Metabolic Acidosis Assessment in High-Risk Surgeries: Prognostic Importance

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BACKGROUND: Metabolic acidosis frequently is present in surgical patients; however, different types of metabolic acidosis (hyperlactatemia, hyperchloremia, and others) may have different relationships to perioperative outcomes. We hypothesized that in postoperative surgical patients, distinctive types of metabolic acidosis would correlate differently with the outcomes of high-risk surgeries.

METHODS: A prospective, multicenter observational study was performed in 3 different tertiary care hospitals. Patients who required postoperative admission to the intensive care unit (ICU) were included in this study. Patients with a short life expectancy (those with untreated cancer and limited treatment), hepatic failure, renal failure, or a diagnosis of diabetes were excluded. Patients were classified at ICU admission according to the presence and type of metabolic acidosis into 4 groups: those without acidosis, those with a base excess <−4 mmol/L and albumin-corrected anion gap ≤12 mmol/L (hyperchloremic), those with a base excess <−4 mmol/L and increased albumin-corrected anion gap >12 mmol/L, and those with a base excess <−4 mmol/L and hyperlactatemia >2 mmol/L. Furthermore, patients were reclassified 12 hours after admission to the ICU to verify the metabolic acidosis behavior and outcome differences among the groups.

RESULTS: The study included 618 patients. The incidence of acidosis at ICU admission was 59.1%; 23.9% presented with hyperchloremia, 21.3% with hyperlactatemia, 13.9% with increased anion gap, and 40.9% of the patients presented without metabolic acidosis. Patients whose metabolic acidosis persisted for 12 hours had an incidence of ICU complications rates in hyperlactatemia group of 68.8%, increased anion gap of 68.6%, hyperchloremic of 65.8%, and those without acidosis over 12 hours of 59.3%. A Cox regression model for postoperative 30-day mortality showed: in hyperlactatemic acidosis, hazard ratio (HR) = 1.74, 95% confidence interval (CI) = 1.02–2.96; increased anion gap acidosis, HR = 1.68, 95% CI = 0.85–3.81; hyperchloremic acidosis, HR = 1.47, 95% CI = 0.75–2.89, and 10.3% of 30-day mortality rate in patients without acidosis. An adjusted survival curve by Cox regression found a worse 30-day survival in the hyperlactatemic group compared with the other groups ($P = .03$). Furthermore, in multiple comparisons among groups, patients with hyperlactatemic acidosis were more likely to develop renal dysfunction ($P < .001$) up to the seventh day postoperatively.

CONCLUSIONS: We found that among patients with different types of acidosis, patients who developed hyperlactatemic metabolic acidosis postoperatively showed greater rates of renal dysfunction within 7 days and hyperlactatemic acidosis represented an independent factor on 30-day mortality in high-risk surgical patients. (Anesth Analg 2016;123:1163–71)

Metabolic acidosis frequently is present in postsurgical critically ill patients[1,2]; however, the clinical significance of postoperative metabolic acidosis is unclear. Although some studies have found an independent association between low pH or base excess and mortality rate,[3–5] others have not.[6]

In a 2006 retrospective study, Gunnerson et al[7] observed that critically ill patients with lactic acidosis had a greater rate of mortality than patients with hyperchloremic acidosis; however, mortality did not differ between patients with hyperchloremic acidosis and those without acidosis.

Recent data also have suggested the adverse effects of hyperchloremia.[8] A trial in surgical patients in 2001 randomized intravenous fluids in either a 9% saline solution or a balanced solution (Hartmann's solution and 6% hetastarch in balanced electrolyte and glucose), and found greater rates of hyperchloremic acidosis and reduced gastric mucosal perfusion in those who received 0.9% saline solution.[9] Other studies[10,11] also have reported greater rates of renal dysfunction with hyperchloremic solutions.

In contrast, in a double-blind randomized comparison of 9% saline solution with Ringer's lactate in patients undergoing aortic reconstruction surgery, researchers found greater rates of acidosis in the 9% saline solution group but found no difference in mortality or complications.[12]

To clarify the potential role of metabolic acidosis in high-risk postoperative patients, we assessed the incidence of metabolic acidosis in high-risk surgical patients. We

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hypothesized that different types of acidosis would have different relationships with postoperative complications and 30-day mortality.

METHODS

This observational multicenter study was approved by the Research Ethics Committee of the School of Medicine, University of São Paulo, the Ethics Committee for the Analysis of Research Projects of the Hospital das Clinicas, the Hospital do Servidor Público Estadual, and the Hospital do Câncer de Barretos. It was registered in the National System of Information on Ethics in Research Involving Humans (Opinion No. CAAE-0084.1.338.000-09). The participating hospitals have a total of 90 intensive care unit (ICU) beds, and the functional organization charts of all ICUs were similar in the referred hospitals.

Patients who had undergone high-risk surgeries and been admitted to the ICU between September 3, 2012, and December 3, 2013, were enrolled in this study. We modified the previously published criteria[13] to identify the high-risk surgeries and included patients with a requested ICU postoperative stay and at least one of the following clinical conditions: severe cardiorespiratory illness (coronary artery disease or some problem with the aorta, chronic obstructive pulmonary disease, or ischemic stroke), extensive surgery for carcinoma (esophagectomy, total gastrectomy, liver resection, pancreatectomy, colectomy, rectal resection, or cystectomy), a duration of surgery greater than 6 hours, or severe multiple trauma. Intraoperative criteria for high risk included acute massive blood loss (hematocrit <20%), circulatory shock (mean arterial blood pressure <60 mm Hg) requiring the use of vasopressors, or previously severe nutritional disorder. In addition, those aged >65 years with limited physiological reserve in at least 1 vital organ (liver, bilirubin above normal range; kidney, creatinine above normal range; heart, New York Heart Association II to IV; and lungs, dyspnea after walking on level ground).

We obtained signed informed consent from all patients. If the patient was unable to provide consent preoperatively, a responsible adult (legal representative) provided informed consent for the patient.

Patients were excluded from the study if their ICU length of stay was <24 hours, or if they had a short life expectancy (such as those with cancer without treatment perspective or treatment limitations, such as do not intubate and resuscitate). In addition, we excluded patients with liver failure (Child–Pugh class B or C), patients with renal insufficiency (50 mL/min creatinine clearance as assessed by the Cockcroft–Gault formula or prior hemodialysis), or those with a previous diagnosis of diabetes or 2 measured glucose levels of >126 mg/dL after 8 hours of fasting during the perioperative period.[14] We excluded patients in these last 2 groups because they may have developed metabolic acidosis from the underlying disease and not the surgical process. Moreover, greater rates of hyperlactatemia could still occur during liver failure because of the low lactate clearance.[15] Exclusion criteria were evaluated in all patients until 12 hours from ICU admission, except for patients with an ICU stay <24 hours, who were automatically excluded.

All patients underwent 2 blood sample collections, 1 at the time of admission to the ICU (D1) and the other 12 hours after admission (D2), to determine the levels of arterial blood gases, lactate, serum sodium, albumin, and chlorine. Upon admission to the ICU, pH and base difference results were used to divide patients into 2 groups—those with metabolic acidosis and those without. At the same time, patients with metabolic acidosis were classified further according to their lactate and albumin-corrected anion gap (AG) values into 3 groups: hyperlactatemic metabolic acidosis, metabolic acidosis with increased AG, and metabolic acidosis with normal AG (hyperchloremic).

According to the prespecified standardized protocol, patients with metabolic acidosis were defined as those with a base excess of arterial blood gas <−4.0 mmol/L.[1] Hyperlactatemia was diagnosed when serum lactate values exceeded 2.0 mmol/L.[16] The measurement of AG was corrected by albumin and was considered as elevated when values were >12 mmol/L.[17] To avoid the overlap among acidosis groups, the lactate values in the nonhyperlactatemia groups were ≤2.0 mmol/L. By definition, if a patient presented with increased AG and hyperlactatemia, then that patient was not classified as having hyperchloremic acidosis. If the patient had an increased AG and normal lactate values (≤2.0 mmol/L), then they were not classified as hyperlactatemic or hyperchloremic.

We used the AG to estimate the presence of unmeasured anions and considered a value of 12 mmol/L to be normal. We thus corrected the AG for abnormal albumin levels using the following equation[18] (taking 4.5 as the normal concentration of albumin in g/dL):

$$\text{Adjusted AG} = \text{Observed AG} + 2.5\left[4.5 - \text{Measured Albumin } (\text{g/dL})\right].$$

All patients were followed until hospital discharge or for 30 days after surgery, regardless of duration of hospital stay. The primary outcome of the study was 30-day postoperative mortality rate. Secondary outcomes included in-hospital mortality, and the incidence of postoperative ICU complications defined as follows. (1) Cardiovascular dysfunction—the need for vasoactive drugs for more than 1 hour despite a central venous pressure of 8.0 mm Hg and pulse pressure variation <13% and titrated to achieve a mean arterial blood pressure >60 mm Hg.[19,20] In any instance in which the monitoring of central venous pressure or pulse pressure variation was not used, fluid challenge with crystalloids was applied up to 1000 mL before any vasopressor drug was administered. (2) Respiratory dysfunction—Pao_2/fraction of inspired oxygen ratio <200 in patients with no previous cardiac disease or need for reintubation or difficulty removing the endotracheal tube during the postoperative period (defined by >1 failed spontaneous breathing trial). Trials were conducted once patients were judged as being ready for extubation. A spontaneous breathing test was performed with 7 cm H_2O pressure support and a positive end-expiratory pressure of 5 cm H_2O for at least 30 minutes. Success was defined as tidal volumes at least 6–8 mL/kg of the ideal body weight and a respiratory frequency below 25 breaths per minute. (3) Renal insufficiency—creatinine increase of 30% or urine output of less than 400 mL over

24 hours or the need for renal replacement therapy or renal Sepsis-Related Organ Failure Assessment (SOFA) score of 2 or greater.[21] Renal dysfunction was determined by a renal SOFA score >2 during the first 8 postoperative days. (4) Neurologic disorder—assessed by changes in the Richmond Agitation-Sedation Scale (RASS) score[22]: acute and fluctuating change in RASS over 24 hours, <>0 and psychomotor agitation was determined if the patient received a RASS score of 2+ or greater. (5) Coagulation dysfunction—30% drop in platelets with respect to preoperative values, and platelet count value below 100,000 μL^{-1}.[23] To minimize possible errors and differentiate chronic and acute postsurgical complications, a specially trained physician and nurse team evaluated all patients before and after surgery.

In addition, we assessed each patient for the presence of infection during his or her ICU stay, as well as the length of ICU and hospital stays. Infections were classified according to the locations of the infectious foci, etiologic agents, and severity. The characterization of foci and infectious agents were based on the criteria of the Centers for Disease Control and Prevention.[24]

All outcomes were analyzed by group classification during period D2, which determined the persistence of patients in each group after a 12-hour ICU stay, thus allowing the assessment of behavior associated with metabolic acidosis and of outcomes between groups.

In addition to acid–base tests, we also calculated the Simplified Acute Physiology Score (SAPS 3)[25] at the time of admission, and the clinical and laboratory variables during the perioperative period were used to calculate the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM).[26] The assessment of organ dysfunction was determined by use of the SOFA score.[21] The American Society of Anesthesiology physical status classification[27] was used to identify the severity of the patient's illness.

An initial pilot study[28] was used to estimate the sample size. In this pilot study, the mortality for the patients with acidosis was 15%, compared with 2% for the patients without acidosis. These data are in accordance with the mortality rate for surgical patients in the general population (~5%)[29] and in the high-risk population (15%).[30–33] Using a 1:1 ratio in accordance with the data from the pilot study and the minimal clinically significant difference between the groups, we calculated the required sample size to detect a 15% mortality rate in patients with acidosis and a 5% mortality rate in patients without acidosis. With a 95% confidence interval and 80% statistical power, it was determined that a sample size of at least 310 patients would be required (155 patients per group) to compare the mortality rates for 30 days (MedCalc 11.5.1; sampling: comparison of proportions).

Statistical Analysis

All data were entered into an electronic database (Microsoft Excel; Microsoft, Redmond, WA) and subsequently analyzed with the statistical programs SPSS Version 20.0 (IBM Corp., Armonk, NY) and MedCalc version 13.2.0 (MedCalc Software, Ostend, Belgium). Initially, we described the demographic, clinical, and physiological characteristics of the patients included in the study. Frequencies and percentages were calculated for the description of categorical variables. Quantitative variables were described by the use of measures of central and dispersion tendencies.

The characteristics of patients with metabolic acidosis were compared with those of patients without acidosis. Assumptions that variables were normally distributed were tested with the analysis of histograms by skewedness and kurtosis value and by the Shapiro–Wilk test. Continuous variables with asymmetric distributions were assessed using the Kruskal–Wallis test when comparing more than 2 variables and when comparing 2 variables Mann–Whitney *U* test was applied. When analysis of variance was used, the assumption of normality was assessed plotting standard residuals for each group. The χ^2 test was used to measure associations in categorical variables. The χ^2 test for linear trends was used for categorical variables ordered in some sense. This procedure assesses whether there was a trend in the proportions with the characteristic over the categories of the second factor.

For multiple comparisons of categorical variables, we used Log-linear analysis in a saturated model to verify the main effects and interactions from groups compared with centrals outcomes. This process allowed comparing the outcome in the highest order effect among acidosis groups. The goodness-of-fit test was used to assess model fit; this statistic was nonsignificant. All statistical tests were 2-tailed, and for multiples comparison, the nonmetabolic acidosis group was the reference. In addition, the level of significance was performed among groups of comparison and in pairwise combinations of independent group proportions. The Bonferroni correction set the significance cutoff *P* value; it was used to detect the time points at which the differences were significant in multiple comparisons.

Homogeneity between the groups with regard to age, SAPS 3, and POSSUM scores was assessed with analysis of variance. Statistical differences between the acidosis groups, nonacidosis group, and with respect to 30-day mortality rates postoperatively were assessed via the Log-linear analysis, as well as with respect to renal dysfunction until 8 days postoperatively.

We performed a Cox progressive and conditional regression model, applying stepwise selection with backward elimination to determine the risk of death, comparing patients who remained or did not remain in the metabolic acidosis groups after a 12-hour ICU stay.

Variables considered for Cox regression analysis were used if they exhibited a statistically significant association ($P < .05$) in univariate analysis or if they presented pairwise interaction possibilities (sex, age, and prognosis score SAPS 3). Afterward, variables with interactions were tested in the main regression model.

Centers were included in the regression model to verify any possible confounding effects of variability in the clinical practices of the 3 hospitals. *P* value and confidence intervals (CIs) of the groups in comparison with 30-day mortality were obtained from this regression model. Subsequently, estimates of survival after 30 days were calculated for the groups using the Kaplan–Meier curve adjusted by Cox regression, with comparisons made using Mantel Cox test for linear trends.

RESULTS

From September 2012 to December 2013, 2638 high-risk surgical patients were admitted to the ICU. Of these patients, 1839 were excluded from the study, with the main reason for exclusion being diabetes (Figure 1).

On admission to the ICU, 59.1% of the patients were diagnosed with metabolic acidosis, and 40.9% of the patients were classified as not having acidosis. Approximately 23.9% of the patients with acidosis were hyperchloremic, 21.3% were hyperlactatemic, and 13.9% had increased AG acidosis (Figure 2).

No significant differences were observed in the severity scores (SAPS 3, POSSUM, and American Society of Anesthesiologists), age, sex, and length of surgery between the groups (Table 1). The median (interquartile range) base difference in the patients with acidosis was −6.5 (−9.3 to −4.3) mmol/L vs −0.6 (−1.5 to 0.6) mmol/L in the patients without acidosis (Mann–Whitney *U* test, $P < .001$).

Patients with normal AG acidosis (hyperchloremic) received more 0.9% saline solution during the intraoperative period and exhibited greater chloride levels during the postoperative period. The amount of other types of fluids received did not differ between groups (Table 2).

More patients with persistent acidosis (67.8%) exhibited postoperative complications than did patients without acidosis (59.3%; χ^2 test, $P = .03$). The types of complications also differed between the different acidosis groups. Patients who had hyperlactatemia that persisted in the postoperative period had worse overall outcomes in terms of cardiovascular and renal dysfunction (Table 3). In Log-linear analysis, patients with hyperlactatemic acidosis were more likely to develop renal dysfunction in the first 7 days (higher-order effects, $P < .001$; Figure 3).

ICU and hospital mortality were both greater in individuals whose acidosis persisted 12 hours postsurgery. The ICU mortality rate in the hyperlactatemic group was 22.6% vs 15.7% in the increased AG group and 14.5% in the hyperchloremic group. Mortality in the nonacidosis group was 10.3% (χ^2 for trend test $P < .001$). Hospital mortality was also greater (χ^2 for trend test $P < .001$) in the individuals with persistent hyperlactatemia (30.1%) compared with other groups—increased AG (22.8%), hyperchloremia (17.1%), and nonacidosis (10.3%) during the postoperative period (Figure 4).

By the 30-day follow-up, 110 patients (17.8%) had died. The hyperlactatemic metabolic acidosis group had a mortality rate of 30.1%, the increased AG group had 24.3%, and the hyperchloremic acidosis group had 18.4%. The nonacidosis patients had a 10.3% rate of mortality. Log-linear analysis—interaction acidosis groups × 30 days' mortality rate likelihood ratio $\chi^2 = 15.59$, $P = .001$.

In patients who were still acidotic after 12 hours, multivariate Cox regression, adjusted for confounding factors, such as sex, age, SAPS 3 score, gastrointestinal and neurological surgeries, and the centers involved, identified an independent mortality effect in the group with hyperlactatemic

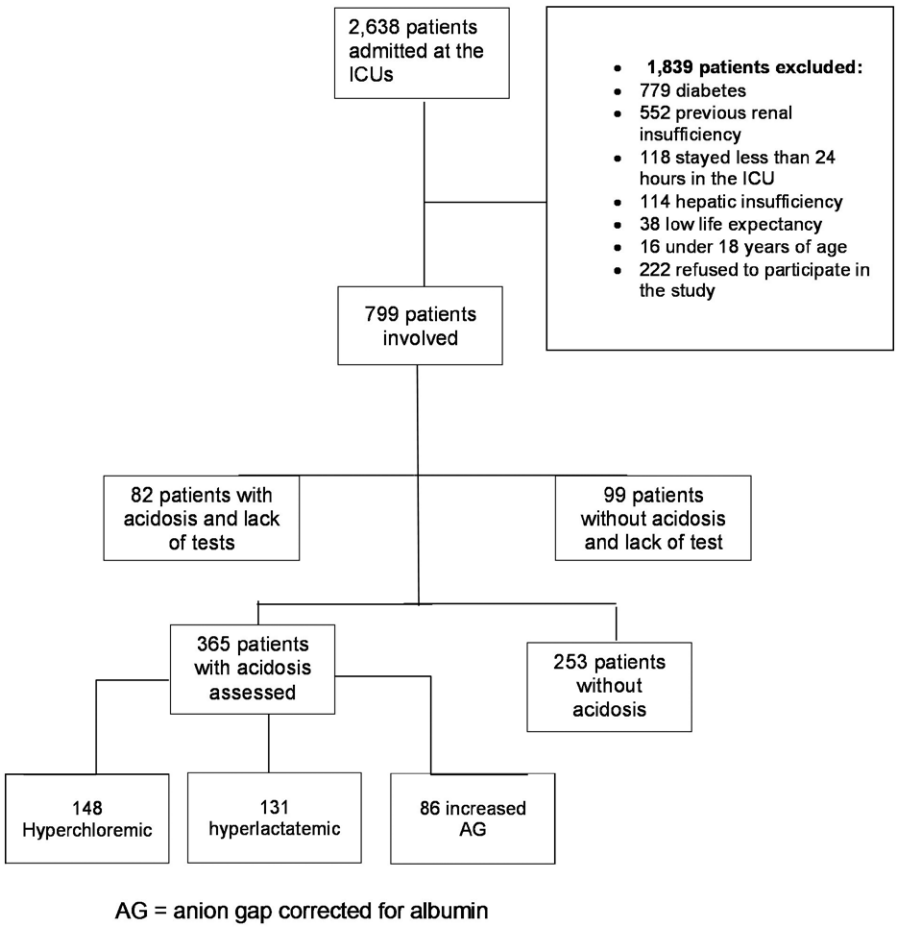

Figure 1. Distribution of patients with and without acidosis.

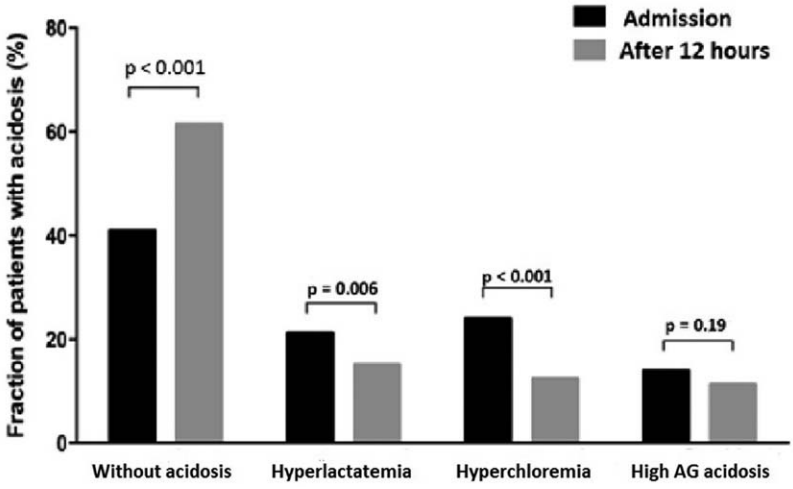

Figure 2. Occurrence in the different groups with and without metabolic acidosis at admission to the intensive care unit (ICU) and 12-h postoperative; AG, anion gap corrected for albumin. *P* value determined using χ^2 test.

Table 1. Baseline Characteristics of the Patients in Each Group

Variables	Without Metabolic Acidosis (n = 253)	Metabolic Acidosis			*P*
		Hyperchloremic (n = 148)	Hyperlactatemic (n = 131)	Increased AG (n = 86)	
Age (years)	59.0 ± 17.9	58.6 ± 18.3	62.1 ± 17.5	61.2 ± 16.6	.98
Sex: male (%)	51.2	58.8	41.2	47.7	.69
General anesthesia (%)	88.5	92.5	88.8	91	.89
White race (%)	73.6	79.7	85.5	71.6	.94
Surgeries (%)					.001
Gastrointestinal	19.8[a]	43.2[b]	47.2[b]	50.0[b]	
Vascular	16.5	12.8	11.0	6.0	
Orthopedic	12.9	11.5	15.0	11.9	
Neurologic	19.8[a]	10.8[a]	3.9[b]	6.0[a,b]	
Urologic	4.0	6.1	5.5	1.2	
Other	26.9	15.7	17.3	25	
SAPS 3	54.7 ± 14.6	54.9 ± 15.8	52.3 ± 14.5	52.6 ± 14.5	.66
POSSUM	36.3 ± 8.7	37.4 ± 9.6	36.6 ± 9.8	35.1 ± 7.4	.12
SOFA	4.0 (2.0–7.0)	4.0 (1.0–7.0)	3.0 (1.0–6.0)	3.0 (1.0–5.0)	.39
ASA (%)					.76
P1	11.1	15.5	10.7	16.3	
P2	47.0	52.0	56.5	53.5	
P3	32.4	20.9	28.2	27.9	
P4	9.5	11.5	4.6	11.5	

For values in percentages, χ^2 test was used to compare groups; values in brackets represent the median (25–75 interquartile range), in these variables, the Kruskal–Wallis test was used to compare groups; values shown as median ± SD, the analysis of variance test was used to compare groups.

Abbreviations: AG, anion gap corrected for albumin; ASA, American Society of Anesthesiologists; n, number of individuals in the groups; POSSUM, Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity; SAPS 3, Simplified Acute Physiology Score; SOFA, sepsis-related organ failure assessment.

[a,b]Each superscript letter indicates Bonferroni correction about *P* value of a subcategory groups whose proportions column does not differ significantly from each other in level .01. If the same superscript letter is present, it is not different statically, by other hand, if the superscript letter is different, the subcategory groups are different statistically.

metabolic acidosis (*P* = .029, hazard ratio [HR] 1.7, 95% CI 1.02–2.97) compared with the group without acidosis after the 30-day follow-up period; however, results obtained in patients with hyperchloremic metabolic acidosis (*P* = .380, HR 1.47, 95% CI 0.75–2.90) and in those with an increased AG (*P* = .157, HR 1.68, 95% CI 0.85–3.32) were not statistically significant in Cox regression model. In addition, no substantive interaction with SAPS 3 was observed, and the proportional hazards assumption was satisfied (Table 4).

We also used an adjusted survival curve by Cox regression to assess the trend in the 30-day follow-up among the groups; it showed a worse 30-day survival in hyperlactatemic group compared with the other groups (*P* = .03; Figure 5).

DISCUSSION

This study showed that surgical patients exhibiting different types of postoperative acidosis had different morbidity and 30-day mortality rates and that patients with persistent hyperlactatemic metabolic acidosis had worse outcomes than those with other forms of acidosis.

Previous studies that assessed the relationship between metabolic acidosis and outcomes in critically ill patients have focused on specific types of acidosis, for example, lactate acidosis,[34,35] or the severity of the acidosis.[3,36,37] Some studies[38], however, have raised the question as to whether acidosis is a marker or cause of postoperative complications.

Table 2. Characteristics of the Patients in Each Group During the Intraoperative Period and at ICU Admission

Variables	Without Metabolic Acidosis (n = 253)	Metabolic Acidosis			*P*
		Hyperchloremic (n = 148)	Hyperlactatemic (n = 131)	Increased AG (n = 86)	
Number of intraoperative blood transfusion (%)	20.2	28.4	25.2	16.3	.44
Concentrated red blood cells	2.3 ± 1.4	2.5 ± 1.0	2.0 ± 1.2	2.1 ± 1.1	.75
Total intraoperative 0.9% saline solution (mL)	1500.0 (1000.0–3000.0)[a]	3000.0 (2000.0–4000.0)[b]	2250.0 (1250.0–4000.0)[a,b]	2000.0 (1500.0–3000.0)[a]	<.001
Total Ringer lactate received during the intraoperative period (mL)	2000.0 (1000.0–3500.0)	2000.0 (1000.0–3500.0)	1500.0 (1000.0–3000.0)	1500.0 (1000.0–2250.0)	.24
Total colloids (third generation) received during the intraoperative period (mL)	500.0 (500.0–625.0)	500.0 (500.0–1000.0)	750.0 (500.0–1000.0)	500.0 (500.0–500.0)	.05
Surgical time (h)	4.0 (3.0–5.5)	4.5 (3.4–6.0)	5.0 (3.0–6.0)	4.5 (3.0–5.5)	.08
ICU admission					
Requiring mechanical ventilator (%)	43.3	36.4	40.0	33.3	.14
pH	7.37±0.1[a]	7.29±0.1[b]	7.28±0.1[b]	7.31±0.1[b]	.004
Bases differences (mmol/L)	−1.4(−2.7 to 0.12)[a]	−5.8(−7.5 to −4.8)[b]	−7.8(−10.9 to −5.6)[b]	−6.9(−9.30 to −5.3)[b]	<.001
Pco_2 (mm Hg)	41.3 ± 8.4	41.6 ± 8.4	39.2 ± 7.4	39.0 ± 8.3	.07
Serum sodium	139.9 ± 4.9	139.6 ± 3.6	140.6 ± 4.6	140.0 ± 3.9	.06
Serum albumin	2.9 ± 0.6	2.9 ± 0.7	2.7 ± 0.6	2.8 ± 0.6	.13
Arterial lactate (mmol/L)	1.9 (1.2–2.3)[a]	1.3 (1.0–1.9)[a]	2.8 (2.3–4.3)[b]	1.45 (1.0–1.7)[a]	<.001
AG (mEq/L)	11.9 ± 5.4[a]	11.4 ± 5.0[a]	13.2 ± 5.6[b]	13.2 ± 5.6[b]	<.001
Chlorine (mEq/L)	109.0 ± 5.2	115.0 ± 5.7[b]	110.9 ± 4.9[a]	110.6 ± 4.5[a]	<.001

For values in percentages, the χ^2 test was used for trend to compare groups; values in brackets represent the median (25–75 interquartile range), in these variables, the Kruskal–Wallis test was used to compare groups; values represent median ± SD, the analysis of variance test was used to compare groups.

Abbreviations: AG, anion gap corrected for albumin; ICU, intensive care unit; n, number of individuals in the groups.

[a,b]Each superscript letter indicates Bonferroni correction about *P* value of a subcategory groups whose proportions column does not differ significantly from each other in level .01. If the same superscript letter is present, it is not different statically, by other hand, if the superscript letter is different, the subcategory groups are different statistically.

Table 3. Clinical Evolution During ICU Hospitalization of Patients Who Exhibited Acidosis After 12 Postoperative Hours

Variables	Without Metabolic Acidosis (n = 379)	Metabolic Acidosis (n = 239)			*P*
		Hyperchloremic (n = 76)	Hyperlactatemic (n = 93)	Increased AG (n = 70)	
Total complications in the ICU (%)	59.3	65.8	68.8	68.6	.032
Circulatory shock in the ICU (%)	43.1[a]	47.4[a,b]	57[b]	50[a,b]	.04
Acute renal injury (%)	11.9[a]	19.7[a,b]	34.4[b]	31.4[b]	<.001
Altered coagulation (%)	10.8	11.8	12.9	7.1	.83
Neurologic changes (%)	26.5	30.3	18.3	15.7	.04
Acute respiratory injury (%)	21.2	26.3	21.5	18.8	.91
Infection in the ICU (%)	31.2	27.6	43	34.3	.50
ICU days	3 (2–6)	4 (2–8.5)	4 (2–8.25)	4 (2–10)	.08
Hospital days	13 (7–26)	14.5 (10–22)	18 (8–32.5)	16 (10–29)	.17

For values in percentages, the χ^2 test was used for trend to compare groups; values in brackets represent the median (25–75 interquartile range), in these variables, the Kruskal–Wallis test was used to compare groups.

Abbreviations: AG, anion gap corrected for albumin; ICU, intensive care unit; n, number of individuals in the groups.

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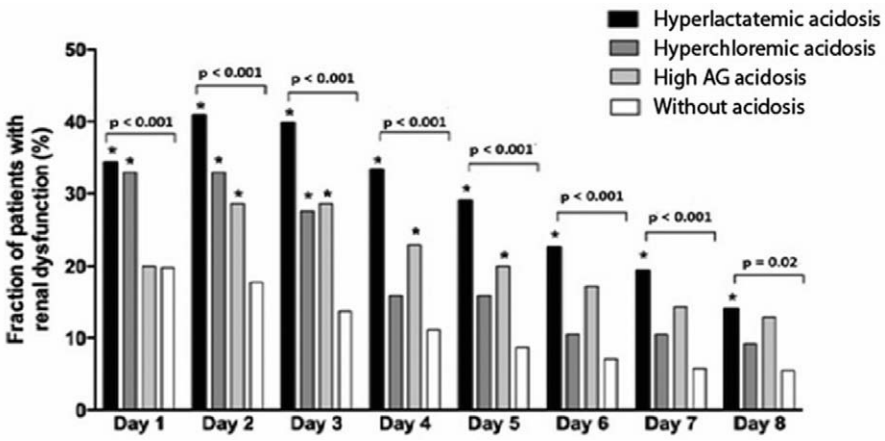

Figure 3. Percentage of renal dysfunction in the different groups with and without metabolic acidosis at admission to the intensive care unit (ICU) and up to the eighth postoperative day. *Represents Bonferroni correction for significance cutoff at $P < .01$ in comparison with the groups without acidosis. The interactions among groups and renal dysfunction on each day were verified by Log-linear analysis.

Evidence suggests that acidosis may interfere with hemodynamics[39] and innate immunity.[40] Research also suggests that different types of acidosis are associated with different clinical consequences.[41] Although observational studies cannot show a causal relationship, our study indicates that different types of metabolic acidosis in high-risk surgical patients are associated with different mortality and complication rates.

If the severity of metabolic acidosis (characterized by base deficit) is the primary determinant of perioperative outcome, the type of metabolic acidosis should not play a significant role. However, we found that the type of acidosis has an independent effect on the outcomes of high-risk surgical patients.

In comparison with the other etiologies of metabolic acidosis, we found that hyperlactatemic acidosis resulted in the greatest 30-day and hospital mortality rates, a finding that is not surprising as lactic acidosis has been associated with high mortality rates in critically ill patients.[16,32,34,42] The relevance of high perioperative lactate levels, however, may differ between surgical patients and other types of critically ill patients.[43] During surgery, cellular oxygen consumption may be lower,[44] and liver clearance may be reduced.[43] Thus, in the immediate postoperative period, serum lactate levels may not represent the actual clinical conditions of surgical patients. Our study demonstrates that patients with persistent hyperlactatemic acidosis after surgery also have poorer outcomes when compared with patients with other types of acidosis.

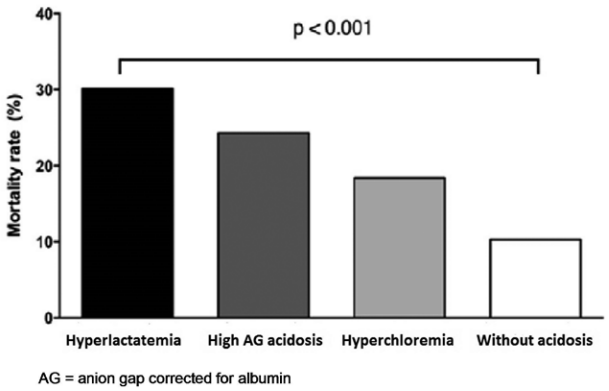

Figure 4. Occurrence of hospital mortality in the different groups with and without metabolic acidosis. *P* value determined via a χ^2 test for trend.

Although recent evidence suggests that hyperchloremic acidosis also may adversely affect outcomes,[45,46] our study found no effect of hyperchloremic acidosis on mortality. This finding is consistent with that of others[47] and suggests that the clinical relevance of hyperchloremic acidosis requires further study.

Our study has some limitations. Because of the observational design, we were unable to establish a causal relationship between acidosis and outcomes. Another limitation with our study was the exclusion of diabetic patients, because they are frequently subjected to high-risk surgeries. These patients were excluded from the study because lactate levels in diabetics correlate with glucose levels.[48] This relationship raises the possibility that lactic acidosis in diabetic patients may be because of either altered glucose metabolism or hypoperfusion. The ability of epinephrine to stimulate muscle Na^+/K^+ pumps may play an enhanced role in diabetic patients, because stress and insulin deficiency enhance the production of counter-regulatory adrenergic hormones, including epinephrine.[49] We chose to exclude diabetic patients from the study because of this alternative

Table 4. Cox Regression Model for 30-Day Mortality

				95.0% CI for HR	
Variables		***P***	**HR**	**Lower**	**Upper**
Step 1	Age (per year)	.893	1.001	0.987	1.015
	Male gender	.072	1.581	0.960	2.603
	SAPS 3 (per unit)	.000	1.039	1.021	1.057
	Gastrointestinal surgery	.126	0.483	0.190	1.226
	Neurologic surgery	.634	0.797	0.314	2.024
	Center 1	.175	0.523	0.205	1.334
	Center 2	.457	2.224	0.270	18.299
	Center 3	.280	1.531	0.707	3.314
		Groups			
	Hyperlactatemic	.021	1.740	1.113	2.740
	Increased AG	.155	1.531	0.800	3.548
	Hyperchloremic	.366	1.399	0.676	2.895
Step 2	SAPS 3 (per unit)	.000	1.039	1.022	1.057
		Groups			
	Hyperlactatemic	.029	1.739	1.021	2.975
	Increased AG	.157	1.684	0.851	3.321
	Hyperchloremic	.380	1.471	0.747	2.901
Step 3	SAPS 3 (per unit)	.000	1.058	1.041	1.076
		Groups			
	Hyperlactatemic	.017	1.740	1.470	1.973
	SAPS 3 by hyperlactatemic	.051	0.970	0.941	1.001

Steps, represented each time that a predictor was added to the equation; SAPS 3 by hyperlactatemic, interaction term; Step 1—a removal test was made of the least useful predictor if $P > .05$. As such the regression equation was constantly being reassessed to see whether any redundant predictors could be removed; Step 2—the contribution of the remaining predictors was then reassessed; Step 3—the contribution of the interaction term in remaining predictors. Test of proportional-hazards assumption final model was $\chi^2 = 0.19$, $P = .979$.

Abbreviations: AG, anion gap corrected for albumin; CI, confidence interval; HR, hazard ratio; SAPS 3, Simplified Acute Physiology Score.

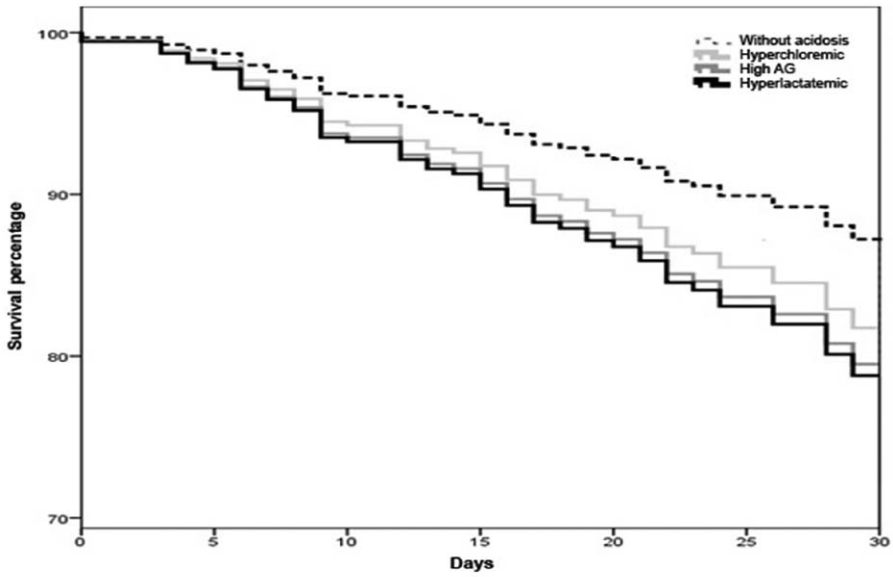

Figure 5. Survival curves of the groups until 30 days.

mechanism for lactic acidosis beyond tissue hypoperfusion. We also excluded patients with short ICU stays and low life expectancies (such as those with cancer without treatment perspective) because their outcomes could not be measured properly. Moreover, we excluded those with Child–Pugh class B or C cirrhosis and those with creatinine clearance <50 mL/min because they may have developed metabolic acidosis from the underlying disease and not because of the surgery. Because of these exclusions, our data may not be generalizable to all patient groups.

In addition, we did not classify acidosis using stronger ion definitions; however, several studies[7,50,51] have reported good correlations between the model of AG adjusted for albumin and other models for the characterization of metabolic acidosis, apart from the fact that the model adjusted for albumin is easier to use. Finally, procedures conducted during the postoperative period and the possible influences on patient outcomes were not assessed. This effect was minimized, however, because outcome assessments were adjusted for confounders and were based on the states of the patients 12 hours after ICU admission. Although some issues were discussed, few prospective multicenter studies on surgical patients in the literature have assessed the effect of different causes of metabolic acidosis on the prognosis of this population.

CONCLUSIONS

High-risk surgical patients frequently exhibit metabolic acidosis during the postoperative period. We found that patients with postoperative hyperlactatemic acidosis had worse outcomes than patients with other types of acidosis or without acidosis. Different types of acidosis, however, are associated with divergent outcomes, with hyperlactatemic and elevated anion gap acidosis having the worst outcomes compared with patients without acidosis. In our study, persistent hyperlactatemia represented an independent effect on mortality in the high-risk surgical population. More studies are needed to determine the mechanisms and clinical significance of perioperative metabolic acidosis.

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DISCLOSURES

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