Role of methemoglobin and carboxyhemoglobin levels in predicting COVID-19 prognosis: an observational study

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Abstract

World Health Organization has declared coronavirus disease-19 (COVID-19) as a pandemic. Although there are studies about this novel virus, our knowledge is still limited. There is limited information about its diagnosis, treatment and prognosis. We aimed to investigate the effect of methemoglobin and carboxyhemoglobin levels on the prognosis of COVID-19. In this observational study, patients who were diagnosed with COVID-19 during March 1–April 31, 2020 in a secondary-level state hospital in Turkey were included in the study. COVID-19 diagnosis was confirmed with reverse transcription polymerase chain reaction method, with nasal, oral or sputum specimens. During the period this study was performed, 3075 patients were tested for COVID-19 and 573 of them were hospitalized. Among the hospitalised patients, 23.2% (133) of them had a positive polymerase chain reaction result for COVID-19. A total of 125 patients, 66 (52.8%) males and 59 (47.2%) females, with an average age of 50.2 ± 19.8 years, were included in the study. The most common findings in chest radiogram were ground-glass areas and consolidations, while one-third of the patients had a normal chest radiogram. Computed thorax tomography was performed for 77.6% (97/125) of the patients. The 24.7% of computed tomographies (24/97) did not reveal any pathological findings, and the most common findings were ground-glass appearance and consolidation. Those who needed intensive care had statistically significantly lower platelet count ($P = 0.011$) and higher lactate dehydrogenase levels ($P < 0.001$). No statistically significant difference was found in carboxyhemoglobin ($P = 0.395$) and methemoglobin ($P = 1.000$) levels. We found that carboxyhemoglobin and methemoglobin levels had no effect on COVID-19 prognosis, but low platelet level played a role in predicting COVID-19 prognosis. This study was approved by the Ethical Committee of Harran University Faculty of Medicine on May 11, 2020 with approval No. 09.

Key words: carboxyhemoglobin; COVID-19; methemoglobin; pandemic; prognosis

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Introduction

Coronavirus disease-19 (COVID-19) was diagnosed first in Wuhan, China in December 2019 and then it has an outbreak all over the world. The virus has become an important cause of mortality and morbidity.[1] World Health Organization has declared it as a pandemic. Although there are studies about this novel virus, our knowledge is still limited. There is limited information about its diagnosis, treatment and prognosis. In the current literature, it is reported that it mostly affects the respiratory tract and mortality occurs due to this.[2]

Carbon monoxide (CO) is a colorless, odorless gas that binds to the same point where oxygen is bound in the hemoglobin (Hb) molecule and can therefore separate oxygen from Hb.[3] By this way, it reduces the oxygen carrying capacity of the blood. All people have some CO-linked Hb in their blood. An increased level of exhaled CO is seen in inflammatory lung diseases such as asthma, bronchiectasis, and upper respiratory tract infection.[4] CO is produced endogenously by hemo xygenase enzymes. The hemo xygenase enzyme is stimulated by cytokines and nitric oxide (NO). Three enzymes take part in Hb catabolism: heme oxygenase-1, heme oxygenase-2 and heme oxygenase-3.[4-6] The heme oxygenase enzyme is most commonly found in the spleen, bone marrow, brain, liver, kidney and lungs, respectively. Heme oxygenase-1 can be induced by biochemical or biophysical stress and is the common isoform of the enzyme.[6]

In order for Hb to reversibly bind oxygen and carry oxygen to tissues, iron must be kept in a ferrous (Fe^{2+}) state. Hb which is carrying oxidized iron atoms in the form of ferri (Fe^{3+}) and lacking oxygen carrying capacity is called methemoglobin (MetHb). MetHb may be formed in some medical conditions such as sepsis, gastrointestinal infections, and sickle cell anemia crisis, and after exposing to toxic drugs and chemicals.[7] Inhaled NO is often used to correct arterial oxygenation in acute respiratory distress syndrome patients. In one study, in patients where inhaled NO was withdrawn, MetHb and COHb values decreased accordingly.[7] Therefore, increasing NO levels may cause an increase in MetHb and COHb levels.[8-11] It has been shown that in clinical situations causing NO activation such as sepsis and septic shock, the large amount of NO released into circulation causes formation of MetHb.[12] In this context, in a study conducted in patients diagnosed with sepsis, increased MetHb level was shown to be related to the severity of sepsis. In this study, we aimed to investigate the effect of MetHb and COHb levels on the prognosis of COVID-19.

Subjects and Methods

This observational study was approved by the Ethical Committee of Harran University Faculty of Medicine on May 11, 2020 with approval No. 09.

Patient selection

Patients diagnosed as COVID-19 during March 1–May 31, 2020 in a second-level public hospital were included in the study. Names and protocol numbers of patients with the diagnosis code U07.3 (2019-nCov) were obtained from the hospital information system. Clinical data were noted to the data collection form, and the data were obtained from patients' files from policlinics and emergency department. For hospitalized patients, inpatient files were reviewed. COVID-19 diagnosis was confirmed with reverse transcription polymerase chain reaction (PCR) method from nasal, oral or sputum specimens. Initial blood tests were performed, and chest radiograms were analyzed. Socio-demographic information of the patients, results of their tests, whether they have a contact with a person with COVID-19, and whether or not the patient met the Turkish Ministry of Health criteria of a possible COVID-19 case were recorded to data collection form. The Turkish Ministry of Health defined possible COVID-19 cases according to the following categories[13]: a) fever and respiratory symptoms and either 1) a history of being abroad or 2) contact within 14 days prior to the onset of symptoms with relatives who have a history of being abroad; or b) at least one of the symptoms of fever or respiratory symptoms and close contact with a verified COVID-19 case within 14 days prior to the onset of symptoms; or c) fever and findings of severe respiratory failure requiring hospitalization and no other obvious cause to explain the patient's clinical condition; or d) abrupt onset of fever accompanied by cough or shortness of breath and not having nasal discharge.

Initial venous blood gas analysis results of pH, partial pressure of carbon dioxide, partial pressure of oxygen values and MetHb, COHb and lactate levels were noted to the data collection form. Patients who have COVID-19 findings clinically or radiologically and were diagnosed as COVID-19 by PCR method were included in the study. Those with missing patient file information, active smokers, those with PCR negative and who had negative PCR results besides a positive rapid test were excluded from the study.

Imaging

The imaging findings of the patients were analyzed through the hospital information system and were recorded on the data collection forms. The chest radiographs taken at the time of admission or soonest after admission were interpreted. Radiological features were recorded according to Fleischner guide[14]: infiltration, ground-glass areas, effusion, and nodules. Distribution according to tomographic images were recorded as; peripheral, central; upper, middle, lower lobe and lingula; right, left and bilateral.

Quantitative reverse transcription PCR

Oral and nasopharyngeal swab samples were taken by the doctor at admission and at various times during hospitalization. Respiratory samples of patients meeting the COVID-19 possible case definition were studied for SARS-CoV-2 in the Microbiology Laboratory of Kastamonu State Hospital, approved by the General Directorate of Public Health of Turkey. Routine confirmation of nucleic acid amplification tests for the SARS-CoV-2 virus was performed by real-time reverse transcription PCR. With this, specific sequences of the virus RNA were determined and, if necessary, confirmed by nucleic acid sequence analysis method. RNA extraction was performed in BSL-2 or equivalent biosafety cabinet. Those who have positive real-time reverse transcription PCR test are considered as COVID-19 patients. If the test was negative, the test was repeated for patients clinically and radiologically suspected to have COVID-19.

Statistical analysis

Statistical analysis of the data was performed with SPSS 19.0 program (IBM, Armonk, NY, USA). Categorical variables were defined as frequency and percentage; continuous variables were defined as the mean ± standard deviation (SD). The suitability of the data to normal distributions was evaluated with the Kolmogorov Smirnov test. Mann Whitney *U* test was used to compare the median of binary groups that did not fit the normal distribution, and chi-square significance test was used in the analysis of categorical variables. The relationship of continuous variables was evaluated with Spearman Correlation test. Statistical significance level was accepted as 0.05 in the study.

Results

General characteristics and laboratory parameters of the COVID-19 patients

During the period this study was performed, 3075 patients were tested for COVID-19 and 573 of them were hospitalized. Among the hospitalized patients, 23.2% (133) of them had a positive PCR result for COVID-19 and 10.4% (60) of them had a positive rapid antibody test result. Patients with a positive rapid antibody test and eight patients with missing file data were excluded. A total of 125 patients, 66 (52.8%) males and 59 (47.2%) females, with an average age of 50.2 ± 19.8 years, were included in the study. Forty patients had at least 1 comorbid disease, 15 patients had at least 2 comorbid diseases, and 4 patients had at least 3 comorbid diseases. General characteristics and laboratory parameters of the patients are listed in **Table 1**.

Radiological findings of the COVID-19 patients

The most common findings in chest radiogram were ground-glass areas and consolidations, while one-third of the patients had a normal chest radiogram. The least common findings were atelectasis and pleural effusion with 1.5% (2 cases for each). Computed tomography of the thorax was performed for 77.6% (97/125) of the patients, 24.7% (24/97) of them did not reveal any pathological findings, and the most common findings were ground-glass appearance and consolidation. When the computed tomography findings are evaluated, most frequent distributions were bilateral (56/97, 57.7%), inferior lobes (65/97, 67.0%) and peripheral (83/97, 85.5%). Central involvement alone was not detected in any patients. Least common lobe to be involved was detected as lingula (13/97, 13.4%).

Table 1: General characteristics and laboratory parameters of the COVID-19 patients

	Data
Gender	
Female	59(47.2)
Male	66(52.8)
Comorbidity	
Yes	40(32.0)
No	85(68.0)
Survived	
Yes	120(96.0)
No	5(4.0)
Need for intensive care	14
Intubated	6(4.8)
Not intubated	8(6.4)
Mean age (yr)	50.2±19.8
Body temperature (°C)	37.3±0.9
Duration of hospitalization (d)	11.8±5.6
Duration of symptoms (d)	6.0±3.7
Hemoglobin (g/dL)	13.1±1.7
Leukocytes (µL)	6088.4±2452.6
Neutrophils (µL)	3974.8±2195.8
Lymphocytes (µL)	1550.4±904.0
Lymphocyte (%)	26.4±12.7
Platelet (µL)	201736.0±69833.6
D-dimer (mg/L)	0.7±0.1
Lactate dehydrogenase (U/L)	277.5±121.0
pH	7.38±0.04
Partial pressure of carbon dioxide (mmHg)	43.6±6.3
Partial pressure of oxygen (mmHg)	29.9±11.6
Carboxyhemoglobin (%)	1.0±0.2
Methemoglobin (%)	1.1±0.6
Lactate (mM)	1.6±0.6

Note: Categorical variables are expressed as number (percentage), and continuous variables are expressed as the mean ± SD. COVID-19: Coronavirus disease-19.

Clinical symptoms of the COVID-19 patients

When the patients were evaluated according to the symptoms, 21.6% (27/125) of them were asymptomatic, 18.4% (23/125) had fever, 18.4% (23/125) had cough, 8.8% (11/125) had myalgia, 15.2% (19/125) had shortness of breath, 4% (5/125) had sore throat, 1.6% (2/125) had gastrointestinal complaints and 1.6% (2/125) had loss off odor. It was found that 54.4% of the cases had contact with a COVID-19 diagnosed patient. According to the possible case scenarios of the Ministry of Health of the Republic of Turkey,13 26.4% (33/125) of the patients were group A, 42.2% (53/125) were group B, 4.8% (6/125) were group C and 24.8% (31/125) were group D.

Those who needed intensive care had statistically significantly lower platelet count (P = 0.011) and higher lactate dehydrogenase levels (P < 0.001). No statistically significant difference was found between COHb (P = 0.395) and MetHb (P = 1.000) levels (**Table 2**). Laboratory values of the patients according to their survey are given in **Table 3** and receiver operating characteristic analysis of mortal COVID-19 patients is present in **Table 4**.

Discussion

Researches are being continued on this global issue of COVID-19. Studies for a vaccine, diagnosis and treatment are ongoing, as well as the prognosis of the disease. In this study we investigated the correlation between COVID-19 prognosis and blood gas analysis, which is an easily accessible laboratory test. In our study, although the number of intensive care patients was low, we found that the decrease in platelet level and increase in lactate dehydrogenase level predicted the need for intensive care, but the CoHb and MetHb levels were not sufficient to foresee the need for intensive care. Endogenous CO is known to be formed by the enzyme heme oxygenase-1. Heme oxygenase-1 enzyme is thought to be an indicator of oxidative stress.[5] Conditions such as sepsis, septic shock, severe pneumonia cause oxidative stress. Zegdi et al.[15] found

Table 2: General characteristics of COVID-19 patients with or without need intensive care

	Need intensive care (n = 14)	Do not need intensive care (n = 111)	P-value
Age (yr)	59.2±16.9	49.1±19.8	0.07
Hemoglobin (g/dL)	13.2±1.7	13.1±1.7	0.836
Leukocytes (µL)	6855.7±2452.6	5991.6±2207.5	0.175
Neutrophils (µL)	4912.1±3430.6	3856.5±1943.5	0.086
Lymphocytes (µL)	1455.7±622.7	1562.4±928.8	0.676
Lymphocyte (%)	23.6±10.8	26.7±12.8	0.388
Platelet (µL)	157785.7±61420.3	207279.2±68540.0	0.011
D-dimer (mg/L)	0.7±0.4	0.8±1.0	0.712
Lactate dehydrogenase (U/L)	408.4±175.3	261.3±100.3	< 0.001
pH	7.4±0.0	7.38±0	0.952
Partial pressure of carbon dioxide (mmHg)	42.9±6.1	43.8±6.3	0.614
Partial pressure of oxygen (mmHg)	26.2±9.3	30.4±11.7	0.233
Carboxyhemoglobin (%)	0.8±0.5	1.0±1.3	0.395
Methemoglobin (%)	1.0±0.5	1.0±0.6	1.000
Lactate (mM)	1.5±0.5	1.6±0.6	0.551

Note: Categorical variables are expressed as number (percentage) and were analyzed by chi-square significance test. Continuous variables are expressed as the mean ± SD and were analyzed by Mann Whitney U test. COVID-19: Coronavirus disease-19.

Table 3: General characteristics of mortal and survived COVID-19 patients

	Survived (*n* = 120)	Mortal (*n* = 5)	*P*-value
Hemoglobin (g/dL)	13.1±0.1	12.8±0.4	0.686
Leukocytes (μL)	6001.8±204.5	8176.0±2660.0	0.054
Neutrophils (μL)	3874.6±179.1	6388.0±2417.3	0.012
Lymphocytes (μL)	1559.4±83.3	1346.0±419.1	0.609
Lymphocyte (%)	26.7±1.1	19.2±7.7	0.200
Platelet (μL)	201521.0±6519.4	210600.0±18898.6	0.778
D-dimer (mg/L)	0.7±0.0	0.7±0.2	0.937
Lactate dehydrogenase (U/L)	266.6±9.5	535.6±97.5	0.001
pH	7.3±0.0	7.3±0.0	0.907
Partial pressure of carbon dioxide (mmHg)	43.8±0.5	38.6±3.5	0.072
Partial pressure of oxygen (mmHg)	30.1±1.0	29.0±4.7	0.849
Carboxyhemoglobin (%)	1.0±0.1	0.7±0.1	0.537
Methemoglobin (%)	1.0±0.0	0.7±0.0	0.310
Lactate (mM)	1.6±0.0	1.5±0.2	0.518

Note: Continuous variables are expressed as the mean ± SD and were analyzed by Mann Whitney *U* test. COVID-19: Coronavirus disease-19.

Table 4: Receiver operating characteristic analysis of mortal COVID-19 patients

Factors	AUC (95%)	Cut off	*P*-value	Sensitivity (%)	Specificity (%)
Age	0.656 (0.370–0.942)	55.5	0.237	60	59.7
Duration of hospitalization	0.556 (0.210–0.901)	12.5	0.707	50	49.5
Hemoglobin	0.434 (0.279–0.590)	12.65	0.62	60	42.9
Leukocytes	0.521 (0.178–0.864)	5025	0.874	40	39.5
Neutrophils	0.571 (0.257–0.886)	3205	0.589	60	41.2
Lymphocytes	0.446 (0.131–0.762)	1295	0.684	60	48.7
Lymphocyte	0.292 (0.000–0.592)	15.45	0.115	40	17.8
Platelet	0.583 (0.383–0.783)	209000	0.53	60	59.7
D-dimer	0.539 (0.290–0.787)	0.555	0.77	60	54.6
Lactate dehydrogenase	0.923 (0.845–1.000)	332	0.001	80	79.8
pH	0.496 (0.177–0.814)	7.381	0.975	40	40.3
Partial pressure of carbon dioxide	0.319 (0.105–0.533)	42.3	0.172	40	39.5
Partial pressure of oxygen	0.491 (0.241–0.740)	25.65	0.944	40	40.3
Carboxyhemoglobin	0.460 (0.292–0.628)	0.75	0.76	40	48.7
Methemoglobin	0.402 (0.256–0.547)	0.85	0.457	40	47.1
Lactate	0.487 (0.259–0.714)	1.65	0.919	60	56.3

Note: AUC: Area under the curve of receiver operating characteristics. COVID-19: Coronavirus disease-19.

that endogenous CO production increased in severe sepsis in intensive care patients, while Scharte et al.[5] found that endogenous CO increased in patients with multiorgan failure. COVID-19 pneumonia can cause multiple organ failure and result with severe sepsis and mortality. We found that COHb levels did not increase in patients requiring intensive care and having a mortal course, although we report a low number of cases. Previous studies measured direct exhaled CO and correlated with the severity of the disease, but the COHb in our study was measured from blood gas and indirectly shows the endogenous COHb level.[5,6,15] This may be the main reason why there was no difference between the groups in our study. MetHb level is thought to predict the severity of the disease in severe sepsis. In the study where Schuerholz et al.[12] evaluated more than 600 intensive care patients, it was found that the level of MetHb increased parallel to the sequential organ failure assessment score in sepsis. Apart from this, various studies reported that acquired methemoglobinemia can be seen especially in the pediatric age group.[16-19] Although most of these studies were performed by measuring MetHb levels with pulse oximetry, this was also supported by arterial blood gas samples.[12,16,17] In our study, there was no statistically significant increase in the level of MetHb in both the group requiring intensive care and in the cases with mortal course.

During the days this study was conducted, the mortality rate in Turkey was 2.7% and rate of those who need intensive care was 3.6%, according to the official data.[20] In studies conducted in China, it was reported that the need for intensive care varies between 5–32%, and mortality is between 0.9–4.3%.[21-25] In our study, those who developed intensive care needs were 11.2% and those with mortality were 4%. In the study of Wang et al.,[21] it was stated that intensive care patients had decreased lymphocyte count and percentage, increased urea, creatine and lactate dehydrogenase levels compared to other patients. They linked these findings to the disruption of the cellular immune mechanism. In the study of Guan et al.,[25] it was reported that lymphopenia and leukopenia can be seen in severe patients. In our study, it was found that the group in need of intensive care had older age, the number of platelets was lower, and the level of lactate dehydrogenase was higher. In addition, neutrophils and lactate dehydrogenase levels were higher in patients with mortality. There was no statistically significant difference between the groups in terms of COHb and MetHb levels.

The most significant limitation of our study is the low number of patients. Particularly, fewer cases with mortality may have affected statistical significance of our findings. Another important limitation is that patients were not evaluated for the scores indicating severity of sepsis, such as acute physiology and chronic health evaluation II and sequential organ failure assessment scores.

To conclude, although the studies emphasized that the levels of MetHb and COHb may be related to the severity of sepsis, those levels were not found to be related with the severity of COVID-19 in our study. We suggest that the authors who want to conduct further studies on this subject may evaluate our findings. COVID-19 is a new disease and needs to be investigated. The diagnosis and prognosis of this disease are still under investigation. With this study, we want to give an idea to the authors who will work on this topic.

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Author contributions
Study conception and design: FÜ; data collection: BÖ; data processing: BÖ, FÜ, İK; data analysis: MT; manuscript writing: BÖ, FÜ; manuscript review: BÖ, FÜ, FMKG, İK; manuscript supervision: FMKG. All the authors read and approved the final version of the manuscript for publication.

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The authors report no conflict of interest.

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Declaration of patient consent
The authors certify that they have obtained patients consent forms. In the form, patients have given their consent for the images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

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The statistical methods of this study were reviewed by the biostatistician of Kastamonu University Faculty of Medicine, Turkey.

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The data and statistical analysis that support the findings of this study are available from the corresponding author, upon reasonable request.

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