cl ≥ 110 mEq/L) on ICU admission, higher Cl levels and worsening within-subject hyperchloremia at 72 hours of ICU stay were independently associated with all-cause hospital mortality. The avoidance of chloride-rich solutions in this specific subgroup of patients may have a greater impact on mortality outcomes. Although the effect of hyperchloremia on mortality appears independent of metabolic acidosis, a potential causal relationship between hyperchloremia and mortality requires further exploration.

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