Original Article

Can Affinity of Hemoglobin to Oxygen to be a Prognostic Marker in Critically ill COVID-19 patients?

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Abstract

Background: This study's objective is to determine the slope of the hemoglobin oxygen dissociation curve in critically ill patients who have COVID-19 along with blood gas measurements and how mortality might be impacted by this circumstance. **Aim:** It has been reported that the hemoglobin oxygen dissociation curve is not different from healthy patients in COVID-19. However, there are insufficient data on the behavior of the curve in patients who require intensive care. **Patients and Methods:** This retrospective study was conducted between 01.03.2021 and 01.07.2021 with patients who were followed up due to COVID-19 in adult intensive care unit. P50 and lactate value obtained from *in vitro* calculated blood gas analysis. The survival status of the patients was recorded. **Results:** The mean P50 value at the admission of nonsurvivors was significantly higher than survivors. In correlation analysis, a significant positive correlation was seen between P50, mortality, and lactate level at admission. SpO_2, PaO_2/FiO_2 ratio, and length of stay in intensive care unit were significantly negatively correlated with P50 levels. **Conclusion:** A right shift in the hemoglobin oxygen dissociation curve is associated with mortality. Lactate levels were also associated with a right shift. Prospective experimental studies are needed to provide a better understanding of this process.

Keywords: *Acute respiratory distress syndrome, COVID-19, critical illness, hemoglobin oxygen dissociation curve, mortality*

Introduction

The acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection reduces the lung's oxygen diffusing capacity, resulting in hypoxemia. Patients with COVID-19 have an extremely low oxygen (O_2) blood saturation without dyspnea in 20%-40% of instances.[1]

An imbalance between O_2 consumption and O_2 delivery causes tissue hypoxia.[2] The ability to release oxygen into the cells, as determined by the oxygen-carrying capacity of the blood as determined by the hemoglobin (Hb) level, and the affinity for Hb-O_2, is largely responsible for the final amount of oxygen reaching the cell or rather the mitochondria for oxidative metabolism. The oxygen dissociation curve (ODC), which depicts the blood's O_2 saturation (sO_2) at various O_2 (pO_2) partial pressures, indicates Hb-O_2 affinity. The S-shaped ODC has two distinguishing characteristics: first, its location in semi-saturated pO_2, defined as P50, which is used to describe HbO_2 affinity, and second, its slope (as determined by the logarithmic Hill plot). The pCO_2, pH (H+ level), temperature, and organic phosphates, particularly 2,3-bisphosphoglycerate, all alter Hb-O_2 affinity (2,3-BPG, ex 2,3-DPG). At pH 7.4 and 37°C, the typical P50 in humans is 26.9 mmHg.[3]

Increased oxygen loading of Hb in the pulmonary system is linked to a left shift of ODC (low P50). Respiratory alkalosis, for example, generates higher affinity for Hb-O_2 and consequently increased oxygen loading at high altitude. A shift of ODC to the left, on the other hand, is linked to decreased oxygen delivery to the tissue. The right shift of ODC improves cellular oxygen availability and occurs, for example, when muscles are under a lot of stress.[4]

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The enzyme 2,3-Bisphosphoglycerate mutase produces 2,3-BPG, and its activity is controlled by pH: acidosis reduces bisphosphoglycerate mutase activity, whereas alkalosis raises it. Interestingly, despite the fact that COVID-19 causes anemia, the few studies that have been published so far have found no change in P50 as expected. However, because 2,3-BPG levels are typically elevated in anemia, this was likely higher in the control group and even in COVID-19. Finally, Böning *et al*.[3] emphasized in their study that more measurements in more severe patients would be of great interest to acquire a better understanding of the changes in erythrocyte composition that may impair oxygen binding and transport in COVID-19.

In this study, we aimed to investigate the slope of the curve in critically ill patients due to COVID-19 with blood gas parameters and how mortality would be affected by this situation.

Method

This retrospective study was conducted between 01.03.2021 and 01.07.2021 with patients who were followed up due to COVID-19 in adult intensive care unit (ICU) in a tertiary healthcare institution. After the approval of the hospital ethics committee for the study (ethical approval number: 2021.07.146, date: 25.08.2021), the data of the patients hospitalized in the ICU between the specified dates were scanned retrospectively.

Inclusion criteria for the study: (1) cases with confirmed diagnosis of COVID-19 by real time polymerase chain reaction (RT-PCR), (2) patients diagnosed with acute respiratory distress syndrome (ARDS) according to the Berlin criteria, and[5] (3) patients aged 18 years and more. Exclusion criteria: (1) Patients aged less than 18 years (n: 1), (2) patients without ARDS (n: 8), (3) pregnant patients (n: 6), (4) with chronic obstructive pulmonary disease (n: 16), (5) patients with a history of heart failure (n: 5), (6) patients with acute renal failure at admission (n: 4), (7) patients with a radiological diagnosis with negative COVID-19 RT-PCR test (n: 10), (8) patients who had been vaccinated (n = 3), and (9) patients who had been intubated before admission (n: 12). One hundred eighty nine patients were analyzed retrospectively. One hundred and thirty six patients were included in the study after individuals who met the exclusion criteria were excluded.

During the COVID-19 pandemic, two adult pandemic intensive care units, each with 16 beds in our hospital, and collected data for the period it served. In our hospital, which is a tertiary education and research hospital, symptomatic patients with positive COVID-19 RT-PCR tests are followed in pandemic inpatient services. In this process, patients in need of intensive care due to respiratory distress, tachypnea, hypoxia, impaired consciousness, and hypotension are taken to the pandemic ICU and their follow-up continues. In addition, COVID-19 PCR positive patients who need intensive care from other hospitals are also accepted to our hospital for treatment.

The data of the patients were obtained from the hospital's computer database and patient files. Sociodemographic data of the patients including age, gender, body mass index, and comorbid diseases were recorded. The body mass index was calculated by dividing weight to the square of the height in meters.

On the day of admission to the ICU, complete blood count and arterial blood gas analysis were performed. P50 and lactate value obtained from *in vitro* calculated blood gas analysis. The FiO_2 values of the patients were obtained from the archive records. Sequential Organ Failure Assessment Score and The Acute Physiology and Chronic Health Evaluation scores were also recorded when patients are admitted to the ICU. Lenght of stay in ICU was defined as number of days spent in ICU. Patients' intubation status at ICU were recorded.

During the follow-up period, the survival status of the patients was recorded. Clinical and laboratory parameters were also compared between survivors and nonsurvivors.

Statistical analysis

Statistical analysis of the study data was performed using the SPSS (IBM SPSS Statistics for Windows, Version 20.0.: IBM Corp.) program. One sample Kolmogorov-Smirnov test was used to evaluate whether the continuous data fit the normal distribution. The quantitative variables were expressed as mean and standard deviation or median (min-max) according to their distribution. Categorical variables were expressed as numbers and percentages. In two group comparisons, the Student's *t*-test was used for continuous data with normal distribution, and the Mann-Whitney U test was used for continuous data with the abnormal distribution. The Chi-square test was used to compare categorical data between two groups. Spearman and point biserial correlation analysis were performed to evaluate the correlation between mortality, intubation status, length of stay, P50, hemoglobin, and lactate levels.

Results

One hundred and thirty six patients, 74 males and 62 females, were included in the study. During the study period, 98 of 136 patients (72.1%) died. The

Table 1: Sociodemographic and clinical characteristics of study population

	Mean±sd *n*=136	Min-max *n*=136
P50	28.8±4.0	22.8-47
Age	59.7±13.9	25-89
BMI	27.5±4.8	19.5-51.9
Mortality	98 (*n*)	72.1 (%)
Hemoglobin (g/dL)	11.6±2.3	7-18.3
LOS	18.6±17.7	1-110
SOFA	4.8±2.0	3-13
APACHE	17.5±4.8	7-30
SpO_2 Admission	89.9±7.5	55-98
PaO_2/FiO_2 Admission	96.2±25.0	41-200
Lactat Admission	2.2±2.2	0.6-16
Gender	(*n*)	(%)
• Male	74	54.4%
• Female	62	45.6%
Entubation	102 (*n*)	75 (%)
Comorbid Diseases	(*n*)	(%)
Diabetes mellitus	30	22.1%
Hypertension	42	30.9%
Hyperlipidemia	6	4.4%
Malignity	22	16.2%
Cerebrovascular Disease	4	2.9%
Neurodegenerative Disease	12	8.8%
Coronary Arter Disease	10	7.4%
Chronic Renal Disease	12	8.8%
Hypothyroidi	4	2.9%
Heart Rytm Disfuncion	4	2.9%

BMI, Body Mass Index; LOS, Lenght of stay; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation

Table 2: Comparison of clinical characteristics of patients according to mortality

	Dead *n*=98	Alive *n*=38	*P*
P50	30.0±4.0	25.9±2.4	**0.001**
LOS	20.5±20.2	13.7±6.8	0.382
Lactate	2.4±2.5	1.6±0.8	0.053
SpO_2	89.7±6.7	90.4±9.2	0.270
PaO_2/FiO_2 ratio	92.6±26.5	105.7±17.8	**0.006**
SOFA admission	5.3±2.1	3.7±0.9	**0.001**
APACHE	19.1±4.2	13.3±3.6	**0.001**
Age	61.0±13.7	56.6±13.9	0.100
BMI	26.8±5.2	29.3±3.3	**0.001**

Bold values: Statistically significant. BMI, Body Mass Index; LOS, Lenght of stay; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation

mean age of the study population was 59.7 ± 13.9 years. The most common comorbid disease of the patients was hypertension with a rate of 30.9%. Intubation was required in 102 (75%) patients. The sociodemographic and clinical characteristics of the study population are shown in Table 1.

The mean P50 value of the patients was 28.8 ± 4.0 and there was no statistically significant difference between male and female patients (male 29.2 ± 4.6 vs. female 28.4 ± 3.3; P =0.368). However, the mean P50 value at the admission of nonsurvivors was significantly higher than survivors as seen in Table 2. Lactate and SpO_2 levels of dead and survival patients were not statistically significant. PaO_2/FiO_2 ratio of survivors was significantly higher than nonsurvivors (105.7 ± 17.8 vs. 92.6 ± 26.5; P =0.006).

In correlation analysis, a significant positive correlation was seen between P50, mortality, and lactate level at admission. On the other hand, SpO_2, PaO_2/FiO_2 ratio, and length of stay in ICU were significantly negatively correlated with P50 levels. However, there was no significant correlation between P50 and hemoglobin values. The correlation analysis was shown in Table 3.

Discussion

In our study, we found that the hemoglobin ODC tended to shift to the right and showed a positive correlation with mortality in COVID-19–associated ARDS patients who were admitted to the ICU due to increased oxygen demand and had not yet been intubated.

Vogel *et al*.[6] performed several repeated measurements under *in vivo* conditions (native arterial or venous blood at 37°, no balance) in intubated and mechanically ventilated patients (3,518 samples in 43 patients with COVID-19, other causes of respiratory failure; 15,945 samples in 828 patients). In COVID-19 disease, these nonstandardized PO_2/SO_2 points were shifted to the left compared to the Severinghaus standard curve (P50 26.7 mmHg), except that it was below 50% SO_2.[6] The measurements made in our study were *in vitro* measurements. In mechanically ventilated patients with corrected oxygenation, the curve is expected to shift to the left. The initial P50 values of the patients who required intensive care were not determined by Vogel *et al*. in their investigation. This approach does not illuminate the need for intensive care in patients with COVID-19.

Some publications evaluating the possible damage of coronavirus to erythrocyte functions have reported that the absence of ACE2 receptors on the surface of erythrocytes cannot allow the virus to enter the erythrocyte cell.[7,8] In addition, there are some experimental publications showing that erythrocytes are severely damaged.[9-11] However, it is clear that the

Table 3: Correlation analysis between mortality, ICU duration, and P50 value

	P50		Mortality		LOS	
	r	*P*	*r*	*P*	*r*	*P*
P50	.	.	0.55	**0.001**	-0.21	**0.011**
SpO_2	-0.290	**0.001**	-0.095	0.271	0.048	0.579
Lactate Admission	0.428	**0.001**	0.166	0.053	-0.222	**0.009**
PaO_2/FiO_2	-0.405	**0.001**	-0.324	**0.001**	0.138	0.109
Hemoglobin	0.054	0.536	-0.103	0.234	-0.112	0.194

LOS, Length of stay *Spearman correlation analysis.
Bold Values: Statistically significant

anemia seen in COVID-19 may result from hemolysis and blood coagulation. Other critical variables include hemodilution with infusions, dietary insufficiency, bleeding, and phlebotomy.[12,13] Besides these structural damages, the function of Hb is affected by the formation of methemoglobin and CO-Hb (eventually more than 20%), which cannot bind oxygen reversibly.[14] P50 is frequently increased during anemia due to stimulated synthesis of 2,3-BPG resulting from decreased venous O_2 saturation during tissue migration (decreased free BPG due to better binding to Hb) or hyperventilation (increased pH). This effect is independent of the type of disease, but low pH may prevent P50 change.[15-18] An additional factor in hemolytic anemia or renal anemia during erythropoietin therapy is the increased proportion of young erythrocytes containing a high concentration of 2,3-BPG.[19] The importance of additional factors (hemodilution with infusions, malnutrition, bleeding, and phlebotomy) is of course variable. Additional measurements in more severe cases would be of considerable interest, according to Böning D *et al*.,[3] to gain a better understanding of the alterations in erythrocyte composition that may impair oxygen binding and transport in COVID-19.

DeMartino *et al*.[7] measured pO_2/SO_2 pairs in venous blood from 17 patients (SO_2 range 20%-95%); measured data points tended to be to the right of the standard curve, but there was no significant difference. However, it is unclear whether the pO_2 values measured in this study are corrected for standard conditions. The authors concluded that "patients with COVID-19 did not exhibit any hemolytic anemia", but the mean [Hb] was low (~13 g/dL, 7 to 17 g/L relative to the numbers) and ferritin (indicator of hemolysis) had moderately reached high values (mean value 500 ng/mL).

Daniel *et al*.[20] investigated 14 COVID-19 patients (seven males and seven females) with significant anemia ([Hb] 9.3 ± 2.3 g/dL) and compared them to 11 subjects (five males and six females) without apparent lung or blood pathologies (diagnosis not communicated, [Hb] 14.3 ± 1.1 g/dL). They also found no difference in the standard P50, which was relatively high in both groups (29.0 ± 2.3 mmHg vs. 28.5 + 1.8 mmHg). In our study, patients did not have significant anemia and there was no correlation between hemoglobin level and P50 value.

Renoux *et al*.[21] measured P50 with a similar standard Hemox-Analyzer in seven patients (median [25–75] percentile: 29.7 [27.2; 31.0] mmHg) and had results that were not significantly different from healthy subjects. Unfortunately, the median can deviate significantly from the mean in such a small sample. The P50 value presented in our study was obtained from data measured *in vitro* with Radiometer ABL90 Flex devices. In our cohort of patients with severe disease conditions in terms of number of patients, there was no control group consisting of non–COVID-19 patients, but we observed that the curve shifted to the right, and this right shift was positively correlated with mortality.

Hb-O_2 affinity is lower in females than in males on average. Males compensate for their high Hb-O_2 affinity with a high oxygen-carrying capacity; thus, cellular oxygen availability should be equivalent (Hb level). However, such a wide individual variation in baseline Hb-O2 affinity could be linked to a higher risk of tissue hypoxia, especially in the case of acute hypoxemia as COVID-19. When low oxygen in the blood is paired with inhibition of oxygen release to the tissue, the situation is likely to become even worse.[22] The P50 value between males and females did not differ significantly in our research. One disadvantage of all these studies on ODC is that data are not presented separately for males and females. In healthy premenopausal women, the mean P50 tends to be higher, while the Bohr effect decreases. However, this effect is probably not large as the mean age of the patients is more than 50 years.[23-25]

In our study, serum lactate levels showed a positive correlation with both P50 level and mortality. In the literature, it has been associated with the severity of the disease and the elevation of lactate in COVID-19.[26,27] Although serum lactate and its kinetics have been used as the main diagnostic and target parameter in septic patients for more than 20 years, the evidence for pneumonia and ARDS patients is insufficient. Despite this lack of evidence, current guidelines recommend the use of lactate and lactate kinetics in COVID-19.[28] So far, the value of serum lactate and its kinetics in predicting a severe course in COVID-19 is uncertain. This lack of evidence is particularly relevant in the particularly vulnerable population of very elderly ICU patients. However, this subgroup was disproportionately

affected by the need for ICU admission and high mortality.[29–32]

The limitations of our study are the *in vitro* measurement of the data used in the study and the lack of sufficient data on standardization. Also, it does not convey any information about drugs that may affect the affinity of oxygen administered to patients. Since the study was retrospective, detailed and blind information about these data could not be obtained; therefore, concomitant drug data were not included in the evaluation to ensure standardization. Again, carboxyhemoglobin levels were not evaluated in our study. The strengths of the study are that the number of patients is significantly higher than other studies in the literature and that it consists of patients with severe disease conditions who have not yet been intubated.

In conclusion, a right shift in the hemoglobin ODC is associated with mortality. Lactate levels were also associated with a right shift. Prospective experimental studies are needed to provide a better understanding of this process, which affects oxygen delivery and binding and causes mortality.

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Conflicts of interest

There are no conflicts of interest.

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