Unmeasured anions as predictors of mortality in medical intensive care unit

Ânions não mensuráveis podem predizer mortalidade em unidade de terapia intensiva clínica

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ABSTRACT

BACKGROUND AND OBJECTIVE: The present study aimed to evaluate the utility of variables that represent unmeasured anions (anion gap, anion gap corrected for albumin, anion gap corrected for albumin and lactate, base excess and modified base excess) to predict mortality in medical intensive care unit patients. **METHODS:** This prospective study included 156 consecutive patients admitted to a medical intensive care unit in a Medical school hospital between August 2006 and June 2007. Serum levels of potassium, sodium, chloride, C-reactive protein, albumin, and lactate were measured. Variables that represent unmeasured anions and APACHE II score were calculated. **RESULTS**: Among the studied patients, 60.9% were male, and mean age was 59.2±17.2 years. Mortality rate was 31.4%. Spearman's test showed correlation among unmeasured anions and lactate. Comparison between survivors and non-survivors showed differences in length of intensive care unit stay, APACHE II score, albumin, C-reactive protein, lactate, anion gap corrected for albumin, base excess, and modified base excess. Anion gap corrected for albumin, base excess, and modified base excess are predictors of medical intensive care unit mortality; however, theirs areas under the ROC curves are smaller than APACHE II score and C-reactive protein. **CONCLUSION:** Variables that estimate unmeasured anions, such as anion gap corrected for albumin, base excess, and modified base excess, can be used to predict mortality in medical intensive care unit patients.

Keywords: Acidosis; Acid-base equilibrium; C-reactive protein; APACHE; Critical care; Intensive Care Units; Mortality

RESUMO

JUSTIFICATIVA E OBJETIVO: O presente estudo teve como objetivo avaliar a utilidade de variáveis que representam ânions não mensuráveis (ânion gap, ânion gap corrigido para a albumina, ânion gap corrigido para a albumina e lactato, excesso de base e excesso de base modificado) para prever a mortalidade em pacientes de unidade de terapia intensiva. **MÉTODOS:** Foram incluídos 156 pacientes consecutivos admitidos na unidade de terapia intensiva em um hospital escola de Medicina entre agosto de 2006 e junho de 2007. Os níveis séricos de potássio, sódio, cloreto, proteina C-reativa, albumina e lactato foram medidos. Foram calculadas variáveis que representaram os ânions não mensuráveis e APACHE II. **RESULTADOS:** Entre os pacientes estudados, 60,9% eram do sexo masculino, e a idade média foi de 59,2±17,2 anos. A taxa de mortalidade foi de 31,4%. O teste de Spearman mostrou correlação entre ânions não mensuráveis e lactato. A comparação entre sobreviventes e não sobreviventes mostrou diferenças no tempo de permanência na unidade de terapia intensiva, APACHE II, albumina, proteína C-reativa, lactato, ânion gap corrigido para a albumina, excesso de base e excesso de base modificado. Ânion gap corrigido para a albumina, excesso de base e excesso de base modificado foram preditores de mortalidade na unidade de terapia intensiva médica, mas as áreas sob as curvas ROC foram menores do que o escore APACHE II e a proteína C-reativa. **CONCLUSÃO:** Variáveis que estimam ânions não mensuráveis, como o ânion gap corrigido para a albumina, o excesso de base e o excesso de base modificado, podem ser usados para prever a mortalidade em pacientes em unidade de terapia intensiva clínica.

Descritores: Acidose; Equilíbrio ácido-base; Proteína C-reativa; APACHE; Cuidados críticos; Unidades de Terapia Intensiva; Mortalidade

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INTRODUCTION

Acid-base equilibrium disorders are common in the critically ill[1]. In particular, metabolic acidosis is a significant marker of poor outcomes[2]. Lactic acidosis is one of the most important causes of metabolic acidosis due to frequency of shock and hypoxia in the intensive care unit (ICU)[3].

Metabolic acidosis is not easily determined in routine clinical practice. Nevertheless, it is possible to estimate metabolic acidosis by the Henderson-Hasselbalch and Stewart approaches. Henderson-Hasselbalch is the traditional way to predict metabolic acidosis, and the Stewart approach is limited by having many variables that are not practical to measure on a daily basis[4].

With the intention of facilitating the estimated diagnosis of acidosis, some investigators suggested improving the anion gap (AG) accuracy by correcting it for albumin (AG alb), and for albumin and lactate (AG alb+lact); and the accuracy of base excess (BE) by modifying it for sodium, chloride, and albumin (BEm)[4-6]. All these approaches can be used to estimate unmeasured anions.

Unmeasured anions are negatively charged compounds that interfere with the relationship between pH, bicarbonate and carbon dioxide tension. Many diseases and interventions are associated with unmeasured anions elevation. Sepsis, hepatic dysfunction, shock, renal failure, balanced fluids used in cardiopulmonary bypass and colloids containing gelatin are some examples[7-11]. Although the presence of unmeasured anions is frequent in critically ill patients, few studies addressed their chemical nature and significance[12].

Recently, some authors started to address the potential utility for unmeasured anions in predicting mortality in different clinical situations. However, the clinical relevance of detecting approaches that estimate unmeasured anions is unclear, and their correlation with elevated mortality and poor outcomes remains incompletely defined in critically ill patients.

The present study aimed to evaluate the utility of some variables that represent unmeasured anions to predict mortality in critical ill patients, including those without acidosis.

METHODS

Subjects

The present study included 156 consecutive patients admitted to a medical ICU in a Medical school hospital, between August 2006 and June 2007. The hospital's Research Ethics Committee approved the study protocol.

Demographic data and Acute Physiology And Chronic Health Evaluation (APACHE II) score were recorded on the day of ICU admission. Arterial blood samples were collected at the time of ICU admission. Biochemical and blood gas analyses were performed. Total serum levels of potassium, sodium, chloride, C- reactive protein (CRP), and albumin were measured using the dry chemistry method (Ortho-Clinical Diagnostics VITROS 950®, Johnson & Johnson). The pH, partial pressure of carbon dioxide (PCO_2), oxygen pressure (PO_2) and lactate were also measured (Roche OMNI® S Blood Gas Analyzer). Lactate was determined with pirolusite/carbon and Ag-Ag/Cl electrode.

Unmeasured anions determination

The AG was defined as AG= $[Na^+]$ + $[K^+]$ - $[Cl^-]$ - $[HCO_3^-]$. Corrected AG to compensate for abnormal albumin and lactate was also calculated. AG alb was determined according to AG alb = AG+0.25*(40 – [albumin]), and AG alb+lac was calculated as AG alb+lac = AG+0.25*(40-[albumin])- [lactate]. BE modified for unmeasured anions (BEm) was defined as BEm = BE-[modified Na^+]-[modified Cl^-]-[modified albumin]. Modified Na^+ = 0.3*($[Na^+]$-140), modified Cl^- = 102-($[Cl^-]$*140/$[Na^+]$), and modified albumin = 0.34*(45- [albumin]). In these equations, potassium, sodium, chloride and bicarbonate ionic concentrations are in mmol/L, lactate concentration is in mmol/L, and albumin concentration in g/L.

Statistical analysis

Mean ± standard deviation or medians (lower quartile, upper quartile) for continuous variables were calculated and for comparison of two groups according to mortality. Student's *t* test for normal or Mann-Whitney for non-normal distribution was employed. Percentage was calculated for categorical variables, and chi-square test was performed to compare proportions and test collinearity among our variables.

Spearman's test was conducted to study correlations between continuous variables. Receiver operating characteristic (ROC) curves were obtained to predict mortality and determine cutoff values. Multivariate logistic regression analysis for outcome prediction was not considered due to collinearity among our variables. Significance level was set at $p \leq 0.05$. Statistical analysis was accomplished with SigmaStat for Windows v 3.5 (Systat Software Inc) and MedCalc (7.2).

RESULTS

During the present study 156 patients (60.9% males) were admitted to the ICU, and their characteristics are shown in Table 1. Mean age was 59.2 ± 17.2 years. Mean APACHE II score was 17.1±8.3 and median length of ICU stay was 4.0 (2.0-7.0) days. Mortality rate was 31.4%. The reasons for their admission were septic shock for 23.7%, respiratory failure/chronic obstructive pulmonary disease (COPD) for 23.7%, acute coronary syndrome/hypertensive crisis for 23.7%, gastrointestinal hemorrhage/pancreatitis/hepatic encephalopathy for 10.9%, diabetic ketoacidosis for 3.8%, post-cardiac arrest for 3.2%, drug overdose for 1.9% and miscellaneous for 9.1% (Table 2).

Comparison between survivors and non-survivors showed significant differences in length of ICU stay, APACHE II score, serum albumin, serum CRP, serum lactate concentration, AG alb, BE, and BEm (Table 3).

Areas under the ROC curves were constructed for mortality prediction and cutoff values were determined (Table 4). Lactate concentrations, APACHE II score, CRP concentrations, AG alb, BE and BEm were predictors of ICU mortality in this univariate model.

DISCUSSION

The present study assessed the utility of variables that estimate unmeasured anions to predict mortality in medical

Table 1. Demographic and laboratory characteristics of the 156 patients

Demographic and laboratory characteristics	
Age, years	59.2 (17.2)
Sex; M: F	95 : 61
APACHE II score	17.1±8.3
ICU stay, days	4 (2.0 -7.0)
Mortality rate, n	49 (31.4%)
Albumin, g/dL	27.8 (8.0)
CRP, mg/L	66 (25.5-90.0)
Lactate, mmol/L	2.0 (1.5-3.2)
Bicarbonate, mmol/L	20.7 (16.0-23.8)
Sodium, mmol/L	138 (133.7-141)
Potassium, mmol/L	4.1 (3.6-4.6)
Chloride, mmol/L	104 (100-109)
AG, mmol/L	17.1 (13.1-20.7)
AG alb, mmol/L	19.8 (16.0-24.3)
AG alb+lac, mmol/L	16.8 (14.0-21.2)
BE, mmol/L	-3.1 (-7.6-0.1)
BEm; mmol/L	-4.8 (-9.4 - -0.3)

Mean ± standard deviation, median, (quartile 1 - quartile 3). M: male; F: female; APACHE II: Acute Physiology And Chronic Health Evaluation; ICU: Intensive Care Unit; CRP: C-reactive protein; AG: anion gap; AG alb: albumin corrected anion gap; AG alb+lac: albumin and lactate corrected anion gap; BE: base excess; BEm: excess base corrected for unmeasured anions.

Table 2. Reason for intensive care unit admissions

Admission diagnoses	Number (n=156) n (%)
Septic shock	37 (23.7)
Respiratory failure/chronic obstructive pulmonary disease	37 (23.7)
Acute coronary syndrome/hypertensive crisis	37 (23.7)
Gastrointestinal hemorrhage/pancreatitis/ hepatic encephalopathy	17 (10.9)
Diabetic ketoacidosis	6 (3.8)
Post-cardiac arrest	5 (3.2)
Drug overdose	3 (1.9)
Miscellaneous	14 (9.1)

ICU patients. In our data, variables that estimate unmeasured anions such as AG alb, BE and BEm were predictors of medical ICU mortality.

Metabolic acidosis can be predicted by Henderson-Hasselbalch and Stewart approaches. Henderson-Hasselbalch is the traditional way to predict metabolic acidosis. Analysis of blood gas and serum electrolytes permits the Henderson-Hasselbalch approach that describes the relationship between pH, bicarbonate and carbon dioxide tension ($PaCO_2$)[13]. These measures associated with AG and BE calculations reveal the metabolic status of acid-base equilibrium. This method predicts the quantity of lactic acids, ketoacids and sulfuric acids, by the increase in unmeasured anions. Despite this, the Henderson-Hasselbalch method is unable to quantify metabolic acidosis correctly because bicarbonate may be falsely elevated in hypoalbuminemic patients and BE might also be affected by albumin and electrolytes[4,6,13,14].

The Stewart approach is an elegant method to predict metabolic acidosis. This approach involves the strong ion gap (SIG) calculation. The SIG is the difference between apparent strong ion difference (SIDa) and effective strong ion difference (SIDe). SIDa involves the difference between strong cations and strong anions, and SID takes into account weak acids like albumin, phosphate and CO_2. However, it is limited because many variables are not practical to measure on a daily basis[4]. Dubin et al., showed in a university-affiliated ICU hospital that diagnostic performance of Stewart approach exceeded that of bicarbonate and BE, but when AG alb was included in analysis, the Stewart approach did not offer any diagnostic or prognostic advantages[15]. Despite that, previous studies showed that SIG seems to have the best correlation with lactate concentrations[3-5].

Recently, some authors started to address the potential utility for unmeasured anions in predicting mortality. In fact, Rocktaeschel et al., found that AG, AG alb, BEm, and SIG predict hospital mortality[3]. In other study SIG was the most strongly predictive of mortality following vascular trauma[16]. Likewise, in pediatric ICU, Balasubramanyan et al. compared AG alb, BEm, SIG and lactate, and found that BEm predicts mortality better than the other unmeasured anions[6]. Antonini et al. showed that metabolic acidosis by unmeasured anions is a clinically relevant phenomenon, which is correlated with mortality[17]. Abramowitz et al. described AG alterations in kidney disease is associated with mortality[18]. On the other hand, Cusack et al. in a mixed medical and surgical ICU found no prognostic value for SIG[19].

In our data, AG alb, BE, and BEm were associated with mortality prediction in univariate analysis. Interestingly, areas under the ROC curves for these variables were higher than for lactate. One reason could be that lactate level is not always associated with microcirculation perfusion impairment, although it is one of the most important causes of metabolic acidosis and a marker of poor outcomes in critically ill patients[2,3,20]. These findings reinforce the importance of other unmeasured anions in outcome prediction.

It should be pointed out that, in our data, all patients were studied at ICU admission, and colloid solutions such as albumin and gelatin were not used for intravenous resuscitation or maintenance. This is a crucial point to be considered, since the study from Himpe et al., showed that succinylated gelatin in colloid solutions was acidifying and increased the concentration of unmeasured anions[11].

Many studies highlighted the presence of unmeasured anions in critically ill patients, but only few have attempted to address their chemical nature. Organic acids, amino acids, intermediates of the tricarboxylic acid cycle and uric acid might explain part of SIG because most of then are negatively charged at physiologic pH. However, Moviat et al., showed that amino acids, uric acids and organic acids together accounted for only 7.9% of SIG in ICU patients with metabolic acidosis[12]. CRP is another protein that could increase unmeasured anions concentration.

Table 3. Comparisons between survivors and non-survivors

	Survivors (107)	Non-survivors (49)	p-value
Age, years	58.5 (18.3)	60.8 (14.4)	0.427
Male, n (%)	61 (57.0)	34 (69.4)	0.196
APACHE II score	14 (7)	22 (9)	<0.001
ICU stay, days	3.0 (2.0, 6.0)	6.0 (2.0, 8.0)	0.028
Albumin, g/dL	29.3 (7.5)	24.7 (8.3)	<0.001
CRP, mg/L	46(19-83)	87 (64-224)	<0.001
Lactate, mmol/L	1.8 (1.3-2.9)	2.4 (1.8-4.5)	0.003
Bicarbonate, mmol/L	21.5 (17.4-23.9)	18.5 (13.7-23.6)	0.070
Sodium, mmol/L	137.0 (133.2-140.0)	139.0 (133.7-143.0)	0.076
Potassium, mmol/L	4.1 (3.5-4.5)	4.1 (3.7-5.2)	0.346
Chloride, mmol/L	104.0 (98.2-108.7)	105.0 (101.0-111.0)	0.074
AG, mmol/L	16.9 (12.7-20.4)	17.9 (14.5-23.6)	0.057
AG alb, mmol/L	18.7 (15.3-23.0)	21.7 (18.3-26.9)	0.005
AG alb+lac, mmol/L	16.5 (12.9-21.0)	17.9 (15.8-22.5)	0.068
BE, mmol/L	-2.1 (-6.1-0.3)	-5.6 (-11.3 - -1.3)	0.004
BEm, mmol/L	-3.5 (-7.7-0.6)	-7.6 (-11.8 - -3.8)	<0.001

Mean ± standard deviation, median, (quartile 1 - quartile 3). Significance level p<0.05. APACHE II: Acute Physiology And Chronic Health Evaluation; ICU: intensive care unit; CRP: C-reactive protein; AG: anion gap; AG alb: albumin corrected anion gap; AG alb+lac: albumin and lactate corrected anion gap; BE: base excess; BEm: excess base corrected for unmeasured anions.

Table 4. Areas under receiver operation characteristics (ROC) curves for mortality prediction

	Areas under ROC curve	95% Confidence Interval	Cutoff	p-value
Lactate, mmol/L	0.648	0.567-0.722	>1.70	0.0026
APACHE II score	0.772	0.698-0.835	>18.00	0.0001
AG alb+lac, mmol/L	0.591	0.510-0.669	>15.80	0.0679
CRP, mg/L	0.731	0.654-0.799	>6.40	0.0001
AG alb, mmol/L	0.642	0.561-0.717	>18.25	0.0039
AG, mmol/L	0.595	0.514-0.673	>14.00	0.0574
BE, mmol/L	0.642	0.562-0.717	≤-7.00	0.0018
BEm, mmol/L	0.680	0.600-0.752	≤5.35	0.0001

Significance level p<0.05. APACHE II: Acute Physiology And Chronic Health Evaluation; AG alb+lac: albumin and lactate corrected anion gap; CRP: C-reactive protein; AG alb: albumin corrected anion gap; AG: anion gap; BE: base excess; BEm: excess base corrected for unmeasured anions.

Experimental and clinical studies suggest that acute phase proteins, such as CRP, might account for elevation of the SIG, although Kneidinger et al., did not confirm this finding[21]. Thus, the mechanisms underlying unmeasured anions elevation and their significance require further clarification[22,23].

As CRP concentrations and APACHE II score are commonly used to predict mortality in medical and surgical ICU, we also evaluated area under ROC curves for APACHE II score and CRP concentrations. Our results showed that area under ROC curve for CRP was higher than for unmeasured anions for predicting mortality. Moreover, serum concentrations of CRP were associated with AG alb, AG alb+lac and BEm. CRP, an acute-phase protein synthesized by the liver following stimulus by various cytokines including tumor necrosis factor alpha and interleukine-6, markedly increase within hours after infection or inflammation[24]. Numerous studies have demonstrated increased CRP concentrations in patients with sepsis[24-26]. Importantly, CRP is easily obtainable by the dry chemistry method, and it is elevated in shock as is serum lactate. Our study also showed that CRP concentrations were higher and albumin concentration lower among non-survivors, suggesting that the intensity of inflammatory response is a marker of poor ICU outcome. In a review, Faix[27] reports that combinations of pro- and anti-inflammatory biomarkers may help identify patients who are developing severe sepsis before organ dysfunction advance.

As for CRP concentrations, the area under ROC curve for APACHE II score is higher than for unmeasured anions for predicting mortality. This suggests that unmeasured anions are not superior to APACHE II score and CRP concentrations for mortality prediction in critically ill patients.

Finally, we should consider the major limitations of this study. Potential limitations of our study include small number of nonsurvivors, a single ICU sample tabanalysis, and absence of multivariate analysis due to collinearity among unmeasured anions.

CONCLUSION

Our data suggest that variables that estimate unmeasured anions, such as anion gap corrected for albumin, base excess, and modified base excess, can be used to predict mortality in medical intensive care unit patients.

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