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Original article

Analysis of endogenous oxidative damage markers and association with pulmonary involvement severity in patients with SARS-CoV-2 pneumonia

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ABSTRACT

Introduction: The SARS-CoV-2 virus affects many organs, especially the lungs, with widespread inflammation. We aimed to compare the endogenous oxidative damage markers of coenzyme Q10, nicotinamide dinucleotide oxidase 4, malondialdehyde, and ischemia-modified albumin levels in patients with pneumonia caused by SARS-CoV-2 and in an healthy control group. We also aimed to compare these parameters between patients with severe and non-severe pulmonary involvement.
Methods: The study included 58 adult patients with SARS-CoV-2 pneumonia and 30 healthy volunteers. CoQ10 and MDA levels were determined by high-pressure liquid chromatography. NOX4 and IMA levels were determined by ELISA assay and colorimetric method.
Results: Higher levels of CoQ10, MDA, NOX4, and IMA and lower levels of COQ10H were observed in patients with SARS-CoV-2 pneumonia than in the control group. MDA, IMA, NOX4, and CoQ10 levels were significantly higher in patients with severe pulmonary involvement than in patients with non-severe pulmonary involvement, but no significant difference was observed in CoQ10H levels. CoQ10 levels were significantly and positively correlated with both ferritin and CRP levels.
Conclusion: SARS-CoV-2 pneumonia is significantly associated with increased endogenous oxidative damage. Oxidative damage seems to be associated with pulmonary involvement severity.

1. Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in China and spread throughout the world within a few months, resulting in a pandemic [1]. Interaction mechanisms of SARS-CoV-2 with human biological markers have been identified [2]. However, the mechanism of action of SARS-CoV-2 is quite complex and is not fully understood. SARS-CoV-2 continues to have a strong worldwide epidemic effect. The interaction of SARS-CoV-2 with the immune system and its consequences seem to be much more complex.

Reactive oxygen species (ROS) are produced as part of the normal physiological activity. ROS mediators include molecules such as hydroxyl radical (·OH), superoxide radical ($O_2^{\cdot}$), and hydrogen peroxide (H_2O_2). These molecules disrupt the membrane structures of foreign pathogens and cause them to lose membrane integrity [3]. The production of ROS may increase due to endogenous or exogenous reasons [4,5]. The human body has a natural antioxidant defense system against the increased ROS production, and oxidative stress occurs when the balance between ROS and the antioxidant defense system shifts in favor of ROS [5].

One of the crucial endogenous sources of ROS is the electron leakage that occurs in the electron transport chain (ETC) in the inner membrane of the mitochondria. This electron leakage causes the formation of radicals and can occur due to two main reasons. The first is when the electron concentration exceeds the ETC capacity, and the second occurs when the structure of ETC molecules, carrying electrons, is degraded or when their synthesis decreases [6]. The only lipemic molecule found in ETC is Coenzyme Q10 (CoQ10), also known as ubiquinone. The reduced form of CoQ10 is CoQ10H, also known as ubiquinol. CoQ10H acts as an antioxidant and is used in many areas, including as a biomarker to determine oxidative damage [7].

Another source of the endogenous oxidative damage system is the nicotinamide adenine dinucleotide phosphate oxidase (NOX) enzyme family. The NOX family is made of seven members (NOX

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1–5, DUOS 1 and 2) [8]. NOX4 has been shown to stimulate intracellular signal cascades, such as mitogen-activating protein kinase (MAPK) [9]. NOX4 is also a biomarker used to determine endogenous oxidative damage, as it shows activity without the need of inducers [10]. Ischemia-modified albumin (IMA) is called the modified form of albumin and is measured using spectrophotometry by the Albumin Cobalt Binding test. Additionally, serum IMA levels have been reported to be affected by clinical conditions, such as stroke and mesenteric ischemia [11]. Malondialdehyde (MDA) is an aldehyde product formed as a result of lipid peroxidation that is often used as a biomarker in determining oxidative stress [12]. Associations between viral infections and oxidative stress have drawn the attention of researchers [13]. The replication of influenza viruses in lung epithelial cells is associated with redox-sensitive pathways activated by NOX4-derived ROS [14]. It was also suggested that antioxidants can be used in the treatment of COVID-19 [15]. No detailed data is available. However, studying endogenous oxidative damage caused by SARS-CoV-2 in the human organism is likely to provide methods to guide COVID-19 disease treatment.

2. Objective

We aimed to evaluate endogenous oxidative stress and to compare results with a healthy control group by determining IMA, CoQ10, and NOX4 serum levels in patients with SARS-CoV-2 pneumonia. We also aimed to compare these parameters between patients with severe and non-severe pulmonary involvement.

3. Material and methods

3.1. Study population

The study included 58 patients who were consecutively hospitalized in our COVID-19 clinic and 30 healthy individuals from April to November 2020. Nasal swab samples were taken from patients over 18 years of age with SARS-CoV-2 pneumonia. All consenting patients were included in the study. Patients not only had clinical and laboratory findings, but also presented with pulmonary involvement compatible with SARS-CoV-2 pneumonia. Accurate diagnosis of SARS-CoV-2 pneumonia was obtained by reverse transcription polymerase chain reaction (RT-PCR) from oral or nasopharyngeal swab specimens. The control group included 30 healthy individuals of similar age and smoking rates without chronic disease or complaints of lower respiratory tract infection during the previous month.

3.2. Radiological involvement

All patients underwent chest tomography evaluated with thin-sliced, high-resolution computed tomography. Severe and non-severe pulmonary involvement was evaluated with a prevalence score described by Fausto *et al.* [16]. Findings included ground-glass opacities, consolidation and nodular opacities in all lobes and segments of the lungs. Subjects with class 3 or 4 findings were defined as having severe pulmonary involvement and those with class 1 or 2 as having non-severe pulmonary involvement.

3.3. Analysis of parameters

Blood samples were taken from all patients on the day of hospitalization. Approximately 3 ml of blood was collected per dry biochemistry tube with gel under personal protective equipment conditions. Blood samples were centrifuged at 3,500 rpm for 10 minutes after waiting 20 minutes for clotting. Serum samples obtained after centrifugation were immediately frozen using liquid nitrogen and stored at -80 °C until time of analysis. Serum analysis of reduced and oxidized CoQ10 was performed as described by Litarru *et al.* [17]. For chromatographic measurements, the Agilent 1200 Series (LabX, Ontario, Canada), a high-pressure liquid chromatography-electrochemical detector (HPLC-ECD) system with an auto sampler, gradient pump, and column frame, was used. Oxidized and total CoQ10 levels were determined using electrochemical detector (ECD) at 0.35 volt. CoQ10 concentrations were determined by comparing peaks obtained from the samples with standard peaks. Oxidized and reduced CoQ10 levels were expressed in μM. The MDA analysis in serum samples was performed using HPLC and fluorescence detector (HPLC-FLD), as described by Khoschsorur *et al.* This method is based on detection of the complex formed by MDA and thiobarbituric acid in a fluorescent detector after HPLC separation in alkaline medium (excitation at 527 nm, emission at 551 nm) [18]. Serum IMA levels were measured using the colorimetric method defined by Bar-Or *et al.* and results of IMA measurements were defined by the absorbance unit (ABSU) [19]. NOX4 analysis was determined by commercially available enzyme-linked immunosorbent measurement (ELISA) kits (Cat. no. YLA4202HU, YLbiont, Shanghai, China).

4. Statistical analysis

The IBM-SPPS 23 package statistical program (IBM Corp., Armonk, NY, USA) was used to analyze data. Data distribution was determined by Shapiro-Wilk test and an independent sample t-test was used to compare normally distributed numerical data. The non-normally distributed numerical data were compared using Mann-Whitney U test, and Chi-square test was used to compare categorical data, such as gender and smoking. We also determined the Pearson correlation coefficient (r) to show the correlation between parameters. P-values below 0.05 were considered statistically significant.

5. Results

Baseline characteristics and clinical findings of the SARS-CoV-2 pneumonia group are summarized in Table 1. No significant difference was observed in terms of age and gender between the SARS-CoV-2 group and the healthy control group.

The levels of CoQ10, MDA, NOX4, and IMA observed in the SARS-CoV-2 pneumonia patient group were significantly higher than those observed in the healthy control group (P <0.001), but the level of CoQ10H was significantly lower. In addition, the CoQ10H/CoQ10 ratio in the SARS-CoV-2 pneumonia patient group was significantly lower than in the healthy control group. Oxidative stress biomarker results in the SARS-CoV-2 pneumonia patient and healthy control groups are summarized in Table 2.

We investigated all parameters in the non-severe and severe pulmonary involvement groups based on radiological findings. No significant difference was observed between the groups in terms of gender, comorbidity, hospital stay, and smoking status (P = 0.855, P = 0.245, P = 0.423, and P = 0.196, respectively). Patients in the non-severe group were significantly younger than those in the severe group. CRP, fibrinogen, D-dimer, ferritin, and LDH levels were significantly higher in the severe group than in the non-severe group (P = 0.017, P = 0.029, P = 0.027, P = 0.036, and P = 0.018, respectively). There was no significant difference between the groups in terms of WBC levels (P = 0.924). SaO_2 level in the severe group was significantly lower than in the non-severe group (P = 0.001). Clinical and laboratory findings are summarized in Table 3.

CoQ10, MDA, and IMA levels were significantly higher in the severe pulmonary involvement group than in the non-severe group (P = 0.023, P = 0.001, P = 0.007). However, no difference was

Table 1
Characteristics and clinical findings of patients with SARS-CoV-2 pneumonia and healthy control groups.

		SARS-CoV-2 pneumonia group	Healthy control group	*P*-value
		n = 58	*n* = 30	
Gender (count [%])	Male	37 (69.8)	16 (30.2)	0.265
	Female	21 (58.3)	15 (41.7)	
Age (years ± SD)		54.1 ± 19.2	57.4 ± 11.3	0.377
Smoking condition (count [%])	None	44 (75.9)	20 (66.6)	0.387
	Quit	3 (5.2)	4 (13.4)	
	Active	11 (19)	6 (20)	

SARS-CoV-2 pneumonia group (*n* = 58)

Comorbidity (count [%])	Hypertension	7 (20)
	Diabetes mellitus	11(31.6)
	Asthma	8 (22.8)
	COPD	6 (17.1)
	ASCVD	3 (8.5)
Radiological findings (count [%])	Non-severe	35 (60.3)
	Severe	23 (39.7)
WBC (cell/μL ± SD)		10,230 ± 7,972
CRP (mg/L ± SD)		49.8 ± 63.7
Fibrinogen (mg/dL ± SD)		421.2 ± 189.3
D-Dimer (μg/mL ± SD)		2.36 ± 6.74
Ferritin (ng/mL ± SD)		334.7 ± 495.7
LDH (U/L ± SD)		322.3 ± 127.2
SaO_2 (% ± SD)		88.2 ± 4.77
Hospital stay (days ± SD)		8.62 ± 0.61

SD: standard deviation; WBC: white blood count; CRP: C-reactive protein; LDH: lactic acid dehydrogenase; SaO_2: oxygen saturation; COPD: chronic obstructive pulmonary disease; ASCVD: atherosclerotic cardiovascular disease.

Table 2
Oxidative stress parameters between SARS-CoV-2 pneumonia patients and healthy control groups.

	SARS-CoV-2 pneumonia group	Healthy control group	*P*-value
	n = 58	*n* = 30	
CoQ10 (μM ± SD)	4.45 ± 1.24	2.63 ± 0.63	<0.001
CoQ10H (μM ± SD)	5.35 ± 1.91	11.1 ± 2.02	<0.001
CoQ10H/CoQ10	1.38 ± 0.62	4.44 ± 1.39	<0.001
MDA (μM ± SD)	7.91 ± 1.88	4.46 ± 0.81	<0.001
NOX4 (μmol/L ± SD)	16.9 ± 5.54	5.71 ± 1.29	<0.001
IMA (ABSU ± SD)	3.79 ± 0.86	2.02 ± 0.73	<0.001

SD: standard deviation; CoQ10: Coenzyme Q10; MDA: malondialdehyde; NOX4: nicotinamide adenine dinucleotide phosphate oxidase 4; IMA: ischemia-modified albumin; ABSU: absorbance units.

observed in terms of CoQ10H levels and CoQ10H/CoQ10 ratio ($P = 0.25$ and $P = 0.109$, respectively) (Table 4).

In the correlation analysis, we observed statistically significant negative correlations between CoQ10H and CoQ10. Similarly, a negative correlation was observed between CoQ10H and MDA, NOX4, or IMA. A significant positive correlation was observed between CoQ10 and NOX4, MDA, or IMA. We also observed positive correlations between MDA and NOX4 or IMA and a significant positive correlation between NOX4 and IMA (Table 5).

We found a significant positive correlation between CoQ10 and CRP and ferritin levels (r = 0.336, $P = 0.01$, and r = 0.371, $P = 0.01$, respectively) (Figs. 1 and 2).

6. Discussion

COVID-19 disease, which emerged at the end of 2019 in Wuhan province of China's Hubei city, spread to almost every country in the world in a short time and was then declared a pandemic by the World Health Organization (WHO) on March 11, 2020. By December 3, 2020 according to the WHO, 63,965,092 people had been infected and 1,488,120 people had died from COVID-19 disease worldwide [20]. SARS-CoV-2 disease is epidemiologically similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), but its longer incubation period compared to these two homologous viruses has caused it to spread much faster worldwide. Research has been rapidly carried out on SARS-CoV-2, and keeps on being conducted. Although the effects of SARS-CoV-2 on the human body have been studied in many ways, its effects on oxidative damage have not been studied yet.

ROS has long thought to be toxic to cells, but ROS produced in normal cell physiology, especially H_2O_2, can easily diffuse through the cell membrane and play an important role as a secondary messenger in signal transduction [21]. ROS also have an important role in the immune system. For instance, a large amount of H_2O_2 is produced by phagocytic cells to activate dendritic cells, resulting in an antigen-specific immune response [22]. Studies reported an association between the produced ROS levels and the adaptive immune response. A minimal increase in ROS level in the immune system may lead to the emergence of normal immune function, whereas high ROS production increases proinflammatory cytokine production through the loss of nuclear factor erythroid 2-related factor 2 (NRF2) [23]. Moderate levels of ROS can act as a biochemical mediator in various cellular functions, such as proliferation, aggregation, and bacterial defense system [24]. It should not be forgotten that ROS disrupts the structure of many biomolecules, such as lipids, proteins, and nucleic acids in the cell, and may cause loss of function. ROS are therefore thought to play a role in the pathogenesis of cancer, diabetes, aging, and many other diseases [25]. The level of ROS produced in our body or as a result of environmental factors is of great importance for normal cell function. One of the most important factors in keeping ROS at a certain level is the antioxidant defense system.

Previous studies showed that viral infections induce ROS production [26]. Strengert *et al.* reported that ROS production synthesized by Duox1 and 2 (members of the NADPH oxidase enzyme family) was induced to inhibit the replication of Influenza A virus and to protect the host cell [27]. Soucy-Faulkner *et al.* found that NOX2 and ROS are required for the efficiency of RIG-I-mediated antiviral response [28]. These findings show that the increase in

Table 3
Baseline characteristics and laboratory findings in non-severe and severe pulmonary involvement groups based on radiographs.

		Non-severe group $n=35$	Severe group $n=23$	*P*-value
Gender (count [%])	Male	22 (61.9)	15 (38.1)	0.855
	Female	13 (59.5)	8 (40.5)	
Comorbidity (count [%])	Hypertension	5 (71.4)	2 (28.6)	0.720
	Diabetes mellitus	5 (45.5)	6 (54.5)	
	Asthma	4 (50)	4(50)	
	COPD	3 (50)	3(50)	
	ASCVD	1 (66.7)	1 (33.3)	
Smoking status (count [%])	None	29 (65.9)	15 (34.1)	0.196
	Active	2 (66.7)	1 (33.3)	
	Quit	4 (36.4)	7 (63.6)	
Age (years ± SD)		49.1 ± 20.5	61.6 ± 15.7	0.12
WBC (cell/μL ± SD)		10,312 ± 9,417	10,104 ± 5,251	0.924
CRP (mg/L ± SD)		33.8 ± 44.8	74.2 ± 79.8	0.017
Fibrinogen (mg/dL ± SD)		367.6 ± 209.9	491.9 ± 132.6	0.029
D-Dimer (μg/mL ± SD)		0.79 ± 0.87	4.76 ± 10.3	0.027
Ferritin (ng/mL ± SD)		222.2 ± 249.2	500.9 ± 695.5	0.036
LDH (U/L ± SD)		290.7 ± 94.1	370.3 ± 155.8	0.018
SaO_2 (% ± SD)		90.2 ± 4.09	85.4 ± 4.05	0.001
Hospital stay (days ± SD)		8.97 ± 5.12	7.95 ± 3.84	0.423

SD: standard deviation; WBC: white blood count; CRP: C-reactive protein; LDH: lactic acid dehydrogenase; SaO_2: oxygen saturation; COPD: chronic obstructive pulmonary disease; ASCVD: atherosclerotic cardiovascular disease.

Table 4
Oxidative stress parameters in non-severe and severe pulmonary involvement groups based on radiographs.

	Non-severe	Severe	*P*-value
	$n=35$	$n=23$	
CoQ10 (μM ± SD)	4.15 ± 1.25	4.91 ± 1.09	0.023
CoQ10H (μM ± SD)	5.12 ± 1.77	5.71 ± 2.09	0.25
CoQ10H/CoQ10	1.49 ± 0.65	1.22 ± 0.54	0.109
MDA (μM ± SD)	7.16 ± 1.59	9.05 ± 1.73	0.001
NOX4 (μmol/L ± SD)	15.5 ± 6.05	19.6 ± 3.21	0.007
IMA (ABSU ± SD)	3.51 ± 0.74	4.21 ± 0.88	0.002

SD: standard deviation; CoQ10: Coenzyme Q10; MDA: malondialdehyde; NOX4: nicotinamide adenine dinucleotide phosphate oxidase 4; IMA: ischemia-modified albumin; ABSU: absorbance units.

ROS production initiated by viral infections plays an important role in activating the innate immunity.

Oxidative stress is expected to occur in viral and bacterial pneumonia, based on the evidence of increased ROS production in these infections and resultant oxidative stress. Previous studies investigated the levels of oxidative stress markers, especially in patients with community-acquired pneumonia (CAP) [29,30,31]. Trefler *et al.* reported that the levels of thiobarbituric acid reactive substances (TBARS) in patients with CAP caused by bacteria were higher than in controls. They also observed lower TBARS levels in patients with CAP caused by H1N1 compared to controls [29]. Molotov-Luchanskiy *et al.* reported that plasma samples of CAP patients were found to have higher levels of MDA and advanced oxidation protein products compared to control samples [30]. Chen *et al.* observed that oxidative stress, tumor necrosis factor alpha (TNF-α) and intelukin-6 (IL-6) increased with the increase in CAP severity [31]. The results of these studies showed that oxidative stress caused by ROS can play an important role in the pathogenesis of patients with pneumonia.

While advances in vaccination are promising, there may be many unknown factors involved in the development and progression of SARS-CoV-2 pneumonia, currently lacking effective treatment. Our study is the first to investigate endogenous oxidative stress biomarkers in patients with SARS-CoV-2 pneumonia. We observed that CoQ10, MDA, NOX4, and IMA levels were higher in patients with SARS-CoV-2 pneumonia than in the control group. CoQ10H levels of those patients were lower than in the control group. These results show that endogenous oxidative damage is increased in patients with SARS-CoV-2 pneumonia. We believe that the increase in NOX4 serum levels suggests unknown reactions that play some important role in the host's immune response or in the worsening of the clinical presentation by increasing some innate immune mediators, such as H2O2, through increased NOX4 expression. This finding is an important indicator of endogenous oxidative damage in patients with SARS-CoV-2 pneumonia.

Table 5
Oxidative stress parameters in non-severe and severe pulmonary involvement groups based on radiographs.

		CoQ10H (μM)	MDA (μM)	NOX4 (μmol/L)	IMA (ABSU)
CoQ10 (μM)	r	−0.484[a]	0.672[a]	0.717[a]	0.473[a]
	p-value	0.001	0.001	0.001	0.001
	n	88	88	88	88
CoQ10H (μM)	r		−0.572[a]	−0.658[a]	−0.592[a]
	p-value		0.001	0.001	0.001
	N		88	88	88
MDA (μM)	r			0.773[a]	0.461[a]
	p-value			0.001	0.001
	n			88	88
NOX4 (μmol/L)	R				0.542[a]
	p-value				0.001
	n				88

CoQ10: Coenzyme Q10; MDA: malondialdehyde; NOX4: nicotinamide adenine dinucleotide phosphate oxidase 4; IMA: ischemia-modified albumin; ABSU: absorbance units; r: Pearson correlation coefficient; n: number of all subjects.

[a] Correlation is significant at 0.01 level (2-tailed).

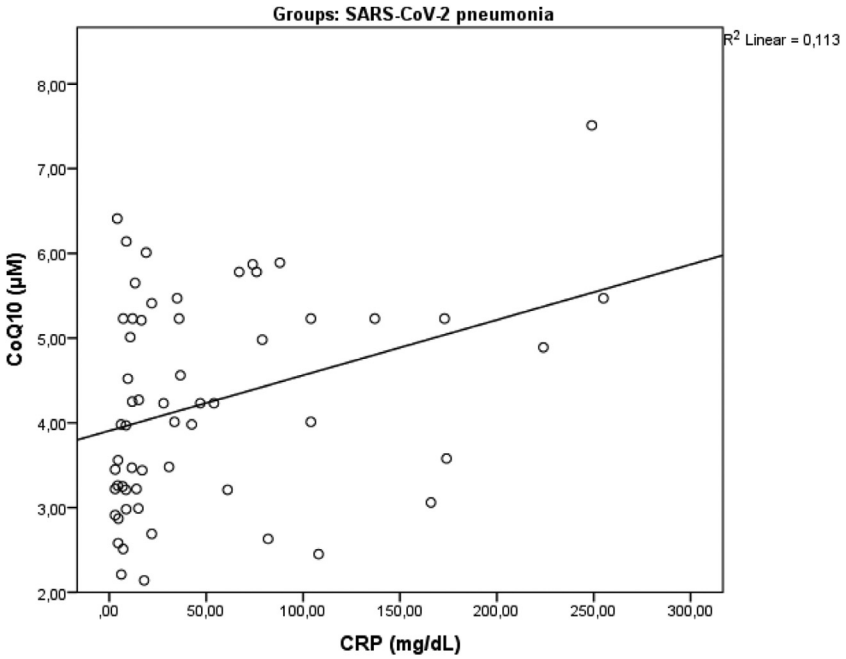

Fig. 1. Correlation between CRP and CoQ10 levels (r = 0.336 and *P* = 0.01). CRP = C-reactive protein; CoQ10 = Coenzyme Q10.

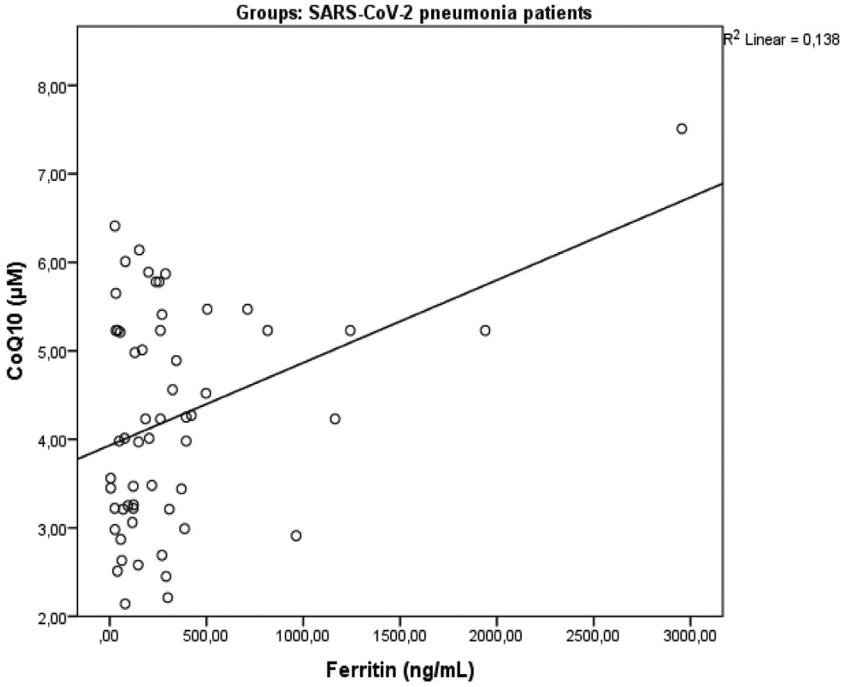

Fig. 2. Correlation between CoQ10 and ferritin levels (r = 0.371 and *P* = 0.004). CoQ10 = Coenzyme Q10.

When comparing our patients based on their severe and non-severe pulmonary involvement, we found that CoQ10, MDA, NOX4, and IMA levels were higher in patients with severe pneumonia than in those with non-severe pneumonia. The correlation analysis also revealed a significant correlation between endogenous oxidative stress markers. We therefore believe that these parameters can be used to predict the severity of pulmonary involvement in patients with SARS-CoV-2 pneumonia. Additionally, CoQ10 showed a strong positive correlation with both CRP and ferritin levels. These findings suggest that endogenous oxidative damage plays an important role in the pathogenesis of SARS-CoV-2 pneumonia. The immune system may respond by increasing the level of sources involved in ROS production, such as NOX4 and CoQ10. However, in the case of an uncontrolled increase and inadequate antioxidant defense system, the disease may progress more severely. This situation may shed light on the pathogenesis of the formation of cytokine storm in these patients.

Although our study did not evaluate endogenous oxidative damage in patients with SARS-CoV-2 pneumonia, it provides important data. It may, however, have limitations. In our patient group, only

serum was used as a sample. In further studies, oxidative damage marker levels could also be examined in alveolar fluid or tissue samples.

7. Conclusion

This is the first study investigating endogenous oxidative damage and its association with the degree of pulmonary involvement in patients with SARS-CoV-2 pneumonia. The study found that endogenous oxidative damage significantly increases in patients with SARS-CoV-2 pneumonia. It also showed that patients with severe pulmonary involvement have a higher degree of endogenous oxidative damage. Additionally, a significant positive correlation was observed between CoQ10 with CRP and ferritin levels. Our study provides useful information for finding the causal factors underlying the development and progression of SARS-CoV-2 pneumonia.

Ethical Approval

All procedures carried out for participants complied with the 1964 Helsinki Declaration and later changes. The study was initiated after approval from the Ethics Committee of the Faculty of Medicine, University of Van Yüzüncü Yıl, was received (Approval no. 05.05.2020/10).

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Disclosure of interest

The authors declare that they have no competing interest.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

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