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Association of Chloride Ion and Sodium-Chloride Difference With Acute Kidney Injury and Mortality in Critically Ill Patients

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Objectives: Derangements of chloride ion concentration ($[Cl^-]$) have been shown to be associated with acute kidney injury and other adverse outcomes. For a physicochemical approach, however, chloride ion concentration should be considered with sodium ion concentration. This study aimed to examine the association of chloride ion concentration and the main strong ion difference (difference between sodium ion concentration and chloride ion concentration) during the first 24 hours after admission into ICU with the development of acute kidney injury and mortality.

Design: Retrospective analyses using the eICU Collaborative Research Database.

Setting: ICUs in 208 hospitals across the United States between 2014 and 2015.

Patients: Critically ill patients who were admitted into the ICU.

Interventions: None.

Measurements and Main Results: A total of 34,801 patients records were analyzed. A multivariable logistic regression analysis for the development of acute kidney injury within 7 days of ICU admission shows that, compared with main strong ion difference 32–34 mEq/L as a reference, there were significantly high odds for the development of acute kidney

injury in nearly all groups with main strong ion difference more than 34 mEq/L (main strong ion difference = 34–36 mEq/L, odds ratio = 1.17, $p = 0.02$; main strong ion difference = 38–40 mEq/L, odds ratio = 1.40, $p < 0.001$; main strong ion difference = 40–42 mEq/L, odds ratio = 1.46, $p = 0.001$; main strong ion difference > 42 mEq/L, odds ratio = 1.56, $p < 0.001$). With chloride ion concentration 104–106 mEq/L as a reference, the odds for acute kidney injury were significantly higher only in chloride ion concentration less than or equal to 94 mEq/L and chloride ion concentration 98–100 mEq/L groups. Analyses conducted using inverse probability weighting showed significantly greater odds for ICU mortality in all groups with main strong ion difference greater than 34 mEq/L other than the 36–38 mEq/L group, as well as in the less than 26 mEq/L group.

Conclusions: Main strong ion difference measured on ICU presentation to the ICU predicts acute kidney injury within 7 days, with low and, in particular, high values representing increased risk. The association between the chloride levels and acute kidney injury is statistically insignificant in models incorporating main strong ion difference, suggesting main strong ion difference is a better predictive marker than chloride on ICU admission.

Key Words: acute kidney injury; chloride ion; intensive care; strong ion difference

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Chloride is the most abundant anion in the extracellular fluid and plays an important role in numerous physiologic functions (1). Recently, researchers have described an association between hyperchloremia and acute kidney injury (AKI) after abdominal surgery (2), after noncardiac surgery (3), in septic shock (4), with subarachnoid hemorrhage (Sadan, 28504980), and in unselected ICU patients (5,6,7). Hyperchloremia has also been associated with increased mortality in postsurgical and ICU populations (3, 8–11).

Stewart (12) proposed an alternative approach to acid-base physiology, which considered serum bicarbonate a dependent variable, with “strong ions” (ions that completely dissociate from hydrogen in physiologic conditions) as well as “weak nonvolatile acids” (ions that can exist either associated with or dissociated from their hydrogen

ion) as the independent variables along with plasma carbon dioxide. “Apparent strong ion difference” (aSID) could be calculated by subtracting the sum of serum chloride and lactate from the sum of serum sodium, potassium, calcium, and magnesium, and could be used to determine the presence of an acidosis or alkalosis. This can be thought of as analogous to the calculation of the anion gap using a traditional bicarbonate-based approach, to reveal the presence of an unmeasured acid, although the Stewart approach incorporates lactate as well as weak acids (albumin and phosphate) that are not always corrected for in clinical practice using the bicarbonate-based approach. Subsequently, studies have shown that “main strong ion difference” (mSID), the difference between sodium ion concentration ($[Na^+]$) and chloride ion concentration ($[Cl^-]$), can be used as surrogate for aSID (13, 14).

Prior studies have shown strong ion difference calculations using the Stewart approach can be useful as a prognostic marker for mortality in ICU populations, although with no clear advantage over the more common bicarbonate-centric acid base approach when incorporating correction for albumin and lactate (15–17). However, many of the previous studies correlating $[Cl^-]$ with AKI did not evaluate whether $[Cl^-]$ is merely acting as a proxy for strong ion difference, which may be better evaluated using calculations such as mSID. (2, 4–7, 18–20). In this multicenter retrospective study, we evaluate the association of mSID and $[Cl^-]$ at admission to the ICU with subsequent development of AKI and ICU mortality.

MATERIALS AND METHODS

Study Population and Data Source

Data were analyzed from patients admitted into ICU in 208 hospitals across the United States between 2014 and 2015, as captured in the eICU Collaborative Research Database v2.0 (21). The study is exempt from Institutional Review Board approval due to the retrospective design, lack of direct patient intervention, and the security schema, for which the reidentification risk was certified as meeting safe harbor standards by an independent privacy expert (HIPAA Certification 1031219-2).

Inclusion criteria were: 1) first admission into the ICU during the study period, 2) 18 years old or older, and 3) medical ICU patients. Exclusion criteria were: 1) patients who received renal replacement therapy before ICU admission, 2) patients who had creatinine concentration more than 3.0 mg/dL at admission, 3) patients who underwent surgery before ICU admission, and 4) patients without data for mSID calculation for the first 24 hours after ICU admission.

Study Variables

The primary outcome was defined as the development of AKI within 7 days of ICU admission. AKI was diagnosed and classified by Kidney Disease Improving Global Outcomes consensus criteria (22). According to this classification and staging system of AKI, serum creatinine concentration greater than or equal to 1.5 times the baseline or increase in serum creatinine greater than or equal to 0.3 mg/dL from baseline creatinine concentration constitutes stage 1, serum creatinine concentration greater than or equal to 2.0 times the baseline

constitutes stage 2, and serum creatinine concentration greater than or equal to 3.0 times the baseline or initiation of renal replacement therapy constitutes stage 3. Baseline creatinine, as in previous studies, was considered to be creatinine at admission or the previous creatinine value before ICU admission when available (23, 24).

The secondary outcomes were mortality in the ICU and in the hospital. ICU mortality was defined as death prior to discharge from the ICU, with hospital mortality defined as death prior to discharge from hospital. Baseline characteristics including age, gender, weight, and ethnicity, and past medical history were extracted. Information on vital signs such as heart rate, blood pressure, and temperature was also extracted from the database.

$[Cl^-]$ at admission was defined as the first serum chloride ion measurement within 24 hours of ICU admission. $[Na^+]$ measured at the same time as the $[Cl^-]$ measurement was also extracted and used to calculate mSID at admission: $[Na^+] - [Cl^-]$. Low SID and high SID were defined as SID less than 31 mEq/L and greater than 37 mEq/L, respectively. Hypochloremia and hyperchloremia were defined as $[Cl^-]$ less than 98 mEq/L and greater than 110 mEq/L, respectively. Both mSID and $[Cl^-]$ were stratified into bins of 2 mEq/L in width and represented as a categorical variable.

Statistical Analyses

All results for continuous variables are expressed as mean \pm SD, or median (interquartile range; 25% quartile, 75% quartile) as appropriate. Shapiro-Wilk test was used to test for normal distribution. For groupwise comparisons of continuous variables, Student *t* test (two groups) or one-way analysis of variance (*n* groups) was used when variables were normally distributed. Wilcoxon rank-sum test (two groups) or Kruskal-Wallis test (*n* groups) was used when variables were not normally distributed. For categorical variables, Fisher exact test or the chi-square test was used.

An adjusted odds ratio for an outcome was calculated by a logistic regression model, adjusting for factors that could be related to both mSID and $[Cl^-]$ and the outcomes. mSID and $[Cl^-]$ were treated as categorical variables in the case of nonlinear relationship with the outcomes. Missing values in continuous covariates in the model were replaced with mean values. Inverse probability weighting was used to estimate causal effects in a sensitivity analysis. Since treating mSID and $[Cl^-]$ as categorical variables ignores the order and could decrease power, four subgroups were created and analyzed separately: 1) low mSID (≤ 34 mEq/L) and low $[Cl^-]$ (≤ 106 mEq/L), 2) low mSID (≤ 34 mEq/L) and high $[Cl^-]$ (> 106 mEq/L), 3) high mSID (> 34 mEq/L) and low $[Cl^-]$ (≤ 106 mEq/L), and 4) high mSID (> 34 mEq/L) and high $[Cl^-]$ (> 106 mEq/L). In another sensitivity analysis, mSID and $[Cl^-]$ were treated as continuous variables.

All statistical comparisons were two-sided and a significant level was defined as a *p* value of less than 0.05. All statistical analyses were performed using R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Data were queried from R using the package bigquery Version 1.2.0.

RESULTS

Participant Characteristics

Of an initial pool of 65,855 patients, there were 19,844 postoperative patients, 5752 patients whose creatinine concentration

TABLE 1. Comparison of Patients' Demographics and Hemodynamic and Laboratory Values Based on Main Strong Ion Difference Classification

Variable	31 ≤ mSID < 37 mEq/L (n = 21,573, 62%)	mSID < 31 mEq/L (n = 7,030, 20%)	mSID > 37 mEq/L (n = 6,198, 18%)	p
Age, yr, mean (sd)	63.3 (17.7)	61.6 (18.8)	64.8 (16.2)	<0.001
Male, n (%)	11,752 (54.5)	3,391 (48.2)	3,185 (51.4)	<0.001
Height in cm, mean (sd)	169.5 (10.9)	167.9 (10.8)	168.7 (11.1)	<0.001
Weight in kg, mean (sd)	83.1 (24.6)	78.3 (22.2)	88.1 (31.3)	<0.001
Ethnicity, n (%)				
African American	1,975 (9.2)	503 (7.2)	724 (11.7)	< 0.001
Asian	205 (1.0)	62 (0.9)	33 (0.5)	
Caucasian	16,574 (76.8)	5,419 (77.1)	4,888 (78.9)	
Hispanic	1,386 (6.4)	419 (6.0)	307 (5.0)	
Other/unknown	1,433 (6.6)	627 (8.9)	246 (4.0)	
Congestive heart failure, n (%)	2,419 (13.4)	549 (9.4)	1,454 (26.7)	< 0.001
Peripheral vascular disease, n (%)	822 (4.6)	260 (4.5)	316 (5.8)	< 0.001
Hypertension, n (%)	8,447 (47.0)	2,424 (41.5)	2,893 (53.2)	< 0.001
Chronic obstructive pulmonary disease, n (%)	4,075 (22.7)	1,133 (19.4)	2,045 (37.6)	< 0.001
Diabetes, n (%)	2,325 (12.9)	830 (14.2)	931 (17.1)	< 0.001
Malignancy, n (%)	0.00 (0.06)	0.00 (0.05)	0.00 (0.04)	0.13
mSID in mEq/L, med (IQR)	34 (32–35)	29 (27–30)	40 (38–42)	< 0.001
Serum chloride ion concentration in mEq/L, med (IQR)	105 (102–108)	110 (107–113)	99 (95–102)	< 0.001
Serum sodium concentration in mEq/L, med (IQR)	139 (136–141)	138 (135–141)	139 (136–142)	< 0.001
Serum creatinine in mg/dL, med (IQR)	0.93 (0.71–1.30)	0.97 (0.72–1.45)	1.00 (0.72–1.40)	< 0.001
Albumin in g/dL, med (IQR)	3.1 (2.5–3.6)	2.8 (2.3–3.3)	3.2 (2.7–3.8)	< 0.001
Bilirubin in mg/dL, med (IQR)	0.6 (0.4–0.9)	0.6 (0.4–1.0)	0.6 (0.4–0.9)	0.001
Serum blood urea nitrogen in mg/dL, med (IQR)	18 (12–28)	20 (13–32)	21 (14–34)	< 0.001
WBC per 10 ³ /L, med (IQR)	10.3 (7.4–14.4)	10.9 (7.4–15.7)	10.8 (7.8–15.0)	< 0.001
Platelets per 10 ³ /L, med (IQR)	207 (153–272)	196 (132–270)	217 (161–283)	< 0.001
Hematocrit %, med (IQR)	35.7 (30.2–40.6)	32.7 (27.4–38.3)	37.1 (31.8–42.0)	< 0.001
Hemoglobin in g/dL, med (IQR)	11.8 (9.8–13.6)	10.8 (9.0–12.8)	12.0 (10.1–13.8)	< 0.001
Glucose in mg/dL, med (IQR)	127 (103–171)	126 (101–170)	137 (109–189)	< 0.001
Serum potassium concentration in mEq/L, med (IQR)	4.0 (3.7–4.4)	4.1 (3.7–4.5)	4.0 (3.6–4.5)	< 0.001
Uric acid in mg/dL, med (IQR)	5.8 (4.0–7.8)	5.8 (4.0–7.5)	7.0 (5.2–9.0)	0.02
Heart rate in beats/min, mean (sd)	89.61 (22.13)	92.21 (22.43)	92.74 (22.46)	< 0.001
Systolic blood pressure in mm Hg, mean (sd)	127.94 (27.67)	119.57 (26.42)	129.62 (28.08)	< 0.001
Temperature in °C, mean (sd)	36.78 (0.76)	36.77 (0.87)	36.73 (0.77)	< 0.001

IQR = interquartile range, med = median, mSID = main strong ion difference.

was more than 3.0 mg/dL at admission, 106 patients who received renal replacement therapy before admission, and 5,352 patients without data for mSID calculation who were excluded, resulting in a final cohort of 34,801 participants. Mean age was 63 years old, 53% were male, and 77% were Caucasian. At admission, 7,030 patients (20.2%) had low mSID and 6,198 patients (17.8%) had

high mSID. About 4,167 patients (12.0%) had hypochloremia and 5,336 patients (15.3%) had hyperchloremia. **Table 1** shows demographics and hemodynamic and laboratory parameters for patients based on mSID classification.

Three-thousand sixty-one patients (8.8%) developed AKI within 7 days of admission. Of those patients with AKI, 2,443

TABLE 2. Comparison of Outcomes Based on Main Strong Ion Difference Classification

Outcome	31 ≤ mSID < 37 mEq/L (n = 21,573)	mSID < 31 mEq/L (n = 7,030)	mSID > 37 mEq/L (n = 6,198)	p
AKI, n (%)	1,695 (7.9)	633 (9.0)	733 (11.8)	< 0.001
Kidney Disease Improving Global Outcomes AKI stage (%)				
Stage 1	1,362 (7.7)	488 (8.3)	593 (11.1)	< 0.001
Stage 2	239 (1.4)	112 (1.9)	102 (1.9)	
Stage 3	94 (0.5)	33 (0.6)	38 (0.7)	
Death in ICU, n (%)	936 (4.3)	375 (5.3)	389 (6.3)	< 0.001
Death in Hospital, n (%)	1,447 (6.7)	547 (7.8)	624 (10.1)	< 0.001

AKI = acute kidney injury, mSID = main strong ion difference.

patients were classified as AKI stage 1, 453 patients were classified as AKI stage 2, and 165 patients were classified as AKI stage 3. There were 5,907 patients (17.0%) who could not be evaluated for AKI due to missing values. There were 1,700 deaths (4.8%) in the ICU and 2,618 deaths (7.5%) in the hospital.

Univariate Analyses of Primary and Secondary Outcomes

In univariate analysis, there were significant differences in AKI development, AKI stage, ICU mortality, and hospital mortality among groups classified based on mSID. AKI frequency and mortality were both highest in the mSID greater than 37 mEq/L, followed by the mSID less than 31 mEq/L group and lowest in the group with mSID between 31 and 37 mEq/L (Table 2). Figure 1A illustrates the frequency of AKI among groups stratified into 2-mEq/L-wide mSID bins. The frequency of AKI was the lowest (7.2%) in patients with mSID 32–34 mEq/L and increased as SID increased and decreased. Figure 1B illustrates the frequency of AKI among groups stratified into 2-mEq/L-wide [Cl⁻] bins, showing the similar U-shaped relationship. Figure 2, A and B, shows

the ICU mortality among groups stratified by mSID and [Cl⁻], again showing a U-shaped curve.

Supplemental Figure 1 (<http://links.lww.com/CCX/A397>) shows mSID plotted against serum bicarbonate in the same individual, demonstrating an absence of a linear relationship between the two variables. **Supplemental Figure 2** (<http://links.lww.com/CCX/A398>) shows [Cl⁻] plotted against mSID in the same individual. **Supplemental Figure 3** (<http://links.lww.com/CCX/A399>) shows correlation matrix between the continuous variables.

Multivariable Analyses

A multivariable logistic regression analysis with development of AKI as the outcome is shown in Supplemental Table 1 (<http://links.lww.com/CCX/A400>). Compared with mSID 32–34 mEq/L as a reference, the odds for AKI increased for nearly all mSID range groups above 34 mEq/L. There was no significant difference in the odds for AKI for mSID range groupings below 32 mEq/L compared with the reference range of 32–34 mEq/L. With [Cl⁻] 104–106 mEq/L as a reference, the odds for AKI were significantly higher only in [Cl⁻] ≤ 94 mEq/L and [Cl⁻] 98–100 mEq/L. Age,

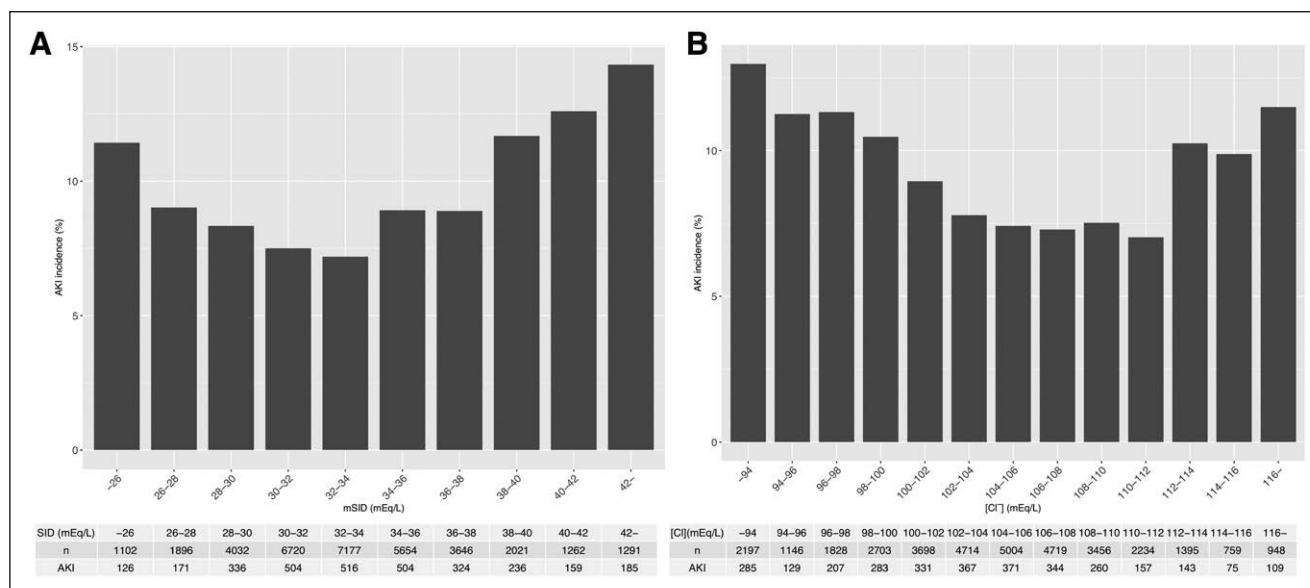


Figure 1. Frequency of acute kidney injury (AKI) among stratified groups based on: (A) main strong ion difference (mSID) and (B) serum chloride ion concentration ([Cl⁻]).

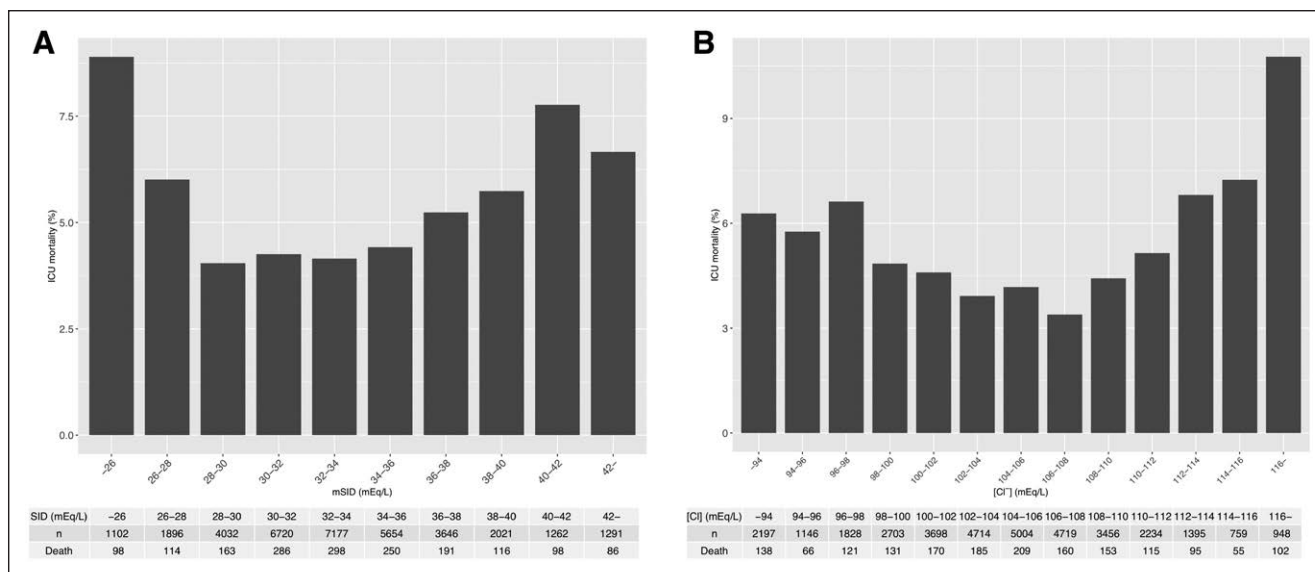


Figure 2. ICU mortality among stratified groups based on (A) main strong ion difference (mSID) and (B) serum chloride ion concentration ($[Cl^-]$).

weight, Black race, a diagnosis of congestive heart failure, and a number of hematologic and laboratory parameters were also associated with increased odds for AKI. Analyses using inverse probability weighting demonstrated similar findings compared with unweighted analyses for both mSID and $[Cl^-]$.

A multivariable logistic regression analysis for ICU mortality is shown in **Supplemental Table 2** (<http://links.lww.com/CCX/A401>). Compared with mSID 32–34 mEq/L as a reference group, odds for ICU mortality were significantly higher in the mSID 36–38 mEq/L and mSID 40–42 mEq/L groups, and significantly lower in the mSID 28–30 mEq/L group. Analyses conducted using inverse probability weighting showed significantly greater odds for ICU mortality in all groups with mSID greater than 34 mEq/L other than the 36–38 mEq/L group, as well as the less than 26-mEq/L group. Using $[Cl^-]$ 104–106 mEq/L as a reference group, the odds for ICU mortality were greater in the 112–114 mEq/L and $[Cl^-]$ greater than 116-mEq/L groups. However, these associations were not significant with inverse probability weighting. Similar trends were seen using multivariable logistic regression analysis for overall hospital mortality; mSID groups greater than 36 mEq/L and $[Cl^-]$ groups less than 98 and greater than 110 mEq/L were associated with increased hospital mortality. A multivariable logistic regression analysis for hospital mortality is shown in **Supplemental Table 3** (<http://links.lww.com/CCX/A402>).

Supplemental Table 4 (<http://links.lww.com/CCX/A403>) and **Supplemental Table 5** (<http://links.lww.com/CCX/A404>) shows logistic regression models with mSID and $[Cl^-]$ as continuous variables within four subgroups of mSID and $[Cl^-]$ ranges. In the group with high mSID and low $[Cl^-]$, both increased mSID and decreased $[Cl^-]$ were associated with AKI. Decreased mSID but not $[Cl^-]$ had significant association with AKI in the low mSID/high $[Cl^-]$ group. Increased mSID but not $[Cl^-]$ had significant association with AKI in the high mSID/high $[Cl^-]$ group. The only significant associations seen in sensitivity analyses for mortality were increasing $[Cl^-]$ and mSID in the high

mSID/high $[Cl^-]$ group and increasing $[Cl^-]$ in the low mSID/high $[Cl^-]$ group.

DISCUSSION

The hospital mortality from this large, predominantly Caucasian United States-based population was 7.5%, which is somewhat lower than previous studies of ICU populations using the Acute Physiology and Chronic Health Evaluation database (25). Studies of AKI rates in ICU populations of this size have not been published, but smaller studies have demonstrated substantially higher rates of AKI than the 8.8% seen in this study (6, 7). Discrepancies in mortality and AKI rates could be explained by differences in exclusion criteria, specifically those with significant elevation in creatinine or the need for renal replacement therapy prior to admission. Although some studies computed serum creatinine concentration based on a formula by assuming a normal glomerular filtration rate for patients without baseline creatinine concentration before admission (4, 6, 26), this assumption could overestimate AKI frequency after admission.

Both low and high mSID values are associated with an increased risk of AKI, severe AKI, ICU mortality, and hospital mortality overall compared with normal mSID values. Subdividing mSID values into smaller groups both above and below normal range reveals a U-shaped relationship, with greater risk as mSID deviates further from the normal range. Risk for AKI was greater for mSID values above normal range compared with values below normal range, which was corroborated in multivariate analysis of the subdivided dataset showing nearly all groups with elevated mSID values with increased risk for AKI, whereas only the lowest mSID group among depressed mSID groups was associated with increased risk for AKI.

Prior studies have shown strong ion difference calculations using the Stewart approach can be useful as a prognostic marker for mortality in ICU populations (15–17). Here, we demonstrate a similar roughly U-shaped relationship between mSID and both ICU and inhospital mortality. Low mSID values in the case of

mortality were even more tenuously associated with increased mortality in either the hospital or ICU, and significant only in inverse probability weighted analysis.

Prior studies have also demonstrated an association between abnormal serum chloride concentration and development of AKI in critically ill patients (4–7, 20, 27–31). However, these studies considered $[\text{Cl}^-]$ as a continuous variable, assuming a linear relationship between $[\text{Cl}^-]$ and log odds of AKI development. This study shows a U-shaped association between $[\text{Cl}^-]$ and AKI, suggesting that representing $[\text{Cl}^-]$ as a continuous variable in a regression model may be a simplification of the relationship. Prior studies that treated $[\text{Cl}^-]$ as a categorical variable to evaluate a nonlinear relationship with AKI subdivided $[\text{Cl}^-]$ only into two or three bins due to sample size considerations (2, 18, 19, 26, 32–34), a limitation we were able to overcome with the large size of our dataset.

Many of the studies correlating $[\text{Cl}^-]$ and AKI have not evaluated whether abnormal $[\text{Cl}^-]$ is merely a proxy for strong ion difference (2, 4–7, 18–20). In this study, $[\text{Cl}^-]$ was not significantly associated with AKI when included in multivariate models that also contained mSID other than at the less than or equal to 94 level; it was also not significantly associated with ICU mortality except at the less than or equal to 94 level in inverse probability weighted models. These findings suggest mSID may be a better predictor for both AKI and ICU mortality than $[\text{Cl}^-]$ alone.

Sensitivity analyses were done to evaluate each combination of mSID and $[\text{Cl}^-]$ deviation from normal range: low mSID and high $[\text{Cl}^-]$, most consistent with metabolic acidosis; high mSID and low $[\text{Cl}^-]$, most consistent with metabolic alkalosis; and low mSID/high $[\text{Cl}^-]$ and high mSID/low $[\text{Cl}^-]$ pairings, which are less consistent with pure metabolic processes. These analyses corroborated the advantage of mSID over $[\text{Cl}^-]$ as a predictor of AKI. The sensitivity analyses also supported but less conclusively the association between increased mSID and mortality.

mSID was originally conceived as a simplified way of evaluating acid-base physiology using the Stewart approach (13, 14). In this study, there were nearly equal numbers of individuals with mSID above and below a normal range, yet the majority of patients had a metabolic acidosis based on serum bicarbonate levels. Although the majority of individuals with metabolic alkalosis based on serum bicarbonate levels had high mSID values, individuals with metabolic acidosis based on serum bicarbonate levels had a broad range of mSID values. This deviation does not appear to be driven by variation in $[\text{Na}^+]$, which were largely similar across mSID groups, and may reflect more complex acid-base disorders.

There are several limitations in this study. First, mSID incorporates $[\text{Cl}^-]$ in its calculations, so there is some degree of collinearity between the two features. However, the data do demonstrate a significant degree of discordance with the variables and their relationship to the outcomes. Second, baseline creatinine was unavailable and so the initial serum creatinine was considered baseline; although this allows for the assessment of subsequent worsening of kidney function, it does not capture processes that may have started before arrival to the ICU, including the lag time for creatinine to reach steady state in the cases where the cause of AKI was addressed before arrival to the ICU. More broadly, this analysis is unable to take into account any medical interventions done prior

to ICU arrival, which could affect the risk of AKI and mortality. Finally, the use of mSID, while clinically appealing due to its simplicity, is limited in its ability to allow inference about the underlying physiology. This study raises additional questions about the relationship between mSID, acid-base status, and clinical outcomes, which will require further investigation to better answer.

CONCLUSIONS

mSID measured on presentation to the ICU could be a useful consideration in predicting AKI and mortality risk on initial patient evaluation, with low and, in particular, high values representing increased risk. The association between $[\text{Cl}^-]$ and AKI or mortality largely became insignificant in models incorporating mSID, suggesting mSID is a better predictive marker than chloride on ICU presentation. However, mSID deviations from normal did not appear to correlate with changes in serum bicarbonate alone, a finding that merits further exploration.

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