Retrospective Cohort Study
Physico-Chemical Characterization of Acid Base Disorders in Patients with CoVID-19: A Cohort Study

Acid Base disorders in COVID 19

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Abstract

BACKGROUND

Acid-base imbalance has been poorly described in patients with coronavirus disease 2019 (COVID-19). Study by the quantitative acid-base approach may be able to account for minor changes in ion distribution that may have been overlooked using traditional acid-base analysis techniques. In a cohort of critically ill COVID-19 patients, we looked for an association between metabolic acidosis surrogates and worse clinical outcomes, such as mortality, renal dialysis, and length of hospital stay.

AIM

To describe the acid-base disorders of critically ill COVID-19 patients using Stewart’s approach, associating its variables with poor outcomes.

METHODS

This study pertained to a retrospective cohort comprised of adult patients who experienced an intensive care unit stay exceeding 4 d and who were diagnosed with severe acute respiratory syndrome coronavirus 2 infection through a positive PCR analysis of a nasal swab and typical pulmonary involvement observed in chest computed tomography scan. Laboratory and clinical data were obtained from electronic records. Categorical variables were compared using Fisher’s exact test. Continuous data were presented as median and interquartile range. The Mann-Whitney U test was used for comparisons.

RESULTS

In total, 211 patients were analyzed. The mortality rate was 13.7%. Overall, 149 patients (70.6%) presented with alkalosis, 28 patients (13.3%) had acidosis, and the remaining 34 patients (16.2%) had a normal arterial pH. Of those presenting with acidosis, most had a low apparent strong ion difference (20 patients, 9.5%). Within the group with alkalosis, 128 patients (61.0%) had respiratory origin. The non-survivors were older, had more
comorbidities, and had higher Charlson’s and Simplified Acute Physiology Score 3. We did not find severe acid-base imbalance in this population. The analyzed Stewart’s variables (effective strong ion difference, apparent strong ion difference, and strong ion gap and the effect of albumin, lactate, phosphorus, and chloride) were not different between the groups.

CONCLUSION
Alkalemia is prevalent in COVID-19 patients. Although we did not find an association between acid-base variables and mortality, the use of Stewart’s methodology may provide insights into this severe disease.

**Key Words:** COVID-19; Physicochemical approach; Acid-base status; Critically ill patients; Acute respiratory syndrome


**Core Tip:** In this retrospective study, alkalemia was the most prevalent acid-base disturbance in critically ill coronavirus disease 2019 patients. It was mainly of respiratory origin. The results suggested that there was no association between acid-base disturbances and mortality. However, the physicochemical approach appeared to furnish supplementary information concerning the etiological factors involved in assessing metabolic acid-base imbalances in critically ill patients with coronavirus disease 2019. Nevertheless, ascertaining their correlation with mortality remains pending.

**INTRODUCTION**
Acid-base disorders are commonly found in the intensive care unit (ICU)[1]. Maintaining blood homeostasis and pH regulation is crucial for normal physiology and cellular metabolism and function. The significance of this regulation is demonstrated by various physiological abnormalities that occur when plasma pH is either too high or too low. The body tightly controls acid balance through the respiratory and renal systems, both of which are essential for maintaining acid-base equilibrium.

The identification of severe acute respiratory syndrome coronavirus 2, the virus responsible for coronavirus disease 2019 (COVID-19), occurred in December 2019. The pulmonary manifestations of COVID-19 are typically characterized by bilateral ground-glass opacities, with or without consolidations. Extensive pneumonia can be a serious infectious disease, as it impairs the exchange of respiratory gases and alters minute ventilation. Consequently, respiratory-related acid-base imbalances are expected complications in COVID-19 patients. Additionally, acute tubular injury is a common complication of the disease. The pathophysiology of COVID-19 acute tubular injury involves local and systemic inflammatory and immune responses, endothelial injury, activation of coagulation pathways, and the renin-angiotensin system. There is also debate surrounding the possibility of direct viral infection with renal tropism. Therefore, renal involvement in COVID-19 may play a significant role in the development of acid-base disturbances.

The incidence and effects of acid-base disorders in COVID-19 patients have not been well studied thus far. Since these disorders serve as markers for underlying pathological conditions that can have severe consequences on multiple organs, it is crucial to accurately describe and assess acid-base disorders. Small differences in correcting for anion gap, variations in analytical methods, and different approaches to diagnosing acid-base imbalances can result in significantly different interpretations and treatment strategies for the same disorder. By utilizing a quantitative acid-base approach, clinicians may be able to account for minor changes in ion distribution that may have been overlooked using traditional acid-base analysis techniques.
Given that renal and pulmonary changes are commonly observed in COVID-19 patients, we hypothesized that these changes significantly affect acid-base status but may go unnoticed due to counteracting effects. Thus, the primary objective of this study was to analyze acid-base balance using the physicochemical method of Stewart. The secondary objective was to identify any potential association with outcomes such as dialysis need, vasopressor use, duration of hospital stay, and mortality.

**MATERIALS AND METHODS**

**Population**

This was a retrospective study conducted in a tertiary 600-bed hospital in Salvador, northeastern Brazil from March to December 2020. All adult patients who were more than 18 years of age at their first admission to the ICU at our hospital were screened for eligibility. The inclusion criteria were an ICU stay of more than 4 d, blood gas collection on the same day of ICU admission, a COVID-19 diagnosis by a positive test from a nasal swab, and a typical pulmonary involvement observed in the chest computed tomography scan. We excluded patients with chronic kidney disease stages 4 and 5, patients with acute kidney injury on dialysis, pregnant women, and patients with a kidney transplant. The swab was collected on the ICU admission day, and the viral RNA was detected by quantitative real-time RT-PCR to confirm severe acute respiratory syndrome coronavirus 2 infection.

All patients were followed until discharge, death, or hospital transference. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee for Analysis of Research Projects of the Hospital São Rafael, Salvador, Brazil (CAAE 34428920.0.0000.0048). A waiver of informed consent was granted by the Ethics Committee.

**Data extraction and analysis**

We obtained demographic (age, sex, Simplified Acute Physiology Score 3, Sequential Organ Failure Assessment, and Charlson's comorbidity index scores, hospital mortality), laboratory, radiological, treatment, and clinical outcome data from electronic
medical records. Acute kidney injury was diagnosed by the Kidney Disease: Improving Global Outcomes criteria.

At ICU admission, an arterial blood sample was analyzed using a Siemens RAPID Point 500 blood gas analyzer (Siemens Health Care, Erlangen, Germany) to investigate acid-base disorders using both Henderson-Hasselbach and Stewart’s methodologies. From these data, the base deficit, anion gap, apparent and effective strong ion difference (SIDa and SIdE respectively), and strong ion gap (SIG) were calculated as described previously: (1) Anion gap = (Na⁺ + K⁺) - (Cl⁻ + HCO₃⁻); (2) SIDa = (Na⁺ + K⁺ + Ca²⁺ + Mg²⁺) - (Cl⁻ + lactate); (3) SIdE = 2.46 × 10⁻⁸ × PCO₂/10⁻⁷⁺ [Albumin] x (0.123 x pH - 0.631) + [PO₂²⁻] x (0.39 x pH - 0.469), where PCO₂ is the partial pressure of carbon dioxide; and (4) SIG = SIDa - SIdE.

According to the physicochemical approach (Stewart’s), we classified acidosis, alkalosis, and no pH disorder based on the partial pressure of carbon dioxide (PCO₂) and the electrolyte composition of blood (SIDa) as follows: (1) A pH of less than 7.38 was categorized as acidosis, a pH of more than 7.42 was categorized as alkalosis, and a pH between 7.38 and 7.42, with PCO₂ between 38-42 mmHg and SIDa between 38-42 mEq/L, was categorized as no disorder; (2) Respiratory acidosis: pH < 7.38, PCO₂ > 42 mmHg, and SIDa between 38-42 mEq/L; (3) Metabolic acidosis secondary to SIDa: pH < 7.38, PCO₂ between 38-42 mmHg, and SIDa < 38 mEq/L; (4) Other metabolic acidosis: pH < 7.38, PCO₂ between 38-42 mmHg, and SIDa between 38-42 mEq/L; (5) Respiratory alkalosis: pH > 7.42, PCO₂ < 38 mmHg, and SIDa 38-42 mEq/L; (6) Metabolic alkalosis secondary to SIDa: pH > 7.42, PCO₂ between 38-42 mmHg, and SIDa > 42 mEq/L; (7) Other metabolic alkalosis: pH > 7.42, PCO₂ between 38-42 mmHg, and SIDa between 38-42 mEq/L; and (8) Mixed disorder pH 7.38-7.42 with PCO₂ > 42, and SIDa > 42 mEq/L or PCO₂ < 38 and SIDa < 38 mEq/L.

Statistical analysis

Categorical variables were compared using Fisher’s exact test. Continuous data were presented as median and interquartile range or mean ± standard deviation, as appropriate. The Mann-Whitney U test or the Student’s t test was used for comparisons.
P values < 0.05 were considered significant. Data were analyzed with the PSPP®
statistical package, version 1.2.1 (GNU Project; www.gnu.org/software/pspp/).

RESULTS

Clinical data

During the evaluation period, a total of 799 patients had a positive COVID-19 nasal
swab by RT-PCR in our hospital, and 456 were admitted to the ICU. Among them, 254
patients had an ICU stay longer than 4 d. Forty-three patients were excluded due to age
less than 18 years, advanced chronic kidney disease, and no arterial blood gas analysis
at ICU admission.

Demographic, laboratory, and acid-base variables are shown in Table 1. The mean age
of the population was 59.7 ± 17.1 years with a higher predominance of males (60.0%).
Overall, the non-survivors were older (79.0 ± 9.7 years vs 58.3 ± 15.0 years, P = 0.000)
and had more comorbidities such as high blood pressure (74.0% vs 49.0%, P = 0.040),
diabetes mellitus (50.0% vs 30.0%, P = 0.050), or chronic pulmonary disease (26.0% vs
12.0%, P = 0.100). We found higher Charlson’s and Simplified Acute Physiology Score 3
scores in non-survivors. Secondary infections were diagnosed more frequently in this
group of patients (100% vs 46.0%, P = 0.000). Vasoactive drugs, mechanical ventilation,
acute kidney injury, and dialysis were associated with mortality. As expected, patients
who did not survive had a longer hospital and ICU stay (median of 19.0 d vs 12.5 d and
18.5 d vs 8.0 d, respectively) but a shorter disease duration at hospital admission (4.5 d
vs 7.0 d).

Laboratory data

The blood gas and acid-base variables are shown in Table 2. Overall, 149 patients
(70.6%) presented with alkalosis, 28 patients (13.3%) had acidosis, and the remaining 34
patients (16.2%) had a normal arterial pH. From those presenting with acidosis, most
had a low SIda (20 patients, 9.5%). Within the group with alkalosis, 128 patients (61% of
all patients) had respiratory origin. We found no statistically significant differences in
pH, PCO₂, bicarbonate, or lactate levels between survivors and non-survivors. Serum
sodium and chloride levels were slightly higher in survivors ($P < 0.010$ and $P < 0.030$, respectively). We also searched for differences in Stewart’s variables between these two groups. The values of SIDe, SIDa, and SIG and the effect of albumin, lactate, phosphorus, and chloride were not different between the groups.

**DISCUSSION**

In this cohort of critically ill COVID-19 patients, the quantitative approach to acidosis demonstrated that the main acid-base disorder was alkalosis, with the majority of these being of respiratory origin. The remaining patients had either metabolic acidosis or alkalosis. Among patients with metabolic acidosis, the majority had low SIDa. The results of this study were consistent with other studies that addressed this topic. Alfano et al described metabolic and respiratory alkalosis as the main acid-base disorders, but metabolic alkalosis was the most frequent finding without specification of the etiology. In patients with respiratory failure treated with noninvasive mechanical ventilation, the most frequent acid-base disorder described was alkalosis, also of metabolic or respiratory origin. As an additional finding, the patient’s diagnosis was only possible through the quantitative method in 12% of patients. This innovative methodology seems more suitable for studying the complex acid-base abnormalities in critically ill patients. Some authors argue that this mechanistic approach may resolve several inconsistencies in the traditional model, give rise to novel clinical applications, and enhance understanding of pharmacological manipulation of electrolytes and clinical fluid management.

Respiratory alkalosis was the main acidosis-based disorder identified in our population. This disturbance involves an increase in respiratory rate and/or tidal volume. In patients admitted with respiratory failure, this finding has already been correlated with the presence of a greater extent of pulmonary inflammatory involvement identified by chest computed tomography. In this way, it can be a sign of greater severity and the need for a faster decision-making process. Patient self-inflicted lung injury might be one of the many factors that can explain progression of lung disease in COVID-19. Patients
who have injured lungs typically experience a heightened respiratory drive due to the impairment of gas exchange and respiratory mechanics. If the neuromuscular transmission is intact, this increased respiratory drive leads to powerful inhalations that may have physiological effects, such as a risk of over-distension, pendelluft, or atelectrauma, and an increase in vascular transmural pressure. Consequently, these effects are likely to worsen the existing lesions. This further deterioration of gas exchange and respiratory mechanics results in an even higher respiratory drive, which then exposes the lungs to the risks of even stronger inspiratory efforts. Therefore, the concept of patient self-inflicted lung injury incorporates a dynamic aspect that functions as a vicious circle. The presence of respiratory alkalosis in these patients can be justified by excessive ventilatory effort and increased breath work. It can be used as a marker of underlying severity and should be approached with a sense of urgency and be judiciously corrected.

In our study, the diagnosis and variables involved in the quantitative assessment of acid-base disorders were not associated with mortality and other outcomes. The performance of the quantitative approach for determining the prognosis of critically ill patients has been questioned due to the impact of lactate, other measured ions, and even therapeutic interventions from the Stewart equation.

Benzuidenholt et al, in a single-center African retrospective observational study, found that most patients admitted to the ICU had alkalosis and a lower partial pressure of oxygen, which was associated with survival. They suggested that alkalosis could be caused by the activation of the traditional branch of the renin-angiotensin system and the resulting rise in the effects of aldosterone.

Aldosterone levels in critically ill patients are abnormally low despite an increase in plasma renin activity. This dissociation of aldosterone is not caused by a decrease in angiotensin II synthesis or alterations in plasma adrenocorticotrophic hormone and potassium ions. This phenomenon has been linked to a higher mortality rate during critical illness.
All-Azzam et al.\textsuperscript{[19]} found that mixed metabolic and respiratory acidosis were associated with increased mortality in COVID-19 patients. These findings may have been influenced by the higher prevalence of patients with diabetes mellitus, chronic kidney disease, and severe respiratory failure with hypercapnia in this patient population.

\textit{Limits of the study}

Our study was designed to investigate the acid-base and electrolyte disturbances in COVID-19 patients with severe pulmonary involvement admitted to the ICU unit and the complications that may occur following these disorders in the patients. Possible limitations were the retrospective nature of the study and the limited number of patients included. However, our study had several strengths. To date, it is the largest COVID-19 cohort to describe the acid-base status with Stewart's methodology and the first report of a search for mortality predictors using this innovative approach. Our study population included 211 patients in the year 2020 before vaccination was available. This represented an opportunity to study the clinical and metabolic effects of the virus in a non-immunized population. We also excluded chronic kidney patients and did not detect corticosteroid or alkaline fluid administration before blood gas collection in the ICU, eliminating these potential biases. As the median time from emergency department presentation to ICU admission was 0 d, another possible interference in the acid-base status was very unlikely. Thus, our cohort likely describes the effects of serious COVID-19 on acid-base status.

\textbf{CONCLUSION}

In summary, patients with COVID-19 who were admitted to the hospital had a high incidence of acid-base disorders. They had all types of acid-base changes that were not related to outcomes. The most common acid-base disorders in these patients were metabolic and respiratory alkalosis.
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