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Oxyhemoglobin Dissociation Curve in COVID-19 Patients

COVID-19 Hastalarında Oksihemoglobin Disosiasyon Eğrisi

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Abstract

Objective: Coronavirus disease-2019 (COVID-19) is a disease that can progress with hypoxemia and severe respiratory distress in some patients. The oxyhemoglobin dissociation curve (ODC) is critical to understanding the effects of O2 exchange. This study aimed to evaluate the relationship between the ODC and oxygen-carrying capacity of hemoglobin (Hb) in COVID-19 patients.

Materials and Methods: In the study, ODCs were created by examining the data obtained from the arterial blood gas analyses of 686 intensive care unit (ICU) and non-ICU COVID-19 patients retrospectively.

Results: It was concluded that patients with COVID-19 and other respiratory distress patients had a slight right-leaning trend in the ODC compared with the standard curve. The P50 value of the ICU group was higher than the other groups (mean: 30.74 mmHg, n=131, p=0.047). While the percentage of oxyhemoglobin (mean: 65.44% vs 69.81%, p=0.015), the amount of glucose (mean: 163.39 mg/dL vs 195.36 mg/dL, p=0.002) and pH (median: 7.38 vs 7.41, p=0.007) in the non-ICU group was higher compared with the control group, the carboxyhemoglobin percentage (mean: 1.66% vs 1.13%, p=0.000), PCO_2 (42.02 mmHg vs 39.44 mmHg, p=0.015), potassium (mean: 4.33 mmol/L vs 4.04, p=0.026), and sodium (mean: 138.10 mmol/L vs 135.80 mmol/L, p=0.000) were lower. The methemoglobin percentage of the ICU group was lower (p=0.000) than the other groups.

Conclusion: The ODC of COVID-19 and other respiratory distress patients shifts slightly to the right, indicating that patients have partial respiratory difficulties.

Keywords: COVID-19, hematological parameters, oxygen affinity, SARS-CoV-2

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19), hipoksemi ve bazı hastalarda ciddi derecede solunum sıkıntısı ile seyredebilen bir hastalıktır. Oksihemoglobin disosiasyon eğrisi (ODC), O2 değişiminin etkilerini anlamak için çok önemlidir. Bu çalışmanın amacı; COVID-19 hastalarında ODC ve hemoglobin (Hb) arasındaki oksijen taşıma kapasitesi ilişkisini değerlendirmektir.

Gereç ve Yöntemler: Çalışmada, yoğun bakım ünitesi (YBÜ) COVID-19, yoğun bakım dışı (non-YBÜ) COVID-19 ve COVID-19 olmayan diğer solunum sıkıntılı toplam 686 hastanın arter kan gazından elde edilen veriler retrospektif olarak incelenerek oksihemoglobin eğrileri oluşturuldu.

Bulgular: COVID-19 tanılı ve diğer solunum sıkıntılı hastaların ODC'lerinin standart eğriye göre hafif sağa eğilim gösterdiği belirlendi. YBÜ grubunun P50 değeri, diğer gruplara kıyasla daha yüksekti (ortalama: 30,74 mmHg, n=131, p=0,047). Kontrole kıyasla non-YBÜ grubunun; oksihemoglobin yüzdesi (ortalama: %65,44 vs %69,81, p=0,015), PO_2'ı (46,98 mmHg vs 48,98 mmHg, p=0,001), glikoz miktarı (ortalama: 163,39 mg/dL vs 195,36 mg/dL, p=0,002) ve pH'sı (medyan: 7,38 vs 7,41, p=0,007) daha yüksek iken karboksihemoglobin yüzdesi (ortalama: %1,66 vs %1,13, p=0,000), PCO_2'ı (42,02 mmHg vs 39,44 mmHg, p=0,015), potasyum (ortalama: 4,33 mmol/L vs 4,04, p=0,026) ve sodyum (ortalama: 138,10 mmol/L vs 135,80 mmol/L, p=0,000) seviyesi daha düşüktü. YBÜ grubunun methemoglobin yüzdesi ise diğer gruplara kıyasla daha düşüktü (p=0,000).

Sonuç: COVID-19 ve diğer solunum sıkıntılı hastaların ODC'si hafif sağa kaymaktadır, bu sonuç hastaların kısmen solunum güçlüğü çektiğini göstermektedir.

Anahtar Kelimeler: COVID-19, hematolojik parametreler, oksijen afinitesi, SARS-CoV-2

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Introduction

Coronaviruses form a large family of viruses that can cause diseases in humans and animals (1). The coronavirus disease-2019 (COVID-19) pandemic, from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in 2019 and spread globally. It's primarily transmitted through droplets and contact with mucous membranes after exposure to infected surfaces (2). COVID-19 symptoms are nonspecific and can't be reliably distinguished from other viral respiratory infections. Initial patients had fever (98%), cough (76%), fatigue/myalgia (44%), sputum (28%), headache (8%), hemoptysis (5%), diarrhea (3%), and half reported shortness of breath (2).

SARS-CoV-2's damage mechanism to cells, tissues, and organs is unclear. COVID-19 patients exhibit severe atypical respiratory distress with hypoxemia, preceding other symptoms like radiological changes and dyspnea (3). Hypoxemia is critical in COVID-19, causing organ failure and death (4). The virus enters cells via ACE2 receptors, found in alveolar epithelial and vascular endothelial cells, triggering a strong immune response and widespread endothelial dysfunction (5).

Hemoglobin (Hb) is a heterotetramer with two alpha and two beta chains, an iron ion, and a porphyrin ring, essential for oxygen transport in vertebrates. About 97% of oxygen is transported from lungs to tissues by Hb in erythrocytes, while 3% dissolves in plasma and blood cells. Oxygen binds to Hb at high partial pressure (PO_2) in lungs and releases at low PO_2 in tissues due to consumption (6,7) Hb tetramer structure changes impact oxygen affinity and tissue oxygenation. Oxygen affinity relates to PO_2 and can be read from the oxyhemoglobin dissociation curve (ODC), with P50 representing 50% Hb oxygen saturation. Hb's molecular cooperation results in ODC's sigmoid shape. ODC shifts left or right in clinical situations. A right shift decreases oxygen affinity, improving tissue oxygenation; a left shift does the opposite. Decreased affinity raises P50, increasing tissue oxygenation. Factors like 2,3-DPG, pH, and temperature affect Hbs oxygen affinity (6-8).

With COVID-19 affecting over 22 million globally, theories explore the pathophysiology. One suggests that SARS-CoV-2 proteins interact with human Hb, facilitating iron removal, leading to functional Hb loss and iron accumulation (9).

Understanding respiration and gas exchange principles is key for diagnosing and treating respiratory illnesses. Some diseases stem from poor ventilation, membrane diffusion disorders, or gas transport issues (6). Arterial blood gas analysis assesses lung function and oxygenation, providing crucial information on patient's respiratory and metabolic status to guide treatment decisions (6,10,11)

The aim of this study was to determine whether there is a direct interaction between the viral proteins that cause COVID-19 and Hb that may lead to loss of oxygen carrying capacity in the oxygen Hb dissociation curve obtained from the artery blood gas.

Materials and Methods

Study Design

In the study, lab data of patients admitted to Erzincan Binali Yıldırım University Mengücek Research Hospital's intensive care unit (ICU) between May 2020 and February 2021, diagnosed with COVID-19 (polymerase chain reaction positive for SARS-CoV-2), non-ICU, and non-COVID-19 respiratory distress (control) were retrospectively examined. The study was approved by the Ethics Committee for Clinical Research at Erzincan University Faculty of Medicine (decision no: 05/05, date: 22.03.2020). Patients' demographic information and arterial blood gas values were recorded. Arterial blood gas samples were analyzed using ABL 700 (Radiometer, Copenhagen, Denmark).

Statistical Analysis

Descriptive statistics for patient and control groups' demographic and laboratory findings were presented. Quantitative variables were defined by average, median, interquartile range, and standard deviation; categorical variables as frequency and percentage. Categorical variables were analyzed using the χ^2 test. Shapiro-Wilk test checked normality hypothesis for quantitative variables between groups. Levene test was used to hypothesize variances' homogeneity. Parameters meeting parametric test assumptions were analyzed with one-way ANOVA, while Kruskal-Wallis analyzed those without. Tukey and Dunnett post-hoc tests determined significant changes' sources. Differences between groups were denoted by symbols, with different symbols signifying significant differences. Box-Plot charts summarized deterministic statistical characteristics, distribution, and parameter differences by groups. SPSS (version 20.0) was used for data analysis, with a p-value <0.05 considered significant.

Results

The study involved 343 COVID-19 patients and 343 control patients with different respiratory etiologies without COVID-19. O_2-Hb dissociation curves were generated using COVID-19 patient data and control group data, then compared (12). Table 1 shows average ages of ICU, non-ICU, and control groups as 71.51, 68.79, and 66.00 respectively; gender distributions were 80 males/51 females, 122 males/90 females, and 209 males/139 females. In ODC evaluations (Figure 1), non-ICU and control group curves without COVID-19 were similar; ICU group's ODC slightly tilted right, and all groups trended right compared to the standard curve. ICU group's P50 value was higher (mean: 30.74 mmHg, n=131, p=0.047). Non-ICU group had higher oxyhemoglobin percentage (mean: 65.44% vs 69.81%, p=0.015), PO_2 (46.98 mmHg vs. 48.98 mmHg, p=0.001), glucose (mean: 163.39 mg/dL vs 195.36 mg/dL, p=0.002),

Table 1. Summary of results from patients with ICU COVID-19, non-ICU COVID-19 and control group without COVID-19																
	Non-ICU					ICU					Control					p-value
Sex																
Male N (%)	122 (57.5)					80 (61.1)					209 (60.9)					0.699
Female N (%)	90 (42.5)					51 (38.9)					134 (39.1)					
Parametreler	**Mean**	**Median**	**SD**	**Min.**	**Max.**	**Mean**	**Median**	**SD**	**Min.**	**Max.**	**Mean**	**Median**	**SD**	**Min.**	**Max.**	
Age	68.79*	71.00	14.47	20.00	96.00	71.51*	73.00	13.57	20.00	96.00	62.31#	66.00	20.07	19.00	102.00	**0.000**
P50 (mmHg)	29.25#	28.79	3.71	21.28	53.74	30.74*	29.66	5.86	21.74	74.39	29.38*#	28.52	6.67	20.65	110.98	**0.047**
Bicarbonate plasma (mEq/L)	24.18	24.25	4.19	10.30	37.70	24.48	23.80	5.84	11.60	51.00	23.66	23.90	4.42	5.30	42.00	0.252
Bilirubin (mg/dL)	1.60	1.45	1.06	0.00	8.00	2.43	1.50	4.04	0.00	33.00	1.57	1.50	0.93	0.10	7.00	0.838
Deoxyhemoglobin (%)	27.67	21.40	20.73	1.20	92.00	28.62	25.70	22.63	0.50	83.20	31.51	28.30	20.63	0.70	94.30	0.107
Glucoce (mg/dL)	195.36*	147.50	123.35	40.00	695.00	185.44	158.00*#	104.38	64.00	879.00	163.39#	131.00	96.39	55.00	743.00	**0.002**
HCO_3 (mEq/L)	24.46	24.35	3.92	15.50	33.60	23.84	25.05	6.32	7.40	43.50	24.00	23.90	3.81	13.20	38.70	0.771
Hematocrit (%)	42.48	41.95	12.41	0.90	82.60	40.35	40.40	11.78	5.50	73.90	42.69	43.00	10.25	10.10	78.60	0.118
Hemoglobin (g/dL)	13.85	13.70	4.10	0.01	27.20	13.06	12.90	3.91	4.00	24.10	13.94	14.10	3.40	3.10	25.70	0.086
Carboxyhemoglobin (%)	1.13#	1.00	0.61	-0.30	4.80	1.02#	1.00	0.52	-0.30	2.90	1.66*	1.30	1.45	-0.40	11.40	**0.000**
Chlorine (mmol/L)	106.26	106.00	6.85	74.00	136.00	107.35	107.00	9.65	86.00	145.00	106.09	106.00	8.58	2.60	142.00	0.367
Lactate (mmol/L)	2.09	1.80	1.21	0.10	6.90	2.23	1.80	1.52	0.50	9.30	2.07	1.70	1.35	0.00	13.70	0.506
Methemoglobin (%)	1.36*	1.30	.45	-1.10	3.30	1.20#	1.20	0.49	0.10	3.20	1.42*	1.40	0.44	-1.40	4.60	**0.000**
Oxyhemoglobin (%)	69.81*	75.70	20.60	5.70	96.50	69.20#*	72.15	22.54	15.40	96.80	65.44#	68.10	20.52	4.00	97.10	**0.015**
Oxygen saturation (%)	71.73	78.20	21.16	5.80	98.80	70.76	73.75	23.06	15.60	99.50	67.53	70.90	21.15	4.10	99.30	0.076
Osmalarite (mOsmol/L)	283.36	283.60	11.61	233.50	340.90	286.14	283.65	18.28	243.20	353.50	285.24	285.65	11.70	237.60	359.30	0.147
pH (7.35-7.45)	7.407*	7.415	0.079	7.019	7.557	7.390#*	7.408	0.101	7.047	7.590	7.384#	7.383	0.080	6.819	7.649	**0.007**
Potassium (mmol/L)	4.04#	3.90	1.37	2.30	16.80	4.14#*	4.00	0.86	2.40	7.00	4.33*	4.10	1.55	2.40	20.10	**0.026**
Sodium (mmol/L)	135.80#	136.00	5.92	111.00	164.00	137.61#*	137.00	8.11	117.00	171.00	138.10*	139.00	5.51	113.00	163.00	**0.000**
Standard base (±3 mmol/L)	0.12	0.25	5.10	-17.50	18.70	0.17	0.20	6.62	-18.80	22.80	0.03	0.30	5.71	-24.50	36.00	0.970
Total O_2 (mEq/L)	13.80#	13.80	5.19	2.30	30.10	12.47*	12.10	5.40	2.70	25.90	12.71#*	12.80	4.98	0.90	30.50	**0.033**
pCO_2 (mmHg)	39.44*	39.00	9.78	12.20	113.00	41.78#*	39.70	12.92	12.70	101.00	42.02#	41.90	9.79	5.40	89.30	**0.015**
pO_2 (mmHg)	48.98#*	44.05	24.26	11.00	177.00	56.86#	45.80	36.30	16.00	295.00	46.98*	40.00	31.08	5.70	281.00	**0.001**
Ionized calcium (mg/dL)	1.15*	1.16	0.12	0.58	1.86	1.10#	1.10	0.10	0.82	1.47	1.15*	1.15	0.12	0.69	1.96	**0.000**

The values in Table 1 are presented as mean and standard deviation (SD). Differences between groups with the same symbol were not statistically significant, while differences between groups with different symbols were found to be significant at a p-value of less than 0.05. ICU: Intensive care unit, COVID-19: Coronavirus disease-2019, SD: Standard deviation, min-max: Minimum-maximum

and pH (median: 7.38 vs 7.41, p=0.007) than the control group, but lower carboxyhemoglobin percentage (mean: 1.66% vs 1.13%, p=0.000), PCO_2 (42.02 mmHg vs 39.44 mmHg, p=0.015), potassium (mean: 4.33 mmol/L vs 4.04, p=0.026), and sodium (mean: 138.10 mmol/L vs 135.80 mmol/L, p=0.000). ICU group had lower methemoglobin percentage (p=0.000).

ICU and non-ICU patients had similar deoxyhemoglobin, Hb, hematocrit, total bilirubin, bicarbonate plasma, chlorine, lactate, and osmolarity levels compared to control patients (no significant differences, Table 1, Figure 2).

Discussion

The ODC, which connects oxygen saturation (SO_2) and PO_2 in blood, is crucial for understanding blood's oxygen transport and release (13). P50 measures Hb's oxygen affinity, determining oxygen release from microcirculation to tissues. An increased P50 (rightward ODC shift) indicates reduced Hb-oxygen binding affinity, promoting oxygen release into tissues (7). Normal Hbs P50 is around 26 mmHg at 40 mmHg PCO_2 pressure (14).

In this study, examining arterial blood gas samples, all groups had higher P50 values compared to the standard. ICU COVID-19 patients had a higher P50 value than non-ICU COVID-19 patients (mean: 29.25 mmHg, p=0.047), with a slight ODC right shift. This suggests ICU COVID-19 patients require greater tissue oxygenation due to low O_2-Hb affinity. While Severinghaus's standard curve (12) indicates systemic arterial blood oxygen saturation separating from lungs is around 95 mmHg, Figure 1 shows all three groups' dissociation curves averaging 98 percent systemic arterial blood oxygen saturation.

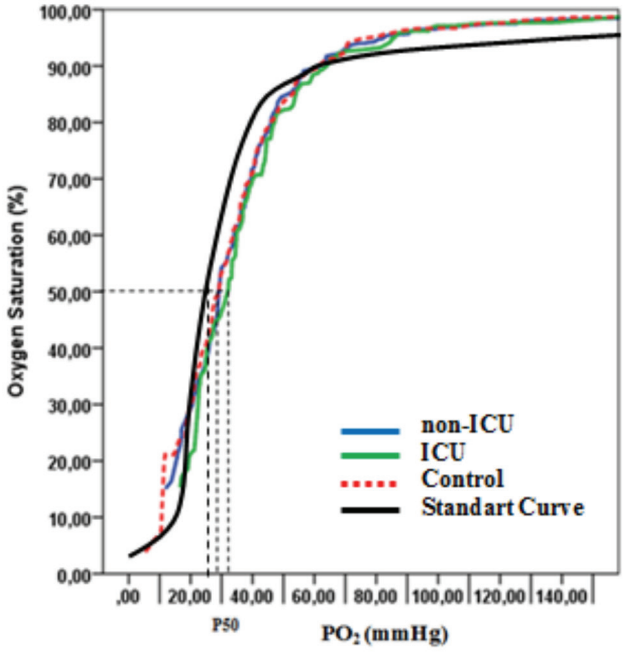

Figure 1. Comparative oxygen dissociation curves to the standard curve for all groups: the standard curve as described by JW Severinghaus (black curve), values of oxygenation saturation plotted versus PaO2 for patients admitted to the intensive care unit (ICU) with coronavirus disease-2019 (COVID-19) (green curve), and control patients without COVID-19 (control; red curve)

Daniel et al. (15) found no difference in Hb-O_2 affinity between 14 COVID-19 patients and 11 controls using an *in vitro* Hemox analyzer with standardized pH and temperature. P50 values were directly obtained from blood gas analyzers without adjustment for CO_2 or pH changes in COVID-19. They hypothesized that *in vivo* Hb-O_2 affinity could be affected by other factors in COVID-19. Vogel et al. (16) conducted a retrospective, observational study of blood gas analyses (n=3,518) from COVID-19 patients to investigate changes in Hb-O_2 affinity. They reported that this condition may play a role in adjusting to hypoxemia due to the lengthy disease process. Compared to patients with other causes of severe respiratory failure, COVID-19 patients had significantly higher Hb-O_2 affinity. Our findings show higher P50 and lower Hb-O_2 affinity in ICU COVID-19 patients. This may result from patients receiving oxygen support via ventilators, masks, or nasal cannulas. There are limited ODC-related studies in COVID-19 patients in the literature.

In critical illnesses, arterial blood gas (ABG) tests are vital for assessing lung function, diagnosis, and patient follow-up (17). Our study showed patients' pH values were within the normal range, allowing ODC evaluation at normal pH. All three groups displayed hypoxemia with ICU and non-ICU groups having higher PO_2 values than controls. Oxygen therapy may have increased arterial blood PO_2 in COVID-19 patients, which is a study limitation. No significant abnormalities were found in partial oxygen pressure against Hb oxygen saturation. All groups showed a slight right shift in ODC. Lower PCO_2 levels in non-ICU and ICU groups may be related to respiratory support therapy (18). Further *in vitro* and *in vivo* studies are needed to validate our hypothesis and understand the ODC mechanism during COVID-19 infection.

In our study which also evaluated the glucose, electrolyte, bicarbonate, bilirubin, Hb and hematocrit levels in the ABG analysis; had high blood glucose levels (mean: 195.36 mg/dL, 185.44 mg/dL, 163.39 mg/dL respectively) outside the normal range were detected in all patients in the ICU, non-ICU and control groups. This indicates that patients glucose metabolism is impaired. In the cross-group comparison of other data, there were similar levels of Hb, hematocrit, total bilirubin, bicarbonate plasma, chlorine, lactate and osmolarity.

Most coronavirus non-structural proteins are mainly found in infected cells, playing a key role in RNA replication (19). The virus is unlikely to access significant Hb, and there is no evidence of infiltration into red blood cells (20). Liu and Li (9) suggest interactions may occur after immune hemolysis, but some studies report no significant hemolysis in COVID-19 patients (21-23). Our study's clinical data

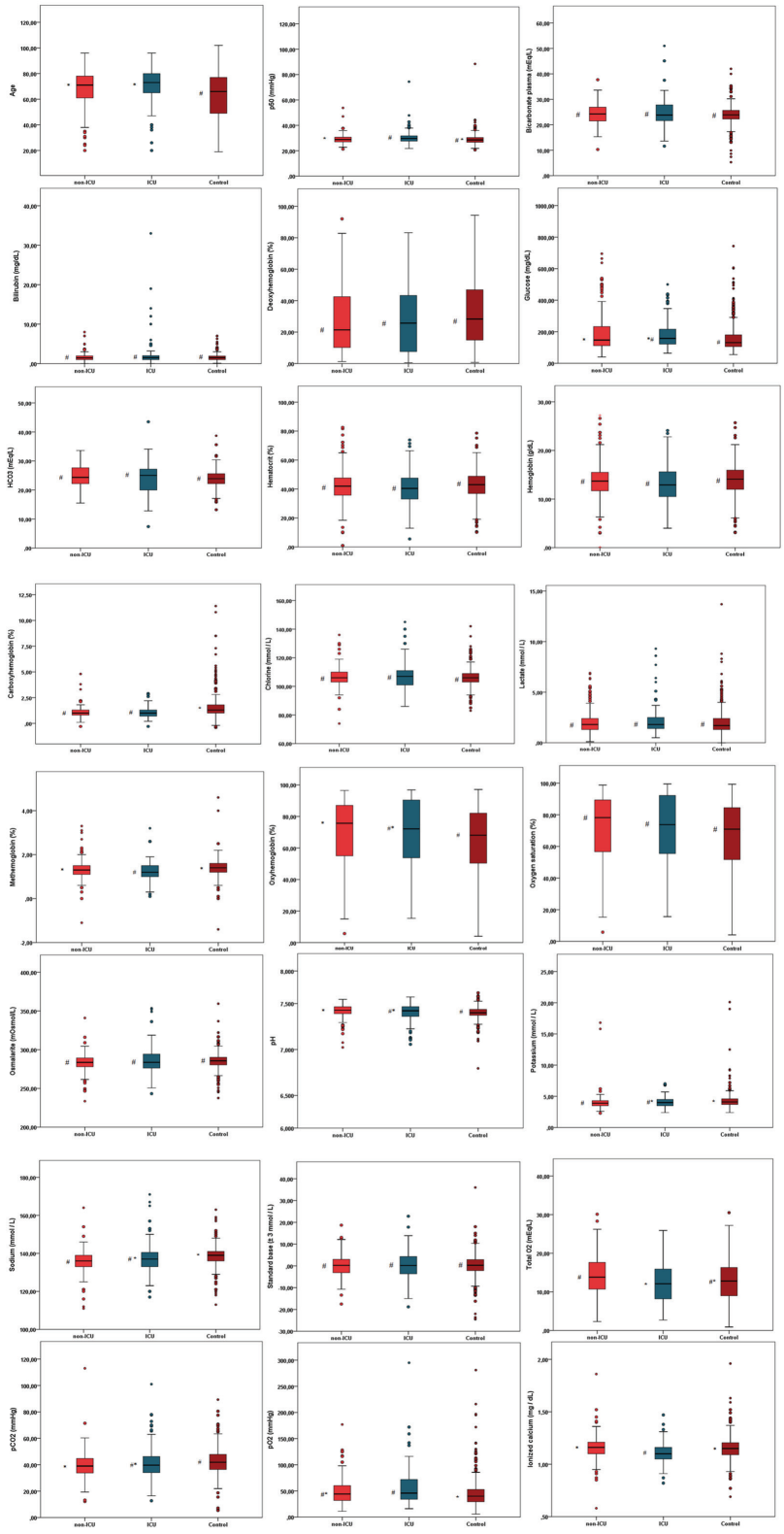

Figure 2. Corresponding laboratory values of age, P50, bicarbonate plasma, bilirubin, deoxyhemoglobin, glucose, HCO_3, hematocrit, hemoglobin, carboxyhemoglobin, chlorine, lactate, methemoglobin, oxyhemoglobin, oxygen saturation, osmolarity, pH, potassium, sodium, standard base, Total O_2, pCO_2, pO_2, and ionized calcium. The importance of the differences between the groups was indicated by the symbols. While the differences were found to be insignificant between groups with the same symbol, the differences between groups with different symbols were found to be significant

doesn't show significant hemolysis or abnormal Hb-oxygen decomposition. Similarly, another study evaluating ABG data of thirty COVID-19 patients found no significant clinical effect (24). Recent reports show similar mortality rates and mechanical ventilation needs for COVID-19 as other respiratory failure forms (3,25). Additionally, there's no evidence in the literature of significant anemia or excessive iron load caused by COVID-19 (21-23).

Our study has limitations due to small sample size, single-center, and retrospective design. The patient population receiving respiratory support and various medications in the service and intensive care unit may not fully reflect the impact of oxygen on Hb in COVID-19. The Control group was created from other patients with respiratory distress, limiting statistical significance. Therefore, larger sample sizes and *in vivo* and *in vitro* experimental studies are required for further verification.

Conclusion

The medical field and the global scientific community are making rapid strides in comprehending the underlying mechanisms of COVID-19 to effectively control its spread, provide proper care for patients, and ultimately discover definitive treatment options. In our study, which was carried out in order to contribute to the enlightenment of the physiological mechanism of the disease, it was concluded that patients diagnosed with COVID-19 and other respiratory distress patients were slightly right-leaning in the Hb-O_2 dissociation curve and had a higher percentage of oxygen saturation of arterial blood in all three groups.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee for Clinical Research at Erzincan University Faculty of Medicine (decision no: 05/05, date: 22.03.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.Ü., Design: H.Ü., C.M., Data Collection or Processing: C.M., M.T.H., Analysis or Interpretation: H.Ü., C.M., M.T.H., Literature Search: H.Ü., C.M., M.T.H., Writing: H.Ü., M.T.H.

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