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Avaliação prognóstica da acidemia grave em pacientes criticamente doentes

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RESUMO

Acidose é uma condição potencialmente fatal e o conhecimento sobre acidose extrema no cenário da doença crítica é incompleto e pouco estudado. Com isso, o presente estudo propõe-se a realizar uma análise do perfil dos pacientes criticamente doentes com acidose extrema. Uma coorte retrospectiva dos pacientes internados na unidade de terapia intensiva nos últimos 10 anos com gasometria arterial com pH inferior a 7,0 foi realizada. Dados clínicos e análises de gases sanguíneos foram obtidos de prontuários eletrônicos. O desfecho primário foi a mortalidade intra-hospitalar. Os desfechos secundários foram necessidade de vasopressores, ventilação mecânica (VM) e/ou terapia renal substitutiva (TRS), tempo gasto em VM e TRS e tempo de permanência na UTI e no hospital. Além disso, a abordagem simplificada do método de Stewart para avaliação de distúrbios ácido-básicos foi aplicada para analisar as causas da acidose. No período de janeiro de 2012 a dezembro de 2021 houve 371 gasometrias arteriais com pH menor que 7,0 em 231 pacientes. A acidose metabólica foi o subtipo mais frequente. A mortalidade geral foi de 42,8% (n=95). Não houve diferença na mortalidade entre os grupos com distúrbios primários respiratórios, metabólicos ou mistos, mas a necessidade de vasopressores, a necessidade e a duração da VM e o tempo de permanência no hospital e na UTI foram diferentes entre os grupos. Pacientes com acidose extrema causada por ânions não medidos com lactato ≥4 mmol/L tiveram maior mortalidade em comparação com pacientes com acidose extrema causada por ânions não medidos com lactato <4 mmol/L.

Palavras-chave: Acidose extrema; paciente criticamente doente; prognóstico; método de Stewart.

ABSTRACT

Acidosis is a potentially fatal condition and knowledge about extreme acidosis in the setting of critical illness is incomplete and not well understood. With this, the present study proposes to analyze the profile of critically ill patients with extreme acidosis. A retrospective cohort of patients admitted to the intensive care unit in the last 10 years with arterial blood gas pH below 7.0 was performed. Clinical data and blood gas analyzes were obtained from electronic medical records. The primary outcome was in-hospital mortality. Secondary outcomes were need for vasopressors, mechanical ventilation (MV) and/or renal replacement therapy (RRT), time spent on MV and RRT, and length of stay in the intensive care unit (ICU) and hospital. In addition, a simplified Stewart approach to acid-base disorders was applied to analyze the causes of acidosis. From January 2012 to December 2021 there were 371 arterial blood gasses with pH less than 7.0 in 231 patients. Metabolic acidosis was the most frequent subtype. Overall mortality was 42.8% (n=95). There was no difference in mortality between groups with primary respiratory, metabolic, or mixed disorders, but the need for vasopressors, the need for and duration of MV, and the length of stay in the hospital and ICU were different among groups. Patients with extreme acidosis caused by unmeasured anions with lactate ≥4 mmol/L had higher mortality compared with patients with extreme acidosis caused by unmeasured anions with lactate <4 mmol/L.

Keywords: Extreme acidosis; critical illness; prognosis; Stewart approach.

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LISTA DE ABREVIATURAS E SIGLAS

pH	Potencial hidrogeniônico/ Potential hydrogen
ICU	Intensive care unit
MV	Mechanical ventilation
VM	Ventilação mecânica
RRT	Renal replacement therapy
TSR	Terapia substitutiva renal
HCO_3^-	Bicarbonato
CO_2	Gás carbônico
$PaCO_2$	Pressão parcial de CO_2 / partial pressure of carbon dioxide
SDI	Strong ion difference
UTI	Unidade de terapia intensiva
SAPS 3	Simplified Acute Physiology Score 3
SD	Standard deviation
FIPE	Fundo de incentivo à Pesquisa e Ensino
BMI	Body mass index
COPD	chronic obstructive pulmonary disease
CI	Confidence interval

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1 INTRODUÇÃO

O funcionamento do organismo humano é o resultado de reações químicas a nível molecular e o bom funcionamento celular é dependente das condições físico-químicas do ambiente. Nesse sentido, a manutenção da concentração de íons H^+, mensurada por meio do pH, é essencial para a manutenção da homeostase [1]. Embora haja uma grande produção de ácidos no funcionamento celular, as concentrações de íons H^+ são baixas e constantes, devido aos mecanismos de defesa do organismo, baseados em três componentes: o sistema tampão, o centro respiratório e a excreção renal. Os tampões são a primeira linha de defesa contra a acidose, que tem a função de tamponar os íons H^+ até sua via final de excreção e reabsorção, seja pulmonar ou renal [2].

O sistema de tampão extracelular mais importante do organismo é o tampão de bicarbonato (HCO_3^-) [1-2]. Ele consiste em uma solução de água que contém dois componentes: um ácido fraco, o H_2CO_3, e um sal bicarbonatado, como o $NaHCO_3$ (Figura 1) [1]. Na presença de um ácido forte, como o HCl, o aumento de íons H^+ é tamponado pelo HCO_3^-, com produção de CO_2 e H_2O, que estimula o centro respiratório para a eliminação de CO_2. Já na presença de uma base forte, o OH^- reage com solução tampão de bicarbonato formando HCO_3^- adicional. O consumo de CO_2 na produção de bicarbonato, deprime o centro respiratório buscando um aumento na concentração de CO_2. [1]

$$\mathbf{CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO^-_3 + Na^+}$$

Figura 1. Tampão de bicarbonato.

A acidemia é definida, de acordo com abordagem fisiológica tradicional da teoria da neutralidade de Henderson Hasselbalch (Figura 2), como o acúmulo de ácido (CO_2) ou a perda da reserva alcalina ($HCO3^-$) do sangue e dos tecidos e mensurada pelo pH (co-logaritmo da atividade dos íons hidrônio) plasmático menor que 7,35 [3-4]. A acidemia divide-se em causas respiratórias e causas metabólicas. A acidose respiratória decorre do acúmulo de CO_2, um ácido volátil, como evento desencadeador da acidose. A fisiopatologia para este distúrbio se alicerça na disfunção respiratória aguda do tipo II, em que o mecanismo de eliminação de CO_2

está prejudicado. Já a acidose metabólica ocorre pelo acúmulo de ácidos não voláteis, que é mensurada pela redução de bicarbonato pelo método fisiopatológico tradicional [5].

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO^-_3$$

Figura 2. Equação de Henderson Hasselbalch.

Contudo, essa avaliação é limitada, uma vez que a mensuração do bicarbonato é produto do pH e da pCO_2 sendo assim uma variável dependente. Ou seja, não há como avaliar uma acidose metabólica de forma independente. Nesse sentido surgiram métodos alternativos e aditivos de avaliação das alterações ácido-básicas, entre eles o excesso de base (do inglês, *base excess*) e o método de Stewart de [6-7]. O excesso de base é definido como a quantidade de ácido forte que deve ser adicionado à amostra de sangue para que ela retorne a um pH de 7,4 [8]. Nenhuma alteração do excesso de base metabólica é esperada com alterações respiratórias agudas e para alterações respiratórias crônicas existe correção de 0,4 mmol/l para cada 1 mmHg na pressão parcial de dióxido de carbono [21]. Salienta-se que $PaCO_2$ e pH são as únicas mensuradas diretamente, sendo $HCO3^-$ e o excesso de base variáveis derivadas. Nesse sentido, por entender a abordagem centrada no bicarbonato confusa e inadequada, o fisiologista canadense Peter Stewart propôs uma abordagem da fisiologia ácido-básica dos fluidos corporais centrada na dissociação da água, onde ele introduz o termo SDI (do inlgês, *strong ion difference*), que é a diferença entre da concentração de cátions fortemente dissociáveis menos a concentração de ânions fortemente dissociáveis [7,22]. O pH de qualquer fluido corporal é uma função da dissociação da água modificada por PCO_2, outros ácidos fracos e certos eletrólitos. Assim estabeleceu seis equações que, em equilíbrio simultâneo, e sob as restrições das Leis de Ação em Massa, Conservação de Massa e Neutralidade Elétrica podem ser usadas para definir a relação PCO_2/pH, conforme a figura abaixo [22].

$$[H^+]^4 + ([SID^+] + K_a)\,[H^+]^3 + [K_a\,([SID^-] - [A_{TOT}]) - K_W' - K_1'S\,PCO2][H+]2 - [K_a\,(K_W' + K_1'S\,pCO_2) - K_3K_1'S\,pCO_2][H^+] - K_aK_3K_1'S\,pCO_2 = 0$$

Figura 3. Equação de Stewart.

Sumarizando as equações, se chega à conclusão que as concentrações de bicarbonato e de íons de hidrogênio (pH) são dependentes de três variáveis de controle independentes: 1- a pressão parcial de CO_2 (componente respiratório); 2- a diferença de íons fortes; 3- a concentração total de ácido fraco em associação com as constantes de dissociação dos ácidos fracos e da água [9]. Íons fortes são aqueles que estão completamente dissociados em uma solução. A diferença de íons fortes é medida pela soma dos cátions com dissociação completa no plasma (sódio, potássio, cálcio e magnésio) menos os ânions com dissociação completa no plasma (cloreto e lactato). Com base no princípio da eletroneutralidade, presume-se que o íon que preenche a diferença de íons fortes de forma majoritária é o bicarbonato (variável dependente) [4]. Ácidos fracos são ácidos parcialmente dissociados (albumina e fosfato) e também contribuem para alterações do pH e do bicarbonato. Assim, a acidose metabólica é causada por uma diminuição da diferença de íons fortes e um aumento na concentração total de ácido fraco [7].

Um método simplificado combina a avaliação do excesso de base e a abordagem de Stewart com o escopo de facilitar a avaliação da acidose metabólica à beira do leito, onde o excesso de base é inferido com base na diferença entre íons fortes, ressaltando a importância do lactato com ânion forte, e ácidos fracos, sobretudo a albumina, podendo ser simplificada na seguinte equação: base excess = [Na - Cl - 35] + [1 - lactato] + [0,25 x 42 - albumina] + outros íons. O objetivo dessa avaliação é a melhor compreensão da acidose metabólica em pacientes com múltiplas doenças associadas, nos quais diversas condições poderiam gerar o distúrbio. Ao se identificar a causa do distúrbio, o manejo clínico mais adequado é possível [21]. Por exemplo, frente a um paciente em ventilação mecânica e cirrose hepática que realizou reanimação com solução salina e apresenta a seguinte gasometria arterial e eletrólitos: pH 7,2, PCO_2 40 mmHg, bicarbonato 15 mmol/l, lactato 5 mmol/l, sódio 133 mmol/l, cloreto 110 mmol/l e albumina 22 g/l, à primeira vista a acidose metabólica tem causa presumida na hiperlactatemia, mas a análise pelo método de Stewart simplificado mostra que a diferença de íons fortes é o fator com maior impacto na acidose do paciente, que pode ser consequência da ressuscitação com solução salina com indução de acidose hiperclorêmica.

Acidose é uma condição potencialmente fatal, que afeta o funcionamento de diversos sistemas orgânicos e tem elevada incidência em pacientes em unidades de

terapia intensiva (UTI), com taxas que chegam a 40% em alguns estudos [10-11]. Acidemia grave é definida pela presença de pH plasmático <7,2, que se associa a alta mortalidade [11]. Acidemia com pH extremo abaixo de 7,0 é geralmente fatal, salvo em casos de cetoacidose diabética [23]. Tem-se debatido se a acidose é um marcador de disfunção orgânica ou um fator independentemente relacionado a ela. [11]. Grandes reduções do pH afetam a distribuição de cargas de proteínas, podendo levar à desnaturação proteica, com um potencial catastrófico para o organismo [12]. Estudos em modelos animais comprovaram o efeito deletério da acidose, como a redução da contratilidade cardíaca e redução de resposta dos receptores adrenérgicos às catecolaminas. Além disso, a hipercapnia aguda gera redução de contratilidade diafragmática e aumento do fluxo sanguíneo cerebral, estando relacionada a aumento da pressão intracraniana e à perda de consciência e convulsões [13]. Além dessas evidências em modelos animais, um estudo recente em humanos mostrou os efeitos nocivos da acidemia na função cardíaca, avaliada pela técnica de termodiluição transpulmonar com análise integrada do débito cardíaco pelo contorno do pulso (PiCCO™; Pulsão, Grupo Maquet Getinge, Feldkirchen, Alemanha), de uma coorte de pacientes graves no Reino Unido [14]. Neste estudo, um ponto de corte de pH de 7,28 diferenciou dois grupos, separando-os por gravidade dos parâmetros cardíacos avaliados.

Embora haja um amplo entendimento fisiológico dos malefícios da acidose no funcionamento celular, existem algumas evidências clínicas de que certo grau de acidose possa ser benéfica em alguns contextos [15-16]. O efeito protetor da hipercapnia permissiva na lesão pulmonar, por exemplo, foi atenuado em estudos experimentais quando houve tamponamento do pH, inferindo, dessa forma, um papel da acidose *per se* [17]. Nesse sentido, existe discussão sobre o manejo ideal da acidose no contexto de doença crítica aguda. Considerando a teoria da neutralidade, seria esperado que em um contexto de acidemia, a suplementação de uma solução tampão teria benefício, com melhora de desfechos clínicos. Contudo, as evidências são controversas. No BICAR-ICU trial, um estudo multicêntrico com 389 pacientes, avaliou a reposição de bicarbonato de sódio para manejo da acidose, não havendo diferença no desfecho composto de morte por qualquer causa em 28 dias ou disfunção orgânica nova em sete dias [18]. A falta de associação clara entre acidose plasmática e acidose celular parece ser o principal fator da compreensão incompleta dos distúrbios ácido-básicos no cenário da doença crítica [13].

Existe um conhecimento incompleto da acidose extrema (pH < 7,0) no cenário da doença crítica e entender sua incidência e associação com desfechos clínicos é importante para a melhor compreensão do metabolismo da doença crítica, orientando investigações futuras. Com isso, o presente estudo propõe-se a realizar uma análise do perfil dos pacientes criticamente doentes com acidose com pH extremo e os desfechos da doença crítica, como mortalidade, taxa de disfunção orgânica, tempo de hospitalização e suporte de vida, como o uso de ventilação mecânica e de terapia de substituição renal. Além disso, não há estudos de avaliação da acidose extrema pelo método de Stewart e sua relação com prognóstico entre os subgrupos de causa de acidose em pacientes criticamente doentes.

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2 DESENVOLVIMENTO

2.1 INTRODUCTION

Potential hydrogen (pH) corresponds to the molar concentration of hydronium cations in a solution. A range of serum pH between 7.35 - 7.45 is considered normal [1]. The maintenance of this narrow range results from the intersection of buffer systems with the hydrogen ion excretion pathways (renal or respiratory) [2]. The dysregulation of this finetune acid-base balance leads to deleterious effects in physicochemical reactions in the organism, being potentially fatal.

In addition to the insult leading to acidemia, changes in hemodynamic, respiratory, and immune function are direct complications associated with the state of acidosis [3-4,6]. Thus, in cases of severe and extreme acidosis, the direct administration of tampons to correct the disorder is controversial [7]. Case series of patients with extreme acidosis reported high mortality rates [4,5], but with little information about the type of acidosis, underlying causes, associated comorbidities, and treatment. A retrospective study showed that the use of bicarbonate occurs more frequent in more severe patients, with no benefit associated with its use [10]. Moreover, the BICAR-ICU study, which aimed to evaluate whether sodium bicarbonate infusion would improve outcomes in critically ill patients with severe metabolic acidosis (pH <7.2) showed no benefit in survival or multiorgan dysfunction, except for a benefit in mortality in a prespecified subgroup of patients with acute renal failure [8]. Even in patients with respiratory acidosis, the use of buffer solutions is questionable [9]. Then, the impact of tampon use in severe and extreme acidosis needs further studies, with no guidelines for management at the present [10].

Besides the uncertainties regarding treatment, the most appropriate approach to diagnose acidosis, especially metabolic acidosis, is a matter of debate [2,11-12]. The traditional acid-base calculation uses serum bicarbonate level, anion gap, and base excess for analysis. The Stewart approach proposes that pH is determined by three independent controllers of acid-base status: the partial pressure of carbon dioxide ($PaCO_2$), the strong ion difference (SID), and the total amount of nonvolatile weak acids [12]. The Stewart approach adds to the traditional model by analyzing each variable independently to indicate the cause of the acid disorder [13]. Moreover, hypoalbuminemia, a common condition in critically ill patients, may lead to errors in the analysis of acidosis using traditional methods [2,11-13]. Comparisons of the traditional method with the Stewart approach shows that the latter is superior, both in identifying metabolic acidosis and grading the severity of the disorder [14].

Disturbances in acid-base balance, especially acidosis, are very common in critically ill patients [3]. However, data on extreme acidosis defined as a pH <7 is lacking [4,5]. This study aims to evaluate the impact of extreme acidosis subtypes on mortality and clinical outcomes of critically ill patients.

2.2 MATERIAL AND METHODS

Population

This is a single center retrospective cohort study developed at the Hospital de Clínicas de Porto Alegre, a tertiary university hospital with 45 mixed medical-surgical ICU beds. We conducted an electronic search to identify critically ill patients with extreme acidosis defined as a pH <7.0 [4]. Patients were considered eligible if they were >18 years, were admitted to the ICU, and had at least one arterial blood gas analysis with pH <7.0. Each patient was included once. Patients with more than one

gasometry with pH <7.0, the first one was analyzed. The main exclusion criteria was previously defined end-of-life directions, data error as venous or non-patient collection , and missing primary outcome data. The study was approved by the Ethics Committee at Hospital Clínica de Porto Alegre and was in agreement with the Helsinki Declaration. Informed consent was waived by the institution for reasons of the retrospective design and anonymization of patient identifiers before analysis.

Data collection

Clinical and laboratory data were obtained from electronic medical records for all patients. Variables included age, gender, ethnicity, body mass index (BMI), comorbidities, reason for ICU admission, presence of sepsis, occurrence of cardiac arrest, relationship between acidosis and an immediate post-cardiac arrest period, bicarbonate infusion to correct acidosis, and the definition of the cause of acidosis according to the traditional method and the simplified Stewart approach. Simplified Acute Physiology Score 3 (SAPS 3), ranging theoretically from a minimum of 0 points to a maximum of 271 points was used to score disease severity [15]. Arterial blood gas analyses, serum electrolytes, and albumin values were recorded. Blood gas analyses were performed on a ABL800 flex system (Radiometer Ibérica, Madrid, Spain). The number of arterial blood gas analyses with extreme acidosis (pH<7.0) was computed for each patient. We classified acidosis according to previous studies, as follows: 1- metabolic disorder if $PaCO_2$ <40 mmHg and $HCO3^-$ <24 mmol/L; 2- respiratory disorder if $PaCO_2$ >40 mmHg and $HCO3^-$ >24 mmol/L; 3- mixed metabolic and respiratory disorder if $PaCO_2$ >40 mmHg and $HCO3^-$ <24 mmol/L [4]. The anion gap was considered increased if >12mEq/L [2]. A simplified Stewart approach was applied for gas analysis using a calculator for smartphones (Stewart Acid-Base,

Brazil) [16] to classify acidosis according to the presence of unmeasured anions, chloride, or lactate. The independent variable with the greatest impact on acidosis was considered as the cause of acidosis.

Outcomes

In-hospital mortality was the primary outcome. The secondary outcomes were need for vasopressors, mechanical ventilation (MV), and/or renal replacement therapy (RRT), time spent on MV and/or on RRT, and length of ICU and hospital stay.

Statistical analysis

Considering a total mortality rate of 54% [7] we estimated a sample size of 646 patients (316 patients with respiratory, 264 with metabolic, and 61 with mixed acidosis subtypes) to find a 20% reduction in mortality in patients with respiratory acidosis [17], with a power of 80% and an alpha-error of 5%.

Categorical variables were expressed as percentages. Data were expressed as mean and standard deviation (SD) if normally distributed, or as median and interquartile range otherwise. Patients were classified according to the primary disorder as having respiratory, metabolic, or mixed acidosis. Groups were compared using one-way analysis of variance with Bonferroni's post-hoc test, Kruskal–Wallis test, or chi-square test as appropriate. To assess the impact of the primary disorder subtype on mortality, we constructed a multivariate logistic regression model adjusting for age and SAPS 3 score, variables with biological plausibility to associate with the primary outcome. Values were considered statistically significant if $p < 0.05$. Statistical analyses were conducted in SPSS 23.0 (Chicago, IL, USA).

2.3 RESULTS

Between January 2012 to December 2021, 231 patients had 371 arterial blood gas analyses with pH <7. Nine eligible patients were excluded: seven due to laboratory error, and two due to missing data, resulting in 222 patients included in the study. The total number of ICU admissions during the study period was 33.245 patients, with a mean of 3017 ± 1028 per year. Considering the rate of admissions during the 10-year study period, 0.67% of patients (n=222) presented with extreme acidosis.

The main characteristics of the study population are summarized in Table 1. Briefly, 49.5% were male, with a mean age of 55 ± 16, and a SAPS 3 score of 76 ± 18. Hypertension was the most common previous medical condition (53.2%). The main organ dysfunctions at ICU admission was shock (76.6 %), followed by acute respiratory failure (68%), and acute renal failure (66.2%). Twenty-seven patients had COVID-19 (12.2%).

Minimum pH detected was 6.68. As expected, PaCO2, HCO3, anion gap and base excess was different between groups. Higher serum lactate levels were found in the group with metabolic acidosis and mixed acidosis compared to the group with respiratory acidosis (5.8 [1.4 - 16] vs. 3.2 [1 - 11.4] vs. 1.1 [0.9 to 1.3] mmol/L, respectively, p <0.001). Although not significant, there was a higher incidence of renal failure in patients with metabolic and mixed acidosis and, consequently, serum creatinine, urea and potassium levels were higher in these groups compared to the group with respiratory acidosis (Table 2). Sixteen patients (7.2%) had pH <6.8. Of them, three had diabetic ketoacidosis (18.7%), and 11 survived to hospital discharge (68.7%).

Table 1. Baseline demographic and clinical characteristics of patients with extreme acidosis.

Demographics	All (n=222)	Respiratory acidosis (n=25)	Metabolic acidosis (n=75)	Mixed acidosis (n=122)	p
Age (years)	55 ± 16	52 ± 17	57 ± 16	54 ± 16	0.3
Male gender (n, %)	110 (49.5)	12 (48)	39 (52)	59 (48.4)	0.8
BMI (kg/m^2)	26.8 ± 7	29.5 ± 9.5	26.7 ± 6.5	26.3 ± 6.5	0.1
Caucasian (n, %)	181 (81.5)	20 (80)	60 (80)	101 (82.8)	0.7
SAPS 3 score	76 ± 18	70 ± 17	77 ± 19	77 ± 18	0.2
Comorbidities					
Hypertension (n, %)	118 (53.2)	13 (52)	45 (60)	60 (49.2)	0.3
Diabetes (n, %)	64 (28.8)	3 (4.7)[a]	33 (51.6)[a]	28 (43.8)[a]	**<0.001**
Obesity (n, %)	58 (26.1)	10 (40)	18 (24.3)	30 (25)	0.26
Heart failure (n, %)	39 (17.6)	3 (12)	14 (18.7)	22 (18)	0.7
Chronic kidney disease (n, %)	70 (31.5)	3 (12)[a]	31 (41.3)[a]	36 (29.5)	**0.01**
COPD (n, %)	36 (16.2)	6 (24)	5 (6.7)[a]	25 (20.5)	**0.02**
COVID-19 (n, %)	27 (12.2)	9 (36)[a]	5 (6.7)	13 (10.7)	**<0.001**
Immunosuppression (n, %)	35 (15.8)	2 (8)	10 (13.3)	23 (18.9)	0.3
Cancer (n, %)	43 (19.4)	2(8)	17 (22.7)	24 (19.7)	0.27

Reasons for ICU admission					
Shock (n, %)	170 (76.6)	20 (80)	55 (73.3)	95 (77.9)	0.7
Septic (n, %)	107 (48.2)	17 (89.5)	35 (64.8)	55 (59.1)	0.4
Hypovolemic (n, %)	26 (11.7)	0 (0)	10 (18.5)	16 (17.2)	
Cardiogenic (n, %)	12 (5.4)	1 (5.3)	3 (5.6)	8 (8.6)	
Obstructive (n, %)	14 (6.3)	1 (5.3)	4 (7.4)	9 (9.7)	
Mixed (n, %)	7 (3.2)	0 (0)	2 (3.7)	5 (5.4)	
Presence of sepsis (n, %)	144 (64.9)	21(84)	44 (59.5)	79 (64.8)	0.08
Cardiac arrest (n, %)	47 (21.2)	3 (12)	12 (16)	32 (26.2)	0.1
Acute respiratory failure (n, %)	151 (68)	23 (92)[a]	43 (57.3)[a]	85 (69.7)	**0.005**
Coma (n, %)	122 (55)	11 (44)	38 (50.7)	73 (59.8)	0.2
Acute renal failure (n, %)	147 (66.2)	12 (48)	53 (70.7)	82 (67.2)	0.1
Ketoacidosis (n, %)	13 (5.9)	0 (0)	12 (16)[a]	1 (0.8)	**<0.001**
Post-operative care (n, %)	77 (34.7)	7 (28)	18 (24)[a]	52 (43)[a]	**0.02**
Biochemistry profile					
Calcium (mg/dL)	8.7 ± 1.1	9.1 ± 0.4	8.5 ± 1.2	8.9 ± 1	0.08
Magnesium (mg/dL)	2.1 ± 0.5	2 ± 0.4	2.1 ± 0.5	2.1 ± 0.5	0.8
Potassium (mEq/L)	5.2 ± 1.3	5.7 ± 1.3[d]	5.6 ± 1.6[c]	4.9 ± 1[c,d]	**< 0.001**
Urea (mg/dL)	109 ± 88	72 ± 52[b]	144 ± 119[b,c]	95 ± 61[c]	**< 0.001**
Creatinine (mg/dL)	2.1 (1.2 - 3.9)	1.8 (0.6 - 3.8)[b]	4 (2.1 - 12.3)[b,c]	2.5 (1.7 - 4.2)[c]	**0.002**

BMI: body mass index; SAPS 3: Simplified Acute Physiology score 3; COPD: chronic obstructive pulmonary disease; Values are mean ± SD or median and interquartile range. Analyses of categorical variables were performed using the chi-square test and of continuous variables using ANOVA test or Kruskall-Wallis test, as appropriate.a: Chi-square test with adjusted residue >1.96; b: difference between respiratory acidosis and metabolic acidosis groups; c: difference metabolic acidosis and mixed acidosis groups; d: difference between respiratory acidosis and mixed acidosis groups.

The causes, characteristics, and treatment of extreme acidosis are presented in Table 2. The primary disorder was respiratory acidosis in 11.3% of patients (n=25), metabolic acidosis in 33.8% (n=75), and mixed respiratory and metabolic acidosis in 55% (n=122). Acidosis was present at the time of ICU admission in 72% of patients (n=160) and 31% of patients (n=69) had extreme acidosis immediately after an episode of cardiac arrest. The mean anion gap was 22 ± 8 and most patients presented values >12 mEq/L. Acidosis was corrected in 71.6% (n=159) of the patients, with infusion of bicarbonate in 55.9% (n=124) of patients. The median time to correct acidosis was 17 (8 - 45) hours.

Primary outcome

Overall in-hospital mortality was 42.8% (n=95). No difference in mortality was observed among groups with respiratory, metabolic, and mixed primary disorders (28% vs. 42.7% vs. 45.9%, p=0.26) (Table 3). Similarly, when we adjusted for age and SAPS 3 score using a multivariate logistic regression model, no association between the primary disorder and mortality was detected (Table 4).

The reasons for ICU admission did not impact the survival rate, except for surgical patients admitted in the postoperative period (42.2% died vs. 27.8% survived, p=0.01). Besides, no patient (n=13) with diabetic ketoacidosis died.

Table 2. Causes, characteristics, and treatment of extreme acidosis (pH <7.0).

Variable	Respiratory acidosis (n=25)	Metabolic acidosis (n=75)	Mixed acidosis (n=122)	p
pH	6.92 ± 0.07	6.92 ± 0.06	6.92 ± 0.07	0.9
$PaCO_2$ (mmHg)	146 ± 27[a]	26 ± 15[a]	72 ± 23[a]	**< 0.001**
HCO_3 (mmol/L)	28 ± 3[a]	5 ± 3[a]	14 ± 4[a]	**< 0.001**
Anion gap (mEq/L)	13 ± 4[a]	27 ± 7[a]	20 ± 7[a]	**< 0.001**
Base excess (mEq/L)	-9 ± 5[a]	-26 ± 4[a]	-18 ± 4[a]	**< 0.001**
Lactate (mmol/L)	1.1 (0.9 - 1.3)[b,d]	5.8 (1.4 - 16)[b]	3.2 (1 - 11.4)[d]	**< 0.001**
Sodium (mEq/L)	140 ± 5	139 ± 7	140 ± 7	0.2
Chloride (mEq/L)	100 ± 8	102 ± 7	103 ± 7	0.5
Albumin (g/dL)	2.9 ± 0.6	3 ± 1	2.7 ± 0.8	0.1
Phosphate (mg/dL)	3.9 (2.3 - 12.3)	5.6 (4.2 - 8.5)	4.9 (3.4 - 6.8)	0.4
Acidosis at ICU admission (n, %)	16 (10)	60 (37.5)	84 (52.5)	0.2
Post-cardiac arrest acidosis (n, %)	4 (5.8)	16 (23.2)[e]	49 (71)[e]	**0.005**
Use of bicarbonate (n, %)	2 (1.6)[e]	59 (47.6)[e]	63 (50.8)	**<0.001**
Acidosis resolved (n, %)	24 (15.1)[e]	51 (32.1)	84 (52.8)	**0.02**
Acidosis correction time (hours)	121 (40 - 193)	16 (10 - 29)	23 (9 - 40)	0.7
Time between acidosis and death (days)	9.5 (0 - 50)	1 (0 - 11)	3 (0 - 51)	0.5

ICU: intensive care unit. $PaCO_2$:CO2 partial pressure; HCO_3 : bicarbonate. Analyses of categorical variables were performed using the chi-square test and of continuous variables using ANOVA test or Kruskall-Wallis test, as appropriate. a: difference between all groups; b: difference between respiratory acidosis and metabolic acidosis groups; c: difference between metabolic acidosis and mixed acidosis groups; d: difference between respiratory acidosis and mixed acidosis groups; e:Chi-square test with adjusted residue >1.96

Secondary outcomes

Clinical outcomes of patients with extreme acidosis according to the primary disorder are summarized in Table 3. Patients with metabolic acidosis used less vasopressors than patients with respiratory acidosis or mixed acidosis (77% vs. 88% vs. 91% respectively, p=0.02). As expected, patients with respiratory acidosis needed MV more frequently than patients with metabolic acidosis (96% vs. 82.4%, p=0.001) and spent a longer time on MV than the other groups (21 [9 to 47] vs. 8 (5 to 16) vs. 9 [4.5 to 17.5] days, p <0.001). The need and duration for RRT was not different among groups. The length of hospital stay and ICU stay were shorter and the need for ICU readmission were lower in patients with metabolic acidosis, but similar in patients with respiratory and mixed acidosis (Table 3).

Patients who survived used less supportive therapy than non-survivors (vasopressor use 81% vs. 93%, p=0.01; need for MV 88% vs. 97%, p=0.02; ICU readmission 18% vs. 53%, p <0.001).

Table 3. Outcomes of patients with extreme acidosis according to the primary disorder subtype.

Outcomes	Respiratory acidosis (n=25)	Metabolic acidosis (n=75)	Mixed acidosis (n=122)	p
Mortality (n, %)	7 (28)	32 (42.7)	56 (45.9)	0.26
Need for vasopressors (n, %)	22 (88)	57 (77)[a]	111 (91)[a]	**0.02**
Need for MV (n, %)	24 (96)	61 (82.4)[a]	118 (96.7)[a]	**0.001**
Time spent on MV (days)	21 (9 to 47)[b,d]	8 (5 to 16)[b]	9 (4.5 to 17.5)[d]	**< 0.001**
Need for RRT (n, %)	10 (40)	44 (59.5)	69 (56.6)	0.2
Time spent on RRT (days)	7.5 (5 to 44)	12 (2 to 27)	21 (12.5 to 38)	0.4
ICU readmission (n, %)	8 (32)	17 (22.7)	48 (39.3)	0.05
Hospital length of stay (days)	37 (27 to 50)	34 (14 to 66)[c]	41 (23 to 78)[c]	**< 0.001**
ICU length of stay (days)	18 (5 to 28)[b]	15 (7 to 18)[b,c]	18 (10 to 36)[c]	**< 0.001**

MV: mechanical ventilation; RRT: renal replacement therapy; ICU: intensive care unit. Values are median and interquartile range. Analyses of categorical variables were performed using the chi-square test and of continuous variables using ANOVA test or Kruskall-Wallis test, as appropriate.
a: Chi-square test with adjusted residue >1.96;
b: difference between respiratory acidosis and metabolic acidosis groups;
c: difference between metabolic acidosis and mixed acidosis groups;
d: difference between respiratory acidosis and mixed acidosis groups.

Exploratory analyses

The simplified Stewart method was applied in 113 patients (50.9%) with complete data for acid-base calculation. Unmeasured anions were the major component of extreme acidosis in 81.4% of patients (n=92), followed by hyperlactatemia in 15.9% (n=18), and chloride in 2.7% (n=3). Of the 92 patients with unmeasured anions as the main component of acidosis, 45 (48.9%) also had lactate ≥4 mmol/L contributing to worsening acidosis. No difference in mortality was detected regarding the ion analysis using the simplified Stewart method (unmeasured anions 41% vs. hyperlactatemia 39% vs. chloride 33%, p=0.9). Interestingly, patients with extreme acidosis caused by unmeasured anions with lactate ≥4 mmol/L had a higher mortality compared to patients with extreme acidosis caused by unmeasured anions with lactate <4 mmol/L (55.6% vs. 27.7%, p=0.007). The median contribution of lactate to the extreme acidosis among survivors was lower than in non-survivors (-2.2 [-10.8 - -0.3] vs. -9.15 [-14.0 - -1.13], p=0.001). In contrast, the mean contribution of unmeasured anions to extreme acidosis did not differ between survivors and non-survivors (-19.5 ± 8.3 vs. -19.3 ± 8, p=0.899).

Table 4. Adjusted odds ratio for in-hospital mortality of primary disorder subtypes, age, and SAPS 3 score using logistic regression.

Variable	OR	CI 95%	p
SAPS 3 score	1	0.98 - 1.02	0.96
Age (years)	1.03	1.01 - 1.05	**0.001**
Primary disorder subtype			0.38
Metabolic	1		
Respiratory	0.63	0.22 - 1.74	
Mixed	1.23	0.67 - 2.25	

CI: confidence interval; OR: odds ratio; SAPS 3: Simplified Acute Physiology score 3.

2.4 DISCUSSION

In this retrospective cohort study of 222 critically ill patients, we showed extreme acidosis is a rare event and mixed acidosis was the most common primary disorder subtype determining it. The primary disorder subtype was not associated with mortality, but it did impact the need for vasopressors, need for MV and time spent on MV, and length of hospital and ICU stay. Moreover, hyperlactatemia confers worse prognosis in patients with extreme acidosis.

The in-hospital mortality rate of our sample was lower than expected [4,5]. In a multicenter prospective study conducted in 2011 [7], a mortality rate of 57% was reported in critically ill patients with severe metabolic or mixed acidosis defined as pH <7.2, a much higher pH cut-off than ours. Even for patients with pH <6.8, the mortality was lower compared to the literature (31% vs. 68%) [5]. This lower than expected mortality is not explained by disease severity, as inferred by a very high SAPS 3 score, but might be attributed to the not negligible number of patients with respiratory acidosis as the primary disorder leading to extreme acidosis. The mortality rate of respiratory acidosis described in the literature is around 26% [18,19], similar to ours.

It is biologically plausible to infer different mortality in different subtypes of acidosis. While studies with metabolic and mixed acidosis show a mortality rate around 60% [7], studies with respiratory acidosis have a rate around 25% [19], as the respiratory buffer system is more labile, facilitating intervention through the institution of life support [20]. Mochizuki et al. studied different acidosis subtypes in critically ill patients with any pH <7.38, showing higher mortality for the mixed subtype [17]. At present, mortality rates according to the subtype of primary disorder leading to extreme acidosis have not been compared. We present here, for the first time, the results of a large cohort of patients with extreme acidosis classified by the type of

primary disorder. Surprisingly, the mortality was not affected by the primary disorder subtype, as we expected metabolic acidosis to be more fatal than others. It seems that at a very low pH, the effect of acidosis in the performance of the cardiovascular system is more determinant of the outcomes than it is the subtype of primary disorder. In line with these findings, Jung et al. demonstrated that the delay to recover from severe acidosis impacts mortality, a variable that might stand out the type of acidosis [7].

Regarding the secondary outcomes, patients with metabolic acidosis needed lower doses of vasopressors and less MV. These patients received bicarbonate more frequently and had higher rates of corrected acidosis, but with a similar time spent on correction. Similarly, previous studies using bicarbonate infusions failed to demonstrate increased survival, but showed positive effects on secondary outcomes, such as the need for RRT and vasopressor-free days [21]. In patients with respiratory acidosis, longer times spent on MV were demonstrated, as different ventilation strategies are expected in patients with respiratory failure [22]. While respiratory acidosis is treated with MV, in metabolic acidosis MV is a supportive therapy to allow for the recovery of the underlying condition.

As expected, chronic kidney disease and diabetes were more prevalent in patients with metabolic and mixed acidosis. Besides, ketoacidosis was associated with metabolic acidosis [23]. Conversely, respiratory failure was associated with respiratory acidosis [24] and chronic obstructive pulmonary disease and COVID-19 were more frequent in this subtype [20]. Mixed acidosis was more frequent in patients admitted to the ICU at the postoperative period, in agreement with the literature. At the postoperative period, mixed acidosis might result from the

overlapping of hypoventilation during the anesthetic reversal phase and some degree of persistent hypoperfusion [25].

The Stewart approach demonstrated that unmeasured anions were the major component leading to metabolic acidosis in our sample, followed by hyperlactatemia. Similarly, a prospective observational study enrolling patients with septic shock, showed unmeasured ions and hyperchloremia were the two major components of acidosis [26]. Interestingly, we observed that patients with extreme acidosis due to unmeasured anions alone have better prognosis than those with extreme acidosis due to unmeasured anions with concomitant lactate elevation. Therefore, we demonstrate here that hyperlactatemia negatively impacts survival of critically ill patients presenting with extreme acidosis. This is consistent with the literature, since lactate is described as an independent predictor of mortality in patients admitted to the ICU [27]. The increase in lactate occurs through several pathways and might reflect the systemic inflammatory state leading to hypoperfusion, particularly in sepsis. In sepsis, lactate is an early biomarker for risk stratification, even before clinically evident organic dysfunction is present [28].

The strength of this study is the inclusion of a large sample of critically ill patients presenting with extreme acidosis. This is the best available data regarding mortality in patients with extreme acidosis. However, this study has limitations. First, the study is underpowered. Our results have 35% power to detect 20% difference in mortality in favor of patients with respiratory acidosis. This limitation elapses from the low incidence of extreme acidosis and from the impossibility to identify patients with extreme acidosis before 2012, when full electronic medical records were adopted by our institution. Second, due to the retrospective design, some information was missing, not allowing for the use of the Stewart approach to all patients. However,

this is the largest cohort of patients with extreme acidosis evaluated by the Stewart approach. Third, the study is unicentric, limiting generalization, but the study population included patients admitted to mixed medical-surgical ICUs. Finally, information regarding dose and time of bicarbonate infusion was not available, precluding in-depth conclusions about the impact of treatment according to the acidosis subtypes.

In conclusion, the primary disorder subtype causing acidosis was not associated with mortality, but it did impact the need for vasopressors, need and duration of MV, and length of hospital and ICU stay. More importantly, hyperlactatemia confers worse prognosis in patients with extreme acidosis.

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3 CONCLUSÃO

A acidose é uma condição potencialmente fatal, sobretudo quando em valores extremos. [1-2]. É descrito na literatura que a acidose *per se* pode afetar a performance cardiovascular [3-4], gerar desnaturação proteica [5] e alterações do estado mental [6]. Nesse sentido, considerando a acidose como uma causa de disfunção orgânica e não apenas como um marcador de gravidade, tem se discutido o benefício da correção da acidose no cenário da doença crítica [3-7].

Por outro lado, tem-se avançado o conhecimento sobre a ventilação protetora, que demonstra desfechos positivos em contexto de acidose [8]. Atualmente se advoga o conceito de acidemia permissiva no cenário da síndrome da angústia respiratória aguda, sendo discutido até mesmo efeitos vantajosos dessa condição [9]. Essas evidências geram questionamentos sobre se a acidose do tipo respiratória difere da acidose metabólica, com efeitos distintos no organismo.

A comparação direta dos subtipos de acidose é escassa na literatura. Se percebe, porém, que a mortalidade em estudos com pacientes com acidose metabólica e mista é maior que a mortalidade em estudos com pacientes com acidose respiratória [3,10]. Um estudo recente e multicêntrico que avaliou os subtipos de acidose em pacientes críticos demonstrou que a mortalidade é menor nos pacientes com acidose respiratória [11]. Diante disso, identificar corretamente o subtipo de acidose no paciente crítico é crucial não só para seu correto manejo, mas também pelo impacto prognóstico sugerido pelas evidências atuais. O método de Stewart tem sido descrito como uma ferramenta útil na diferenciação dos fatores causais da acidose, bem como na quantificação da atuação de cada um deles [12].

Não se encontrou dados na literatura da avaliação do impacto dos subtipos de acidose quando em valores extremos de pH (<7,0). Os estudos sobre esta condição são pequenos devido a sua baixa incidência e demonstram alta mortalidade [1-2]. O perfil da acidose extrema também é pouco estudado. Questiona-se se níveis tão baixos de pH teriam um efeito deletério independente, ou se nesses níveis de acidose o subtipo deixa de ser relevante, não impactando nos desfechos.

O subtipo mais frequente em nossa amostra foi a acidose mista e foi possível diferenciar causas de admissão em UTI para cada subtipo de acidose. Não houve diferença de mortalidade entre os subtipos. Contudo, a amostra tem cerca de 30% do tamanho esperado, tendo assim um baixo poder estatístico para confirmação de nossos achados. A baixa incidência de casos de acidose extrema torna desafiante estudos com grandes amostras, necessitando estudos multicêntricos para alcançar amostra considerável.

Os desfechos secundários como necessidade de ventilação mecânica, de vasopressores, tempos de internação hospitalar e em UTI foram distintos entre os subtipos de acidose na nossa amostra, sugerindo que de fato a acidose, mesmo quando extrema, tem prognósticos diferentes na dependência do subtipo. Além disso, a análise pelo método de Stewart mostrou que a maioria dos casos tem como determinante da acidose o aumento de ânions não mensurados, mas apenas aquelas que têm lactato aumentado tem um prognóstico distinto. Assim, não só a acidose respiratória é diferente das demais, como também a acidose mista e metabólica são diferentes entre si, tendo na hiperlactatemia um importante marcador de gravidade.

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