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ORIGINAL ARTICLE

Evaluation of the Relationship between Exhaled CO Levels with Clinical Course and Parenchymal Involvement in COVID-19

Dursun E. Afsin [1] and Bugra Kerget [2]

[1] *Department of Pulmonary Diseases, Health Sciences University Erzurum Regional Education and Research Hospital, Erzurum, Turkey*
[2] *Department of Pulmonary Diseases, Ataturk University School of Medicine, Yakutiye, Erzurum, Turkey*

SUMMARY

Background: **COVID-19, caused by the SARS-CoV-2 virus, has infected nearly 270 million people over the past two years. We aimed to determine the exhaled CO levels of patients hospitalized with COVID-19 pneumonia and its correlation with parenchymal involvement.**
Methods: **Between September 2021 and December 2021, 74 patients who were hospitalized in the infectious diseases service of our hospital and whose delta variant COVID-19 infection was confirmed with real-time PCR method were included in the study. The patients were analyzed in 3 groups: moderate COVID-19 (group 1), severe COVID-19 without macrophage activation syndrome (MAS) (group 2), and severe COVID-19 with MAS (group 3).**
Results: **While it was observed that the exhaled CO levels were higher in patients in Group 3 at the time of hospitalization than in patients in Group 1 and 2, it was determined that no significant difference was observed between the groups at the time of discharge ($p < 0.001$, 0.213). CT scores obtained at the time of hospitalization were also observed to be statistically significantly higher in patients in Group 3 when compared to patients in Group 1 and 2 ($p = 0.002$). In the correlation analysis of the exhaled CO levels and the CT scores at the time of hospitalization, a statistically significant positive correlation was observed ($r = 0.628$, $p < 0.001$).**
Conclusions: **In COVID-19, which has a high affinity for lung tissue compared to other known viral lower respiratory tract infections, the exhaled CO level may be a non-invasive parameter that can be used in the evaluation of parenchymal involvement and clinical course.**
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Correspondence:
Dursun Erol Afsin, MD
Health Sciences University
Erzurum Regional Education and
Research Hospital
25240, Yakutiye, Erzurum
Turkey
Phone: +90 4423447446
Fax: +90 4423446528
Email: bjkerget1903@gmail.com

KEYWORDS

COVID-19, exhaled CO, thorax computed tomography

INTRODUCTION

COVID-19 has infected about 270 million people in the world since December 2019 and, unfortunately, caused about 5.5 million deaths. COVID-19 can be asymptomatic in people infected in the acute period, but it can also be presented with mild symptoms such as weakness, muscle and joint pain, loss of appetite and loss of taste. However, with hypertension, diabetes mellitus, chronic renal failure in older ages as well receiving immunosuppressive therapy might cause severe clinical pictures in patients and pregnant women.

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Acute respiratory distress syndrome (ARDS) and macrophage activation syndrome (MAS) are the leading severe clinical pictures. Although efforts have been made to prevent such severe clinical picture with the acceleration of vaccination studies for COVID-19, such consequences could be inevitable in the unvaccinated population [1]. While some patients are admitted to the emergency service with a radiological and laboratory findings that will create an ARDS picture, in some patients this picture is formed over time. In studies performed on COVID-19 patients, it was observed that CRP, IL-6, IL-1, TNF-alpha, ferritin, fibrinogen, D-dimer, and LDH could be biomarkers that may play a role in clinical follow-up [2,3].

Carbon monoxide is synthesized by the heme oxygenase-1 (HO-1) enzyme from many tissues and organs and causes a significant increase in the synthesis of oxidative stress and inflammation [4]. Since HO-1 is found in alveolar macrophages and vascular endothelium, there are suggestions that the level of exhaled CO could be a marker of inflammation and oxidative stress in the airways [5,6]. Inflammation and oxidative stress can induce HO-1 and the concentration of CO in exhaled air, and therefore CO levels are increased in patients with asthma and other inflammatory lung diseases [7]. In a study conducted in patients with viral upper respiratory tract infection, it was observed that infections increase the exhaled CO levels. Accordingly, when the pre- and post-treatment levels of exhaled CO in patients followed-up with lower respiratory tract infection are compared, it was found out that CO levels show a significant decrease with the treatment [8].

Exhaled CO level is a parameter that has not been studied before in COVID-19 patients, and in our study we aimed to evaluate the correlation of exhaled CO level with clinical course and radiological findings.

MATERIALS AND METHODS

Study design

In our study, patients who returned from abroad in the last 14 days and who came into contact with a suspected COVID-19 patient, especially those with complaints of incipient fever, cough, dyspnea, weakness, decreased sense of taste and smell, and admitted to Erzurum Regional Training and Research Hospital emergency service were included. Before the patients were included in the study, detailed information was given to the patients (or their relatives) about the purpose of the study. An informed consent form was obtained from the participants and they were included in the study. Local ethics committee approval was obtained before starting the study.

Study population

High-resolution computed tomography (HRCT) was performed in a standardized manner on patients at high risk for COVID-19. In accordance with the HRCT results, patients with bilateral ground-glass opacity, subsegmental consolidation or linear opacities, cobblestone appearance, and reverse halo sign, with peripheral localization in the foreground were evaluated as typical findings and patients with radiological atypical findings but with compatible clinical complaints were hospitalized. The diagnosis of COVID-19 was performed by real time PCR method by taking nasopharyngeal swabs from the patients. Seventy-four patients who were hospitalized in the chest diseases intensive care unit and service in Erzurum Regional Training and Research Hospital between September 2021 and December 2021 due to moderate and severe COVID-19 pneumonia were included.

After hospitalization, biochemical parameters including hematological parameters, liver and kidney function tests, coagulation parameters, ferritin, D-dimer, troponin-I and CRP levels were obtained daily. FeNO levels were measured at the hospitalization of the patients.

Study group

The patients included in our study were divided into 3 groups according to their follow-up status due to COVID-19. Group 1: Moderate Illness Patients with clinical signs of pneumonia with no signs of severe pneumonia (severe pneumonia: pneumonia fitting any one of the following conditions: respiratory rate $\geq$ 30 breaths/min; SpO2 $\leq$ 92%; patients with lung infiltration rate > 50%) (n:14), Group 2: Patients hospitalized for severe pneumonia but not followed-up in the intensive care unit due to respiratory failure or macrophage activation syndrome (n:32), Group 3: Patients hospitalized with severe pneumonia and followed-up in the intensive care unit due to development of macrophage activation syndrome or respiratory failure in their follow-up (n:28).

Exclusion Criteria

Patients with chronic or clinically significant infectious or inflammatory conditions in the last month, current smoker, uncontrolled asthma, chronic obstructive pulmonary disease (COPD), malignancy, invasive surgery in the last month, uncontrolled hypertension, high fasting blood glucose, and newly developed cerebrovascular disease, kidney disease and coronary artery disease were excluded. History and laboratory parameters obtained at admission were used to evaluate patients in terms of exclusion criteria. Presence of coronary artery disease, asthma, COPD and diabetes was determined as a result of consultation with cardiology, chest diseases and internal medicine departments.

Exhaled CO measurement

Exhaled CO was measured by a portable micro CO analyzer (Micro Medical Ltd., Rochester, Kent, U.K.) using a single slow exhalation [9].

Thorax computed tomography and analysis

All patients underwent contrast-enhanced CT scans of the chest on a second-generation Somatom Definition

Flash 256-slice dual-source multidetector CT scanner (Siemens Healthcare, Forchheim, Germany). CT examinations were performed with breath holding during deep inspiration. All images were transferred to a commercial workstation (Singo via. Workstation, Siemens, Erlangen, Germany). The images were assessed by two pulmonologist who were blinded to the patients' identities. The first reader had 25 years of experience in pulmonology and the second reader had 10 years of experience in pulmonology. Each reader evaluated the size, location, and number of the lesions and interpreted the findings. Tomographic imaging was evaluated using the terms of international standard terminology such as ground glass opacity, crazy-paving pattern and consolidation, as defined by Fleischner Society dictionary and widely used in the literature on viral pneumonia [10-12]. A semi-quantitative scoring system was used to quantitatively estimate the pulmonary involvement of all these abnormalities on the basis of the area involved. Each of the 5 lung lobes was visually scored from 0 to 5 as: 0, no involvement; 1, < 5% involvement; 2, 25% involvement; 3, 26% - 49% involvement; 4, 50% - 75% involvement; 5, > 75% involvement. The total CT score was the sum of the individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement).

Definitions and diagnosis

Fever was defined as an axillary temperature of 37.3℃ or higher. In patients with high fever while under treatment for COVID-19, blood, urine, and sputum cultures were obtained to test for possible bacterial and fungal superinfections and empiric antibiotherapies were revised according to the culture results. Diagnosis and grading of acute respiratory distress was done using the Berlin 2015 diagnostic criteria [13]. Patients with elevated daily cardiac-specific troponin levels underwent echocardiographic evaluation for nascent cardiac pathologies. Coagulopathy was defined as prothrombin and partial thromboplastin times 3 seconds and 5 seconds longer than normal, respectively. The treatment strategy for each patient was determined based on their clinical severity and the Turkish Ministry of Health COVID-19 adult diagnosis and treatment guidelines. Patients with findings such as refractory fever, persistently high or increasing CRP and ferritin levels, elevated D-dimer level, cytopenia (lymphopenia or thrombocytopenia), abnormal liver function tests, hypofibrinogenemia, or elevated triglyceride levels despite treatment were monitored for MAS. If serial measures demonstrated further deterioration in these parameters that could not be explained by secondary bacterial infection, the patients were treated for MAS with > 250 mg/day methylprednisolone if they had no contraindication. The patients were followed up for 72 hours and those who did not show a clinical response were treated with 400 mg tocilizumab. After 24 hours, patients who still did not exhibit clinical and laboratory response received a second dose of tocilizumab.

Statistical analysis

Analyses were performed using IBM SPSS version 20.0 software (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA). Data were presented as mean, standard deviation, number, and percentage. Shapiro-Wilk test and Kolmogorov-Smirnov test were used to determine whether continuous variables were normally distributed. Continuous variables were compared between more than two independent groups using analysis of variance (ANOVA) if normally distributed and Kruskal-Wallis test if non-normally distributed. Post-hoc tests after ANOVA were performed using Tukey's test when variances were homogeneous and Tamhane's T2 test when variances were not homogeneous. Post-hoc analysis after Kruskal-Wallis test was performed using the Kruskal-Wallis one-way ANOVA (k samples) test. Relationships between two quantitative variables were examined using Pearson's correlation analysis if normally distributed and Spearman's correlation analysis if non-normally distributed. ROC curve analysis was used to evaluate sensitivity and specificity in patients COVID-19. p-values < 0.05 were considered statistically significant.

RESULTS

The mean age of the patients included in our study was 56.7 ± 13.6. The mean age of patients in Group 1 was 55.1 ± 14.2, in Group 2 it was 57.1 ± 12.5, and in Group 3 it was 58.1 ± 13.4. No statistically significant difference was observed between the mean ages of the patients ($p = 0.66$). Fifty-one (68.9%) patients included in the study were male. While 44 of the patients were ex-smokers, 30 were non-smokers. Twenty-four patients had hypertension, 10 had diabetes mellitus, and 2 had coronary artery disease.

Inter-group analysis of laboratory parameters of the patients at the time of the hospitalization, and the hospitalization period for the patients are given in Table 1. Accordingly, it was observed that lymphocyte count and percentage were statistically significantly lower in Group 2 and 3 patients compared to Group 1 patients ($p = 0.001$, 0.04). While it was observed that CRP, LDH, and BUN levels were higher in Group 2 and 3 patients compared to Group 1 patients, CRP, fibrinogen, and ferritin levels were also observed to be higher in Group 3 patients compared to Group 2 patients ($p < 0.001$, < 0.001, < 0.02, < 0.001, < 0.001, < 0.001 respectively). When the groups are compared in terms of the duration of hospitalization, a statistically significant increase was observed in patients in Group 3 when compared to patients in Group 1 and 2 ($p < 0.001$).

The exhaled CO levels of the groups at the time of hospitalization and discharge and the CT scores obtained during hospitalization are shown in Table 2. Accordingly, while it was observed that the exhaled CO levels were higher in patients in Group 3 at the time of hospitalization than in patients in Group 1 and 2, it was deter-

Table 1. Comparison of laboratory parameters of patients obtained at the time of hospitalization and their duration of hospitalization periods.

	Group 1 (n = 14) Mean ± SD	Group 2 (n = 32) Mean ± SD	Group 3 (n = 28) Mean ± SD	p
WBC (/µL)	7,106.6 ± 1,999.2	7,272.3 ± 2,000.6	7,153.8 ± 1,794.8	0.39
Lymphocytes (/µL)	2,579.1 ± 704.8	2,010.8 ± 640.3 [a]	1,903.3 ± 711.9 [a]	0.001
Lymphocyte%	27.3 ± 9.2	21.3 ± 6.5 [a]	20.4 ± 6.5 [a]	0.04
Neutrophils (/µL)	4,420.9 ± 1,781.9	4,298.7 ± 1,864.9 [a]	4,168.5 ± 1,789.2 [a]	0.05
Neutrophil%	60.5 ± 8.6	56.7 ± 8.1 [a]	55.6 ± 14.7 [a]	0.04
Platelets (/µL)	2,623,869.3 ± 72,964.2	261,230.4 ± 39,561.4	260,227.2 ± 74,822.5	0.07
MPV (fL)	10.1 ± 0.9	9.9 ± 0.6	9.8 ± 0.4	0.09
ALT (U/L)	34.2 ± 21.9	33.3 ± 18.9	36.1 ± 19.1	0.27
AST (U/L)	24.4 ± 8.4	22.6 ± 6.4	23.5 ± 7.6	0.38
Albumin (g/dL)	4.2 ± 0.3	4.1 ± 0.3	4.1 ± 0.2	0.11
Fibrinogen (ng/mL)	315.4 ± 142.1	316.9 ± 53.9	370.2 ± 68.7 [a, b]	< 0.001
Procalcitonin (ng/mL)	0.04 ± 0.03	0.04 ± 0.03	0.03 ± 0.03	0.06
D-dimer (ng/mL)	339.2± 223.6	338.1 ± 247.2	341.2 ± 260.4	0.44
CRP (mg/dL)	7.7 ± 10.6	11.8 ± 2.9 [a]	23.8 ± 9.3 [a, b]	< 0.001
LDH (U/L)	219.5 ± 60.5	245.1 ± 22.8 [a]	250.5 ± 53.6 [a]	< 0.001
BUN (mg/dL)	13.3 ± 3.9	16.9 ± 4.7 [a]	16.9 ± 5.1 [a]	0.02
Ferritin (ng/mL)	134.3 ± 140.6	145.6 ± 113.1	303.5 ± 210.6 [a, b]	< 0.001
Troponin-I (ng/mL)	2.2 ± 3.8	2.2 ± 1.2	2.6 ± 2.1	0.44
Length of the hospitalization (days)	7.1 ± 1.4	6.6 ± 1.5	12.5 ± 2.7 [a, b]	< 0.001

SD - Standard deviation, WBC - White blood cells, MPV - Mean platelet volume, AST - Aspartate transaminase, ALT - Alanine transaminase, LDH - Lactose dehydrogenase, CRP - C-reactive protein, BUN - Blood urea nitrogen, Kruskal-Wallis test was used for between-group analyses. p [a] - Compared to group 1, p [b] - Comparison between groups 2 and 3.

Table 2. Comparison of exhaled CO and CT scores between groups at the time of hospitalization and discharge.

	Group 1 admission (n = 14) Mean ± SD	Group 2 admission (n = 32) Mean ± SD	Group 3 admission (n = 28) Mean ± SD	p
Exhaled CO admission (ppm)	2.3 ± 1.4	1.8 ± 0.8	3.8 ± 1.7 [a, b]	< 0.001
CT score admission	6.6 ± 3.5	7.4 ± 3.5	10.3 ± 3.1 [a, b]	< 0.001
Exhaled CO discharged (ppm)	2.1 ± 0.9	1.9 ± 0.8	2.3 ± 0.9	0.21

SD - Standard deviation, WBC - White blood cells, MPV - Mean platelet volume, AST - Aspartate transaminase, ALT - Alanine transaminase, LDH - Lactose dehydrogenase, CRP - C-reactive protein, BUN - Blood urea nitrogen.
Kruskal-Wallis test was used for between-group analyses. p [a] - Compared to group 1, p [b] - Comparison between groups 2 and 3.

mined that no significant difference was observed between the groups at discharge ($p < 0.001$, 0.213). CT scores obtained at the time of hospitalization were also observed to be higher in a statistically significant manner in patients in Group 3 when compared to patients in Group 1 and 2 ($p = 0.002$) (Figure 1). In the follow-up of the patients, 2 patients died. Exhaled CO levels of these patients upon hospitalization were observed to be 8 and 7 ppm.

In the correlation analysis of the exhaled CO levels and the CT scores at the time of hospitalization, a statistically significant positive correlation was observed ($r = 0.628$, $p < 0.001$). In the correlation analysis of the duration of hospitalization with exhaled CO and CT

Table 3. Correlation analysis of exhaled CO, CT score, CRP, and LDH levels.

		Exhaled CO admission	CT score admission	Length of the hospitalization
Exhaled CO admission	**r**	**1.000**	**0.628**	**0.543**
	p	**-**	**< 0.001**	**< 0.001**
	n	**74**	**74**	**74**
CT score admission	**r**	**0.628**	**1.000**	**0.533**
	p	**< 0.001**	**-**	**< 0.001**
	n	**74**	**74**	**74**
Length of the hospitalization	**r**	**0.543**	**0.533**	**1.000**
	p	**< 0.001**	**< 0.001**	**-**
	n	**74**	**74**	**74**

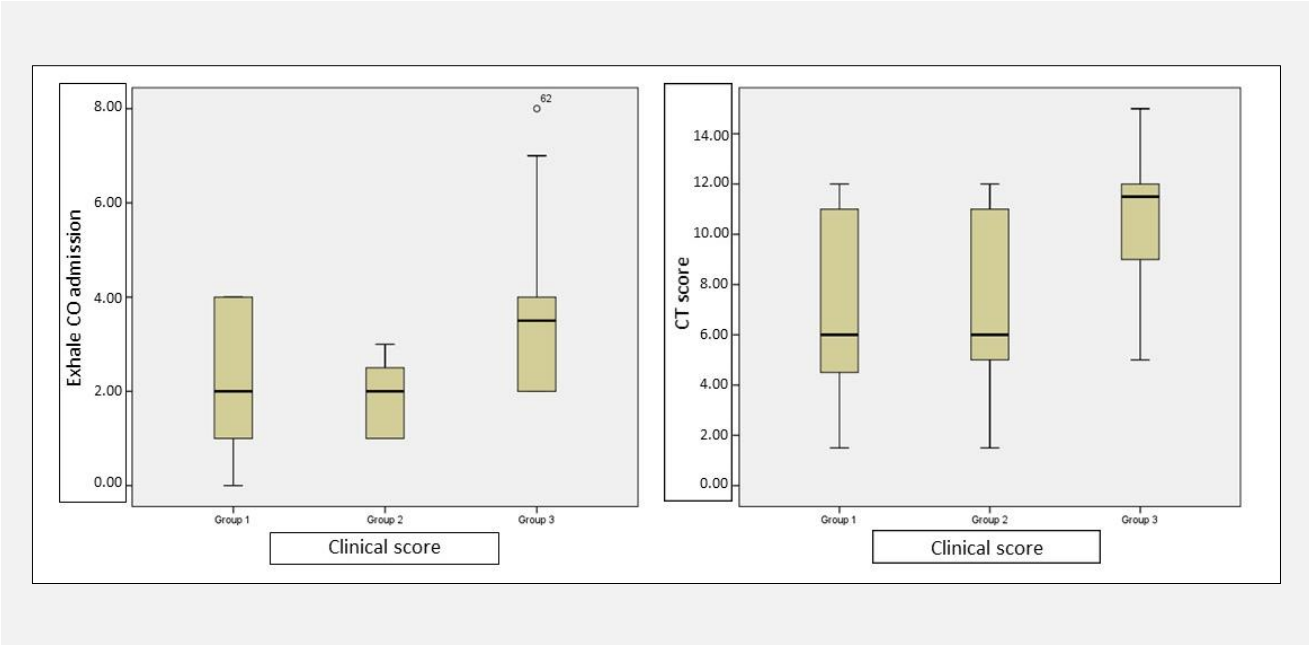

Figure 1. Comparison between the groups of exhaled CO and CT scores obtained at the time of hospitalization.

Independent samples *t*-test was used to compare the groups among themselves. It was observed that both exhaled CO and CT scores at the time of hospitalization were significantly higher in patients in Group 3 when compared to Group 1 and 2 patients ($p \leq 0.001$ for all).

scores, a positive correlation was observed with both parameters ($r = 0.543$, $p < 0.001$, $r = 0.533$, $p < 0.001$) (Table 3). In the ROC curve analysis of the exhaled CO and CT scores of the patients who developed ARDS or MAS compared to the patients who did not develop, while the AUC values were 0.809 and 0.74, when the cutoff value for the exhaled CO level was taken as 2.5 ppb, the sensitivity was 71%, the specificity was 70%, and the cutoff value for the CT score was 7.5, the sensitivity was 79% and the specificity was 65%.

DISCUSSION

In our study, it was observed that the CRP and LDH levels, which have been shown to be associated with prognosis in COVID-19 patients, were high and the lymphocyte level was low in relation to the severity of the disease. In the comparison of exhaled CO levels, it was observed that the baseline levels were high in Group 3 patients with severe clinical course. In addition, a positive correlation was observed with the CT score also in the correlation analysis performed with parenchymal involvement.

COVID-19 has become a major problem worldwide for over 2 years. Mutations of the SARS-CoV-2 virus over time have caused the disease to progress with a more severe clinical course. Acute respiratory distress syndrome (ARDS) and macrophage activation syndrome (MAS) are the leading these clinical pictures [14]. The lack of effective anti-viral treatment and the inability to predict the clinical course in the initial phase of the disease were important disadvantages. In particular, it is clearly observed that the mutations that develop cause the clinical course to be more severe in individuals who are not vaccinated. It was observed that the sensitivity of thorax CT, which is frequently used in detecting lung involvement in COVID-19 patients in studies performed, could be more valuable in PCR testing. However, intensive level of thoracic CT application brought along economic problems as well as unnecessary exposure of the patients to radiation [15]. It has been shown that the use of proinflammatory markers such as CRP, fibrinogen, D-dimer, and ferritin may be important in treatment planning and prognosis in addition to chest radiography, which is a more accessible method in the follow-up of the disease [2].

CO is released together with biliverdin and iron as a result of the breakdown of hem, which is from the metalloporphyrin group, by heme oxygenase (HO). Biliverdin turns into bilirubin, while iron turns into ferritin [16]. Studies on the measurement of exhaled CO level in lower respiratory tract infections have shown that infections activate HO-1 directly or by increasing the level of proinflammatory cytokines in the respiratory tract [7]. As a result of this activation, it was observed that the exhaled CO level increases in lower respiratory tract infections. In studies performed on the physiological pathway of CO, the data have been obtained that it may play an important role in the regulation of vascular functions, inflammation, apoptosis, and cell proliferation [17]. Similar to nitric oxide, it performs guanosine monophosphate production by activating guanylate cyclase [18]. It was observed that CO exposure potentiates bacterial phagocytosis in leukocytes in studies performed by inducing bacterial sepsis in animals. Furthermore, studies in animal models have shown that CO also reduces ventilator-induced lung damage [19-21].

In our study, consistent with previous studies, it was observed that the level of LDH, which has an important place in endothelial dysfunction, as well as CRP, which shows proinflammatory cytokine properties, increased in a correlation with the severity of the disease. Similarly, it was observed that the ferritin level was higher in Group 3 patients than in Group 1 and 2 patients. When the exhaled CO and CT scores obtained at the time of hospitalization were compared between the groups, it was observed that both parameters were higher in patients in Group 3, and there is a high level of positive correlation between these values. Considering the current findings together with previous studies, the exhaled CO level may have increased due to the direct activation of HO-1 by the viral load. Also the increase in ferritin level in patients with high exhaled CO levels may have developed due to the higher metabolism of heme in these patients. The fact that the exhaled CO levels of the patients obtained at the time of discharge did not differ between the groups can be attributed to the decrease in inflammatory activity as a result of the treatment.

One of the most important limitations observed in our study is that the exhaled CO level measured at discharge may have been affected by the treatment protocols applied. However, it was inevitable to use treatments such as dexamethasone and methylprednisolone, which would suppress HO-1 activity in correlation with the severity of the disease. However, what we wanted to observe at the time of discharge was to analyze the decrease of CO level due to or independent of the treatment. In addition, correlation with the endogenous CO level in arterial blood gas, which can be checked at the time of hospitalization, would have provided more efficient results. However, the fact that arterial blood gas could not be obtained from most patients under emergency conditions prevented us from reaching this result. As a result, the exhaled CO level has been a non-invasive, easily accessible method that increases in viral pneumonia due to COVID-19 as in other viral diseases and shows positive correlation with radiological findings. Also its decreased level in line with the decrease in inflammatory activity showed that it can also be utilized during follow-up. For this reason, the exhaled CO level can be a method that can be used in emergency conditions in the evaluation of the severity of COVID-19 patients.

Declaration of Interest:

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