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Research Article

Utility of Stewart's Acid-Base Approach in a Liver Intensive Care Unit: An Observational Study

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ABSTRACT

Background: Stewart's method of acid-base analysis involves analyzing the strong ion difference in the blood. The anion gap (AG), strong ion difference (SID), and strong ion gap (SIG) not only assist in diagnosing underlying acid-base disturbances but also serve as prognostic markers. This study aimed to analyze Stewart's approach in patients with cirrhosis.

Methods: Acid-base parameters of forty-eight cirrhosis patients requiring intensive care were prospectively studied. The primary objective of this study was to evaluate the prognostic value of SIG. The secondary objective was to examine the correlation between acid-base parameters, such as lactate, base excess of arterial blood gas analysis (ABG-BE), base excess of unmeasured anions [BE (UA)], AG, SID, and SIG.

Results: The median SIG was 4.1 (IQR: 2.5 - 5.6). The median albumin-corrected AG (acAG) level was 15 (IQR, 14–20). The median BE (UA) was -4.2 (IQR: -7.1, 1.7). Apparent SID and BE (UA) demonstrated a strong correlation ($r = 0.92$; $p < 0.001$). Effective SID was strongly correlated with ABG-BE ($r = 0.83$, $p < 0.001$). SIG and acAG showed a strong correlation with an r value of 0.94 ($p < 0.001$). An ICU stay of more than 8 days was considered prolonged (75th percentile). ABG-BE, SIG, and acAG on admission day effectively predicted prolonged ICU stay, with AUCs of 0.73, 0.75, and 0.78, respectively.

Conclusion: SIG effectively predicts prolonged ICU stay with good predictive ability. However, the anion gap, when corrected for albumin, is better than SIG in terms of predictive accuracy, requiring fewer variables and offering greater ease of use.

Introduction

Acid-base disorders are commonly encountered in patients in the intensive care unit (ICU) and are assessed and diagnosed through various methodologies, including the Copenhagen approach (base excess or base deficit), the Boston approach (PCO_2–HCO_3), and Stewart's approach [1-3]. The anion gap (AG) methodology is currently used to classify and help us to work on the differential diagnoses for metabolic acid-base disorder. The normal range for AG is 4–12 mEq/L. An elevated AG value indicates the presence of anions apart from bicarbonate and chloride, which cannot be quantified by conventional methods. Subsequently, AG and albumin-corrected AG (acAG) also had predictive ability in intensive care units, patients with aortic aneurysms, and pediatric critically ill patients [4-6]. Traditional arterial blood gas analysis, which utilizes pH and PCO_2 (Boston approach) or base excess

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(Copenhagen approach), does not account for weak ions such as albumin and phosphate. In 1978, Peter A. Stewart, a Canadian physiologist, introduced an approach involving strong ion difference (SID) that applies fundamental physicochemical principles of aqueous solutions to blood. This approach is predicated on the essential laws of electroneutrality, the conservation of mass, and mass action [3]. The SID approach considers the role of all buffer molecules that contribute to acid-base equilibrium in the body. In several studies, acid-base abnormalities not detected by the AG approach were identified using Stewart's approach, as they account for all biochemical elements present in the blood [7]. Consequently, we aimed to evaluate the efficacy of Stewart's approach in our Hepato-pancreato-biliary ICU and compare it with that of AG, albumin-corrected AG (acAG), and the base-excess approach.

Methods

Following approval from the ethics committee (AMH-C-S-036/07-22), a prospective observational study was conducted in the hepatic critical care-based ICU at Apollo Hospital, Chennai, from October 2022 to April 2023. This study included consecutive patients aged > 18 years who were admitted to the ICU. This ICU specializes in hepatic critical care, primarily managing patients with liver diseases presenting with conditions such as upper gastrointestinal bleeding, hepatic encephalopathy, acute kidney injury, and infection-related issues, as well as a few patients with pancreatitis and those requiring post-liver transplant care. Patients with pancreatitis, acute-on-chronic liver failure, or acute liver failure were excluded from analysis. However, data from pancreatitis cases were retained and used as a comparison group to understand the base-excess effect of unmeasured anions in the liver disease cohort. This study was conducted in accordance with the principles of the Declaration of Helsinki. The patients' physiological and biochemical data were prospectively collected. The management of septic shock in all enrolled patients conformed to current critical care guidelines and hospital protocols. Disease severity was evaluated using the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score [8]. Sedation was administered as necessary using a propofol infusion, with the aim of achieving a Richmond Agitation-Sedation Scale score of (-2). The patients underwent goal-directed fluid therapy, which was guided by the collapsibility index of the inferior vena cava or a target stroke volume variation of 8-13%. Fluid resuscitation was directed by clinical assessments, sonographic evaluations, and minimally invasive cardiac output monitoring, at the discretion of the attending clinician. Noradrenaline was used as the initial vasopressor, commencing at a dose of 0.05 micrograms/kg/min and adjusted to maintain a target mean arterial pressure of 65 mm Hg. In cases where the noradrenaline requirement exceeded 0.25 micrograms/kg/min, vasopressin infusion was initiated at 0.01 U/min and titrated to a maximum of 0.04 U/min (2.4 U/hour). Blood tests and values required for AG, SID, and strong ion gap (SIG) were obtained within the first hour of ICU admission, including measurements of inorganic phosphorus and albumin levels, and were recorded in real time. Blood bicarbonate levels were measured in the laboratory using the enzymatic method. The AG was calculated with the inclusion of potassium. All data were stored in a computerized format following patient discharge or death. None of the therapies were guided by SID or SIG. The formulas used to calculate the variables in Stewart's approach were as follows [9-10]:

- Apparent Strong Ion Difference (SIDa), mEq/L = (Na^+) + (K^+) + 2 (Ca^{2+}) + 2 (Mg^{2+}) - (Cl^-) - (lactate$^-$);
- Effective Strong Ion Difference (SIDe), mEq/L = $(HCO_3 -)$ + (A −);
- (A-) = ionized part of weak plasmatic acids = (albuminate) + (phosphate) = [(albumin [g/L]) × (0.123 × pH − 0.631)] + [(phosphorus [mmol/L]) × (0.309 × pH − 0.469)].
- Strong ion gap (SIG) = SIDa – SIDe;

The base excess effect of the unmeasured anion [BE (UA)] was calculated as per the formula BE (UA) = [(Na^+ - K^+ - Cl^-) + (1-lactate in mmol/L) + (0.25 * (42 – Albumin in G/L))]. The base excess effect of individual components was calculated using an online arterial blood gas calculator created for the intensive care network of the Royal North Shore Intensive Care Department (https://intensivecarenetwork.com/calculators/files/gazo.html) by Pierre Janin. Blood gas samples were procured from the radial artery through a catheter that had been inserted for invasive blood pressure monitoring. The initial one milliliter of blood extracted from the catheter was discarded, and the subsequent sample was collected using a heparinized syringe BD A-line™ (BD Biosciences, Franklin Lakes, NJ, USA) syringe. The samples were analyzed immediately after collection using point-of-care analyzers, specifically a benchtop arterial blood gas analyzer (RapidLab 1265; BGA; Siemens Healthcare Diagnostics GmbH, Bad Nauheim, Germany). The patient's temperature was recorded at the time of sample collection, and the data were adjusted for temperature variations. Outcomes including the documentation of acute kidney injury, as defined by the KDIGO criteria [11], the requirement for renal replacement therapy, the necessity for invasive mechanical ventilation, and the assessment of oxygenation as measured by the PaO2/FiO2 ratio (partial pressure of oxygen in arterial blood, fraction of inspired oxygen) are critical parameters. Sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock [12]. The

cumulative fluid balance over a 48-hour period and 30-day mortality rate were also recorded.

Statistical analysis:

For categorical variables, frequencies and percentages were used as summary statistics, while medians and interquartile ranges were used for continuous variables. The chi-square test was used to compare categorical values, and the Mann-Whitney U test was applied to continuous variables. Correlations between continuous variables were examined using the Pearson's correlation test. Initially, the study intended to use 30-day mortality as the outcome; however, owing to its low frequency, the analysis focused on the outcome of prolonged ICU stay, defining patients with prolonged ICU stay as those exceeding the 75th percentile of ICU length of stay. The receiver operating characteristic (ROC) curve and its area under the curve were used to assess the discriminative performance of variables in predicting the outcome. The optimal cutoff for the variables to effectively distinguish between patients with and without prolonged stays was derived from Youden's index of the ROC curve. Statistical analysis was performed using MedCalc for Windows, version 23.0.2 (MedCalc Software, Ostend, Belgium).

Results

During the study period, 78 consecutive patients admitted to the hepato-pancreato-biliary ICU were screened. Subsequently, 30 patients were excluded (Figure 1), leaving 48 patients for the analysis. The parameters of patients with pancreatitis alone were later used to compare the base excess effect of the individual components with those of liver disease patients. Demographic data are presented in (Table 1). The study patients exhibited an overall mortality rate of 6.25% (3 patients), which made us deviate from our initial plan, and we ended up analyzing the outcome based on the length of ICU stay.

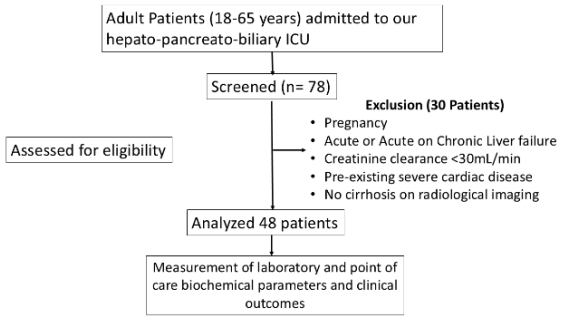

Figure 1- Flowchart of the study.

Patient characteristics

Male patients were the predominant group. Ethanol was the predominant cause of liver disease in our study population. Nineteen patients (39.6%) had type 2 diabetes, and 11 patients (22.9%) had hypertension. The most frequent presentation to our ICU was abdominal pain and/or distention (n = 16, 33.3%), followed by upper gastrointestinal bleeding (n = 15, 31.2%). The additional reasons for admission included encephalopathy and fever. The median MELD score for patients admitted to our ICU was 23 (IQR: 17–28). Six (12.5%) patients presented with circulatory shock upon admission. The biochemical and laboratory test results at admission are shown in (Table 2).

Strong ion gap and anion gap

The median acAG was 15 (IQR: 14–20). The median base excess of unmeasured anions [BE (UA)] was -4.2 (IQR: -7.1, 1.7). The apparent strong ion difference (SIDa) was 35 (33, 38), and the effective SID (SIDe) was 31 (28, 33) upon admission. The median strong ion gap (SIG = SIDa-SIDe) was 4.1 (IQR: 2.5 - 5.6). A histogram of the SIG is shown in (Figure 2).

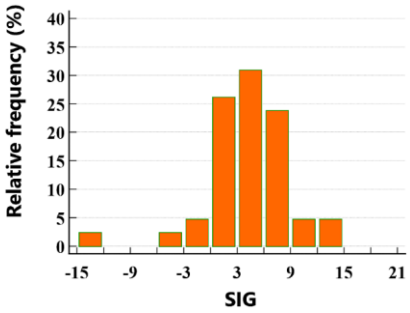

Figure 2- Histogram of the strong ion gap in the study population. SIG – Strong Ion Gap

Among the 48 patients, four individuals were diagnosed with metabolic alkalosis according to the Copenhagen approach, utilizing the base excess from the arterial blood gas (ABG-BE) of the point-of-care device. Ten patients exhibited normal ABG-BE values, ranging from -2 to +2, and thirty-four patients presented with acidosis. For analysis, an SIDa range of 38–42 was considered normal. In patients with alkalosis, SIDa was within normal limits in one patient, and acidosis was present in two patients, resulting in a 75% change in diagnosis (Table 3, Figure 3). In patients with normal ABG-BE, SIDa revealed alkalosis in 30% and acidosis in 50% of patients, revealing additional acid-base disturbances in 80% of cases. In patients with acidosis as per ABG-BE, SIDa was within the normal range in four patients and indicated alkalosis in one patient, implying a change in diagnosis in five patients (14.6%).

Correlation with acidosis

The pH in the ABG analysis correlated moderately with ABG-BE ($r = 0.53$, $p < 0.001$) and BE (UA) ($r = 0.42$, $p = 0.006$). pH showed a poor correlation with SIG ($r = 0.008$, p = NS) and acAG ($r = -0.13$, p = NS). SIDa and

BE (UA) demonstrated a strong correlation, with an r of -0.92 ($p < 0.001$). Effective SID was strongly correlated with ABG-BE ($r = 0.83$, $p < 0.001$). The SIG and acAG showed a strong correlation with an r value of 0.94 ($p < 0.001$) (Table 4, Figure 4). When the acid-base parameters were analyzed for correlation with disease severity scores, MELD and CLIF-SOFA demonstrated moderate correlations with lactate, ABG-BE, and SIDe.

Table 1- Admission characteristics of the study population.

Parameter		Descriptives (n = 48)
Age, years		59 (45, 70)
Sex: Male		42 (87.5%)
Etiology, n	Ethanol	23 (47.9%)
	NASH	11 (22.9%)
	Others	15 (31.2%)
Comorbidities, n	Type 2 Diabetes	19 (39.6%)
	Hypertension	11 (22.9%)
	Coronary artery disease	3 (6.2%)
Presenting complaint, n	Upper gastrointestinal bleed	15 (31.2%)
	Encephalopathy	13 (27.8%)
	Abdominal pain/distention	16 (33.3%)
	Fever	4 (8.3%)
Severity Score	MELD	23 (17, 28)
	CLIF-SOFA	8 (5, 10)

NASH, nonalcoholic steatohepatitis; MELD, model for end-stage liver disease; CLIF-SOFA, chronic liver failure-sequential organ failure assessment.

Table 2- Hemodynamic and biochemical parameters on admission day in the study population.

Admission Parameters	Descriptives (n = 48)	Admission Parameters	Descriptives (n = 48)
Clinical parameters		**Point of care test (arterial blood gas)**	
Mean arterial pressure, mmHg	77 (72, 93)	pH	7.41 (7.38, 7.46)
Heart rate, beats/min	85 (69, 103)	$PaCO_2$, mmHg	31 (25, 36)
Incidence of circulatory shock, n	6 (12.5%)	Sodium, mEq/L	132 (129, 136)
Derived acid-base parameters		Potassium, mEq/L	4.3 (3.8, 4.6)
		Chloride, mEq/L	101 (97, 105)
acAG, mEq/L	15 (14, 20)	Calcium, mmol/L	1.1 (1, 1.13)
Base excess of unmeasured anions	-4.2 (-7.1, 1.7)	Lactate, mmol/L	2.6 (2.2, 4.2)
Apparent Strong Ion Difference (SIDa), mEq/L	35 (33, 38)	Base Excess (Blood gas)	-3.3 (-7.1, -1)
		Laboratory tests	
Effective Strong Ion Difference (SIDe), mEq/L	31 (28, 33)	Bicarbonate, mEq/L	21 (19, 24)
		Phosphorus, mg/dL	3 (2.2, 3.7)
Strong ion gap (SIG = SIDa – SIDe), mEq/L	4.1 (2.5, 5.6)	Magnesium, mg/dL	2 (1.8, 2.2)
		Albumin, g/dL	3.2 (2.8, 3.5)

acAG – albumin-corrected anion gap. $PaCO_2$: Partial pressure of carbon dioxide in the arterial blood.

Table 3- Incidence of acid-base disorders according to different approaches.

Patient characteristics	Change in anion gap and strong ion difference	Frequency
Patients with alkalosis as per ABG-BE, n = 4	Normal acAG (4 to 12 mEq/L)	0
	Normal SIDa (38 to 42 mEq/L)	1 (25%)
	acAG revealed acidosis.	2 (50%)
	SIDa revealed acidosis.	2 (50%)
Patients with normal ABG-BE, n = 10	acAG revealed alkalosis.	0
	SIDa revealed alkalosis.	3 (30%)
	acAG revealed acidosis.	4 (40%)
	SIDa revealed acidosis.	5 (50%)
Patients with acidosis as per ABG-BE, n = 34	Normal acAG (4 to 12 mEq/L)	13 (38.2%)
	Normal SIDa (38 to 42 mEq/L)	4 (11.7%)
	acAG revealed alkalosis.	0
	SIDa revealed alkalosis.	1 (2.9%)

ABG-BE: arterial blood gas-based base excess (Copenhagen approach). acAG, albumin-corrected anion gap; SIDa: Apparent Strong Ion Difference

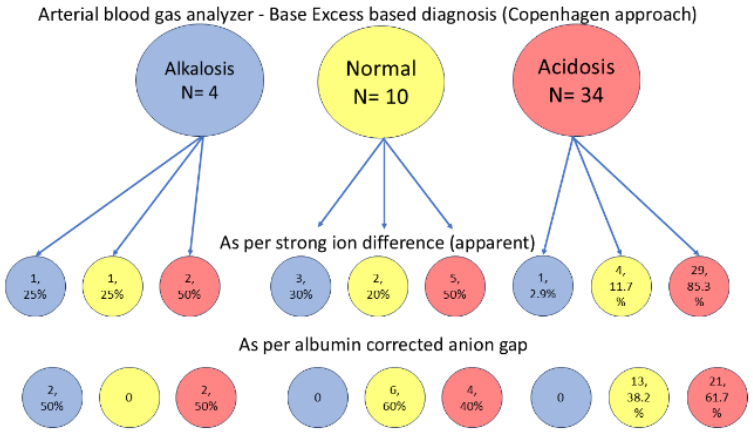

Figure 3- Change in diagnosis by anion gap and strong ion gap approaches with respect to the Copenhagen approach. Blue circles represent patients with alkalosis, yellow circles represent those with normal acid-base status, and red circles represent acidosis. The values mentioned in the circle are frequencies and percentages for each diagnosis.

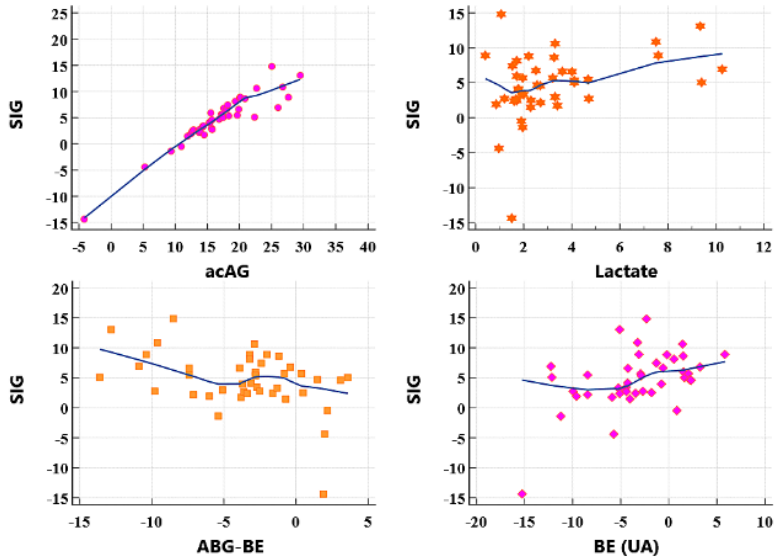

Figure 4- Correlation between strong ion gap and other acid-base parameters. SIG - strong ion gap. acAG - albumin-corrected anion gap. ABG-BE - arterial blood gas-based base excess. BE (UA) - base excess effect of unmeasured anions.

Table 4- Correlation between severity scores and acid-base parameters.

Parameters	BE (UA)	SIDa	SIDe	SIG	acAG	ABG-BE	Lactate
MELD	-0.45*	-0.42*	-0.56**	0.11	0.33	-0.59**	0.63**
CLIF-SOFA	-0.22	-0.30	-0.45**	0.16	0.28	-0.48**	0.38*
pH	0.42**	0.30	0.30	0.008	-0.13	0.53**	-0.42**
Lactate	-0.34*	-0.36*	0.68**	0.35*	0.64**	-0.68**	
ABG-BE	0.48**	0.43**	0.83**	-0.42*	-0.61**		
acAG	0.28	0.27	-0.63**	0.94**			
SIG	0.49**	0.47**	-0.49**				
SIDe	0.43**	0.53**					
SIDa	0.92**						

* = significant at $p < 0.05$ level; ** = significant at $p < 0.01$ level. MELD: Model for End-Stage Liver Disease; CLIF-SOFA: Chronic Liver Failure - Sequential Organ Failure Assessment. ABG-BE: Base excess obtained from arterial blood gas (Copenhagen approach); acAG: albumin-corrected anion gap; SIDa: Apparent Strong Ion Difference. SIDe: Effective Strong Ion Difference. SIG - Strong ion gap.

Comparison with Pancreatitis patients

The base excess effects of free water, chloride, and lactate were comparable between patients with cirrhosis and pancreatitis. While the alkalinizing effect of albumin was more pronounced in patients with liver disease, the alkalinizing effect of phosphorus was more pronounced in patients with pancreatitis (Figure 5).

Outcome analysis

Due to its low frequency, mortality could not be used to analyze the effect of these acid-base parameters on patient outcomes. Therefore, an ICU stay >8 days was considered the outcome of interest. The 8-day threshold represented the 75th percentile of the ICU stay length in our sample. The study population comprised 10 patients with longer ICU stays (>8 days) and 38 patients with shorter ICU stays (≤8 days). Patients with longer ICU stays exhibited higher CLIF-SOFA scores [10 (8, 12) vs. 7 (5, 9), p= 0.002] and comparable MELD scores on admission (Table 5). Patients with extended ICU stays exhibited lower ABG-BE [-8.9 (-12, -2.1) vs. -3.1 (-5.5, -1), P=.04], elevated lactate levels [6.1 (3.6, 8.5) vs. 2.2 (1.7, 3.3), p= 0.02], increased acAG [21 (18, 25) vs. 15 (14, 17), p= 0.04], and higher SIG [6 (5, 8) vs. 3 (2, 6), p= 0.04] on the admission day. Patients with increasing SIG over 48 h were higher in the prolonged ICU stay group (40% vs. 13.2%; p= 0.05).

The incidence of acute kidney injury, the requirement for invasive mechanical ventilation, and the occurrence of sepsis were higher in patients with a longer ICU stay (Table 6).

Predictor of Outcome

BE (UA) and SIDa demonstrated an AUC of 0.50 and 0.52, respectively, in predicting prolonged ICU stay according to the ROC curve analysis. The pH, lactate, and SIDe displayed AUC values of 0.64, 0.68, and 0.70, respectively.

ABG-BE with an AUC of 0.73, SIG with an AUC of 0.75, and acAG with an AUC of 0.78 on the admission day exhibited good efficacy in predicting extended ICU stays (Table 7, Figure 6). The optimal cut-off values that discriminated the patients for lactate, acAG, and SIG were 4, 17, and 4.1 mEq/L, respectively. The AUC of CLIF-SOFA for predicting a poor prognosis was 0.81. The addition of either acAG or SIG to CLIF-SOFA improved the AUC of CLIF-SOFA from 0.81 to 0.84.

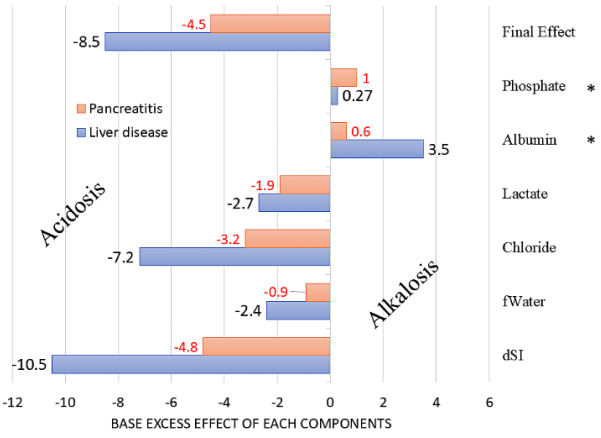

Figure 5- Pattern of acid–base disturbances occurring in critically ill patients with liver cirrhosis and pancreatitis (comparison group for patients without cirrhosis). * = difference was statistically significant at p < 0.05.

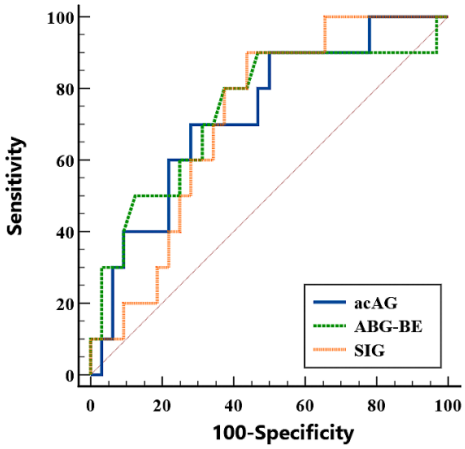

Figure 6- ROC curves of acid-base parameters in the prediction of ICU stay >8 days. Only parameters with AUC > 0.70 are displayed. acAG - albumin-corrected anion gap; SIG - strong ion gap; ABG-BE – arterial blood gas-based base excess.

Table 5- Admission Day characteristics across the two groups.

Patient characteristics	Patients with ICU stays ≤8 days, n= 38	Patient with ICU stay >8 days, n= 10	P value
Age, years	63 (50, 72)	59 (48, 69)	.78
CLIF-SOFA	7 (5, 9)	10 (8, 12)	.002
MELD	18 (16, 26)	29 (20, 39)	.08
Bilirubin, mg/dL	2.8 (1.4, 3.8)	6.2 (3.1, 4.2)	.07
Aspartate aminotransferase, IU/L	78 (52, 101)	49 (30, 287)	.28
Urea, mg/dL	57 (36, 75)	116 (91, 124)	.02

Creatinine, mg/dL	0.9 (0.7, 1.8)	1.8 (1.3, 2.9)	.09
Total leukocyte count, cells/mm³	6.7 (5, 9.7)	4.7 (3.1, 20)	.23

MELD: Model for End-Stage Liver Disease; CLIF-SOFA: Chronic Liver Failure - Sequential Organ Failure Assessment.

Table 6- Acid-base and clinical parameters of the two groups.

Parameter	Patients with ICU stays ≤8 days, n= 38	Patient with ICU stay >8 days, n= 10	P value
Admission day characteristics			
Base excess from arterial blood gas (Copenhagen approach)	-3.1 (-5.5, -1)	-8.9 (-12, -2.1)	.04
Lactate, mmol/L	2.2 (1.7, 3.3)	6.1 (3.6, 8.5)	.02
Albumin-corrected anion gap, mEq/L	15 (14, 17)	21 (18, 25)	.04
Base excess of unmeasured anions	-4.2 (-5.5, -1.7)	-5.7 (-10, -0.3)	.87
SIDa, mEq/L	34 (33, 37)	33 (28, 39)	.81
SIDe, mEq/L	31 (29, 33)	26 (23, 32)	.08
SIG, mEq/L	3 (2, 6)	6 (5, 8)	.04
Events in the course of ICU stay			
Patients with increasing SIG over 48 h, n	5 (13.2%)	4 (40%)	.05
Acute kidney injury, n	9 (23.6%)	8 (80%)	.01
Need of CRRT, n	1 (2.6%)	1 (10%)	.38
Mechanical Ventilation, n	1 (2.6%)	5 (50%)	<.001
PaO_2/FiO_2 ratio	390 (370, 450)	350 (260, 400)	.11
Sepsis, n	5 (13.1%)	6 (60%)	.01
48-hour fluid balance, L	4.6 (2.9, 4.9)	5 (3.1, 6.5)	.35
30-day mortality, n	0	3 (30%)	<.001

SIDa: Apparent Strong Ion Difference. SIDe: Effective Strong Ion Difference. SIG - Strong ion gap. CRRT: Continuous renal replacement therapy. PaO2: Partial pressure of oxygen in arterial blood. FiO_2: Fraction of inspired oxygen.

Table 7- ROC curve for various acid-base parameters on the admission day in predicting the outcome: ICU stay > 8 days (>75th percentile).

Parameter	AUC	Cut-off	Sensitivity	Specificity
Base excess in arterial blood gas (Copenhagen approach)	0.73	≤ (-7)	80%	64%
Lactate	0.68	>4 mmol/L	62%	85%
Albumin-corrected anion gap	0.78	>17 mEq/L	80%	71%
Effective Strong Ion Difference	0.70	≤ 31 mEq/L	70%	68%
Strong ion gap	0.75	>4.1 mEq/L	90%	56%

Discussion

Blood pH reflects the cumulative outcome of multiple concurrent acid-base disturbances within a patient. It serves as an indicator of acidemia or alkalemia, representing the net result of all enhancing and counteractive effects. This complex physiological process, which influences the ultimate state of the blood pH, is referred to as acidosis or alkalosis. Although individuals may experience simultaneous acidotic and alkalotic processes, the blood pH ultimately deviates in one direction, specifically towards the predominant side of the acid-base disturbance.

Acid-base disturbances are common complications among patients admitted to intensive care units and significantly contribute to morbidity and mortality. Prompt and accurate management of these disturbances is essential to optimize patient outcomes and enhance survival rates. Acid-base imbalances can disrupt a patient's internal homeostasis, potentially rendering treatment ineffective or inadequate [13]. Therefore, it is imperative to evaluate, classify, and diagnose acid-base disturbances accurately, facilitating early intervention and preventing severe consequences.

The evaluation, classification, and diagnosis of acid-base disorders were enhanced using AG, SID, and SIG. Albumin-corrected AG (acAG) is widely considered a more effective parameter and is often preferred over conventional AG in the literature. For each g/dL decrease in the serum albumin concentration, AG is expected to decrease by 2.5 mmol/L and needs to be corrected [14-15]. The normal range for acAG is 4-12 mEq/L, but this does not mean that acidosis or alkalosis can't happen. Acid-base changes can happen even when the AG is normal. It is important to note that clinically, diagnosis follows a stepwise approach, beginning with the

identification of acidemia or alkalemia, followed by the detection of acidosis or alkalosis, and the subsequent classification of acidosis based on AG [16]. This systematic approach allows clinicians to establish a diagnosis and formulate a treatment plan. Apart from being diagnostic, elevated AG is reported to be associated with adverse outcomes in patients with aortic aneurysms, those undergoing extracorporeal therapy, and in pediatric intensive care settings [4-5,17-18]. SID is a marker of acid-base disturbances and is used as a diagnostic test, whereas SIG is employed as a predictor in most studies by quantifying unmeasured anions in the blood. The normal SID value in humans is 40 mEq/L. The SIG in healthy controls is approximately zero, with a mean of 1.4 mEq/L reported in a study conducted by Gunnerson et al. in patients who were not critically ill, and none had >5 mEq/L [19]. In the same study, stable Intensive Care Unit (ICU) patients awaiting discharge demonstrated a mean SIG of 5.1 (±2.9). In critically ill patients, the average SIG ranged from 3.6 to 7.7 mEq/L, and it might be as high as 13.4 mEq/L in patients with acute kidney injury [20-21]. The median SIG in our overall cohort was 4 mEq/L, and in patients with longer ICU stays, it was 6 mEq/L. Admission-day SIG is considered a predictor of adverse outcomes in medical ICU, trauma care, and post-cardiothoracic surgery patients [22-25] Dynamic changes in SIG have prognostic significance in critical care settings [15,25] A reduction in SIG over time following admission appears to be a favorable prognostic indicator. Similarly, in our study, a reduction in SIG over time was associated with a shorter ICU stay.

We analyzed the effects of individual components and their effects on BE and found that alterations in phosphate and albumin levels were the primary contributors to alkalosis, whereas the remaining imbalances, including the effects of sodium, dilution, chloride, and lactate, were associated with acidosis. Notably, hypophosphatemia was more prevalent in individuals with pancreatitis, whereas hypoalbuminemia was more pronounced in patients with liver disease. The latter condition exhibited the most significant alkalinizing effect in the liver disease cohort. Our study also identified the coexistence of hyperchloremic acidosis and hypoalbuminemic alkalosis in critically ill patients with cirrhosis, which is consistent with the findings of Drolz et al. In the same study, net metabolic acidosis attributed to lactate and unmeasured anions was more pronounced in cirrhotic patients than in non-cirrhotic patients. Furthermore, the same study indicated that lactate levels, acidemia, and [BE (UA)] serve as predictors of poorer outcomes in critically ill patients with cirrhosis [26]. In 1/3rd of our patients (16 instances), SIDa revealed hidden acid-base imbalances that were not detected by ABG–BE. Correlation tests further confirmed some theoretical aspects, showing that SIG and acAG did not consistently influence the pH levels. Our study reinforces that BE (UA), measured using the Stewart approach, and ABG-BE, measured using the Copenhagen approach, have a more significant impact on pH. Additionally, this study identified three pairs of closely related factors: 1) effective SID and ABG-BE; 2) apparent SID and BE (UA); and 3) acAG and SIG. In our study, SIG exhibited superior performance relative to AG (AUC: 0.75 vs. 0.70). However, when corrected for albumin, acAG demonstrated improved performance compared to SIG (AUC: 0.78 vs. 0.75). AG is more user-friendly because it requires fewer parameters and is commonly available in the outputs of most point-of-care ABG analyzers, making SIG a more complex value to ascertain. Among the acid-base variables, acAG and SIG showed the highest discriminatory ability between patients; however, they did not match the efficacy of the CLIF-SOFA score (AUC = 0.81) in our study. Composite scores, such as APACHE II and SOFA, are anticipated to outperform acid-base parameters [27]. The integration of AG into the SOFA score has been demonstrated to enhance its predictive capability in cardiac ICU settings [28]. The findings of our study corroborate this observation, as inclusion of either acAG or SIG in the prediction model increased the AUC of the CLIF-SOFA from 0.81 to 0.84 in our study. The primary limitation of this study was its small sample size. In addition, as a single-center study, there may be variations in disease severity and management protocols that could impact the generalizability of the findings. Another limitation is the selection of prolonged ICU stay as the outcome of interest, rather than 30-day mortality. Owing to the low mortality rate, we adjusted the outcome of interest during the analysis. Although this study focused on patients with cirrhosis, the initial admission complaints varied, potentially affecting the homogeneity of the study population. The physiological changes associated with upper gastrointestinal bleeding and encephalopathy may differ, and including these conditions in a single category could be misleading in terms of understanding changes in SIG.

Conclusion

In conclusion, this study demonstrated the coexistence of hyperchloremic acidosis and hypoalbuminemic alkalosis in patients with cirrhosis admitted to the ICU. Compared to non-cirrhotic patients, cirrhotic individuals exhibited more pronounced net metabolic acidosis attributed to lactate and unmeasured anions. SIG effectively predicts prolonged ICU stays and has commendable predictive ability. However, the anion gap, when corrected for albumin, outperformed SIG in terms of predictive accuracy, requiring fewer variables and offering greater ease of use.

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