Relationship of at Admission Lactate, Unmeasured Anions, and Chloride to the Outcome of Critically Ill Patients

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Objectives: To investigate the association between the concentration of the causative anions responsible for the main types of metabolic acidosis and the outcome.

Design: Prospective observational study.

Setting: Teaching ICU.

Patients: All patients admitted from January 2006 to December 2014.

Interventions: None.

Measurements and Main Results: Four thousand nine hundred one patients were admitted throughout the study period; 1,609 met criteria for metabolic acidosis and 145 had normal acid-base values. The association between at admission lactate, unmeasured anions, and chloride concentration with outcome was assessed by multivariate analysis in the whole cohort and in patients with metabolic acidosis. We also compared the mortality of patients with lactic, unmeasured anions, and hyperchloremic metabolic acidosis with that of patients without acid-base disorders. In the whole population, increased lactate and unmeasured anions were independently associated with increased mortality, even after adjusting for potential confounders (odds ratio [95% CI], 1.14 (1.08–1.20); $p < 0.0001$ and 1.04 (1.02–1.06); $p < 0.0001$, respectively). In patients with metabolic acidosis, the results were similar. Patients with lactic and unmeasured anions acidosis, but not those with hyperchloremic acidosis, had an increased mortality compared to patients without alterations (17.7%, 12.7%, 4.9%, and 5.8%, respectively; $p < 0.05$).

Conclusions: In this large cohort of critically ill patients, increased concentrations of lactate and unmeasured anions, but not chloride, were associated with increased mortality. In addition, increased unmeasured anions were the leading cause of metabolic acidosis. (*Crit Care Med* 2017; XX:00–00)

Key Words: chloride; lactate; metabolic acidosis; outcome; unmeasured anions

Metabolic acidosis is a common finding in critically ill patients. Its relationship to outcome, however, is not straightforward. Although the development of metabolic acidosis is considered an indicator of poor prognosis, the decrease in arterial pH might only reflect the severity of the disease. Indeed, patients with more critical conditions are more acidotic as an expression of the underlying illness. On the contrary, acidosis might be an independent predictor of mortality because of its own deleterious effects on body homeostasis. Although some studies showed an independent association between low pH or base excess ([BE]) and mortality in critically ill patients (1–3), another study did not find such relation (4).

Some studies suggested that the outcome of patients with metabolic acidosis is more dependent on the causative anion than on the acidosis per se (5). A retrospective observation of 867 patients with suspected lactic acidosis (LA) found that the type of metabolic acidosis on ICU admission, but not its severity, was associated with mortality (6). The highest mortality corresponded to LA (56%), followed by unmeasured anions acidosis (UAA) (39%). In contrast, the mortality of patients

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with hyperchloremic acidosis (HA) was similar to that of patients without acidosis (29 vs 26%). Although the strong prognostic implications of LA are well defined (7–9), there are controversial reports about the effects of UAA and HA on the outcome of critically ill patients (6, 10–13).

For many years, HA has been regarded as a "benign acidosis," a condition without impact on mortality, which results from the administration of large amounts chloride-rich solutions, during shock resuscitation (14). On the other hand, experimental and clinical studies found that hyperchloremia was associated with impaired immune response (15, 16), decreased renal perfusion (17), and increased occurrence rate of acute renal failure and renal replacement therapies (12, 18). Furthermore, observational studies identified hyperchloremia as an independent predictor of outcome in postoperative and septic shock patients (11, 19).

Given these controversies, additional research is needed to clarify the influence of the different types of metabolic acidosis on the outcome of critical illnesses. The goal of this study was to assess the effects of the main anions, which usually account for the development of metabolic acidosis, on the outcome of critically ill patients. For this purpose, we prospectively studied a large cohort of patients on ICU admission. Our hypothesis was that mortality was dependent on the accumulation of particular anions regardless of the changes in pH.

METHODS

Design

Prospective observational study.

Setting

Medical-surgical ICU located in a teaching hospital.

Ethics Approval and Patient Consent

The study was approved by the Institutional Review Board. Informed consent was obtained from the next of kin for all patients admitted to the study.

Patients

All patients greater than 18 years old admitted to ICU from January 2006 to December 2014 were screened. Patients with incomplete or wrong data and those who remained in intensive care less than 24 hours were excluded. All patients were followed up until hospital discharge or death.

Measurements

At admission, epidemiologic data (age, gender, and clinical or surgical admission) and clinical data (vasopressor and mechanical ventilation requirements) were recorded. Acute Physiology and Chronic Health Evaluation (APACHE) II (20) and Sepsis-related Organ Failure Assessment (SOFA) scores (21) were calculated. Condition on discharge (alive or dead) was recorded.

Arterial blood samples were analyzed for gases (AVL OMNI 9 Roche Diagnostics, Graz, Austria) and electrolytes: $[Na^+]$, $[K^+]$, $[Cl^-]$ (electrode ion selective Aeroset; Abbott Laboratories, Abbott Park, IL), $[Ca^{++}]$ (ion selective electrode; AVL OMNI 9), $[Mg^{++}]$ (Arsenazo dye/Mg complex), albumin (bromcresol-sulfonphthaleinyl), inorganic phosphate $[Pi^-]$ (molybdate-vanadate), and lactate (ion selective electrode; AVL OMNI 9).

Calculated Variables

Bicarbonate $[HCO_3^-]$ and extracellular [BE] were calculated using the Henderson-Hasselbalch (22) and Van Slyke equations (23), respectively.

Anion gap ([AG]) was calculated as follows (24):

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

[AG] was corrected for the effect of abnormal albumin concentration (25):

$$[AG]_{corrected}\ (mEq/L) = [AG]_{observed} + 0.25 \times ([normal\ albumin] - [observed\ albumin])\ (in\ g/L)$$

To avoid the confounding effect of both hemoconcentration and hemodilution, $[Cl^-]$ was adjusted to water excess/deficit by multiplying the observed value by a correcting factor as,

$$[Cl^-]_{corrected} = [Cl^-]_{observed}\ ([Na^+]_{normal}/[Na^+]_{observed})$$ (26).

Unmeasured anions ([UA]) concentration was calculated as follows:

$$[UA] = [AG]_{corrected} - [lactate]$$

For the determination of [UA], we used the difference between $[AG]_{corrected}$ and [lactate]. We used $[AG]_{corrected}$ instead of strong ion gap [SIG] because the former is easier to be determined, and both variables are interchangeable. A previous study showed the narrow 95% limits of agreement between $[AG]_{corrected}$ and [SIG] (26). To confirm that this approach is appropriate, the agreement between $[AG]_{corrected}$ and [SIG] was assessed again in the present cohort. [SIG] was calculated as previously reported (26).

Excess of [lactate], [UA], and [Cl-] (Δ[lactate], Δ[UA], and Δ[Cl-], respectively) were calculated as the differences between normal reference and observed values. Normal reference ranges were established according to the results of a previous study (26).

Metabolic acidosis was defined by a pH value less than or equal to 7.36 and [BE] less than or equal to –2. Patients with metabolic acidosis were grouped into categories according to the anion in excess that accounted for over 50% of the decrease in [BE]: 1) HA: $[Cl^-]_{corrected}$ greater than 110 mEq/L plus $\Delta[Cl^-]_{corrected}$ greater than 50% of the decrease in [BE]. 2) LA: [lactate] greater than 1.5 mmol/L plus Δ[lactate] greater than 50% of the decrease in [BE]. 3) UAA: [UA] greater than 18 mmol/L plus Δ[UA]. 4) Indeterminate acidosis (IA): None of the anions by themselves accounted for more than 50% of the decrease in [BE]. Patients without acid-base disorders (normal pH, [BE], [lactate], [UA], and $[Cl^-]_{corrected}$) comprised the control group.

Statistical Analysis

Mortality for the different groups of metabolic acidosis was compared with the control group. In addition, we analyzed the association between each possible causative anion ([lactate],

[UA], and $[Cl^-]_{corrected}$) and outcome. In order to identify independent predictors, multivariate regression analysis was carried out including all variables of interest associated with mortality in the bivariate analysis. The tested variables were age, gender, SOFA score, surgical or medical admission, vasopressor and mechanical ventilation requirements, renal dysfunction (plasma creatinine ≥ 1.4 mg/dL), [lactate], [UA], and $[Cl^-]_{corrected}$. The calibration of the model (goodness of fit) was assessed by the Hosmer-Lemeshow test and the discrimination by the area under the receiver operating characteristic (ROC) curve. The association of individual anions that behaved as independent predictor for mortality, adjusted for the other covariates of the logistic regression model, was graphically shown by means of margins and marginsplot functions.

Data are expressed as percentages, median and interquartile ranges (25–75%), or mean ± SD. Differences were evaluated through chi-square for dichotomous variables or Student *t* test for quantitative variables with normal distribution or Wilcoxon rank-sum test in case of nonnormal distribution. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, 4,901 patients were recruited; 1,609 of them met criteria for metabolic acidosis, and 154 of them had a normal acid-base status. There was a large number of patients with increased [lactate], [UA], and $[AG]_{corrected}$, who were not included in the metabolic acidosis subgroup. This was explained by the presence of associated metabolic or respiratory disorders that modified the criteria of pH and BE.

The main clinical and epidemiologic characteristics and the acid-base and electrolyte values of survivors and nonsurvivors, in the whole cohort and in patients with metabolic acidosis, are shown in **Tables 1** and **2**.

The 95% limits of agreement between $[AG]_{corrected}$ and [SIG] were 3 mEq/L (**Supplementary Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C869).

TABLE 1. Epidemiologic, Clinical, Acid-Base, and Electrolyte Data in the Whole Cohort of Critically Ill Patients

Variables	All	Survivors	Nonsurvivors	*p*
n (%)	4,901	4,311 (88)	590 (12)	
Gender, male, *n* (%)	2,381 (49)	2,083 (48)	298 (51)	0.32
Age (yr), mean ± SD	64 ± 19	63 ± 19	74 ± 14	< 0.001
Medical admission, *n* (%)	2,584 (53)	2,099 (49)	485 (82)	< 0.001
Acute Physiology and Chronic Health Evaluation II score, mean ± SD	11 ± 7	10 ± 6	19 ± 7	< 0.001
Sepsis-related Organ Failure Assessment score, mean ± SD	3 ± 3	2 ± 2	6 ± 4	< 0.001
Shock, *n* (%)	870 (18)	574 (13)	296 (50)	< 0.001
Mechanical ventilation (%)	1050 (22)	694 (16)	356 (60)	< 0.001
ICU length of stay (d), median (IQR)	2 (1–4)	2 (1–4)	4 (2–6)	0.38
Hospital length of stay (d), median (IQR)	8 (5–13)	8 (5–13)	6 (3–12)	0.87
pH, mean ± SD	7.38 ± 0.08	7.38 ± 0.08	7.37 ± 0.10	0.01
[BE] (mEq/L), mean ± SD	−3 ± 4	−3 ± 4	−4 ± 6	0.17
P_{CO_2} (mm Hg), mean ± SD	37 ± 9	37 ± 8	38 ± 12	0.09
$[Na^+]$ (mEq/L), mean ± SD	136 ± 5	136 ± 5	135 ± 7	< 0.001
$[K^+]$ (mEq/L), mean ± SD	3.9 ± 0.7	3.9 ± 0.6	4.1 ± 0.8	< 0.001
$[Cl^-]$ (mEq/L), mean ± SD	103 ± 6	104 ± 6	101 ± 7	< 0.001
$[Cl^-]_{corrected}$ (mEq/L), mean ± SD	106 ± 5	106 ± 5	104 ± 5	< 0.001
[Lactate] (mmol/L), mean ± SD	2.1 ± 1.6	2.0 ± 1.4	2.8 ± 2.0	< 0.001
$[AG]_{corrected}$ (mEq/L), mean ± SD	19 ± 5	19 ± 5	22 ± 6	< 0.001
[UA] (mEq/L), mean ± SD	17 ± 5	17 ± 5	19 ± 5	< 0.001
$[Pi^-]$ (mg/dL), mean ± SD	3.4 ± 1.0	3.5 ± 1.1	3.8 ± 1.5	< 0.001
Plasma urea (mg/dL), mean ± SD	48 ± 40	44 ± 37	73 ± 54	< 0.001
Plasma creatinine (mg/dL), mean ± SD	1.18 ± 1.33	1.13 ± 1.33	1.51 ± 1.30	< 0.001

$[AG]_{corrected}$ = anion gap corrected for abnormal albumin concentration, [BE] = base excess, $[Cl^-]_{corrected}$ = $[Cl^-]$ corrected for abnormal albumin concentration, $[Pi^-]$ = inorganic phosphate concentration, IQR = interquartile range, [UA] = unmeasured anion concentration.

TABLE 2. Epidemiologic, Clinical, Acid-Base, and Electrolyte Data in Patients With Metabolic Acidosis

Variables	All	Survivors	Nonsurvivors	*p*
n (%)	1,609 (100)	1,426 (89)	183 (11)	
Gender, male, *n* (%)	774 (48)	692 (49)	82 (45)	0.34
Age (yr), mean ± SD	63 ± 18	61 ± 18	72 ± 15	< 0.001
Medical admission, *n* (%)	457 (28)	323 (23)	134 (73)	< 0.001
Acute Physiology and Chronic Health Evaluation II score, mean ± SD	12 ± 8	10.7 ± 6	22 ± 8	< 0.001
Sepsis-related Organ Failure Assessment score, mean ± SD	3 ± 3	2 ± 2	7 ± 4	< 0.001
Shock, *n* (%)	362 (22)	236 (17)	126 (69)	< 0.001
Mechanical ventilation, *n* (%)	399 (25)	266 (18)	133 (72)	< 0.001
ICU length of stay (d), median (IQR)	2 (1–4)	2 (1–4)	3 (2–6)	0.92
Hospital length of stay (d), median (IQR)	5 (8–13)	8 (5–13)	5 (2–14)	0.59
pH, mean ± SD	7.29 ± 0.06	7.29 ± 0.05	7.25 ± 0.09	< 0.001
[BE] (mEq/L), mean ± SD	−7 ± 4	−7 ± 3	−9 ± 5	< 0.001
P_{CO_2} (mm Hg), mean ± SD	40 ± 9	40 ± 8	41 ± 13	< 0.001
$[Na^+]$ (mEq/L), mean ± SD	137 ± 5	137 ± 4	136 ± 7	< 0.001
$[K^+]$ (mEq/L), mean ± SD	4.1 ± 0.7	4.0 ± 0.7	4.3 ± 0.9	< 0.001
$[Cl^-]$ (mEq/L), mean ± SD	103 ± 6	104 ± 6	101 ± 7	< 0.001
$[Cl^-]_{corrected}$ (mEq/L), mean ± SD	108 ± 5	108 ± 5	106 ± 5	< 0.001
Lactate (mmol/L), mean ± SD	2.5 ± 2.1	2.3 ± 1.9	3.9 ± 3.3	< 0.001
$[AG]_{corrected}$ (mEq/L), mean ± SD	20 ± 5	20 ± 5	24 ± 6	< 0.001
[UA] (mEq/L), mean ± SD	18 ± 5	17 ± 2	20 ± 5	< 0.001
$[Pi^-]$ (mg/dL), mean ± SD	3.8 ± 1.3	3.6 ± 1.2	4.6 ± 2.0	< 0.001
Plasma urea (mg/dL), mean ± SD	50 ± 49	44 ± 43	90 ± 73	< 0.001
Plasma creatinine (mg/dL), mean ± SD	1.36 ± 1.94	1.28 ± 1.96	1.97 ± 1.70	< 0.001

$[AG]_{corrected}$ = anion gap corrected for abnormal albumin concentration, [BE] = base excess, $[Cl^-]_{corrected}$ = $[Cl^-]$ corrected for abnormal albumin concentration, $[Pi^-]$ = inorganic phosphate concentration, IQR = interquartile range, [UA] = unmeasured anion concentration.

The type of acidosis most frequently found was UAA (53%), followed by HA (23%), LA (22%), and IA (3%). Patients with LA and UAA had higher APACHE II score, higher requirements of mechanical ventilation and vasopressors than control group (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C869). Thirty-four (4%) of the UAA corresponded to diabetic ketoacidosis, and 218 (27%) had plasma creatinine levels greater than or equal to 1.4 mg/dL. Patients with HA were similar to those of control group. Mortality rates were higher for patients with LA and UAA compared to those without acid-base alterations (**Fig. 1**).

[lactate] and [UA] were associated with increased mortality, even after adjusting for potential confounders, both in the whole population (odds ratio [95% CI], 1.14 [1.08–1.20]; $p < 0.0001$ and 1.04 [1.02–1.06]; $p < 0.0001$, respectively) and in patients with metabolic acidosis (1.09 [1.02–1.18]; $p = 0.018$ and 1.05 [1.01–1.09]; $p = 0.014$, respectively). The bivariate analysis and the logistic regression models, as well as the corresponding calibration tests and ROC curves, appear in **Supplementary Tables 2–5** (Supplemental Digital Content 1, http://links.lww.com/CCM/C869) and in **Supplementary Figures 2** and **3** (Supplemental Digital Content 1, http://links.lww.com/CCM/C869). **Figure 2** shows the probability of death associated with increasing [lactate] and [UA] adjusted for the other covariates of the model, in the entire cohort and in the subgroup of metabolic acidosis.

DISCUSSION

This study assessed the effect of the principal causative anions on the outcome of a large cohort of critically ill patients. Our main finding was that at admission [lactate] and [UA] behaved as independent predictors of mortality. As previously reported (9), values of [lactate] usually considered normal were consistently associated with increased mortality, even in the absence of overt metabolic acidosis. The key original contribution, however, was that UAA constituted the leading cause

for metabolic acidosis in critically ill patients. Like [lactate], any increase in [UA] was associated with a worse outcome, even after the adjustments to several potential confounders. In contrast, changes in $[Cl^-]_{corrected}$ were not independent predictors of outcome.

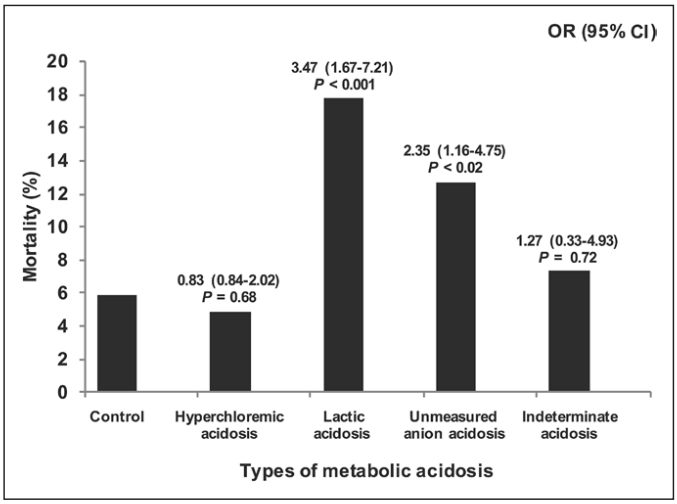

Figure 1. Mortality of the different types of metabolic acidosis. OR = odds ratio.

Our findings are not completely novel. A previous study has also shown that patients with LA and UAA have higher mortality than those with HA and normal acid-base status (6). Nevertheless, this investigation has some drawbacks, such as its retrospective design, the inclusion of only patients with suspected LA, and a relatively small sample. Another study, in 618 surgical critically ill patients, found 30-day mortalities of 30%, 24%, 18%, and 10% for LA, UAA, HA, and patients without acidosis, respectively (10). Although only LA had an independent effect on mortality, the study might have been underpowered to show the effects of the other types of metabolic acidosis because of the small number of patients included in each group. In contrast, our prospective study included a large number of patients and used strict criteria in order to reduce diagnostic overlaps and/or misclassifications. Furthermore, we mainly approached the effects of the causative anions, instead of the type of metabolic acidosis. In this way, multivariate analysis showed that in the whole cohort of critically ill patients and in patients with metabolic acidosis, increased [lactate] and

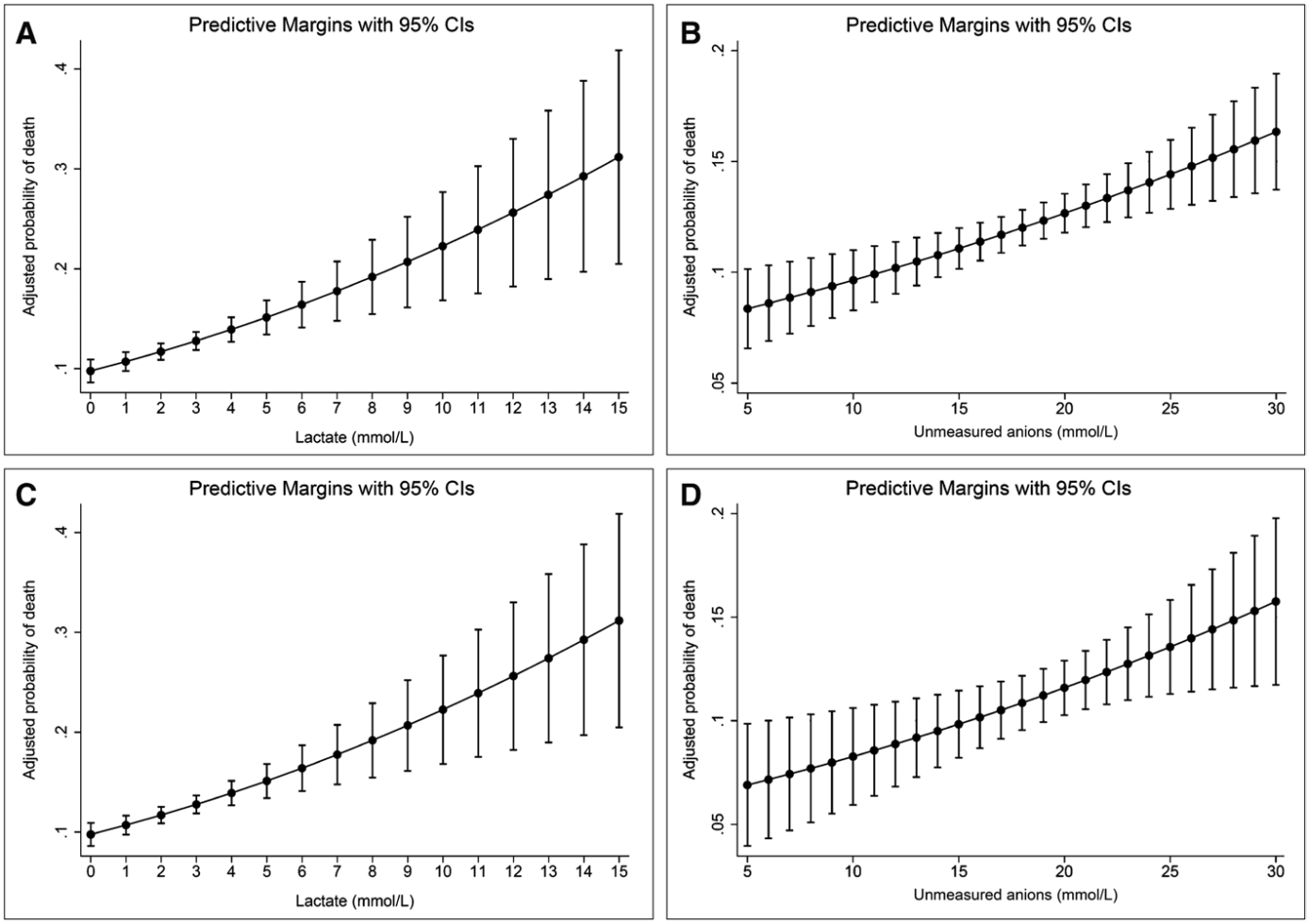

Figure 2. Probability of death associated with increasing lactate and unmeasured anions concentrations ([lactate] and [UA], respectively) adjusted for the other significant covariates of the model (age, clinical admission, shock, mechanical ventilation, and SOFA score). **A**, Relationship between probability of death and [lactate] in the whole series of critically ill patients. **B**, Relationship between probability of death and [UA] in the whole series of critically ill patients. **C**, Relationship between probability of death and [lactate] in the subgroup of patients with metabolic acidosis. **D**, Relationship between probability of death and [UA] in the subgroup of patients with metabolic acidosis.

[UA], but not hiperchloremia, were independent predictors of mortality. These findings suggest that the characteristics of the individual anions themselves, and not only the magnitude of metabolic acidosis, are the primary determinants of outcome.

The relationship between at admission [lactate] and outcome has been previously addressed (7–9). In our series of critically ill patients, LA explained 22% of the metabolic acidosis. Compared with other types of metabolic acidosis, it was associated with the highest mortality. Patients with LA had higher values of APACHE II and SOFA scores and higher occurrence rate of shock and requirements of mechanical ventilation. Nevertheless, [lactate] was an independent predictor of outcome, even after adjusting for those covariates. Our findings are consistent with previous studies, which showed that patients with LA have higher mortality than those with other types of acidosis (6, 10) and that at admission [lactate] can be used to identify patients most likely to die in the hospital (9).

The prognostic ability of [UA], assessed by means of either [SIG] or $[AG]_{corrected}$, has already been described in particular settings (27, 28). In our mixed population of critically ill patients, as well as in the selected group of patients with metabolic acidosis, [UA] also behaved as an independent predictor of outcome. In addition, UAA was the most common type of metabolic acidosis since it explained more than the half of the metabolic acidosis. Its mortality was 13%, significantly higher than that of patients with normal acid-base variables. Despite the fact that [UA] is frequently elevated in critically ill patients and in some chronic diseases (6, 10, 27, 28), its pathogenesis and its implications are not adequately understood. UAA comprises heterogeneous and unrelated conditions. Different anions such as ketoacids, formate, oxalate, salicylate, sulfate, phosphate, and drugs can contribute to its generation. In septic patients, hyperlactatemia only partially explains the elevations in $[AG]_{corrected}$. The origin and characteristics of the causative anions are uncertain. In critically ill patients with diabetic ketoacidosis, LA, or acidosis of unknown cause, Krebs cycle intermediates might enlarge $[AG]_{corrected}$ (29). Another major cause for increased [UA] is renal failure. This condition results in the accumulation of several molecules such as the negatively charged hippurate and other endogenous organic anions, sulfate, and phosphate (30). A survey that included 11,957 participants showed a graded rise in $[AG]_{corrected}$ across different estimated glomerular filtration rate categories beginning with values of 45–59 mL/min/1.73m^2 (28). Furthermore, $[AG]_{corrected}$ was independently associated with increased risk of mortality regardless of the effects of acidosis. In our patients with UAA, the presence of higher concentrations of plasma urea and creatinine, compared with the other groups, suggests that renal failure might have been a main contributing mechanism. Nevertheless, only 27% of the patients with UAA had abnormal plasma creatinine levels. Furthermore, [UA] behaved as an independent predictor of outcome, whereas plasma creatinine levels did not. These data indicate that renal dysfunction did not play a major role in the generation of UAA in most of the patients. Also, diabetic ketoacidosis was an occasional cause for UAA.

Alterations in $[Cl^-]$ has been linked to complications in critically ill patients, especially renal dysfunction, and worse outcome (11–13, 18, 19). Recently, some retrospective studies found an association between hypochloremia and mortality. In 67 patients with chronic obstructive pulmonary disease exacerbation, hypochloremic patients had a longer length of noninvasive mechanical ventilation (31). In a series of 488 critically ill patients, patients with low $[Cl^-]$ had longer ICU and hospital length of stay and higher mortality, but $[Cl^-]$ was not an independent predictor of outcome (32). In 98 postoperative patients, hypochloremia was associated with higher risk of hospital death, even after adjusting for APACHE II score (33). Finally, two large observational studies described a U-shape relationship between plasma chloride concentrations and hospital mortality (34, 35). One of them showed that severe hypochloremia was independently associated with an increased risk of ICU and hospital mortality, length of stay, and acute kidney injury (34). Hypochloremia might evidence the presence of a single or concomitant metabolic alkalosis. It might also express the physiologic renal compensation for a metabolic acidosis (36). In this circumstance, chloride excretion should be increased and the urine [AG] become negative (37). Subsequently, the response will result in further increase in $[AG]_{corrected}$ and decrease in $[Cl^-]_{corrected}$ (38). In our patients with metabolic acidosis, the lowest mortality corresponded to HA, which was similar to that of patients without acid-base disorders. Although, survivors had higher $[Cl^-]_{corrected}$ than nonsurvivors, the adjustment to other risk factors ruled out an independent effect of either hypo- or hyperchloremia on mortality.

Our study has some limitations. This was a single-center study, which included patients with intermediate risk. Consequently, the results might not be extended to more severely ill patients. Since fluid resuscitation was not controlled, its effects on different types of metabolic acidosis could not be evaluated. In addition, acid-base status was only performed at admission. Sequential measurements might probably have provided more information than isolated measurements. Finally, given the observational design of the study, our findings only show associations but cannot establish causality. Despite the fact that we performed a careful multivariate analysis, unmeasured confounders may not have been completely eliminated.

CONCLUSIONS

The main finding in this large series was that UAA constitutes the most common type of metabolic acidosis at the admission of critically ill patients. Like [lactate], [UA] was also an independent predictor of outcome. Any elevation in the concentration of these anions was associated with increasing mortality, even after the adjustment to potential confounders. Although UAA is not usually taken into account in the pathophysiologic approach of metabolic acidosis (39) and only LA, ketoacidosis, renal failure, or toxins are considered as frequent causes for increased $[AG]_{corrected}$, our results show its relevance in the acid-base abnormalities found in critically ill patients. On the contrary, HA had a similar mortality to that of patients without

acid-base alterations, and alterations in $[Cl^-]_{corrected}$ were not independently related to outcome.

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