TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 435-442
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doi:10.3906/sag-1602-100

The effects of the chloride:sodium ratio on acid-base status and mortality in septic patients

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Received: 16.02.2016 • **Accepted/Published Online:** 07.07.2016 • **Final Version:** 18.04.2017

Background/aim: Calculation of the chloride:sodium (Cl^-:Na^+) ratio is proposed to enable a quick evaluation of the effect of Cl^- and Na^+ on the acid-base balance in critically ill patients. In the present study, the relationship of the Cl^-:Na^+ ratio of septic patients with acid-base status and ICU mortality were investigated.

Materials and methods: In our two-center study, 434 patients who were diagnosed with sepsis were included. The patients were divided into three groups: low (<0.75), normal (≥0.75, <0.80), and high (≥0.80) Cl^-:Na^+ ratio groups. Patients' demographic data, blood gas values, length of ICU stay, and ICU mortality were recorded.

Results: In the low and high groups, ICU mortality was significantly higher than in the normal group (29.3%, 37.1%) (P = 0.005). There was a negative correlation between the Cl:Na^+ ratio and each of HCO_3^-, standard base excess, and $PaCO_2$ (r^2 = 0.21, r^2 = 0.19, and r^2 = 0.17) (P < 0.001 for each). In the multivariate analysis, the ICU mortality was increased 2.6-fold (1.2–5.8) by low Cl^-:Na^+ ratio (P = 0.019).

Conclusion: The Cl^-:Na^+ ratio is a useful parameter for showing the relationship between Cl^- and Na^+ and their impact on acid-base status. Low Cl^-:Na^+ ratio at ICU admission can be used as a prognostic indicator for increased ICU mortality in septic patients.

Key words: Chloride:sodium ratio, sepsis, ICU mortality, outcome

1. Introduction

Acid-base disorder is an important issue that requires an urgent solution in the intensive care unit (ICU) (1). Stewart's physiochemical approach provides practical solutions for the understanding of metabolic acid-base disorders (2–4). However, this approach has limitations that prevent intensivists from completing a fast bedside assessment. Therefore, methods enabling fast and accurate bedside assessment are needed. Recently, simpler and more practical approaches, such as assessments of Cl^- and Na^+ differences, Cl^-:Na^+ ratio evaluation, and base excess-chloride (BE_{Cl}) calculations, have been used (5,6). Duward et al. (6) evaluated acid-base disorders in accordance with pH, pCO_2, and Cl^- changes. According to Duward et al. (6), the main reason for the changes in the HCO_3^- pool is changes in Cl^-. Moreover, Cl^- must always be interpreted together with Na^+, and the simplest method of achieving this interpretation is calculation of the Cl^-:Na^+ ratio. Hypochloremia or hyperchloremia should be considered in accordance with the Cl^-:Na^+ ratio. Regardless of the individual Cl^- and Na^+ concentrations, the Cl^-:Na^+ ratio may be low or high. This notion makes the contribution of Cl^- to acid-base disorder more comprehensible. It is indicated that a strong ion difference (SID) is related to mortality (7,8). Hypochloremia, hyperchloremia, and dysnatremia are also known to be associated with increased mortality (9–11). Thus, the Cl:Na^+ ratio can also be associated with increased mortality. In the present study, the relationship between the Cl^-:Na^+ ratio in septic patients at ICU admission and each of the other components of the acid-base balance and ICU mortality was investigated.

2. Material and methods

2.1. Study design

Ethics committee approval was obtained from the Acıbadem University Medical Research Council for the present study. A total of 2691 patients admitted to the Acıbadem International Hospital ICU and Ataşehir Memorial ICU between 1 January 2006 and 31 December 2012 were retrospectively evaluated. Patients who were

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readmitted to the ICU, who were under the age of 18 years, whose ICU admission scores and hospital outcome were unknown, or who were nonseptic and had already received fluid therapy or mechanical ventilation support were excluded (Figure 1).

2.2. Data collection

Laboratory data were collected from the Acıbadem Health Group Database and Ataşehir Memorial Hospital Database. The blood gas data were collected at ICU admission. Blood gas analyses were performed with an ABL 700 (Radiometer, Denmark, Copenhagen) blood gas device. Patients' age, sex, APACHE II (Acute Physiology And Chronic Health Evaluation) and SOFA (Sequential Organ Failure Assessment) scores, pH, arterial carbon dioxide pressure ($PaCO_2$) (mmHg), bicarbonate (HCO_3^-) (mmol L^{-1}), standard base excess (SBE) (mmol L^{-1}), BE_{Cl} (mmol L^{-1}), Na^+ (mmol L^{-1}), K^+ (mmol L^{-1}), Ca^{2+} (mmol L^{-1}), Cl^- (mmol L^{-1}), lactate (mmol L^{-1}), anion gap (AG) (mmol L^{-1}), length of ICU stay (days), and ICU mortality were recorded. Consent forms were not required because only the patient files were investigated. No parameter intervention was performed and no personal data were recorded during the analysis of the cases.

2.3. Sepsis definition

The definitions of sepsis were made in accordance with the International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 (12). The coexistence of infection (probable or documented) and systemic indicators of infection (general, inflammatory, haemodynamic, organ dysfunction, and tissue perfusion) was defined as sepsis. Culture results of the patients obtained within the first 24 h were recorded.

2.4. Classification and calculations

In accordance with their Cl^-:Na^+ ratios at ICU admission, the patients were divided into three groups: low Cl^-:Na^+ ratio (<0.75), normal Cl^-:Na^+ ratio (≥0.75, <0.80), and high Cl^-:Na^+ ratio (≥0.80) (Table 1) (5). AG and BE_{Cl} were calculated with the formulas shown below:

$AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$,

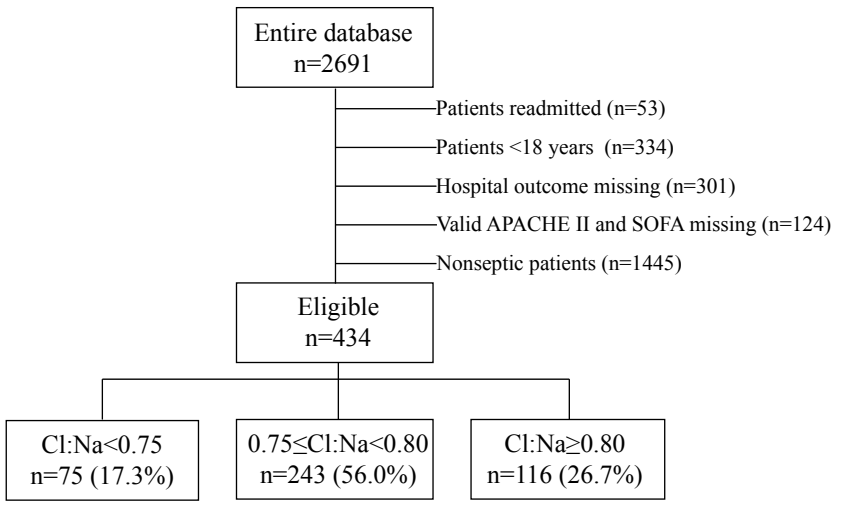
$BE_{Cl} = (Na^+ - Cl^- - 32)$ (6).

2.5. Statistical analysis

The statistical analysis was performed using Wizard Pro Version 1.7.20. Patients' characteristics were compared between the three Cl^-:Na^+ ratio groups using the chi-square and Mann–Whitney U tests. All results are presented as percentages, means (±standard deviations), and median values (interquartiles or minimum and maximum values). A multivariate logistic regression model was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of the Cl^-:Na^+ ratio with ICU mortality. The logistic regression model included age, APACHE II score, SOFA score, pH, $PaCO_2$, SBE, lactate level, Na^+ and Cl^- levels, and Cl^-:Na^+ ratio. A correlation test was used to test for correlations between parameters, and the results are presented as r^2 values. The type 1 error level was set at 5%. According to the Bonferroni correction, $P < 0.025$ was accepted to be statistically significant in the subgroup analysis.

3. Results

A total of 434 septic patients were included in this study. The low Cl^-:Na^+ ratio group included 75 patients (17.3%), the normal Cl^-:Na^+ ratio group included 243 patients (56.0%), and the high Cl^-:Na^+ ratio group included 116 patients (26.7%) (Figure 1). A total of 248 of these 434



APACHE II; Acute Physiology and Chronic Health Evaluation SOFA; Sequential Organ Failure Assessment

Figure 1. Study flowchart.

patients (57.1%) had pneumonia-induced sepsis. Infection areas and microorganism status were not significantly different between any of the groups (P = 0.251, P = 0.120) (Table 1). In the low Cl^-:Na^+ ratio group, Cl^- and lactate concentrations were significantly lower and age, ICU mortality, $PaCO_2$, HCO_3^-, SBE, BE_{Cl}, and AG values were significantly higher than those in the normal Cl^-:Na^+ ratio group (P < 0.025 for each) (Table 1). In the high Cl^-:Na^+

Table 1. Demographic data and clinical outcomes.

	Low (<0.75) (n = 75)	Normal (≥0.75, <0.80) (n = 243)	High (≥0.80) (n = 116)	P
Age, years	76 (22–98) **	63 (18–95)	64.5 (18–98)	<0.001
Male, n (%)	42 (56)	159 (65.4)	65 (56)	0.136
APACHE II	18 (14–23)	17 (13–22)	20.5 (17–27) **	<0.001
SOFA score	4 (0–15)	5 (0–15)	7 (0–16) **	<0.001
Infection areas, n (%) Respiratory Bloodstream Urinary Others Unproven	 48 (64) 12 (16) 8 (10.7) 4 (5.3) 3 (4)	 136 (56) 36 (14.8) 26 (10.7) 21 (8.6) 24 (9.9)	 64 (55.2) 18 (15.5) 12 (10.3) 4 (3.5) 18 (15.5)	0.251
Microorganisms, n (%) Gram-negative Gram-positive Fungi Multiple organisms Unidentified	 17 (22.7) 18 (24) 15 (20) 22 (29.3) 3 (4)	 60 (24.7) 50 (20.6) 45 (18.5) 64 (26.3) 24 (9.9)	 24 (20.7) 20 (17.2) 13 (11.2) 41 (35.4) 18 (15.5)	0.120
Length of ICU stay, days	6 (1–96)	4 (1–96)	7 (1–160) *	0.004
ICU mortality, n (%)	22 (29.3) *	51 (21.0)	43 (37.1) **	0.005
pH	7.42 (6.76–7.61)	7.40 (6.76–7.54)	7.36 (6.8–7.59) **	<0.001
$PaCO_2$	44.4 (34.7–52.1) **	35.8 (31.9–41.0)	31.3 (26.3–36.9) **	<0.001
HCO_3	25.6 (22–29.3) **	22 (19.8–24)	20 (17–22.3) **	<0.001
SBE	2.1 (–2 to 6.2) **	–2 (–5 to –0.3)	–5 (–8.1 to –2) **	<0.001
BE_{Cl}	5 (3–9) **	–1.0 (–3 to 1)	–8 (–10 to –6) **	<0.001
AG	16.0 ± 1.4 **	13.4 ± 0.6	8.4 ± 0.9 **	<0.001
Na^+ #	134 (98–158)	136 (115–158)	134 (115–177)	0.104
Cl^- #	94 (55–118) **	106 (87–122)	107 (94–116) **	<0.001
Cl^-:Na^+ ratio	0.74 (0.71–0.74) **	0.77 (0.76–0.79)	0.82 (0.81–0.84) **	<0.001
K^+	4.0 ± 0.2	4.1 ± 0.2	4.2 ± 0.2	0.337
Ca^{++}	1.11 ± 0.03	1.2 ± 0.18	1.12 ± 0.02	0.729
Lactate	1.1 (0.9–2) *	1.6 (1.1–2.9)	2 (1.1–3.1)	0.003

AG: Anion gap, APACHE II: Acute Physiology and Chronic Health Evaluation, BE_{Cl}: base excess chloride, ICU: intensive care unit, SOFA: Sequential Organ Failure Assessment, SBE: standard base excess. Student t, chi-square, and Mann–Whitney U tests were used for statistical analysis. Results are given as percentage, mean (±standard deviation), or median (interquartiles or minimum and maximum values). P < 0.05 was accepted as significant. According to Bonferroni correction, P < 0.025 was accepted to be statistically significant in the subgroup analyses. * P = 0.001–0.025; ** P < 0.001; # median (minimum–maximum).

ratio group, the Cl^- concentration and APACHE II score were significantly higher and pH, $PaCO_2$, HCO_3^-, SBE, BE_{Cl}, and AG values were significantly lower than those in the normal Cl^-:Na^+ ratio group ($P < 0.025$ for each) (Table 1). There was no statistically significant difference in pH values between the low and normal Cl^-:Na^+ ratio groups ($P = 0.076$). Na^+ values were not significantly different between any of the groups ($P = 0.104$). There was a negative correlation between the Cl^-:Na^+ ratio and HCO_3^-, SBE, and $PaCO_2$ ($r^2 = 0.21$, $r^2 = 0.19$, and $r^2 = 0.17$, respectively) ($P < 0.001$ for each) (Figures 2–4).

In the multivariate analysis, the ICU mortality was increased 1.13-fold (1.08–1.18), 1.4-fold (1.3–1.6), 2.6-fold (1.2–5.8), 2.5-fold (1.1–5.9), 2.5-fold (1.3–4.7), 2.3-fold (1.1–4.6), and 2.1-fold (1.2–3.7) by APACHE II score, SOFA score, low Cl^-:Na^+ ratio, high Na^+ concentration, low and high pH values, and lactate level of ≥2 mmol L^{-1}, respectively ($P < 0.001$, $P < 0.001$, $P = 0.019$, $P = 0.034$, $P = 0.006$, $P = 0.026$, and $P = 0.007$, respectively) (Table 2).

4. Discussion

In the present study, low, high, or normal Cl^- and Na^+ values were detected in all Cl^-:Na^+ ratio groups. There was a negative correlation between the Cl^-:Na^+ ratio and HCO_3^-, SBE, and $PaCO_2$. In the low and high Cl^-:Na^+ ratio groups, ICU mortality was significantly higher than that in

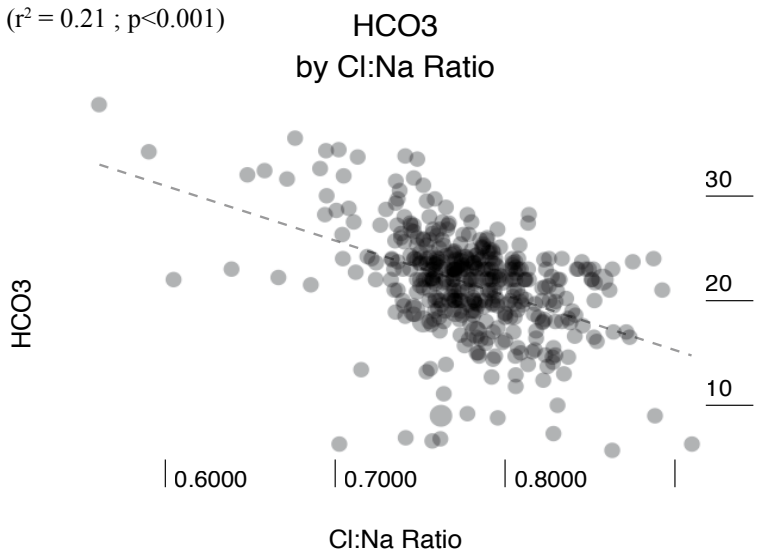


Figure 2. Correlation between Cl^-:Na^+ ratio and HCO_3^-.

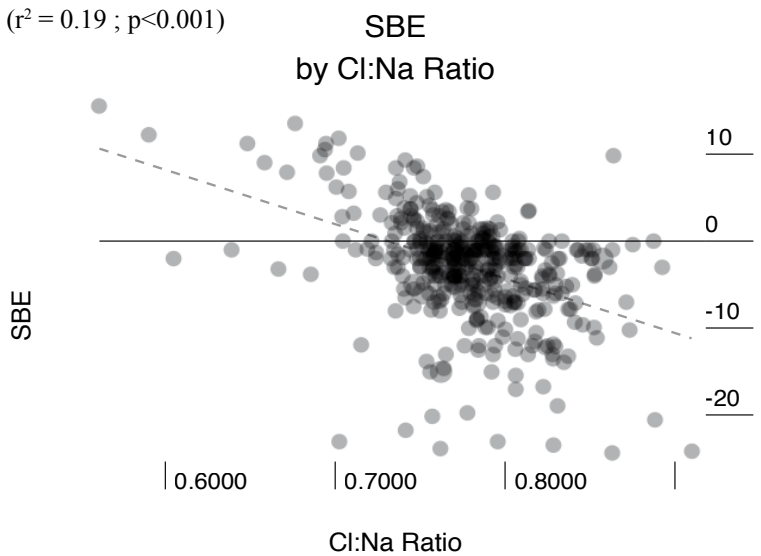


Figure 3. Correlation between Cl^-:Na^+ ratio and SBE.

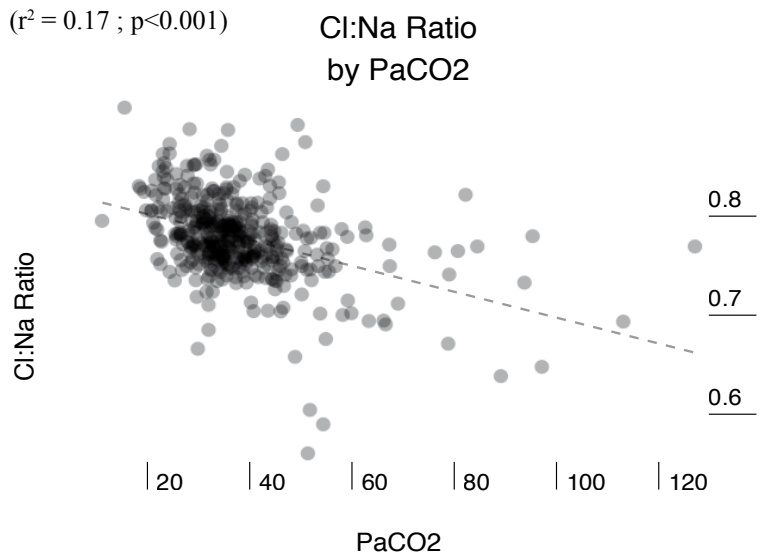


Figure 4. Correlation between $PaCO_2$ and Cl^-:Na^+ ratio.

Table 2. Multivariate logistic regression model for ICU mortality.

	OR (95% CI)	P
Age, years	1.002 (0.99–1.02)	0.764
$PaCO_2$, mmHg	0.98 (0.95–1.01)	0.188
APACHE II	1.13 (1.08–1.18)	<0.001
SOFA score	1.4 (1.3–1.6)	<0.001
Cl^-:Na^+ ratio ≥0.75 and <0.80 <0.75 ≥0.80	 Reference 2.6 (1.2–5.8) 1.3 (0.7–2.5)	 0.019 0.455
Cl^-, mmol L^{-1} ≥95 and ≤105 <95 >105	 Reference 1.8 (0.5–6.4) 0.6 (0.3–1.2)	 0.376 0.175
Na^+, mmol L^{-1} ≥135 and ≤145 <135 >145	 Reference 0.7 (0.4–1.3) 2.5 (1.1–5.9)	 0.285 0.034
pH ≥7.35 and ≤7.45 <7.35 >7.45	 Reference 2.5 (1.3–4.7) 2.3 (1.1–4.6)	 0.006 0.026
Lactate, mmol L^{-1} <2.0 ≥2.0	 Reference 2.1 (1.2–3.7)	 0.007
SBE, mmol L^{-1} ≥ –3.0 and ≤3.0 < –3.0 >3.0	 Reference 0.8 (0.5–1.6) 0.7 (0.2–2.2)	 0.592 0.533

95% CI: 95% confidence interval; OR: odds ratio; SBE, standard base excess; SOFA, Sequential Organ Failure Assessment.

the normal Cl^-:Na^+ ratio group. APACHE II, SOFA score, a low Cl^-:Na^+ ratio, hypernatremia, acidosis, alkalosis, and lactate of ≥2 mmol/L at ICU admission were identified as predictive factors for increased mortality.

According to Duward et al. (6), the main cause of changes in the HCO_3^- pool is a change in Cl^- . In addition, Cl^- must always be interpreted together with Na^+, and the simplest method is using the Cl^-:Na^+ ratio. Hypochloremia or hyperchloremia should be considered in accordance with the Cl^-:Na^+ ratio, which means that regardless of the Cl^- and Na^+ concentrations, the Cl:Na^+ ratio can be high or low. We determined low, high, and normal Cl^- and Na^+ values in all Cl^-:Na^+ ratio groups (Table 1). Thus, we think that the Cl^-:Na^+ ratio is the best parameter for understanding the effect of Cl^- (primary or compensatory) on acid-base status. For example, a low Cl^-:Na^+ ratio can be found in a patient who has normal Cl^- and Na^+ values (Cl: 96 mmol L^{-1}, Na^+: 136 mmol L^{-1}, Cl^-:Na^+ ratio: 0.71), and this clinical status can be compensation for hyperlactatemia, increased unmeasured anions (UAs), or hypercarbia. If the Cl^-:Na^+ ratio is not evaluated, compensations can be overlooked. Therefore, we also think that Cl^- must always be interpreted together with Na^+.

Fencl et al. (4) identified a normal SBE in some patients with metabolic acidosis, and they indicated that metabolic acidosis was compensated by the increased SID. Tuhay et al. (13) observed normal SBE in 20% of hyperlactatemic patients, and they demonstrated hypochloremia in those patients. Thus, they emphasized that Cl^- must always be assessed in acid-base evaluations. Ramadoss et al. (14) demonstrated Cl^- loss from kidneys in the early period of respiratory acidosis in their experimental study. We found that there was a negative correlation between the Cl^-:Na^+ ratio and HCO_3^-, SBE, and $PaCO_2$ (Figures 2–4). This result shows that the Cl^-:Na^+ ratio is an important parameter in acid-base evaluation. An abnormal Cl^-:Na^+ ratio can be the primary reason for a metabolic acid-base disorder, or it can be the result of compensation for metabolic or respiratory acid-base disorders. We think that this notion is most important in septic patients who have increased mortality. Rare combinations can be seen in daily clinical practice, and those combinations were also discussed in previous studies (Table 3) (6,9,13,15–19).

Kurt et al. (15) indicated the presence of hypochloremic metabolic acidosis in 16% of acid-base disorders. We also detected a low Cl^-:Na^+ ratio in 3.6% of patients with acidosis (Table 3). It is observed that a low Cl^-:Na^+ ratio can develop as compensation for hypercarbia. Such an acid-base disorder may be detected in patients diagnosed with chronic obstructive pulmonary disease. In these patients, treatment of a low Cl^-:Na^+ ratio without considering the respiratory component may result in severe acidosis or management of the respiratory component without taking into account the possibility that the low Cl^-:Na^+ ratio may cause severe alkalosis.

Table 3. Combinations of abnormal Cl^-:Na^+ ratios and pH values.

	[a]Acidosis & low Cl^-:Na^+ ratio	[b]Alkalosis & low Cl^-:Na^+ ratio	[c]Acidosis & high Cl^-:Na^+ ratio	[d]Alkalosis & high Cl^-:Na^+ ratio
n (%)	16 (3.6)	19 (4.4)	50 (11.5)	13 (3)
pH	7.24 (7.16–7.32)	7.49 (7.46–7.53)	7.29 (7.22–7.31)	7.49 (7.48–7.55)
$PaCO_2$	66.4 (55.5–89.1)	37.4 (32.6–43.2)	34.5 (26.8–41.6)	26.2 (23.3–29.7)
HCO_3	24 (20–30)	27.2 (22–32)	17 (14.6–20)	22 (19.7–23)
SBE	1 (–5 to 7.9)	2.9 (–2 to 8.4)	–8 (–13 to –5)	-2 (–6 to –1)
BE_{Cl}	7.5 (5–11)	5 (3–9)	–8 (–10 to –6)	–10 (–10 to –6)
Cl^- #	97 (93–109)	97 (93–103)	110 (106–116)	112 (108–115)
Na^+ #	135 (131–146)	135 (129–143)	133 (130–136)	135 (133–137)
Lactate	1.3 (0.8–18)	1.1 (1–2.1)	2.6 (1.3–4.8)	1.5 (1.1–2.6)
Cl^-:Na^+ ratio	0.71 (0.69–0.74)	0.73 (0.71–0.74)	0.82 (0.81–0.84)	0.83 (0.81–0.84)
ICU mortality, n (%)	6 (37.5)	8 (42.1)	24 (48.0)	5 (38.5)

BE_{Cl}: Base-excess chloride; SBE: standard base-excess. Results are given as median (interquartiles). # Median (minimum–maximum). [a] Hypochloremic acidosis; [b] hypochloremic alkalosis; [c] hyperchloremic acidosis; [d] hyperchloremic alkalosis.

Tani et al. (9) showed that in critically ill patients with hypochloremia, SID-related alkalosis can develop and the duration of ICU stay and mortality rate can increase. In this study, 90.8% of the patients were postoperative patients. Thus, iatrogenic electrolyte changes may have occurred and affected the mortality results. We also detected a low Cl^-:Na^+ ratio in 4.4% of the septic patients with alkalosis. It was observed that the main reason for alkalosis in these patients was a low Cl^-:Na^+ ratio. Management of a low Cl^-:Na^+ ratio is the highest priority in these patients.

It has been reported that hyperlactatemia and hyperchloremia cause metabolic acidosis and increase the mortality rate (13,16–19). Story et al. (10) showed a positive correlation between nonlactate SID and HCO_3^- in the hyperchloremic patient group. In the present study, a high Cl^-:Na^+ ratio was detected in 11.5% of the patients with acidosis. Hyperlactatemic-hyperchloremic acidosis has been observed in patients with high lactate levels. The recognition that hyperchloremia is one of the causes of acidosis is important in the determination of fluid management.

The Cl^-:Na^+ ratio is expected to decrease in metabolic alkalosis (6). In the present study, however, a high Cl^-:Na^+ ratio was detected in 3.0% of the patients with alkalosis. Metabolic acidosis caused by hyperchloremia has been observed to be overcompensated by hyperventilation, causing respiratory alkalosis. If normocarbia develops under mechanical ventilation, hyperchloremic acidosis may become apparent.

Recent studies have demonstrated that hypochloremia, hyperchloremia, and dysnatremia are related to increased mortality (9–11). Nevertheless, identifying the Cl^-:Na^+ ratio as a predictor of increased ICU mortality may be premature. However, it is true that APACHE II, SOFA score, low and high pH values, a high Na^+ concentration, a lactate level ≥2 mmol L^{-1}, and a low Cl^-:Na^+ ratio are predictors of increased ICU mortality in the present study. Furthermore, there was no relationship between Cl^- concentration and increased ICU mortality. Duward et al. (6) proposed that a Cl^-:Na^+ ratio below 0.75 is a good indicator of the presence of UA and that a Cl^-:Na^+ ratio greater than 0.79 excludes UAs (6). Thus, the relationship between a low Cl^-:Na^+ ratio and increased ICU mortality may be related to increased UAs.

In conclusion, the Cl^-:Na^+ ratio is a useful parameter for showing the relationship between Cl^- and Na^+ and their impact on acid-base status. APACHE II, SOFA score, hypernatremia, low and high pH values, hyperlactatemia, and a low Cl^-:Na^+ ratio at ICU admission can be used as prognostic indicators for increased ICU mortality in septic patients. The relationship between the Cl^-:Na^+ ratio and increased ICU mortality has to be evaluated with further prospective studies.

Acknowledgment

The authors thank Dr Mehmet Berktaş from Yeditepe University for performing the statistical analysis.

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