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The use of sodium-chloride difference and chloride-sodium ratio as strong ion difference surrogates in the evaluation of metabolic acidosis in critically ill patients☆

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Abstract

Purpose: Inorganic apparent strong ion difference (SIDai) improves chloride-associated acidosis recognition in dysnatremic patients. We investigated whether the difference between sodium and chloride (Na^+-Cl^-) or the ratio between chloride and sodium (Cl^-/Na^+) could be used as SIDai surrogates in mixed and dysnatremic patients.

Patients and Methods: Two arterial blood samples were collected from 128 patients. Physicochemical analytical approach was used. Correlation, agreement, accuracy, sensitivity, and specificity were measured to examine whether Na^+-Cl^- and Cl^-/Na^+ could be used instead of SIDai in the diagnosis of acidosis.

Results: Na^+-Cl^- and Cl^-/Na^+ were well correlated with SIDai ($R = 0.987$, $P < 0.001$ and $R = 0.959$, $P < 0.001$, respectively). Bias between Na^+-Cl^- and SIDai was high (6.384 with a limit of agreement of 4.463-8.305 mEq/L). Accuracy values for the identification of SIDai acidosis (<38.9 mEq/L) were 0.989 (95% confidence interval [CI], 0.980-0.998) for Na^+-Cl^- and 0.974 (95% CI, 0.959-0.989) for Cl^-/Na^+. Receiver operator characteristic curve showed that values revealing SIDai acidosis were less than 32.5 mEq/L for Na^+-Cl^- and more than 0.764 for Cl^-/Na^+ with sensitivities of 94.0% and 92.0% and specificities of 97.0% and 90.0%, respectively. Na^+-Cl^- was a reliable SIDai surrogate in dysnatremic patients.

Conclusions: Na^+-Cl^- and Cl^-/Na^+ are good tools to disclose SIDai acidosis. In patients with dysnatremia, Na^+-Cl^- is an accurate tool to diagnose SIDai acidosis.

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1. Introduction

Metabolic acidosis is common in critically ill patients [1], and it is related to clinical outcomes and disease severity [1,2]. There are several sources of metabolic acidosis during critical illness, and the origin of metabolic acidosis is also related to mortality. An elevated serum lactate level is therefore a relevant outcome predictor [3]. Although hyperchloremic acidosis does not have the same clinical importance in mixed patients [3], it seems to be an outcome marker in septic patients [4]. In this way, hyperchloremia is the most frequent etiology of metabolic acidosis in critically ill patients [5,6].

Three commonly used approaches to acid-base physiology examine different variables for changes in the acid-base

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balance [7]. Each of these variables can be derived from a set of master equations and complete parity can be brought to all 3 acid-base approaches [8]. Standard base excess (SBE) is an old and simple variable used to identify metabolic acidosis; it is associated with clinical outcomes [2,9] and disease severity [1] and can be measured with common, commercially available arterial blood gas analyzers. Currently, there is a trend to reunify the different acid-base approaches [8], and SBE-identified metabolic acidosis can be quantified by the modern physicochemical approach [1]. Changes in SBE can be accurately explained by variations in the inorganic apparent strong ion difference (SIDai); unmeasured anions reflected in the strong ion gap (SIG); and values of lactate, albumin, and phosphate [1]. Inorganic apparent strong ion difference is the net charge balance of all strong ions present; a strong ion is one that is completely (or near-completely) dissociated in the physiologic environment [10]. For practical purposes, SIDai includes $Na^+ + K^+ + Ca^{2+} + Mg^{2+} - Cl^-$. Inorganic apparent strong ion difference is able to reveal and quantify hyperchloremic metabolic acidosis [10].

Hyperchloremic acidosis depends on the chloride concentration, but the sodium concentration is also important; chloride and sodium are the most abundant extracellular ions. Based on the electroneutrality principle, the difference between the positive and negative charges is responsible for the pH changes [10]. Normochloremia can occur alongside hyponatremia and result in acidosis, and hypernatremia can occur alongside hyperchloremia without acidosis [11]. The association between chloride and sodium reflects the importance of SIDai in our understanding of complex acid-base disorders in critically ill patients.

The quantitative approach is not suitable for use at the bedside due to the complex mathematical calculations involved [10]. However, SIG can be substituted by the anion gap corrected for albumin (AGa) [1], and we hypothesized that SIDai can be extrapolated from the 2 most abundant extracellular strong ions, sodium, and chloride. The aim of this study was to investigate whether the difference between sodium and chloride (Na^+-Cl^-) or the ratio between chloride and sodium (Cl^-/Na^+) can be used as SIDai surrogates to diagnose and quantify chloride-associated metabolic acidosis in mixed and dysnatremic patients.

2. Methods

2.1. Patients

This study was approved by the local institutional ethics committee. Because all of the data were collected in the process of daily, routine examinations that were performed on all patients who were admitted to the medical intensive care unit, the requirement for informed written consent was waived. All of the patients admitted to the intensive care unit (ICU) from February to March of 2004 were included in the study. Patients who were admitted from other ICUs were excluded from the analysis.

2.2. Clinical and laboratory data

Clinical and laboratory data were collected from all patients at admission, and laboratory data were recorded again 24 hours later. The following clinical data were recorded: age, sex, Acute Physiological and Chronic Health Evaluation (APACHE) II score, cause of ICU admission, length of stay, and outcome. The following laboratory data were recorded: arterial blood gas (determined with simultaneous arterial lactate measurement), Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, phosphate, and albumin. Colorimetric techniques were used to analyze albumin, phosphate, and serum Mg^{2+} levels. All of the other serum electrolyte levels were measured with an ion-selective electrode. Arterial blood gases and lactate concentrations were measured with an OMNI analyzer (Roche Diagnostics System, F. Hoffmann, La Roche Ltd, Basel, Switzerland). Bicarbonate concentration was calculated according to the Henderson-Hasselbalch equation, and SBE was calculated according to the Van Slyke equation.

2.3. Acid-base calculations

Standard base excess from each blood sample was supplied by the blood gas analyzer, and the calculations were performed with the Siggaard-Andersen Van Slyke equation [12].

$$\mathrm{SBE\ (mEq/L)} = 0.9287 \times (\mathrm{HCO_3\ in\ mEq/L} - 24.4 + 14.83 \times [\mathrm{pH} - 7.4])$$

Physicochemical mathematical calculations were performed with the following standard equations [10;13]:

$$\mathrm{SIDai\ (mEq/L)} = \mathrm{Na^+ + K^+ + Mg^{2+} + Ca^{2+} - Cl^-\ (all\ in\ mEq/L)}$$

$$\begin{aligned}\mathrm{SIG\ (mEq/L)} = {} & \mathrm{SIDai\ (mEq/L) - lactate\ (mEq/L)} \\ & -\{2.46 \times 10^{-8} \times \mathrm{PCO_2(mm\ Hg)} / 10^{-\mathrm{pH}} \\ & + [\mathrm{albumin\ (g/dL)}] \\ & \times (0.123 \times \mathrm{pH} - 0.631) \\ & + [\mathrm{phosphate\ (mEq/L)} \times 0.309 \\ & \times (\mathrm{pH} - 0.469)]\}\end{aligned}$$

2.4. Healthy volunteers and diagnosis of SIDai acidosis

Normal SIDai values were previously recorded from 14 healthy volunteers [1], and arterial blood samples were

collected after informed consent was obtained. Data from the critically ill patients enrolled in the present study were similarly treated and analyzed. The SIDai values were considered to be normal if they were between the 2.5 and 97.5 percentiles of values from the healthy volunteers. We defined SIDai acidosis, that is, metabolic acidosis attributable to disturbances in the inorganic ions, as a SIDai value below the 2.5th percentile (38.9 mEq/L).

2.5. Statistical analysis

All variables were tested for normality with the Kolmogorov-Smirnov goodness-of-fit model. All variables were normally distributed. The data are presented as means and standard deviations. Data acquired from 14 healthy volunteers are shown as medians and interquartile range, as in the original article [1]. The ranges of normal values are expressed as percentiles 2.5th and 97.5th to accomplish 95% of the sample variation. Inorganic apparent strong ion difference was correlated with Na^+-Cl^- and Cl^-/Na^+ with the Pearson correlation test [14]. The agreement between SIDai and Na^+-Cl^- was analyzed with the Bland-Altman plot [15]. The agreement between SIDai and Cl^-/Na^+ was not performed because they are different variables. Sensitivity and specificity, as well as accuracy (the area under the receiver operator characteristic [ROC] curve with a 95% confidence interval [CI]), were calculated to predict the accuracy of diagnosing SIDai acidosis with each surrogate. We calculated the points with the greatest accuracy to predict SIDai acidosis using Youden's index [16]. Inorganic apparent strong ion difference acidosis was defined according to the criteria described previously.

To test whether both surrogates could fit in a model using SBE as a dependent factor, we built 4 mathematical models and completed a multilinear regression. These progressive models were built to determine which surrogate would be easier to use at the bedside. In the first model, we included all physicochemical variables that interfere with SBE with a high determinant coefficient, as already described [1]. In the second model, we substituted SIG with AGa. In the other 2 models, we still used AGa as a SIG surrogate, and SIDai was substituted with Na^+-Cl^- and Cl^-/Na^+, respectively [1]. Single colinearity was identified when 2 independent variables had a Pearson coefficient higher than 0.85 in a matrix of correlations; multicolinearity was identified when the variance inflation factor higher than 10 [17]. All P values of less than .05 were considered to be significant. All statistical analyses were performed with the commercially available statistical package SPSS, version 10.0 (SPSS Inc, Chicago, Ill).

3. Results

A total of 128 patients were included in the study. Two consecutive blood analyses were performed on each patient (at admission and 24 hours afterward), and a total of 256 samples were analyzed. Table 1 shows the patients' general characteristics, reasons for ICU admission and clinical outcomes. Table 2 shows the metabolic characteristics of patients at admission and normal values acquired from healthy volunteers [1]. Both Na^+-Cl^- and Cl^-/Na^+ showed an excellent correlation with SIDai, the mean value of SIDai of 128 patients was 38.9 ± 6.0 mEq/L; as shown in Fig. 1, the Pearson coefficients were 0.995 and −0.972, respectively. A Bland-Altman plot in Fig. 1 also shows that the agreement between Na^+-Cl^- and SIDai was good. The accuracy of both surrogates to diagnose SIDai acidosis was excellent (Fig. 2). Youden's index was used to determine that the best values to predict SIDai acidosis (<38.9 mEq/L) were 0.764 for Cl^-/Na^+ and 32.5 mEq/L for Na^+-Cl^-. The Cl^-/Na^+ and Na^+-Cl^- values had sensitivities of 92.0% and 94.0% and specificities of 90.0% and 97.0%, respectively. If the lowest value (2.5th percentile) of Na^+-Cl^- from normal volunteers was used (<34 mEq/L) as reference to perform SIDai diagnosis, the sensitivity and specificity were 79% and 100%, respectively, and if the highest value (97.5th percentile) of Cl^-/Na^+ ratio from normal volunteers was used (>0.757) as the reference, the sensitivity and specificity were 98.5% and 76.5%, respectively, to perform the diagnosis of SIDai acidosis.

Table 3 shows the models with SBE as a dependent factor. The model with albumin, phosphate, lactate, SIDai, and SIG had a determination coefficient (R^2) of 0.992. When SIG was substituted with AGa, R^2 did not change (0.992). Two additional models kept AGa as a way of revealing unmeasured anions but replaced SIDai with Na^+-Cl^- and

Table 1 Patient characteristics, support, and outcomes

Characteristics	Results (n = 128)
Age (y)	49 ± 20
APACHE II [b]	21 ± 9
Sex, n(%) [a]	
Male	76 (59)
Female	52 (41)
Reason of admission, n (%) [a]	
Septic shock	57 (45)
Respiratory failure	33 (26)
Neurologic syndromes	10 (8)
High-risk postoperative	10 (8)
Severe sepsis	9 (7)
Trauma	5 (4)
Others	4 (2)
Mechanical ventilation, n (%) [a]	115 (90)
Renal replacement therapy, n (%) [a]	8 (6)
Outcomes	
ICU mortality, n (%) [a]	37 (29)
Length of stay (d)	10 ± 7

[a] n (%) denotes the number of patients and the percentage of the sample.
[b] APACHE II denotes Acute Physiological and Chronic Health Evaluation II score.

Table 2 Acid-base variables of patients at admission and normal values acquired from healthy volunteers

Acid-base variables	Patients at admission (n = 128)	Healthy volunteers [a] (n = 14)	
	Mean ± SD	Median (interquartile range)	Percentiles 2.5th⇔97.5th
pH	7.33 ± 0.09	7.36 (7.34, 7.39)	7.32⇔7.45
SIDai, mEq/L	39.0 ± 6.0	42.0 (40.0, 43.0)	38.9⇔48.2
SIG, mEq/L	9.9 ± 7.7	3.8 (1.8, 5.3)	−1.1⇔6.1
Lactate, mEq/L	2.47 ± 2.50	1.3 (0.9, 1.8)	0.7⇔1.9
Albumin, g/dL	2.6 ± 2.4	4.5 (3.9, 4.5)	3.3⇔4.7
PO_4, mg/dL	3.4 ± 1.9	3.7 (3.2, 4.0)	2.6⇔4.8
SBE, mEq/L	−7.4 ± 5.5	0.3 (−1.7, 1.8)	−3.2⇔2.2
AGa, mEq/L	19.8 ± 5.5	15.5 (14.0, 17.0)	12.2⇔19.6
Na^+-Cl^-, mEq/L	33.0 ± 6.0	36.0 (35.0, 37.0)	34.0⇔45.0
Cl^-/Na^+, mEq/L	0.768 ± 0.044	0.742 (0.733, 0.744)	0.679⇔0.757

[a] Adapted from Park et al [1]. Data from healthy volunteers are expressed as median and interquartile range as in the original article [1].

Cl^-/Na^+. The first model had an R^2 value of 0.981, and the second had an R^2 value of 0.928 (Fig. 2). Table 4 shows the sensitivity, specificity, and accuracy of both SIDai surrogates in serum measurements of patients with dysnatremia, that is, Na of less than 135mEq/L (28 measurements) or Na of more than 145 mEq/L (51 measurements).

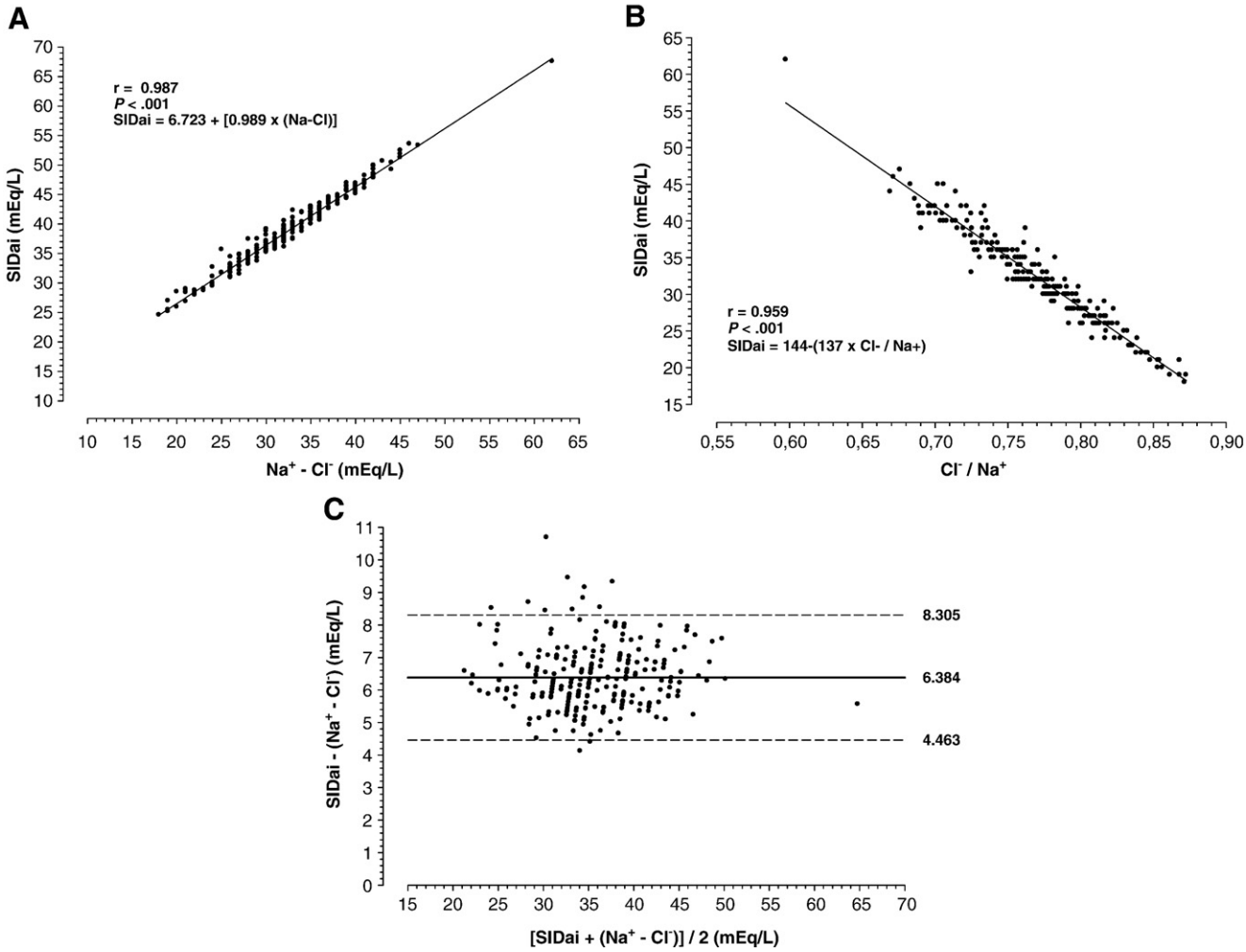

Fig. 1 Correlation and agreement between Na^+-Cl^-, Cl^-/Na^+, and SIDai. Panel A shows the correlation between Na^+-Cl^- and SIDai. Panel B shows the correlation between Cl^-/Na^+ and SIDai, and Panel C shows the agreement between Na^+-Cl^- and SIDai. Bias = 6.384 and limits of agreement 95% = 4.463 to 8.305 mEq/L.

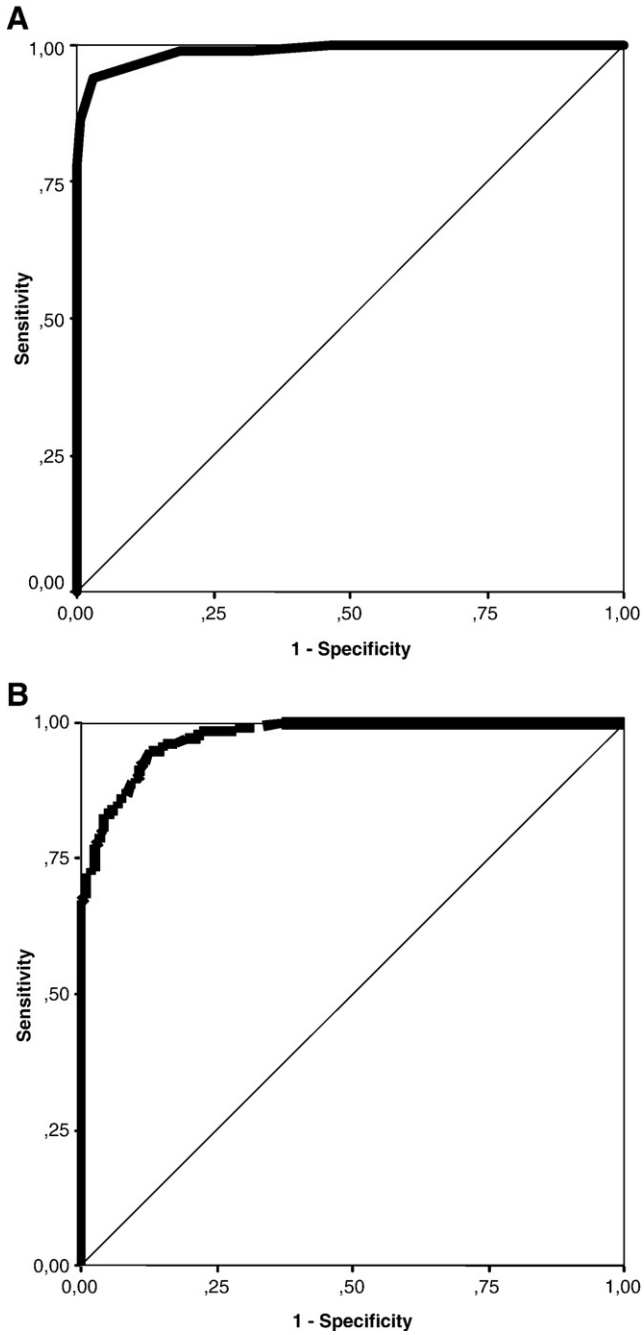

Fig. 2 Receiver operator characteristic curve of SIDai surrogates as predictors of SIDai acidosis (SIDai < 38.9 mEq/L). Panel A shows the ROC curve of Na^+-Cl^- difference as a predictor of SIDai acidosis (SIDai < 38.9 mEq/L); area under curve, 0.989 (95% CI, 0.980-0.998). Panel B shows the ROC curve of Cl^-/Na^+ ratio as a predictor of SIDai acidosis (SIDai < 38.9 mEq/L); area under curve, 0.974 (95% CI, 0.959-0.989).

Table 3 Characteristics of different mathematical models to predict SBE variations from physicochemical variables

Model characteristic	Stewart model	Anion gap (AGa) model	Na^+-Cl^- model	Cl^-/Na^+ model
Determination coefficient (R^2)	0.970	0.954	0.951	0.928
β coefficient [a]				
Constant	−25.10 *	−25.50 *	−19.62 *	115.32 *
Albumin	−2.80 *	−2.40 *	−2.80 *	−0.41 *
Lactate	−1.10 *	−1.04 *	−1.12 *	−0.25 *
Phosphate	−0.70 *	−0.32 *	−0.40 *	−0.15 *
SIDai	1.02 *	1.03 *	–	–
SIG	−1.01 *	–	–	–
AGa	–	−1.02 *	−1.02 *	−0.92 *
Na^+-Cl^-	–	–	1.09 *	–
Cl^-/Na^+	–	–	–	−133.18 *

All variance inflation factors were less than 10, and the Pearson correlation coefficients were less than 0.85.

[a] These are the unstandardized β coefficients.

* $P < .001$.

4. Discussion

In this study, we found that Na^+-Cl^- was well correlated with SIDai. As expected, the bias between Na^+-Cl^- and SIDai was high with short limits of agreement. Cl^-/Na^+ had a good inverse correlation with SIDai; because of the different nature of both variables, agreement was not measured (Fig. 1). The accuracy of Na^+-Cl^- and Cl^-/Na^+ in revealing SIDai acidosis (SIDai < 38.9 mEq/L) was high and was 0.989 (95% CI, 0.980-0.998) for Na^+-Cl^- and 0.974 (95% CI, 0.959-0.989) for Cl^-/Na^+ (Fig. 2). In the mathematical model built to correlate changes in physicochemical variables with SBE variation, the changes of classical variables described by Stewart [10], Figge et al [18], and Kellum et al [13] (SIDai, lactate, $Paco_2$, SIG, phosphate, and albumin) had a determinant coefficient (R^2) of 0.970 in explaining SBE variations; the models using AGa rather than SIG and either Na^+-Cl^- or Cl^-/Na^+ rather than SIDai had R^2 values of 0.951 and 0.928, respectively (Table 3). The ROC curve showed that the best values for determining SIDai acidosis were 32.5 mEq/L for Na^+-Cl^- and 0.764 for Cl^-/Na^+. The Cl^-/Na^+ and Na^+-Cl^- values had sensitivities of 94.0% and 92.0% and specificities of 97.0% and 90.0%, respectively. However, in contrast to the Na^+-Cl^- values, Cl^-/Na^+ values are not a reliable means of identifying SIDai acidosis in patients with hyper and hyponatremia (Table 4).

Several approaches can be used to interpret the physiology of acid-base metabolism. The physicochemical method allows for the quantification of pH variations in proportion to changes in the independent variables [10]. This rationale was extrapolated to explain SBE variations from SIG, lactate, SIDai, albumin, and phosphate changes [1]. The potential advantage of the physicochemical approach is the quantification cited above, which can be used in scientific studies. In practice, however, there is no benefit to using the quantitative approach at the bedside [7], and the quantitative approach is not suitable for use at the bedside due to the complex mathematical calculations required [1,10]. The physico-

Table 4 Sensitivity, specificity, and accuracy of SIDai surrogates in the presence of dysnatremias

	Hypernatremia (Na > 145 mEq/L) (n = 51)		Hyponatremia (Na < 135 mEq/L) (n = 28)	
SIDai acidosis, [a] n (%)	21 (41)		17 (61)	
SIDai surrogate	(Na^+-Cl^-) [b]	(Cl^-/Na^+) [c]	(Na^+-Cl^-) [b]	(Cl^-/Na^+) [c]
Sensitivity (%)	96.7	100	82	64.7
Specificity (%)	95.2	70	100	100
Accuracy (95% CI)	0.995 (0.984-1.000)	0.996 (0.986-1.000)	0.968 (0.910-1.000)	0.968 (0.912-1.000)

[a] SIDai acidosis was considered if SIDai was less than 38.9 mEq/L.
[b] SIDai acidosis was considered if Na^+-Cl^- was less than 32.5 mEq/L, as indicated by the Youden's index.
[c] SIDai acidosis was considered if Cl^-/Na^+ was less than 0.764, as indicated by the Youden's index.

chemical approach highlights the importance of chloride ions in the care of critically ill patients [6]. However, due to its high extracellular concentration, sodium also has an important effect on pH [11,19]. According to the electroneutrality principle, the proportionality between sodium and chloride concentrations is the effective acid-base modulator (SIDai) [11]. Because of this, a patient with hyponatremia can evolve a relative hyperchloremic acidosis with normal values of serum chloride, and the opposite can also occur [11]. There is no consensus in the literature about the clinical meaning of individual components of metabolic acidosis, with the exception of lactate [2]. Although studies of ICU patients have failed to detect a significant effect on survival attributable to hyperchloremic acidosis [3], hyperchloremia has been shown to cause hypotension, renal dysfunction, and incremental change in plasma cytokine levels [20,21].

Inorganic apparent strong ion difference acidosis is common among ICU patients [6], and its early diagnosis is important so that the iatrogenic worsening of metabolic acidosis with fluid resuscitation can be avoided [22]. The calculation of SIDai requires values for magnesium, calcium, and potassium, but magnesium is not routinely measured by commercially available radiometers. At the bedside, the calculation of any variable must be simple and reliable, and a single variable that is dependent on 2 values could be easily used. In this study, Na^+-Cl^- and Cl^-/Na^+ were well correlated with SIDai, and the agreement between Na^+-Cl^- and SIDai was poor (bias = 6.384) (Fig. 1). This poor agreement between Na^+-Cl^- and SIDai is expected because SIDai is a more complete formula in which Na^+-Cl^- is the body of calculation. In contrast, the limit of agreement was short; however, there are several points out of range, probably due to wide variations in others ions (as expected in critically ill patients) or due to errors in multiple measurements [23]. Na^+-Cl^- is therefore a potential tool for simplifying SIDai calculations but has a new limit of normality. The agreement between Cl^-/Na^+ and SIDai was not measured because the nature of the variables differ. The ability of both variables to accurately reveal SIDai acidosis (determined by the ROC curve) was complemented by the insertion of each variable into an already-described mathematical model to explain SBE variations [1]. The high value of determinant coefficient (R^2) of that mathematical model shows the high correlation among the independent variables (SIG, lactate, phosphate, albumin, and SIDai) and SBE. The substitution of SIDai with Na^+-Cl^- or Cl^-/Na^+ has made the model simpler while keeping the R^2 value high (Table 3). These findings show that Na^+-Cl^- or Cl^-/Na^+ are able to identify SIDai acidosis and that variations in Na^+-Cl^- or Cl^-/Na^+ can almost entirely explain SBE changes. When comparing the Na^+-Cl^- value retrieved from the ROC curve through the Youden's index to perform SIDai diagnosis (<32.5 mEq/L), with the lowest value accomplishing 95% of the sample retrieved from the healthy volunteers (<34 mEq/L), the combination of sensitivity and specificity was more interesting for the Youden's retrieved value. The same rationale was valid when using the value retrieved from the ROC curve to the Cl^-/Na^+ ratio (>0.764) and the highest value retrieved from the normal volunteers (>0.757).

Patients with dysnatremia can have SIDai acidosis with normal serum chloride levels or can have hyperchloremia without SIDai acidosis [11]. The 32.5 mEq/L value of Na^+-Cl^- retrieved from the ROC curve was able to identify SIDai acidosis with high specificity and sensitivity in patients with hypo and hypernatremia (Table 4). The same high specificity and sensitivity did not occur when Cl^-/Na^+ is higher than 0.764 (the value retrieved from the ROC curve) in patients with dysnatremia (Table 4).

Both Na^+-Cl^- and Cl^-/Na^+ have been previously analyzed [24,25]. The difference between Na^+ and Cl^- was studied as a component of simple equations that require only mental arithmetic; just as in this study, earlier researchers concluded that Na^+-Cl^- has a good correlation and agreement with more complex Fencl-Stewart equations [24]. The ratio between Cl^- and Na^+ was studied as a marker of tissue acid production and as an anion gap surrogate [23]. The rationale for this idea is based on the presence of metabolic acidosis (standard bicarbonate < 22 mEq/L) and a normal serum chloride level (ie, a normal Cl^-/Na^+ ratio). In the former situation, acidosis due to unmeasurable anions is highly probable because albumin and phosphate are stable ions during the ICU stay of mixed critically ill patients [6]. These studies together have shown that Na^+-Cl^- and Cl^-/Na^+ are easily obtained variables that can be substituted for SIDai in the acid-base diagnosis of critically ill patients; our findings are in line with these

results. In addition, we have shown that changes in both variables can also explain SBE variation in a mathematical model and that Na^+-Cl^- is able to reveal SIDai acidosis in patients with dysnatremia.

This study has several limitations: first, we have not evaluated a different sample of patients to validate the values of Na^+-Cl^- and Cl^-/Na^+; second, the temporal evolution of SIDai surrogates was not adequately tested; third, external reproducibility in other ICUs cannot be examined; and fourth, multiple laboratorial measurements can result in errors, mainly if different analyzers are used [23].

In conclusion, Na^+-Cl^- and Cl^-/Na^+ are good tools for identifying SIDai acidosis. Both allow the partition of SBE disclosed metabolic acidosis, which is related to SIDai, to be monitored. In patients with dysnatremia, Na^+-Cl^- is an easy and accurate tool for SIDai acidosis diagnosis.

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