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An Observational Study of COVID-19 Intensive Care Patients for Abnormalities in Arterial Blood Gas, Acid-Base and Blood Pressure and their Relationship to Patient Outcomes

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ABSTRACT

The increased prevalence of pneumonia and renal complications in individuals afflicted with coronavirus disease 2019 (COVID-19) leads to frequent disruptions in acid-base equilibrium among critically ill patients, thereby influencing their prognosis. The aim of this study was to assess the arterial blood gas (ABG) and acid-base patterns in patients diagnosed with COVID-19 and subsequently admitted to a tertiary care hospital. A retrospective observational study was undertaken at a designated hospital for COVID-19 patients, involving a cohort of 200 individuals who tested positive for COVID-19 using reverse transcription-polymerase chain reaction (RT-PCR) testing. The study collected demographic and laboratory data, including arterial blood gas (ABG) measurements, within the first day of admission. In cases where multiple ABG analyses were conducted, only the initial measurement was considered for statistical analysis. The study also examined the association between the initial ABG measurement and comorbidities. The age group with the highest prevalence among the patients was 51-60 years, accounting for 30% of the total study sample. Additionally, there was a higher proportion of males compared to females, with a male-to-female ratio of 2.7 to 1. The prevalent comorbidities observed in 49% of COVID-19 patients were hypertension, diabetes mellitus and chronic obstructive pulmonary disease. Alkalosis was observed in 54% of the patients, while acidosis was observed in 19% of the patients. The predominant abnormality observed in arterial blood gas (ABG) analysis was primary respiratory alkalosis accompanied by secondary metabolic acidosis, which was observed in 67 patients, accounting for 25.1% of the total sample. This was followed by primary respiratory alkalosis with secondary metabolic alkalosis, observed in 20% of the patients. A statistically significant negative correlation was observed between PaCO2 and pH ($r = -0.530$, $p<0.0001$). Additionally, statistically significant positive correlations were found between pH and base ($r = 0.533$, $p<0.0001$), pH and TCO2 ($r = 0.260$, $p<0.0001$), as well as pH and HCO3 ($r = 0.354$, $p<0.0001$). Acid-base imbalances are commonly observed in individuals diagnosed with COVID-19. The predominant pattern identified in severely afflicted COVID-19 patients, as evidenced by arterial blood gas (ABG) analysis, was respiratory alkalosis, either as an isolated manifestation or in conjunction with other patterns. The examination of arterial blood gas (ABG) upon admission in individuals diagnosed with moderate-to-severe COVID-19 holds promise in expediting intervention for metabolic abnormalities, thereby improving patient outcomes.

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Key Words
COVID-19, abnormalities, blood pressure, outcomes, patients

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INTRODUCTION

Coronaviruses encompass a group of viruses that have been identified as the causative agents of respiratory and intestinal ailments in a wide range of animal species, including humans[1]. These viruses have a predilection for infecting the upper respiratory tract and in severe instances, they can lead to the development of severe pneumonia. Although the majority of COVID-19 cases have been classified as mild, there have been instances where severe manifestations of the disease have resulted in respiratory failure, septic shock and/or multiple organ dysfunction[2]. As the transmission of this infectious disease persists, it is imperative to gain a deeper understanding of its clinical and epidemiological characteristics. This knowledge will enhance our comprehension of the virus's actual scope, enabling us to enhance diagnostic and treatment capabilities and mitigate its adverse effects on morbidity and mortality.

Arterial hypoxemia represents a significant respiratory characteristic observed in individuals affected by COVID-19. The assessment of patients' oxygenation is initially conducted through the utilisation of a pulse oximeter. Pulse oximetry is a method used to estimate the oxygen saturation of arterial blood, known as SaO2, by measuring alterations in the absorption of light by oxyhemoglobin[3]. The saturation of oxygen in the blood (SpO2) as estimated through pulse oximetry may exhibit a discrepancy of up to ±4% when compared to the true arterial oxygen saturation (SaO2) measured using a CO-oximeter[4].

Hypocapnic hypoxia, also known as silent hypoxia, is a condition that has multiple contributing factors in the context of COVID-19. The presence of fever in individuals with COVID-19 leads to a notable shift of the oxygen dissociation curve towards the right. Consequently, a lower saturation of arterial oxygen (SaO2) is associated with a given partial pressure of arterial oxygen (PaO2). Furthermore, it has been observed that Angiotensin-Converting Enzyme 2 (ACE 2), which serves as the cellular receptor for Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), is expressed within the carotid body. This anatomical location is significant as it is where chemoreceptors are responsible for detecting oxygen levels[5]. The carotid bodies play a crucial role in regulating respiratory drive, specifically responding solely to arterial partial pressure of oxygen (PaO2) rather than arterial oxygen saturation (SaO2). As a result of this shift towards the right, a significant decrease in oxygen saturation takes place.

Silent hypoxemia, which is characterised by a lack of noticeable symptoms despite low levels of oxygen in the blood, is not influenced by alterations in carotid body stimulation[6]. Patients with COVID-19 have been observed to exhibit silent hypoxemia, a condition characterised by low levels of oxygen in the blood without noticeable symptoms. This phenomenon is accompanied by an elevated risk of thrombogenesis, the formation of blood clots, within the pulmonary vasculature. This finding has been documented in previous studies[7]. Thrombi located within the pulmonary vasculature have the potential to induce significant hypoxemia. The occurrence of dyspnea is closely associated with the obstruction of the pulmonary vasculature and the subsequent repercussions that ensue. Dyspnea may also occur due to the release of histamine or stimulation of juxtacapillary receptors in the pulmonary vasculature, resulting in potentially severe complications[8].

Various pathological mechanisms, such as fever, inflammation affecting multiple organs, thrombogenesis, respiratory tract infection (both upper and lower) and carotid body suppression, may occur at different stages of the COVID-19 disease. The predominant blood acid-base balance can shift towards either acidosis or alkalosis, depending on the underlying mechanism. Several recent studies have been conducted to investigate the acid-base balance and arterial blood gas (ABG) levels of patients with COVID-19 in various countries, including China, Italy and South Africa[9-12]. The findings of these studies indicate that alkalosis is observed at a higher frequency among COVID-19 patients admitted to the intensive care unit (ICU), which deviates from the typical occurrence of acidosis in ICU patients with other medical conditions. Therefore, the current investigation was undertaken among individuals afflicted with a severe manifestation of the COVID-19 illness. The objective was to ascertain the levels of pH, PaO2, PaCO2 and HCO3 (bicarbonate) through arterial blood gas (ABG) analysis. These measurements serve as indicators of respiratory and metabolic acidosis/alkalosis.

MATERIALS AND METHODS

This was a retrospective cross-sectional study conducted in a tertiary care Hospital of Central India. Patients admitted our Institute, with diagnosis of COVID19 in Intensive Care Units. 200 reverse transcription-polymerase chain reaction-positive COVID-19 patients were taken. According to the institution guidelines, patients were classified as moderate or severe based on the presence of hypoxia (SpO2 <93%) or radiological evidence of pneumonia or ARDS and organ impairment and shock. A high-resolution computed tomographic scan was done for COVID-19 patients with inconclusive chest X-ray and persistent symptoms. All detailed clinical examination and biochemical tests were performed on the day of admission. The study was conducted from the day of

admission in the ICU till the day of discharge or mortality of the patient. The indication for initiation of NIV included standard protocol as followed in our tertiary care institute. Descriptive statistics are used to show the features and characteristics of the collected data. Association of categorical variables are analyzed using chi square test. Quantitative data-expressed as mean+/-SD.Student 't' test are applied on quantitative data. If data found to be normal p<0.05 will be considered statistically significant.

RESULTS

On average, the participants of the study had an age of 58.32+13.4 years. In general, individuals between the ages of 51 and 60 constituted approximately 30.8% of the total population, while those aged 61-70 accounted for 24.8% of the population. A total of 200 patients were included in the study, comprising 146 male participants and 54 female participants. Based on the data presented in Table 1, it can be observed that both female and male individuals exhibit an upward trend in the occurrence of COVID-19 cases requiring hospitalisation between the ages of 21 and 50. Based on statistical data, a strong and statistically significant correlation has been observed between the rise in age groups and the incidence of hospitalised COVID-19 patients (p<0.001). Furthermore, it was observed that 44.9% of the individuals included in the study exhibited a high body mass index (BMI). Out of a total of 200 patients, 98 individuals were found to have co-morbidities. In total, the study included a cohort of 54 individuals diagnosed with hypertension, 31 individuals diagnosed with diabetes mellitus, 4 individuals diagnosed with chronic obstructive pulmonary disease (COPD), 8 individuals diagnosed with both hypertension and diabetes mellitus, 1 individuals diagnosed with both hypertension and COPD and 1 individual diagnosed with all three conditions (Table 1).

The examination of acid-base disorders in the study participants demonstrated the presence of alkalosis (characterised by a high pH >7.45), low pH (7.35) and normal pH in 108 (54%), 38 (19%) and 54 (27.0%) patients, respectively. Out of the total sample size, 48 patients (24%) were found to have developed respiratory acidosis, characterised by an arterial partial pressure of carbon dioxide (PaCO2) exceeding 45 mmHg. Conversely, 111 patients (55.5%) exhibited respiratory alkalosis, indicated by a PaCO2 level below 35 mmHg. Based on the arterial blood gas (ABG) analysis, it was determined that a cohort of 51 individuals, accounting for 25.6% of the total sample, exhibited hypoxemia characterised by a partial pressure of oxygen (PaO2) measuring 75 mmHg. A total of 32 patients, accounting for 15.9% of the sample, exhibited elevated levels of HCO3. Table 2 presents the different parameters and their associations with comorbidities. There was a significant correlation observed between the presence of comorbidities and alterations in pH, PaCO2 and PaO2 (p<0.0001). However, no significant correlation was found between the presence of comorbidities and changes in standard HCO3 levels (p>0.05), (p>0.05).

Table 3 illustrates that upon initial admission, a total of 27 patients, accounting for 13.5% of the sample, exhibited a normal arterial blood gas (ABG) pattern. The most commonly observed acid-base disorder among the patients was respiratory alkalosis, accounting for 23 cases (11.6%). This was followed by metabolic alkalosis, which was observed in 11 patients (5.6%). The most prevalent abnormal arterial blood gas (ABG) pattern observed in 50 (25.2%) patients was primary respiratory alkalosis with secondary metabolic acidosis. This was closely followed by primary respiratory alkalosis with secondary metabolic alkalosis, which was found in 40 (20.2%) patients.

Table 1: Demographic details and comorbidities of the study patients (N = 200)

Parameters	No.	Percentage
Age group (years)		
21-30	4	1.9
31-40	23	11.6
41-50	30	15.0
51-60	61	30.7
61-70	50	24.8
>70	32	16.0
Gender		
Males	146	73.0
Females	54	27.0
Comorbidities		
No comorbidities	102	51.0
Only diabetes mellitus	31	15.4
Only hypertension	54	26.8
Only chronic obstructive pulmonary disease	4	2
Hypertension+diabetes mellitus	8	4.1
Hypertension+chronic obstructive pulmonary disease	1	0.7
Hypertension+diabetes mellitus+chronic obstructive pulmonary disease	1	0.4
Body mass index		
Lower (<18.5)	63	31.5
Normal (18.5-24.9)	47	23.6
Higher (>25.0)	90	44.9

Table 2: Lists the arterial blood gas analysis and comorbidities among study participants (n = 133)

Parameters particular	Sub-particular	Total number of patients n (%)	Comorbidity (n = 98)	No comorbidity (N = 102)	p-value
pH	<7.35	38 (19)	30	8	p<0.0001
	7.35-7.45	54 (27)	50	4	
	>7.45	108 (54)	11	97	
PaCO2 (mmHg)	>45	48 (24)	37	10	p<0.0001
	35-45	41 (20.4)	9	32	
	<35	111 (55.5)	59	52	
PaO2 (mmHg)	<75	51 (25.5)	30	21	p = 0.1842
	75-100	96 (48)	50	46	
	>100	53 (26.5)	25	28	
Standard HCO3 (mmol L^{-1})	<22	61 (30.5)	55	6	p<0.0001
	22-26	107 (53.5)	40	67	
	>26	32 (15.9)	15	17	

Table 3: Type of arterial blood gas disorders in study patients (n = 200)

Type of acid base disorder	Frequency	Percentage
Normal arterial blood gas	27	13.5
Metabolic acidosis	6	3.0
Metabolic alkalosis	11	5.6
Respiratory acidosis	4	2.2
Respiratory alkalosis	23	11.6
Primary respiratory alkalosis with secondary metabolic alkalosis	40	20.2
Primary respiratory alkalosis with secondary metabolic acidosis	50	25.2
Primary respiratory acidosis with secondary metabolic alkalosis	5	2.6
Primary respiratory acidosis with secondary metabolic acidosis	11	5.6
Primary metabolic alkalosis with secondary respiratory alkalosis	7	3.4
Primary metabolic alkalosis with secondary respiratory acidosis	4	2.2
Primary metabolic acidosis with secondary respiratory alkalosis	6	3.0
Primary metabolic acidosis with secondary respiratory acidosis	4	1.9

All of the eight patients who were admitted with isolated metabolic acidosis presented a medical background of kidney disease. A total of seven out of nine patients with a history of COPD exhibited respiratory acidosis or primary respiratory acidosis with secondary metabolic alkalosis on the day of admission. The Pearson correlation coefficient (r) between PaCO2 and pH was found to be -0.530, indicating a statistically significant negative correlation (p<0.0001). The provided diagram (Fig. 1) is presented for reference. The statistical analysis revealed significant correlations between pH and base (r = 0.533, p<0.0001), pH and TCO2 (r = 0.260, p<0.0001) and pH and HCO3 (r = 0.354, p<0.0001).

DISCUSSIONS

The global transmission of COVID-19 is occuring at an alarming rate. The virus undergoes evolutionary processes and manifests novel symptoms. The primary indication observed in the majority of COVID-19 patients who have been admitted to hospitals is the presence of bilateral ground-glass opacities, with or without consolidations as detected through high-resolution computed tomography[13]. Extensive pneumonia, which impacts a substantial proportion of the lungs, can pose a significant threat as an infectious disease due to its impact on respiratory gas exchange and minute ventilation. Consequently, it was anticipated that COVID-19 patients would experience respiratory acid-base imbalances[14]. The objective of this study was to obtain arterial blood images from COVID-19 patients with moderate-to-severe symptoms, with the aim of identifying any indications of respiratory and/or metabolic alkalosis or acidosis[15].

The study population's pathophysiology is elucidated by a noteworthy arterial blood gas (ABG) pattern. The analysis of arterial blood gases (ABG) is crucial in assessing the oxygenation status and acid-base equilibrium of patients. Metabolic acidosis, with lactic acidosis being the prevailing type, is frequently observed in patients admitted to the intensive care unit (ICU). Nevertheless, previous studies conducted in intensive care units (ICUs) have typically excluded patients with COVID-19. A total of 54.3% of the participants in our study exhibited symptoms consistent with alkalosis. A prevalence rate of 55.8% of patients exhibiting respiratory alkalosis suggests a manifestation of severe COVID-19. The study conducted by Alfano *et al*.[14] reported a lower prevalence of metabolic alkalosis compared to our study. This particular study had the highest degree of modification, with a significant decrease of 33.6%. The respiratory acid-base causes were promptly identified. Respiratory alkalosis is a result of hyperventilation induced by hypoxia, whereas respiratory acidosis is caused by hypercapnic respiratory failure[14]. There are multiple theoretical frameworks available to elucidate the underlying reasons for the prevalence of respiratory alkalosis rather than acidosis in individuals afflicted with COVID-19. Hyperventilation can be induced by various conditions such as hypoxemic, pulmonary and central diseases. The ACE2 receptors present in the carotid body have demonstrated a propensity for binding with the virus responsible for COVID-19, indicating their potential involvement. Pulmonary disorders frequently engage in hyperventilation as a means to address hypoxia, albeit at the cost of excessive elimination of carbon dioxide.

The occurrence of respiratory alkalosis may lead to compensatory hyperventilation and rapid deterioration in individuals experiencing mild hypoxemia. It is imperative to closely monitor individuals diagnosed with COVID-19 who exhibit respiratory alkalosis, regardless of the absence of hypoxemia. The majority of patients included in this study exhibited a pH that was skewed towards alkalosis upon admission, as viral pneumonia induces hypoxia in the absence of hypercapnia. As the severity of the disorder increases and the difficulty in breathing intensifies, there is an elevation in PCO 2 levels, resulting in the transformation of respiratory alkalosis into respiratory acidosis. The results of our analysis indicate that renal impairment is associated with the development of metabolic acidosis. The maintenance of optimal pH levels served as a preventive measure in this case. Metabolic acidosis in this specific cohort of patients was attributed to the processes of ammonia excretion and tubular bicarbonate reabsorption. The presence of acute or chronic metabolic acidosis has been found to have a significant impact on the morbidity and mortality rates of both patients with and without chronic kidney disease. Acidosis has been observed to have a detrimental impact on cardiac output and contractility, while also leading to an increase in arterial vasodilation. These effects significantly impair the cardiovascular system's capacity to maintain homoeostasis, as evidenced by previous studies. The prevalence of alkalosis in patients admitted to the intensive care unit (ICU) with COVID-19 remains uncertain. Several study participants who were dependent on ventilators experienced respiratory alkalosis as a result of elevated positive end-expiratory pressure. The administration of corticosteroids has been found to stimulate the mineralocorticoid system, resulting in the development of metabolic alkalosis. A total of 11 patients, accounting for 5.6% of the sample population, exhibited metabolic alkalosis. Metabolic alkalosis can be induced by heightened mineralocorticoid activation or kidney alkalosis. The activation of the conventional RAS pathway by COVID-19 leads to the occurrence of metabolic alkalosis. ACE2 acts as an inhibitor of the renin-angiotensin system (RAS) pathway. The binding and degradation of ACE2 by SARS-CoV-2 could potentially diminish its counter-regulatory effects. The activity of the renin-angiotensin system (RAS) can be stimulated by aldosterone and angiotensin II, potentially resulting in an increase in potassium excretion in urine and the reabsorption of salt in the distal nephron. The Renin-Angiotensin System (RAS) regulates various physiological processes, including blood pressure regulation, electrolyte homoeostasis, water balance and acid-base equilibrium. The two branches, namely the protective pathway and the classic vasoconstrictive pathway, have been the subject of extensive discussion. Aldosterone production, oxidative stress, fibrosis, cell proliferation and vasoconstriction are known to be associated with traditional metabolic alkalosis. The presence of acid-base abnormalities in individuals diagnosed with COVID-19 has been observed to be associated with a range of comorbidities. The prevalence of acid-base imbalances was higher among individuals diagnosed with chronic obstructive pulmonary disease (COPD), diabetes and hypertension. Further investigation is required in order to ascertain the underlying cause of this observed correlation. The study solely focused on the analysis of admission arterial blood gas (ABG) and biochemistry findings at a single site. The limitations of this study, including its retrospective design and absence of a control group, pose challenges in establishing definitive conclusions based on these findings. Another limitation pertains to the absence of chronic substance abuse or prior medication usage prior to hospitalisation. In order to validate the acid-base abnormalities in patients with COVID-19, it is imperative to conduct larger studies that are free from selection bias.

CONCLUSION

Patients who were admitted to the hospital with COVID-19 exhibited significant acid-base imbalances. The presence of comorbidities has been found to be associated with an increased likelihood of experiencing acid-base changes. Respiratory alkalosis emerged as the prevailing arterial blood gas (ABG) pattern among COVID-19 patients exhibiting moderate to severe illness. The analysis of arterial blood gas (ABG) upon admission has the potential to aid in the timely identification and management of metabolic disturbances in individuals with moderate-to-severe cases of COVID-19, consequently leading to enhanced clinical outcomes.

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