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Association between delta anion gap/delta bicarbonate and outcome of surgical patients admitted to intensive care unit

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Abstract

Background Patients undergoing high-risk surgeries with acid-based disorders are associated with poor outcomes. The screening of mixed acid-based metabolic disorders by calculating delta anion gap (AG)/delta bicarbonate (Bic) has a clinically relevant role in patients with high AG metabolic acidosis (MA), however its utility in individuals facing high-risk surgical procedures remains unclear.

Objective Characterize metabolic acidosis using delta-AG/delta-Bic and its associations in patients undergoing high-risk surgeries with possible outcome-related complications.

Design Prospective observational multicentric study.

Setting Three tertiary hospitals in Brazil.

Patients Patients undergoing high-risk surgeries, aged 18 years or older, requiring postoperative critical care.

Main outcome measures Patients undergoing high-risk surgeries monitored during the postoperative phase across three distinct intensive care units (ICUs), with assessment encompassing laboratory analyses upon admission and 24 h thereafter. Patients with MA and with elevated AG within 24 h were separated into 3 subgroups: [G1 – delta-AG/delta-Bic < 1.0] MA associated with hyperchloremia; [G2 – delta-AG/delta-Bic between 1.0 and 1.6] MA and no mixed disorders; and [G3 – delta-AG/delta-Bic > 1.6] MA associated with alkalosis. Primary endpoint was 30-day mortality. The secondary endpoints were cardiovascular, respiratory, renal, neurological, coagulation and infective complications.

Results From the 621 surgical patients admitted to ICU, 421 (51.7%) had any type of acidosis. After 24 h, 140 patients remained with MA with elevated AG (G1: 101, G2: 18, and G3: 21). When compared to patients from subgroups 1 and 3, the subgroup with no mixed disorders 2 showed higher 30-day mortality (adjusted HR = 3.72; 95% CI 1.11–12.89,

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$p=0.001$), cardiovascular complications ($p=0.001$), ICU mortality ($p=0.03$) and sum of all complications during the ICU period ($p=0.021$).

Conclusion In the postoperative time, patients with metabolic acidosis and no mixed disorders present higher ICU-Mortality and higher cardiovascular postoperative complications when compared with patients with combined hyperchloremia or alkalosis. Delta-AG/delta-Bic can be a useful tool to evaluate major clinical outcomes in this population.

Key points

- In the context of high-risk surgeries, patients experiencing metabolic acidosis accompanied by an elevated anion gap exhibit a reduced likelihood of survival in the intensive care unit (ICU).
- The application of the delta-AG/delta-Bic ratio for assessing mixed disorders in patients with elevated anion gap acidosis during the early postoperative phase proves to be a valuable and clinically relevant tool.
- A subgroup of patients presenting metabolic acidosis accompanied by an elevated anion gap although without associated disorders, demonstrate a poorer clinical prognosis within the ICU setting.

Keywords Anion gap, Critical care, Metabolic acidosis, Surgery, Intensive care

Introduction

The maintenance of the acid-base balance during the perioperative period is vital to maintain homeostasis of diverse physiological conditions which have direct implication on surgical outcome. Metabolic acidosis (MA) developed both intraoperatively and postoperatively has been associated with worse clinical outcomes with significantly increased mortality and morbidity [1–5]. The rapid transition to an acidic milieu engenders disruptions in coagulation [6], oxygen delivery [7], vasopressor-receptor coupling [8], and intracellular signaling [9], thus culminating in the onset of organ dysfunction among surgical patients [10].

Surgical and critically ill patients are at higher risk to develop MA with increased anion gap (AG) or with normal AG (hyperchloremic) [1]. A common cause of high AG MA in the perioperative period is increased lactate due to tissue malperfusion [11]. Conversely, in these populations, hyperchloremic acidosis arises as a prevalent consequence of chloride-rich solutions employed for volume replacement, a measure to avert tissue damage [4, 5, 12]. Both forms are associated with increased 30-day mortality and organ dysfunction [1, 2, 4, 5, 12]. Nevertheless, MA may be accompanied by other acid-base disorders [1, 2, 13–16]. One way to assess such disorders is to calculate the delta anion gap ratio (delta-delta), which is ratio between AG increase above expected AG to the decrease in bicarbonate ion (Bic) below the baseline (delta-AG/delta-Bic=ΔAG / $\Delta HCO3^{-}$).The relationship between the increase in AG and the change in bicarbonate is effective in identifying mixed disorders in metabolic acidosis, however, it should be used in conjunction with other clinical and laboratory parameters to correctly diagnose underlining disorders in metabolic acidosis [17, 18], further exploration is required to investigate the utility of delta-AG/delta-Bic in identifying acid-base disorders among surgical patients experiencing metabolic acidosis and its potential implications on prognostic outcomes.

This prospective multicentre study focuses on patients undergoing high-risk surgical interventions and aims to characterize MA using the delta-AG/delta-Bic classification to evaluate the possible presence of subgroups of patients with elevated anion gap metabolic acidosis and mixed disorders. The study examines outcomes within the first 24 h after surgery and analyses how these findings correlate with 30-day mortality and other clinically significant outcomes.

Methods

This prospective multicentre observational study was based on a database of patients undergoing high-risk surgeries who need postoperative ICU from three tertiary hospitals in Brazil, collected from January 2019 to December 2019. This project was approved by the Ethics Committee for the Analysis of Research Projects of the Hospital das Clínicas (HC-FMUSP), Hospital do Servidor Público Estadual (HSPE) - IAMSPE/SP and Hospital do Câncer de Barretos, being registered under number CAAE – 28520820.1.0000.0068 and was conducted according to the Helsinki declaration and STROBE guidelines [19]' [20].This study is registered in the Brazilian trial register (REBEC, Trial-ID U1111-1296-3626).The methodology used in this study was based on a previous study by conducted by our research group [1, 2]. We adapted the criteria previously outlined published elsewhere [2, 21] to identify high-risk surgeries and patients.

Study population

We included patients aged 18 or older who were admitted to the ICU after undergoing high-risk non-cardiac surgery during the designated study period. All participants provided informed consent, and if they were unable to do

so, consent was obtained from a legal representative or family member. Exclusion criteria consisted of ICU stays lasting less than 24 h (Exclusion Criteria Afterward: For patients whose ICU stay ends up being less than 24 h, the exclusion criterion is applied retrospectively), reduced life expectancy, Chronic Obstructive Pulmonary Disease, hepatic insufficiency categorized as Child-Pugh B or C, prior renal insufficiency defined as KDIGO<G3a (creatinine clearance below 59 mL/min/1.73 m^2), previously diagnosed diabetes (both type I and II), or two blood sugar measurements exceeding 126 mg/dL after an eight-hour fasting period around the time of surgery[22]. Figure 1 shows the study setup.

Delta anion gap/delta bicarbonate calculation

Patients were categorized as either having metabolic acidosis (MA) or nonmetabolic acidosis, which was determined by an arterial base excess difference of less than than −2.0 mmol l^{-1} and pH<7.35[23]. The anion gap (AG) measurement was adjusted for albumin to enhance practicality in daily clinical practice and improve the accuracy of the technique compared to using the uncorrected AG [24]. . The correction was performed using the formula: Corrected AG=calculated AG+2.5×(4.5 - measured albumin)[8]. The correlation with the bicarbonate variation was considered normal when falling within the range of 1 and 1.6 [25].

Following the assessment of base differences within the initial 24 h postoperatively, the selected patients were initially categorized into two groups: those with MA and those without. Simultaneously, among those with MA, further analysis was conducted based on their AG, resulting in two subgroups: MA with an increased AG and MA with an unchanged AG. For patients in the increased AG group beyond the initial 24 h, the delta-AG/delta-Bic ratio was calculated and used to create three new groups based on the obtained results. The choice of the 24-hour period after ICU admission was deliberate to account for the potential impact of initial patient care and the natural physiological changes in the acid-base balance during this timeframe.

The delta-AG/delta-Bic calculation was carried out within the first 24 h following admission to the ICU considering the estimated normal values of the variables according to the literature used as well as the laboratory values considered normal (AG=12, and Bicarbonate=24 mmol l^{-1}) [17, 26] and their differences with the result found after 24 h, resulting in the formula:

$$\frac{\text{DeltaAG}}{\text{DeltaBic}} = \frac{\text{correctedAG} - 12}{24 - HCO3^{-}}$$

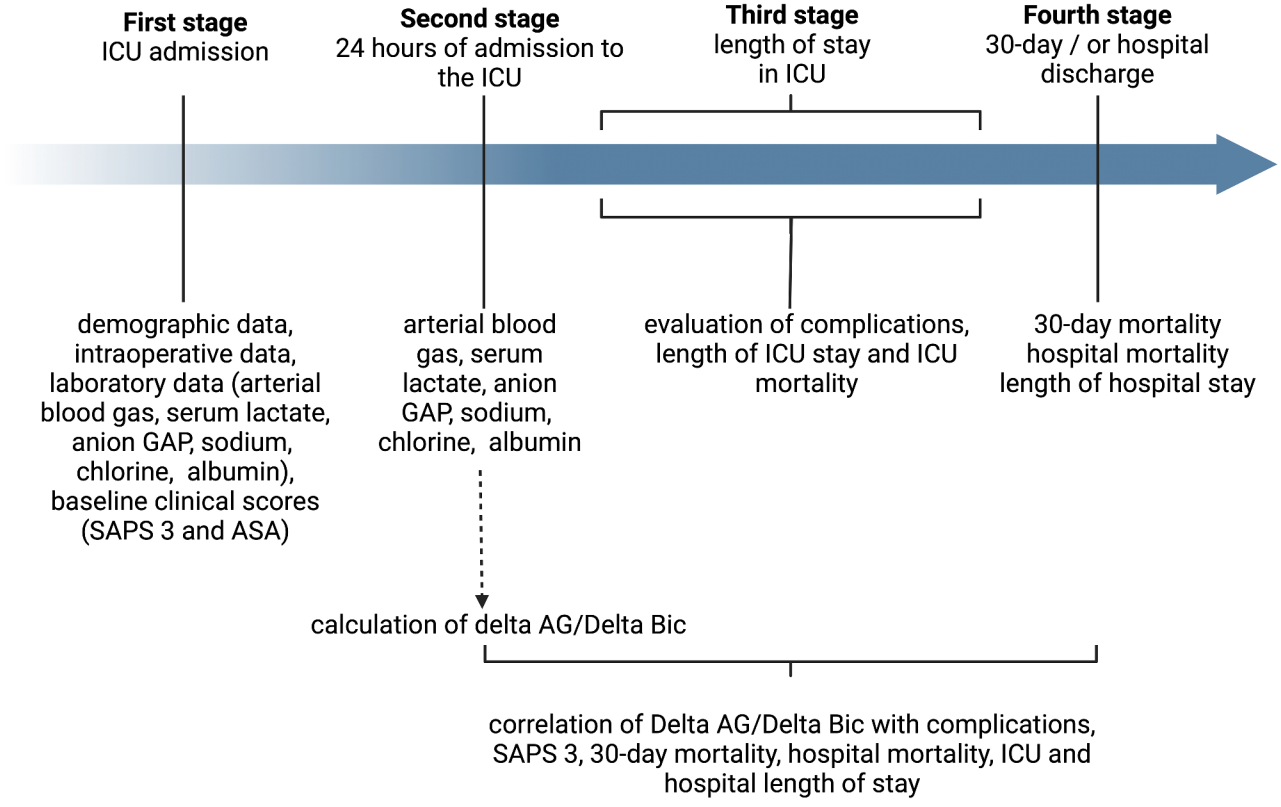

Fig. 1 Represent the Study setup according to the timeline and the respective collected data. ICU: intensive care unit

Study groups based on the delta-AG/delta-Bin sub-division
Consequently, three groups were assessed based on the value of this ratio: [Group 1 – delta-AG/delta-Bic < 1.0] indicating metabolic acidosis associated with hyperchloremia; [Group 2 – delta-AG/delta-Bic between 1.0 and 1.6] denoting metabolic acidosis without mixed disorders; and [Group 3 – delta-AG/delta-Bic > 1.6] signifying metabolic acidosis associated with alkalosis [25]. Additionally, the specific disorder identified based on delta-AG/delta-Bic values was correlated with the complications experienced during the patient's stay in the ICU or hospital.

Study endpoints

The primary objective of this study was to assess in-hospital mortality (30-day mortality and ICU mortality). Secondary objectives included the evaluation of cardiovascular, respiratory, renal, neurological, coagulation, and infective complications. The study followed all enrolled patients throughout their hospitalization until discharge, extending the observation period to 30 days post-surgery.

Definition of complications

a) Cardiovascular: need for vasopressor for more than one hour despite volume resuscitation [27].
b) Respiratory: $PaO/FiO_2 < 200$ in patients without prior respiratory disease, need for reintubation or difficulty in removing from mechanical ventilation during the postoperative period related to failure in the extubation process, even after successful spontaneous breathing on mechanical ventilation according to the institutions' protocols [28].
c) Renal: creatinine increase > 0,3 mg/dl after ICU admission or urine output less than 400 ml in 24 h or need for dialysis during ICU stay [29].
d) Neurological: RASS score acutely fluctuating and different from zero within 24 h. Agitation was determined with RASS score greater than or equal to + 2 [30].
e) Coagulation: 30% drop in platelets compared to the initial ICU admission value, reaching values below 100,000 uL^{-1} associated with spontaneous bleeding [6].
f) Infective: classified according to the location of the infectious focus, etiologic agent, and severity. Characterization of the focus and infectious agents were based on the Center for Disease control and prevention (CDC) criteria [31].

Statistical analysis

The prior studies [1, 2] informed the sample size estimation. Acidosis-associated mortality was 15% in the pilot study, compared to 2% without acidosis. These rates align with general (~ 5%) and high-risk surgical patient mortality (15%) [2, 32, 33]. Using a 1:1 ratio based on pilot data and clinical significance, we calculated the sample size needed to detect 15% acidosis-related and 5% non-acidosis-related mortality differences. 95% CI and 80% power indicated a need for ≥310 patients (≥155 per group) to compare 30-day mortality (MedCalc 11.5.1; sampling: proportions). Categorical variables were described using frequencies and percentages, while quantitative variables were characterized using measures of central tendency and dispersion (median and corresponding interquartile range). Asymmetrically distributed continuous variables were assessed using the Mann-Whitney and Wilcoxon tests for pairwise comparisons, and the Kruskal-Walli's test for multiple comparisons. Normally distributed continuous variables were analyzed using the ANOVA test. Linear trend Chi-square tests were employed for categorical variables. All statistical tests were two-tailed, with a significance level of 0.05. Correction for multiple analyses was performed using the Bonferroni method [34]. The comparability of groups was examined for age, SAPS 3 through analysis of variance (ANOVA), and the distribution of patients by sex [35]. Moreover, survival estimates extending beyond the initial 30-day period were generated using an adjusted Kaplan-Meier curve (e.g., sex, age, SAPS 3 prognosis score), achieved through Cox regression. The statistical significance of observed trends was evaluated utilizing the Mantel Cox test to discern linear patterns. Missing data were minimal in our study and were perceived to be missing at random. To address this, we employed pairwise deletion.

Results

Study population

Figure 2 shows the study population. After surgery, 621 patients admitted to the ICU after surgical procedures were evaluated. On ICU admission, 300 (48.3%) patients presented without acidosis according to the used criteria, and 321 (51.7%) presented some type of acidosis. Of these, 201 (32.4%) had high AG and 120 (19.3%) of them had hyperchloremic acidosis.

Patient characteristics

Table 1 shows the demographic data of the patients 24 h after surgery. From the entire population, 421 (67.8%) patients had no acidosis and 200 (32.2%) met the criteria for the acidosis group. Of the 200 patients with acidosis, 60 (9.7%) had hyperchloremic MA and 140 (22.5%) had MA with high albumin corrected AG. Figure 4. A summarizes the percentage of patients in each group in time-points 0 h and time 24 h and Fig. 4.B Subgroups based on the delta-AG/delta-Bic sub-division.

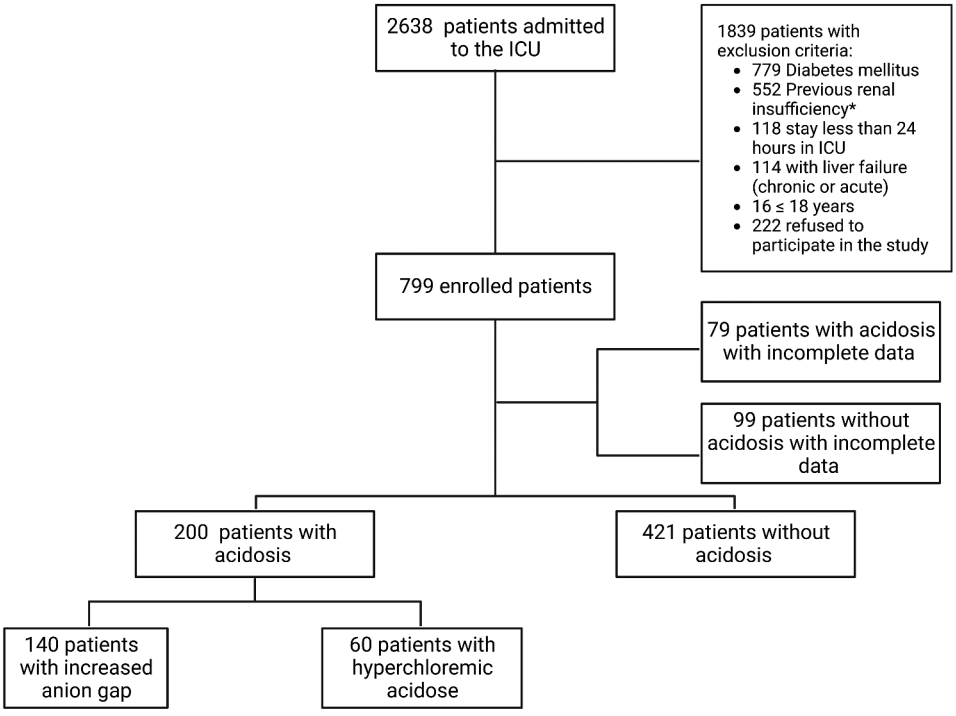

Fig. 2 Study population

Table 1 Demographic variables evaluated at ICU admission

	Entire Population (*n* = 621)	No acidosis (*n* = 421)	Normal AG- hyperchloremia (*n* = 60)	Increased AG (*n* = 140)	*P* value
Age (years)	63 (46–74)	63 (50–74)	63 (46–74)	63 (48–74)	0.96
Male, *n* (%)	312 (50.3)	218 (51.8)	31 (50.8)	67 (45.7)	0.46
Weight (kg)	70 (63.5–80)	70 (63–80)	71 (64–80)	71.8 (65–79)	0.98
Height (cm)	163 (160–169)	163 (161.7–170)	163 (160-169.5)	163 (160–165)	0.17
General anesthesia, *n* (%)	459 (73.9)	311 (73.9)	45 (74.1)	104 (74.0)	0.24
Caucasian, *n* (%)	478 (76.9)	318 (75.6)	41 (67.2)	119 (85.0)	0.09

AG = Anion Gap

Table 2 shows the surgical profile of the patients 24 h after surgery. The SAPS 3 score showed a mean of 38 for patients without acidosis, 41 for patients with hyperchloremic acidosis, and 43.5 for patients with high AG ($p < 0.05$).

Patients undergoing gastrointestinal surgery were associated with higher percentages of MA with elevated AG, being 52.6% versus 33.3% with normal GA and 31.6% without acidosis ($p < 0.05$).

Overall survival analysis

Figure 3A shows a Kaplan-Meier curve at 30 days for the entire population and 3B according to the subgroups. The presence of MA with increased AG (HR = 2.11; 95% CI 1.22 to 3.64), SAPS 3 (HR = 1.03; 95% CI 1.02 to 1.05) and ASA (HR = 1.63; 95% CI 1.25 to 2.14) were factors strongly associated with 30-day mortality, adjusted for time of surgery ($p = 0.17$), type of surgery ($p = 0.25$) and participating centers ($p = 0.45$).

Delta-AG/delta-Bic analsys

Figure 4.B shows the patient profile based on the delta-AG/delta-Bic sub-analysis. Of the patients with MA with elevated AG, delta-AG/delta-Bic was calculated, and they were divided into 3 groups: [Group 1 – delta-AG/delta-Bic < 1.0] MA associated with hyperchloremia 101 (72.1%) patients; [Group 2 – delta-AG/delta-Bic between 1.0 and 1.6] MA and no mixed disorders with 18 (12.9%) patients; and [Group 3 – delta-AG/delta-Bic > 1.6] MA associated with alkalosis and with 21 (15%) patients.

Table 3 shows the intraoperative characteristics of the new sub-division based on delta-AG/delta-Bic. The group 1 (MA associated with hyperchloremia) presented significant higher values of total intraoperative 0.9% saline solution volume, mechanical ventilation requirement and $PaCO_2$ and chloride values when compared with the groups 2 and 3.

Table 2 Surgical profile, SAPS 3 and ASA scores from the groups at ICU admission

Variables	Entire population (*n* = 621)	No acidosis (*n* = 421)	Normal AG- hyperchloremia (*n* = 60)	Increased AG (*n* = 140)	*P*-value
Surgeries, ***n (%)***					**0,03**
Gastrointestinal, *n* (%)	226 (36.4)	133 (31.6)	20 (33.3)	74 (52.6)*	
Vascular, *n* (%)	78 (12.5)	57 (13.5)	7 (11.7)	13 (9.6)	
Orthopedics, *n* (%)	83 (13.3)	64 (15.2)	6 (10.0)	12 (8.9)	
Neurological, *n* (%)	72 (11.6)	50 (11.8)	7 (11.7)	16 (11.1)	
Urological, *n* (%)	30 (4.8)	21 (5.1)	3 (5.0)	5 (3.7)	
Others, *n* (%)	133 (21.4)	96 (22.8)	17 (28.3)	20 (14.0)	
SAPS 3	**40 (31–52)**	**38 (30–50)**	**41 (30.5–49)**	**43.5*(32.5–57)**	**0.003**
ASA, ***n*(%)**					**0.12**
P1	89 (14.4)	58 (13.8)	9 (14.5)	23 (16.4)	
P2	302 (48.6)	214 (50.8)	36 (60.0)*	52 (36.9)	
P3	174 (28.0)	117 (27.8)	9 (14.5)*	48 (34.4)	
P4	45 (7.3)	26 (6.2)	5 (9.1)	14 (9.8)	

Legend n=number of individuals in groups

*represents Bonferroni correction P<0.05 different from the group without metabolic acidosis. Values in parentheses represent median (25-75 interquartile range)

AG represents anion gap; ASA=American Society of Anesthesiology classification; min= minutes; SAPS 3= Simplified Acute Physiology Score 3

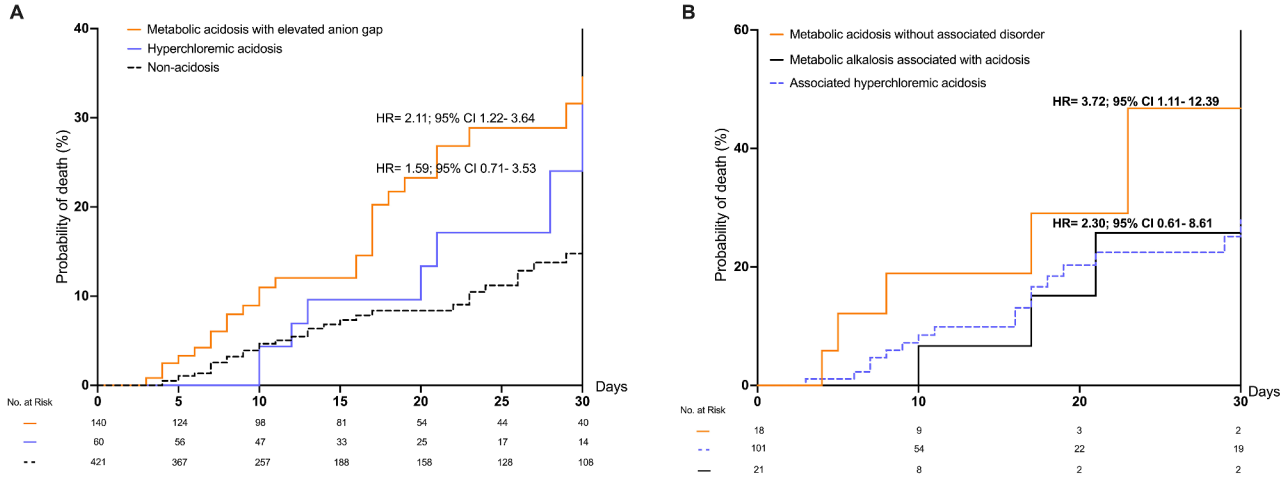

Fig. 3 A Kaplan-Meier curve was constructed for the 30-day period, illustrating distinct groups: those without acidosis, those with hyperchloremic acidosis, and those with elevated anion gap. The curve's values were derived from a Cox regression model. Additionally, a separate Kaplan-Meier curve was generated for various types of metabolic acidosis with an elevated anion gap and mixed disorders, also based on the Cox regression model

Survival analysis based on the delta-AG/delta-Bin subdivision

Figure 3 shows the Kaplan-Meier curve at 30 days for the different types of MA with elevated AG. The presence of MA with increased AG without mixed disorders (group 2) had a higher risk of death during the 30 days (HR=3.72; 95% CI 1.11 to 12.89).

Secondary endpoints

Table 4 shows the diverse perioperative complications. Comparing the MA groups for complications occurring in the ICU, the MA group without mixed disorders (group 2) showed a higher association with cardiovascular complications ($p<0.01$), ICU mortality ($p=0.03$) and in the sum of all complications during the ICU period ($p=0.02$). There were no significant differences regarding the other complications.

Discussion

In this prospective multicentre observational study, during the postoperative period, the presence of metabolic acidosis demonstrated an inverse relationship with survival in high-risk surgical patients, particularly in cases where metabolic acidosis with an elevated anion gap. When examining patients with metabolic acidosis and concurrent mixed disorders, the application of the Delta-AG/delta-Bic calculation revealed distinct outcomes. Specifically, patients experiencing metabolic acidosis without accompanying mixed disorders displayed high risk to ICU mortality and an increased occurrence of postoperative complications, as opposed to those

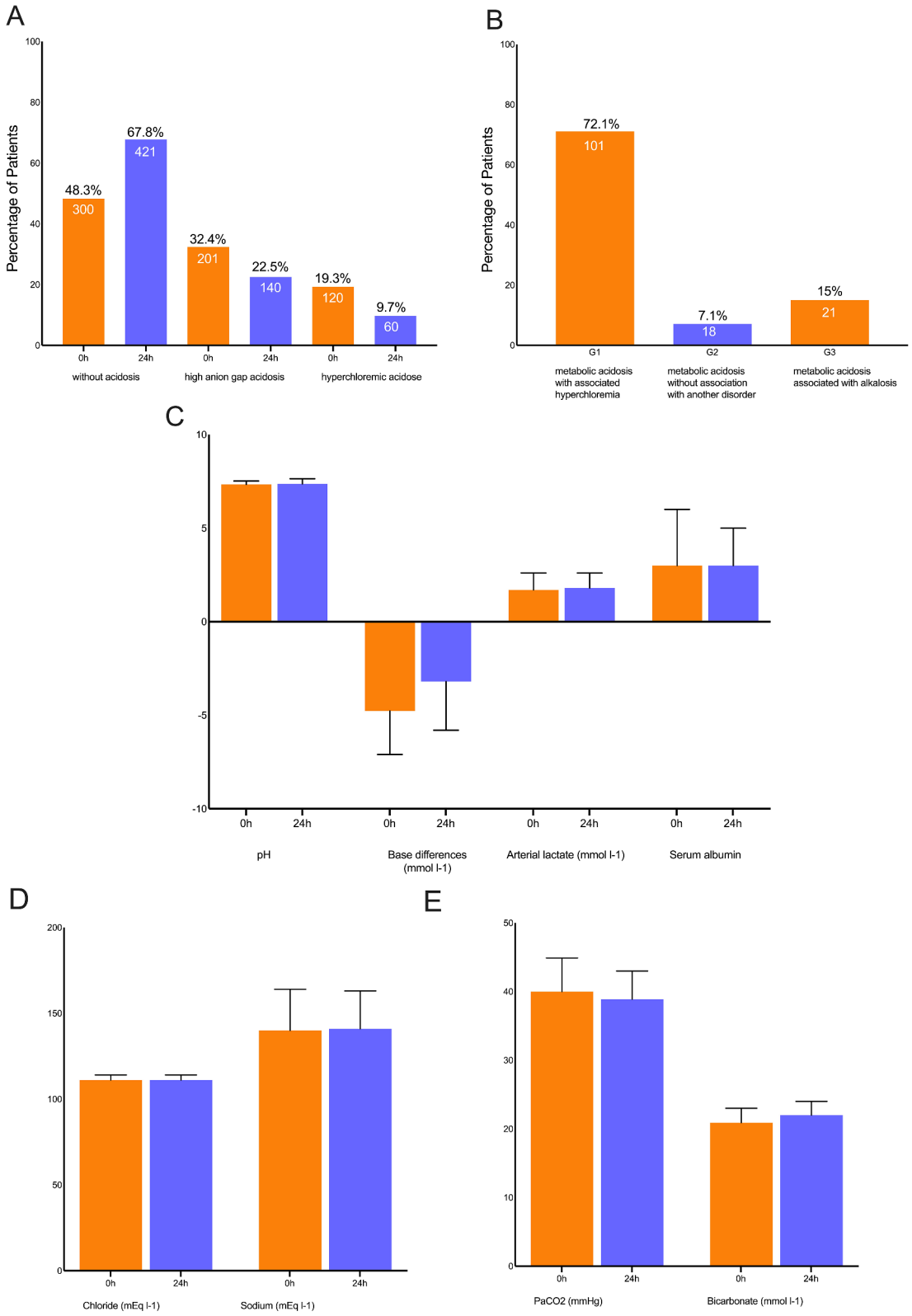

Fig. 4 (**A**) -Represents the percentage of patients in each group in the study timepoints 0 h and time 24 h. (**B**) -Represents patient Subgroups based on the delta-AG/delta-Bic sub-division. (**C**)- Represents p*H*, base differences, arterial lactate, and serum albumin levels at admission (0 h) and after 24 h (24 h). (**D**)-Represents the levels of chloride and sodium in mEq/L at admission and after 24 h, showing little change.(**E**)- the PCO_2 and bicarbonate levels in mmHg and mmol/L respectively, measured at admission and after 24 h

Table 3 Characteristics of intraoperative care until 24 h of ICU admission for patients with high anion gap only

Variables	Metabolic acidosis without associated disorder (*n* = 18)	Associated hyperchloremic acidosis (*n* = 101)	Associated metabolic alkalosis (*n* = 21)	Total (*n* = 140)
Intraoperative				
Number of Intraoperative Blood Transfusion, *n* (%)	4.5 (25.0)	31 (30.9)	4 (21.1)	40 (28.7)
Total intraoperative 0.9% saline solution (ml)	1250.0 (750.0- 2250.0)	3000.0 (1500.0- 4500.0)*	2250.0 (2000.0- 3000.0)	3000.0 (1500.0- 4000.0)
Total ringer lactate received intraoperatively (ml)	2500.0 (1625.0- 5500.0)	2000.0 (1000.0- 3000.0)	1500.0 (1000.0- 3250.0)	2000.0 (1000.0- 3250.0)
Total colloids (3rd generation) received intraoperatively (ml)	750.0 (500.0-1250.0)	500.0 (500.0-1000.0)	500.0 (250.0-500.0)	500.0 (500.0-1000.0)
Surgical time (hours)	295.0 (210.0- 360.0)	296.5 (240–375)	290 (180.0- 360.0)	260 (225.0- 298.25)
24 h after ICU Admission				
MV Requirement	9 (50)	38 (38) *	14 (66.7)	61 (43.9)
*p*H	7.29 (7.23–7.33)	7.29 (7.25–7.31)	7.28 (7.21–7.32)	7.29 (7.25–7.32)
Base differences (mmol l^{-1})	-6.3(-9.0- -4.5)	-7.8(-10.9- -5.1)	-4.4(-9.5- -3.25)	-7.0(-10.1- -4.5)
$PaCO_2$ (mmHg)	43.7 ± 6.9	38.5 ± 7.7*	44.7 ± 7.9	40.3 ± 7.4
Serum sodium	143.2 ± 6.7	140.9 ± 3.9	143.6 ± 6.6	141.6 ± 4.7
Serum albumin	2.5 ± 0.5	2.7 ± 0.6	2.6 ± 0.7	2.6 ± 0.6
Arterial lactate (mmol l^{-1})	2.3 (1.8–3.9)	2.0 (1.35–3.05)	2.2(1.15–3.32)	2.15 (1.4–3.1)
Delta Anion gap/ Delta HCO_3^-	1.26 (1.1–1.4)	0.36 (0.19–0.6)*	2.3 (1.8–4.2)*	0.55 (0.25–1.1)
Corrected AG	17.7 (14.6–19.8)	13.5 (12.9–15.2) *	17.7 (15.8–26.6)	13.0 (12.0-15.2)
Chloride (mEq l^{-1})	111.1 ± 7.1	113.1 ± 4.6	106.3 ± 8.1*	111.8 ± 5.8

Legend n=number of individuals in groups

*represents Bonferroni correction P<0.05 different from the group without associated disorder

Values in parentheses represent median (25-75 percentile)

AG represents anion gap; mL=milliliters; mmol l-1= millimol per liter; MV = mechanical ventilation; AG = anion gap

Table 4 Main complications and their correlation with delta-AG/delta-Bic classification

Complications	Metabolic acidosis without associated disorder (*n* = 18)	Associated hyperchloremic acidosis (*n* = 101)	Metabolic alkalosis associated with acidosis (*n* = 21)	Total (*n* = 140)	*P*-value
Sum of Associated Complications	17 (94.4)	75 (74.3)	13 (61.9)	105 (75)	0.021
Cardiovascular, *n* (%)	17 (94.4) *	60 (59.4)	9 (42.9)	86 (61.4)	**0.001**
Neurological, *n* (%)	6 (33.3)	20 (19.8)	5 (23.8)	16 (22.1)	0.522
Respiratory, *n* (%)	5 (29.4)	22 (21.8)	8 (38.1)	35 (25.2)	0.457
Renal, *n* (%)	8 (41.2)	30 (29.7)	4 (19)	41 (29.5)	0.138
Coagulation, *n* (%)	5 (27.8)	13 (12.9)	2 (9.5)	20 (14.3)	0.118
Infection, *n* (%)	8 (41.2)	40 (39.6)	11 (52.4)	58 (41.7)	0.444
ICU mortality, *n* (%)	8 (44.4) *	18 (17.8)	4 (19.0)	30 (21.4)	**0.038**
Hospital mortality, *n* (%)	8 (44.4)	27 (26.7)	7 (33.3)	42 (30.0)	0.299
ICU time (days), *n*	5.0 (3–8)	5.0 (2–10)	4.0 (1.75–1.25)	4.0 (2–7)	0.748
Mechanical ventilation time (days)	1.5 (0–3)	0.0 (0.0–5.0)	2.0 (0-5.5)	0.0 (0.0-3.30)	0.554
Hospital time (days)	16 (7.75–22.25)	17 (10-32.5)	16.5 (8.5–22.5)	15 (8–27)	0.527

Legend n=number of individuals in groups

*represents Bonferroni correction P<0.05 different from the other groups; Values in parentheses represent median (25-75 percentile)

AG represents anion gap; ICU = Intensive Care Unit. Each patient could have more than 1 complication

presenting with a combination of hyperchloremia or alkalosis.

Our findings are consistent with those observed in our prior study and other investigations conducted on high-risk surgical and critically ill patients [1, 2, 4, 5, 16]. Over half of the patients experienced postoperative acidosis, with the most prevalent type being MA characterized by an elevated anion gap. Metabolic acidosis has been identified as a contributing risk factor for unfavourable outcomes in major surgical procedures [1, 2, 5], particularly those involving the gastrointestinal tract, which was the predominant occurrence of metabolic acidosis in our

analysis. The presence of high AG, in our study, most discriminates the correlation with survival of patients. In our study, the elevated anion gap emerges as the primary discriminator in relation to patient survival. It is noteworthy that specific factors associated with gastrointestinal tract surgeries, including the administration of substantial volumes of saline solution, accumulation of lactate, and depletion of bicarbonate through surgical drainage, are likely contributors to the heightened occurrence of metabolic acidosis observed within this distinct patient subgroup [36].

The presence of metabolic acidosis, whether characterized by elevated levels of chloride (hyperchloremia) or indicated by an increased AG, has been associated with increased morbidity and mortality among surgical and critically ill patients [1, 2, 5]. The simple differentiation between these two types of acidosis has demonstrated prognostic significance and serves as a risk indicator for the development of organ dysfunctions, such as acute kidney injury, across multiple studies [2–4, 12, 14, 16, 21]. Additionally, the initial computation of serum AG within ICU patients is proposed as a sensitive and specific tool for predicting outcomes [16]. Evidence indicates that patients presenting with elevated AG values exhibit a greater frequency of hospital admissions, heightened rates of ICU admission, and augmented severity of illness, independent of concurrent electrolyte abnormalities [37]. However, the simple assessment of acidosis by AG calculation has its limitations [38, 39]. To sustain anionic equilibrium, diverse compensatory mechanisms take place, encompassing the exchange, movement, or transformation of anions, often in response to changes in external conditions or internal factors. Therefore, most of the time metabolic acidosis is accompanied by mixed disorders [23, 25]. In patients with type two diabetes mellitus presenting with metabolic acidosis, the calculation of delta-AG/delta-Bic proved useful in discriminating associated disorders and their associations with clinical outcome, however, it is crucial to note that this diagnostic tool actually is subject to the influence of many factors and should be used only very cautiously and then only as one piece of information among many [18, 40]. The delta-AG/delta-Bic proved to be a feasible tool to discriminated mixed acidosis disturbance in trauma patients [41]. To our knowledge, our study represents the first use of this clinical tool in a patient with high surgical risk.

In the current investigation, upon stratifying subjects according to the delta-AG/delta-Bic ratio, it became apparent that ratios below 1.0 (indicative of associated hyperchloremia) were associated with the least pronounced deviations from baseline values. This observation could potentially be linked to increased volume replacement and a decreased occurrence of inadequate tissue perfusion. Importantly, mortality within this study displayed a noteworthy correlation with the Delta-AG/delta-Bic ratio. It is of significance that patients presenting MA alongside an elevated anion gap, yet without concurrent associated disorders, exhibited a heightened frequency of mortality within the ICU setting when compared to patients with accompanying disorders. One plausible explanation for this observation is the existence of a subgroup of patients with sluggish compensatory mechanisms that may not become apparent within the initial 24 h following surgery. However, further preclinical investigations are required to delve into this potential pathophysiological link and clinical investigations to better characterization of a subtype of patients with slow compensatory mechanism. Additionally, another contributing factor is the variation in treatment administered to the collective. This discrepancy could be attributed to the notion that associated disorders (hyperchloremia or metabolic alkalosis) might be instigated by unintentional intraoperative interventions, such as excessive saline solution administration [12] or blood transfusion [9, 13]. As a result, the correction of these imbalances during the hospitalization period occurs more swiftly and effectively, thereby yielding improved outcomes for these patients.

In relation to complications occurring within the ICU, cardiovascular complications were more prominent among patients with MA in the absence of associated disorders, in comparison to the other groups. Prior research has previously documented that metabolic acidosis assumes the role of a distinctive cardiovascular risk factor among individuals with chronic kidney disease, primarily due to its detrimental impact on the cardiovascular system [42]. This includes factors such as inflammation, which contributes to endothelial dysfunction, as well as the activation of the renin-angiotensin-aldosterone system [42]. In addition, acidosis influences reducing cardiac contractility and reduces the cardiac response to beta-adrenergic stimuli [8].

In the context of surgical and critically ill patients, hyperchloremic MA has been established as being linked to the development of acute kidney injury, as demonstrated in a previous study [3, 37] Consequently, we initially anticipated a stronger association of this outcome within the hyperchloremic MA group. However, our study revealed a higher incidence of kidney injury among patients with metabolic acidosis featuring an elevated AG but not accompanied by associated disorders. Intriguingly, the correlation between ICU-related kidney injury and a Delta-AG/delta-Bic ratio less than 1 was not evident. This lack of correlation may potentially be attributed to the intensive care provided during the initial 24 h [16] and later onset of this organ dysfunction [43]. Further studies with longer observation time are needed to assess this issue.

Study strength and limitations

The study's outcomes require consideration within the context of inherent limitations. First, the study's observational nature lacked a predetermined intraoperative treatment protocol. Second, our definition of metabolic acidosis may not be as sensitive to detect patients in the early stages of acid-base disturbance. Further, the limited postoperative observation duration hindered comprehensive assessment of certain organ dysfunctions, as acute renal failure. Additionally, the study did not explore acidosis's potential impact on adjunct therapeutic modalities, including vasopressors. Finally, the application of the delta-AG/delta-Bic ratio is considered a feasible tool in assessing acid-base disorders; however, it is crucial to exercise caution as acid-base metabolism is complex, and the use of delta-AG/delta-Bic should be approached judiciously, recognizing its limitations in the accurate diagnosis of mixed acid-base disorders within the realm of scientific understanding. It is advised that the delta-AG/delta-Bic ratio not be utilized in isolation but rather in conjunction with additional clinical and laboratory data for the diagnosis of conditions entailing mixed metabolic acidosis. Further research is warranted to ascertain the efficacy of this formula when applied singularly in the context of surgical patients. These limitations underscore the need for cautious interpretation and underscore prospects for future research.

Conclusion

In the postoperative time, patients with MA and no mixed disorders present higher ICU mortality and higher postoperative cardiovascular complications when compared with patients with combined hyperchloremia or alkalosis. The Delta-AG/delta-Bic ratio emerges as a promising and practical tool for the assessment of substantial clinical outcomes within this specific patient cohort.

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Author contributions

Conceptualization, JS, PM and RET; methodology, JS, PM, RETand TC; validation, JS, LM ; formal analysis, RET and TC.; investigation, BCS, AMR, FBH, and CPA; data curation, BCS, AMR, FBH, and CPA.; writing—original draft preparation, RET and TC.; writing—review and editing, LM and JS; supervision, LM and JS.; project administration, RET. All authors have read and agreed to the published version of the manuscript.

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Data availability

All patient-related work data or statistical analysis is available for the next 10 years. The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study received approval from the Ethics Committee for the Analysis of Research Projects at Hospital das Clínicas (HC-FMUSP), Hospital do Servidor Público Estadual (HSPE) - IAMSPE/SP, and Hospital do Câncer de Barretos. The approval is documented under number CAAE – 28520820.1.0000.0068 and the research adhered to the principles outlined in the Helsinki Declaration and followed the STROBE guidelines. Additionally, the study is registered in the Brazilian trial register (REBEC, Trial-ID U1111-1296-3626). Every participant in the study gave informed consent. In cases where individuals were unable to provide consent, approval was sought from a legal representative or a family member.

Consent for publication

Not applicable.

Disclosures

Not applicable

Competing interests

The authors declare no competing interests.

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References

1. Silva JM, Oliveira AM, Marti YN, Gonzaga TB, Ferreira AMP, Maia V, Rezend E. Outcome of surgical patients who present acidosis postoperatively. Crit Care. 2011;15(2):P64.
2. Silva JM Jr., Ribas Rosa de Oliveira, Mendes Nogueira AM, Vianna FA, Amendola PM, Carvalho Carmona CP, LM SM MJ. Metabolic Acidosis Assessment in High-Risk surgeries: Prognostic Importance. Anesth Analg. 2016;123(5):1163–71.
3. Oh TK, Do SH, Jeon YT, Kim J, Na HS, Hwang JW. Association of Preoperative Serum Chloride levels with mortality and morbidity after noncardiac surgery: a retrospective cohort study. Anesth Analg. 2019;129(6):1494–501.
4. Oh TK, Song IA, Kim SJ, Lim SY, Do SH, Hwang JW, Kim J, Jeon YT. Hyperchloremia and postoperative acute kidney injury: a retrospective analysis of data from the surgical intensive care unit. Crit Care (London England). 2018;22(1):277.
5. McCluskey SA, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg. 2013;117(2):412–21.
6. Grottke O, Fries D, Nascimento B. Perioperatively acquired disorders of coagulation. Curr Opin Anaesthesiol. 2015;28(2):113–22.
7. Refsum HE, Opdahl H, Leraand S. Effect of extreme metabolic acidosis on oxygen delivery capacity of the blood–an in vitro investigation of changes in the oxyhemoglobin dissociation curve in blood with pH values of approximately 6.30. Crit Care Med. 1997;25(9):1497–501.

8. Schotola H, Toischer K, Popov AF, Renner A, Schmitto JD, Gummert J, Quintel M, Bauer M, Maier LS, Sossalla S. Mild metabolic acidosis impairs the β-adrenergic response in isolated human failing myocardium. Crit Care (London England). 2012;16(4):R153.
9. Salameh AI, Ruffin VA, Boron WF. Effects of metabolic acidosis on intracellular pH responses in multiple cell types. Am J Physiol Regul Integr Comp Physiol. 2014;307(12):R1413–1427.
10. Thiele RH, Theodore DJ, Gan TJ. Outcome of Organ Dysfunction in the Perioperative Period. Anesth Analg. 2021;133(2):393–405.
11. Kraut JA, Madias NE. Lactic acidosis. N Engl J Med. 2014;371(24):2309–19.
12. Astapenko D, Navratil P, Pouska J, Cerny V. Clinical physiology aspects of chloremia in fluid therapy: a systematic review. Perioperative Med. 2020;9(1):40.
13. Emmett M. Metabolic alkalosis: a brief pathophysiologic review. Clin J Am Soc Nephrol. 2020;15(12):1848–56.
14. Waters JH, Miller LR, Clack S, Kim JV. Cause of metabolic acidosis in prolonged surgery. Crit Care Med. 1999;27(10):2142–6.
15. Kraut JA, Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. Nat Rev Nephrol. 2012;8(10):589–601.
16. Zampieri FG, Park M, Ranzani OT, Maciel AT, de Souza HP, da, Cruz Neto LM, da Silva FP. Anion gap corrected for albumin, phosphate and lactate is a good predictor of strong ion gap in critically ill patients: a nested cohort study. *Rev Bras Ter Intensiva* 2013, 25(3):205–211.
17. Wrenn K. The delta (delta) gap: an approach to mixed acid-base disorders. Ann Emerg Med. 1990;19(11):1310–3.
18. Rastegar A. Use of the DeltaAG/DeltaHCO3- ratio in the diagnosis of mixed acid-base disorders. J Am Soc Nephrol. 2007;18(9):2429–31.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of Observational studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147(8):573–7.
20. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–4.
21. Gurgel ST, do Nascimento P Jr. Maintaining tissue perfusion in high-risk surgical patients: a systematic review of randomized clinical trials. Anesth Analg. 2011;112(6):1384–91.
22. Standards of medical care in diabetes–2013. Diabetes Care. 2013;36(Suppl 1):S11–66.
23. Kraut JA, Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. Nat Rev Nephrol. 2010;6(5):274–85.
24. Wang R, Li J, Chen H, Xiao Z, Xu R, Hu Y, Chen S, Wang X, Zheng S. Preoperative albumin corrected anion gap is associated with in-hospital and long-term mortality in patients undergoing coronary artery bypass grafting in a retrospective cohort study. J Thorac Disease. 2022;14(12):4894–903.
25. Vanmassenhove J, Lameire N. Approach to the patient presenting with metabolic acidosis. Acta Clin Belg. 2019;74(1):21–7.
26. Larkin BG, Zimmanck RJ. Interpreting arterial blood gases successfully. Aorn j. 2015;102(4):343–54. quiz 355 – 347.
27. Sellers D, Srinivas C, Djaiani G. Cardiovascular complications after non-cardiac surgery. Anaesthesia. 2018;73(Suppl 1):34–42.
28. Brazilian recommendations of mechanical ventilation 2013. Part 2. J Bras Pneumol. 2014;40(5):458–86.
29. Park JT. Postoperative acute kidney injury. Korean J Anesthesiol. 2017;70(3):258–66.
30. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–44.
31. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36(5):309–32.
32. Lobo SM, Rezende E, Knibel MF, Silva NB, Páramo JA, Nácul F, Mendes CL, Assunção M, Costa Filho RC, Grion CC, et al. Epidemiology and outcomes of non-cardiac surgical patients in Brazilian intensive care units. Rev Bras Ter Intensiva. 2008;20(4):376–84.
33. Lobo SMA, Salgado PF, Castillo VGT, Borim AA, Polachini CA, Palchetti JC, Brienzi SLA, de Oliveira GG. Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. Crit Care Med 2000, 28(10).
34. Curtin F, Schulz P. Multiple correlations and Bonferroni's correction. Biol Psychiatry. 1998;44(8):775–7.
35. Park E, Cho M, Ki CS. Correct use of repeated measures analysis of variance. Korean J Lab Med. 2009;29(1):1–9.
36. Park CM, Chun HK, Jeon K, Suh GY, Choi DW, Kim S. Factors related to postoperative metabolic acidosis following major abdominal surgery. ANZ J Surg. 2014;84(7–8):574–80.
37. Brenner BE. Clinical significance of the elevated anion gap. Am J Med. 1985;79(3):289–96.
38. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. Clin J Am Soc Nephrol. 2007;2(1):162–74.
39. Salem MM, Mujais SK. Gaps in the anion gap. Arch Intern Med. 1992;152(8):1625–9.
40. Adrogué HJ, Wilson H, Boyd AE 3rd, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med. 1982;307(26):1603–10.
41. Rudkin SE, Grogan TR, Treger RM. The Δ Anion Gap/Δ Bicarbonate Ratio in Early Lactic Acidosis: Time for Another Delta? *Kidney360* 2021, 2(1):20–25.
42. Collister D, Ferguson TW, Funk SE, Reaven NL, Mathur V, Tangri N. Metabolic acidosis and Cardiovascular Disease in CKD. Kidney Med. 2021;3(5):753–e761751.
43. Mo S, Bjelland TW, Nilsen TIL, Klepstad P. Acute kidney injury in intensive care patients: incidence, time course, and risk factors. Acta Anaesthesiol Scand. 2022;66(8):961–8.

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