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Arterial Blood Gas Parameters to Evaluate Oxygenation and Acid-Base Disorders in Corticosteroid-Receiving Severe and Critical COVID-19 Patients

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ABSTRACT

Introduction: Increased inflammation and immune dysregulation in severe and critical COVID-19 trigger oxygen and acid-base disorders, possibly mitigated by corticosteroids. Variations in arterial blood gas (ABG) parameters and the influence of corticosteroid administration have become a concern for clinicians. This study aimed to uncover significant differences in temporal arterial blood gas parameters between severe and critical COVID-19 cases undergoing corticosteroid treatment.

Methods: This case-control study, which adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, analyzed severe (n=27) and critical (n=41) COVID-19 patients treated in the high care unit (HCU) and the intensive care unit (ICU) of Universitas Airlangga Hospital, Surabaya, from May to July 2021. Arterial blood gas results were categorized into three evaluations (E1-E3) based on collection days. The International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) for Macintosh version 27.0 was used for statistical analysis, with a $p<0.05$ considered statistically significant.

Results: Hypoxemia through PaO_2 and P/F ratios was prominent in both groups throughout E1-E3, with differences only in E1 P/F ratios ($p=0.003$). While SaO_2 stayed normal in severe cases, critical cases were low, with differences in E1 ($p=0.012$) and E3 ($p=0.004$). Severe cases maintained normal pH, while critical cases tended towards acidemia, notably differing in E1-E3. Both groups had low HCO_3 levels, differing only in E2 ($p<0.001$). Severe and critical groups exhibited low and high $PaCO_2$ trends, respectively, with distinctions in E2 ($p<0.001$) and E3 ($p=0.003$).

Conclusion: Hypoxemia was prevalent in both groups. Compensated respiratory alkalosis or metabolic acidosis was common in the severe group, while the critical presented with respiratory acidosis.

Highlights:

1. Both severe and critical COVID-19 patients primarily presented with hypoxemia.
2. Severe and critical COVID-19 patients differed through their tendencies towards respiratory alkalosis/metabolic acidosis and respiratory acidosis, respectively.

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Introduction

Pathophysiological mechanisms of COVID-19 are linked to various processes stemming from pulmonary inflammation and oxygenation disorders. Organ-specific complications like renal failure and pneumonia are often observed as well. These disorders disrupt acid-base homeostasis, reflected in arterial blood gas (ABG) analyses. These analyses reveal conditions like acidosis, alkalosis, and acute respiratory distress syndrome (ARDS).[1–3]

The clinical classifications of COVID-19 range from asymptomatic to critical, with 15% and 5% of patients developing severe and critical diseases, respectively.[4,5] Severe and critical diseases are linked with worsened inflammation and immune dysregulation.[6–8] To manage these disorders, clinicians have utilized corticosteroids, including dexamethasone, methylprednisolone, and hydrocortisone, as potent anti-inflammatory and immunomodulatory drugs, either as primary or supportive therapies.[5,9,10]

Few studies compare ABG parameters between severe and critical patients despite established differences in inflammation.[7,8] Moreover, there is a scarcity of studies directly comparing ABG parameters relative to disease severity in the corticosteroid-receiving population, even though studies suggest the drug's influence on ABG parameters.[11,12] Given the close connection between inflammation and ABG parameters and the anti-inflammatory properties of corticosteroids, it is hypothesized that alterations in these parameters correspond to disease severity.[1,8] Thus, this study aimed to uncover significant differences in temporal ABG parameters between severe and critical COVID-19 cases undergoing corticosteroid treatment.

Methods

This case-control study analyzed severe and critical COVID-19 patients admitted to the high care unit (HCU) or intensive care unit (ICU) of Universitas Airlangga Hospital, Surabaya, from May to July 2021. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for case-control studies.[13] Ethical clearance was obtained from the Research Ethics Committee of Universitas Airlangga Hospital, Surabaya. The data was analyzed using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) for Macintosh version 27.0.[13–16]

This study included patients aged 18 years old or older with positive SARS-CoV-2 polymerase chain reaction (PCR) tests, severe or critical disease, at least five days of HCU or ICU therapy, and a minimum of three ABG analyses. Patients must receive one of the following intravenous corticosteroids: 1 x 6 mg/day dexamethasone, 3 x 6.25 mg/day methylprednisolone, or 3 x 50 mg/day hydrocortisone.

The classification of disease severity followed the guidelines set by the Indonesian Society of Respirology (PDPI).[5] Severe patients exhibited symptoms of severe pneumonia, such as fever, cough, dyspnea, and/or tachypnea. Additionally, they manifested a respiratory rate of over 30 breaths per minute, severe respiratory distress, or a SpO_2 level below 93% in room air. Critical patients had conditions like ARDS, sepsis, or other situations that necessitated life-support devices.[4,5]

Patients treated outside the HCU or ICU, were pregnant, initiated treatment outside the timeframe, had insufficient medical record data, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) or long-term use of immunosuppressive drugs and other corticosteroid-affecting medications, were ultimately excluded from the study.[17]

Clinical characteristics comprised of age, length of stay (LOS), sex, outcome, and administered corticosteroids. Prior to analysis, Shapiro-Wilk tests were conducted to assess normality, revealing a normal distribution for age but not for length of stay (LOS). Consequently, an independent t-test was applied for age, while a Mann-Whitney U-test was used for LOS. Additionally, chi-square tests were performed to analyze sex, outcomes, and corticosteroid administration. Chi-square analyses were employed to examine patient comorbidities and complications. For the analysis of arterial blood gas (ABG) parameters, a Shapiro-Wilk test was conducted for each parameter, which did not display a normal distribution.[14,15,18] Consequently, Mann-Whitney U tests were performed. Arterial blood gas analyses were categorized as evaluations (E). E1 was the arterial blood gas analysis upon initiating corticosteroid therapy, E2 was the third day, and E3 was the fifth-to-seventh day. This study utilized the earliest result if multiple results were obtained in a day.[17]

The interpretation of both the Mann-Whitney U test and the independent t-test involves two hypotheses: the null hypothesis and the alternative hypothesis. The null hypothesis ($p \geq 0.05$) indicates that the distributions of the groups are the same, suggesting no significant difference. Conversely, the alternative hypothesis ($p < 0.05$) suggests that there are significant differences between the groups studied. The chi-square test is interpreted in terms of association between variables. The null hypothesis ($p \geq 0.05$) indicates no significant association between the independent and dependent variables. In contrast, the alternative hypothesis ($p < 0.05$) suggests a significant association between the independent and dependent variables.[14,15]

Results

A total of 175 medical records were obtained from the Medical Record Storage Room of Universias Airalngga Hospital, processed and sorted manually from physical records. After excluding duplicate and inaccessible records and ineligible (n=107) patients, 68 patients were included. Subsequently, severity categorization comprised severe (n=27) and critical (n=41) disease.[4,5]

Table 1. Clinical characteristics

Variable	Group, n (%)		p-value
	Severe	Critical	
Age, years*			
Mean ± SD	56.35 ± 11.25	54.00 ± 12.43	0.438
LOS, days†			
Median (IQR)	12.00 (8.50)	9.00 (7.50)	0.047§
Sex‡			
Male	17 (63.0%)	22 (53.7%)	0.448
Female	10 (37.0%)	19 (46.3%)	
Outcome‡			
Deceased	9 (33.3%)	37 (90.3%)	<0.001§
Discharged (improved)	15 (55.6%)	3 (7.3%)	
Discharged (other)	3 (11.1%)	1 (2.4%)	
Administered corticosteroids‡			
DXM	18 (66.7%)	35 (85.4%)	0.220
MTP	4 (14.8%)	3 (7.3%)	
HCT	0 (0.0%)	1 (2.4%)	
DXM/HCT	2 (7.4%)	2 (4.9%)	
DXM/MTP	1 (3.7%)	0 (0.0%)	
MTP/DXM	2 (7.4%)	0 (0.0%)	

*Analyzed using the independent t-test
†Analyzed using the Mann-Whitney U-test
‡Analyzed using the Chi-square test
§Statistically significant values, in accordance to a p<0.050
LOS: length of stay; DXM: dexamethasone; MTP: methylprednisolone; HCT: hydrocortisone; IQR: interquartile range; DXM/HCT: dexamethasone initially, then hydrocortisone; DXM/MTP: dexamethasone initially, then methylprednisolone; MTP/DXM: methylprednisolone initially, then dexamethasone; SD: standard deviation
Source: Research data, processed

Table 1 displays analyses of the patient's clinical characteristics. Shapiro-Wilk normality tests showed normal age distribution but not length of stay (LOS). Mann Whitney U-test for LOS showed a statistically significant difference between the two groups, but the independent t-test for age did not. Chi-square analysis showed significant differences between the outcomes, but not for sex and administered corticosteroids.[14,15,18]

Table 2. Patient's comorbidities, analyzed using the Chi-square test

Comorbidity	Group, n (%)		p-value
	Severe	Critical	
Diabetes mellitus			
Yes	12 (44.4%)	15 (36.6%)	0.517
No	15 (55.6%)	26 (63.4%)	
Hypertension			
Yes	11 (40.7%)	7 (17.7%)	0.030*
No	16 (59.3%)	34 (82.9%)	
Cardiovascular disease			
Yes	6 (22.2%)	0 (0.0%)	0.002*
No	21 (77.8%)	41 (100%)	
Cerebrovascular disease			
Yes	0 (0.0%)	1 (2.4%)	0.414
No	27 (100.0%)	40 (97.6%)	
Orthopaedic disease			
Yes	1 (3.7%)	0 (0.0%)	0.214
No	26 (96.3%)	41 (100%)	

*Statistically significant values, in accordance to a p<0.050
Source: Research data, processed

Table 2 shows the Chi-square analysis of the patient's comorbidities. Based on p-values, significant differences between the groups were observed for hypertension and cardiovascular disease.[14,15,18]

Table 3. Patient's complications, analyzed using the Chi-square test

Complication	Group, n (%)		p-value
	Severe	Critical	
Hyperglycemia			
Yes	12 (44.4%)	22 (53.7%)	0.457
No	15 (55.6%)	19 (46.3%)	
ARDS			
Yes	0 (0.0%)	40 (97.6%)	< 0.001*
No	27 (100%)	1 (2.4%)	
Respiratory failure			
Yes	20 (74.1%)	38 (84.4%)	< 0.001*
No	7 (25.9%)	3 (13.0%)	
Bacterial coinfection			
Yes	4 (14.8%)	18 (43.9%)	0.012*
No	23 (85.2%)	23 (56.1%)	
Sepsis			
Yes	0 (0.0%)	12 (29.3%)	0.002*
No	27 (100%)	29 (70.7%)	
Acute kidney injury			
Yes	1 (3.7%)	5 (12.2%)	0.227
No	26 (96.3%)	36 (87.8%)	
Fungal coinfections			
Yes	1 (3.7%)	2 (4.9%)	0.818
No	26 (96.3%)	39 (95.1%)	
Cardiac arrest			
Yes	0 (0.0%)	2 (4.9%)	0.244
No	27 (100%)	39 (95.1%)	

*Statistically significant values, in accordance to a p<0.050
ARDS: acute respiratory distress syndrome
Source: Research data, processed

Table 3 shows the Chi-square analysis of the patient's complications. Significant differences between the groups based on p-values were found for ARDS, respiratory failure, bacterial coinfections, and sepsis.[14,15,18] Table 4 displays Mann-Whitney U test analyses of ABG parameters at three evaluations. Shapiro-Wilk tests showed a non-normal distribution for all parameters.[14,15] Normal values were described as pH 7.35-7.45, $PaCO_2$ 35-45 mmHg, HCO_3 22-26 mmol/L, SaO_2 94-100%, PaO_2 80-100 mmHg, and P/F ratio ≥300 mmHg.[3]

Table 4. Analysis of ABG parameters, analyzed using the Mann-Whitney U test

ABG	Group, Median (IQR)		p-value
	Severe	Critical	
SaO_2, %			
E1	94.30 (4.90)	91.20 (7.95)	0.012*
E2	94.10 (7.40)	92.70 (10.10)	0.190
E3	95.20 (5.20)	92.30 (10.05)	0.004*
PaO_2, mmHg			
E1	69.70 (27.10)	63.80 (22.20)	0.174
E2	76.60 (28.00)	71.90 (22.15)	0.716
E3	74.60 (32.30)	68.70 (19.90)	0.116
P/F ratio, mmHg			
E1	91.00 (87.05)	65.70 (33.02)	0.003*
E2	89.50 (47.20)	77.50 (41.74)	0.201
E3	99.25 (78.60)	83.37 (56.25)	0.096
pH			
E1	7.42 (0.06)	7.37 (0.14)	0.012*
E2	7.40 (0.06)	7.35 (0.14)	0.003*
E3	7.40 (0.08)	7.33 (0.18)	<0.001*
HCO_3, mmol/L			
E1	20.30 (6.14)	20.10 (6.80)	0.625
E2	20.10 (3.90)	23.20 (6.90)	<0.001*
E3	22.60 (7.10)	23.50 (6.95)	0.319
$PaCO_2$, mmHg			
E1	32.40 (11.70)	33.50 (16.05)	0.693
E2	33.90 (8.40)	47.20 (26.25)	<0.001*
E3	33.90 (10.80)	48.00 (26.35)	0.003*

*Statistically significant values, in accordance to a p<0.050
IQR: interquartile range
Source: Research data, processed

Median SaO_2 values of the severe group were normal, albeit approaching the lower limit. Furthermore, the critical group was consistently hypoxemic.[3] Significant differences were discovered in E1 and E3. Both groups had consistently low median PaO_2 values. While no statistically significant differences were found, critical values were consistently lower. Both groups showed consistently low median P/F ratios, increasing from E1 to E3. Significant differences were observed only on E1, but the critical groups consistently had lower ratios.[14,15]

Median pH values for severe patients remained normal, while critical patients showed a decreasing trend toward acidemia. Significant differences among the groups were discovered in all evaluations. Median $PaCO_2$ showed initial hypocapnia for both groups. Afterward, the severe group exhibited hypocapnia, and the critical group showed hypercapnia, with significant differences in E2 and E3. Median HCO_3 values were initially low for both groups, then both groups presented normal values by E3, with significant differences exclusively on E2.[2,3,14,15]

Discussion

In this study, the severe group persisted with hypoxemia across the three evaluations through all oxygenation parameters and a generally increasing trend. Median SaO_2 values slightly rose to normal by E3, albeit remaining at the lower limit. The outcomes of this study affirmed previous studies that were suggestive of high incidences of hypoxemia.[6,19] Regarding acid-base parameters, severe patients exhibited normal median pH values, while median $PaCO_2$ values suggested a tendency toward hypocapnia. These findings align with previous studies on severe COVID-19 patients in similar cohorts. Conversely, median HCO_3 values were notably low initially but eventually returned to normal levels by E3, showcasing conflicting results compared to previous studies with similar cohorts.[6,20–22]

A collective analysis of the parameters suggests that the severe cohort had a tendency towards fully compensated respiratory alkalosis or metabolic acidosis. If this holds true, it would coincide with prior studies documenting high incidences of primary respiratory alkalosis.[23,24] Respiratory alkalosis in COVID-19 may result from hyperventilation mechanisms triggered by hypoxic stimuli, aligning with the cohort's observed hypoxemic tendencies. This phenomenon increases respiratory efforts to address hypoxia, resulting in excessive CO_2 elimination and decreased $PaCO_2$ values.[1,2,25] On the other hand, current studies on metabolic acidosis in COVID-19 suggest that it is relatively infrequent as a primary disorder among severe patients.[2,21,23,24] Metabolic acidosis primarily develops upon the chronic depletion of acid-base homeostatic mechanisms, which may explain its relative rarity. Nonetheless, heightened metabolic demands, driven by inflammation and hypoxia, could contribute to its development through lactate accumulation (i.e., lactic acidosis). However, as the two acid-base disorders are interconnected and serve as compensatory responses, the precise acid-base disorder findings in the severe group remain uncertain. Additionally, the possibility of mixed acid-base disorders, previously identified in COVID-19 patients, cannot be entirely ruled out.[1,24]

The critical group displayed evident hypoxemia for all oxygenation parameters. Median P/F ratio values displayed an increasing trend, while PaO_2 and SaO_2 displayed fluctuating values but ultimately increased on E3. However, this increase still indicated the presence of hypoxemia. These results aligned with previous studies, affirming the common hypoxemic tendencies among critical patients.[6,26] For the acid-base parameters, median pH values remained within the normal range until the final evaluation, indicating the development of acidemia as the days progressed. Additionally, $PaCO_2$ and HCO_3 values generally exhibited an increasing trend, with $PaCO_2$ values transitioning from hypocapnia to hypercapnia, while HCO_3 values ultimately normalized. These results align with previous studies that demonstrated similar findings in comparable cohorts.[26–28]

The decreasing trend of pH toward acidemia among the critical cohort suggests an acid disorder. Furthermore, despite variations in $PaCO_2$ and HCO_3 values across evaluations, both parameters exhibited an increasing trend, suggesting the potential development of respiratory acidosis. If substantiated, this aligns with a previous study reporting this disorder as the most common acid-base disorder among critical patients.[2] Respiratory acidosis, coupled with the critical group's hypoxemic tendencies, is supported by the high incidences of respiratory failure (n=38, 84.4%) and ARDS (n=40, 97.6%) within the cohort. Typically, respiratory acidosis arises due to ventilatory failure, stimulating an increase in $PaCO_2$ values through CO_2 accumulation. Elevated $PaCO_2$ values stimulate the release of acidic hydrogen (H^+) molecules, followed by HCO_3 production for compensation. This potentially elucidates the upward trend in HCO_3 levels in this study. Furthermore, as prior studies indicated the likelihood of COVID-19 patients developing mixed acid-base disorders, the potential for mixed disorders cannot be entirely excluded.[1,24]

Increasing pulmonary inflammation and immune dysregulations in COVID-19 are believed to contribute to the development of ABG disorders. These pathologies exacerbate the hyperproduction of pro-inflammatory cytokines, triggering the renowned "cytokine storm" phenomenon, where the body excessively releases inflammatory mediators. Ultimately, these changes may directly contribute to the development of hypoxemia through pathologies such as ventilation-perfusion mismatches, alveoli-associated hypoventilation, impaired O_2 diffusion, the formation of intravascular microthrombi, right-to-left pulmonary shunting, and the activation of the Bohr effect. These mechanisms may subsequently induce acid-base disorders.[1,25,29,30] Additionally, these alterations may induce complications like respiratory failure and ARDS, further exacerbating the deterioration of ABG parameters.[31,32]

The diverse pathophysiological mechanisms may account for the various disorders observed in both the severe and critical groups in this study.[31,32] This study

showcased the distinct severities of COVID-19 and their tendencies in ABG parameters. Overall, the statistical differences described through p-values varied between the two groups across most ABG parameters, leading to non-uniform results across evaluation periods.[15] Consistent and significant differences were discovered exclusively in pH, with variations between the two cohorts observed across all three evaluations. Conversely, PaO_2 values were consistently comparable between the two cohorts, indicating no significant differences in this parameter between the two groups were present. Given that disorders in ABG parameters have been associated with heightened inflammation, worsening immune responses, and disease severity, the variations identified could be explained by the differing degrees of inflammation and immune responses between the two cohorts.[7,8,19,24,27,29] Moreover, these differences may have been exacerbated by emerging complications such as respiratory failure, ARDS, sepsis, and nosocomial complications like bacterial coinfections. Additionally, pre-existing comorbidities such as diabetes mellitus, known to induce further inflammation in the body, may have also played a contributing role.[33,34] Therefore, the variations in arterial blood gas parameters between the groups may not be solely attributed to the COVID-19 disease but also individualized patient conditions, emerging complications, and existing comorbidities.[33,34]

The administration of corticosteroids might also play a pivotal role in this study. Corticosteroids are recognized for their effectiveness in the treatment of COVID-19 pneumonia. Previous studies indicated improved prognosis, diminished disease severity, reduced necessity for intubation and ventilation, lower mortality rates, and lower ICU admission rates.[1] These effects are attributed to their ability to improve oxygenation, a vital factor in developing hypoxemia and acid-base disorders.[9] Furthermore, this class of drug has presented promising outcomes in mitigating complications like ARDS and sepsis, which were frequently observed in the critical group.[34,35] By diminishing pro-inflammatory mediators and alleviating lung injuries, correcting these complications is anticipated to improve hypoxemia and acid-base disorders, aligning with previous studies that proposed similar findings.[11,25,28]

The findings of this study, upon the final evaluation, indicated that hypoxemia and acid-base disorders were still common for both groups. However, the overall upward trend in oxygenation parameters could be attributed to corticosteroids' anti-inflammatory and immunomodulatory properties. It should be noted that the persisting acid-base disorders cannot be definitively explained due to unaccounted factors such as renal function and comorbidities, which may have affected the corticosteroid's function in mitigating acid-base disorders.[17,35]

Strength and Limitations

The strength of this study was its thorough analysis of arterial blood gas parameters, providing detailed insights into oxygenation and acid-base disorders in severe and critical COVID-19 patients. However, limitations included the absence of correlational analysis between ABG parameters, hindering more in-depth insights. Moreover, limitations such as incomplete medical records and being a single-center study might have constrained the possibility of a larger sample size. A larger sample would have offered a more comprehensive population representation and yielded more precise outcomes.

Conclusion

In terms of oxygenation disorders, hypoxemic tendencies were observed in both severe and critical patients. Regarding acid-base disorders, variations based on severity suggested potential differences between the groups. The severe group primarily exhibited compensated respiratory alkalosis or metabolic acidosis, while the critical group predominantly showed respiratory acidosis.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Ethical Clearance

This study was ethically approved by the Research Ethics Committee of Universitas Airlangga Hospital, Surabaya (No.129/KEP/2022) on 11/09/2022.

Authors' Contributions

The study was designed by BT, HWS, MR, and ANR. BT collected data, conducted a background literature review, and designed the manuscript. BT performed a statistical analysis. HWS, MR, and ANR supervised the results and discussions. All authors reviewed and approved the final version of the manuscript.

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