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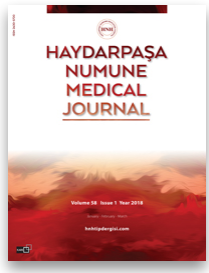

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ORIGINAL ARTICLE

Role of Oxidative Stress and Inflammatory Biomarkers in COVID-19 Pneumonia

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Abstract

Introduction: SARS-CoV-2 causes severe lung damage and respiratory failure through oxidative stress. Biomarkers play a role in inflammation, in revealing the effects of oxidative stress, and in the regulation of treatment. The aim of our study was to reveal oxidative stress in COVID-19 patients by determining oxidative biomarkers and to examine the relationship of these parameters with lung involvement.

Methods: The prospectively designed study included 45 patients hospitalized with the diagnosis of COVID-19 and 38 healthy controls. Total thiol, native thiol, disulfide, myeloperoxidase, ischaemia-modified albumin, and acute phase reactant levels to determine oxidative stress and inflammation were compared between the groups. Thorax tomography scoring was performed to determine the severity of pneumonia. The association of oxidative biomarkers with length of hospital stay and radiological score was evaluated.

Results: We found that native thiol and total thiol levels decreased, and disulfide and myeloperoxidase levels increased in COVID-19 patients compared to the control group. A negative correlation was found between the duration of hospitalization and native thiol and total thiol levels (r=-0.312, p=0.043; r=-0.309, p=0.049). Native thiol and total thiol were negatively correlated with lung involvement on thorax tomography (r=-0.450, p=0.002; r=-0.436, p=0.003). MPO level was positively correlated with the duration of hospitalization (r=0.317, p=0.034).

Discussion and Conclusion: These oxidative/inflammatory parameters play an important role in the lung involvement and disease monitoring of COVID-19 patients and can be used in the management of patients.

Keywords: COVID-19; myeloperoxidase; oxidative stress; pneumonia; thiol.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new type of coronavirus first discovered in December 2019 in China. The disease caused by this pathogen was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) in February 2020 and declared a pandemic in March 2020 [1]. The virus can cause different clinical outcomes ranging from asymptomatic disease to acute respiratory distress syndrome caused by cytokine storm [2]. To understand the cytokine storm and severity of disease that cause multiple organ failure and high mortality, it is necessary to know the inflammation pathways well.

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The main reason for progression to severe disease is the cytokine storm caused by uncontrolled and excessive production of cytokines and pro-inflammatory markers such as IL-1, IL-6, TNF-α, and IL-17 [3]. Interleukin secretion, which plays a role in increased antiviral immunity, has also been shown in infections with other types of coronaviruses, such as SARS-CoV-1 [4]. In some studies, the fact that IL-6 levels are associated with severe COVID-19 disease and are detected as ten times higher in severe critical cases than in severe patients has been interpreted as a reliable marker in showing the severity of the disease [5–7].

In the pathophysiology of COVID-19, reactive oxygen products (ROS) such as hydrochloric acid, hydrogen peroxide, and superoxide are formed, and cytokine levels increase with the increase in the number of neutrophils that play an active role in inflammation and myeloperoxidase (MPO) released from inflamed neutrophils. ROS products are also increased by the consumption of Nitric Oxide (NO), a potent vasodilator, in the course of COVID-19 inflammation [8,9]. Vasoconstriction in pulmonary vessels developed by NO consumption and ROS production associated with increased MPO values trigger tissue damage. It is thought that ROS leads to COVID-19-related lung damage by tissue damage, thrombosis, and red blood cell dysfunction [8,10].

The decrease in protective antioxidants such as thiol against the increase of ROS is important in viral replication and virus-related diseases [11]. Thiols, which are transformed into disulfide bond structures by ROS, are involved in the formation of inflammation, apoptosis, and immune response [12,13]. After the oxidant/antioxidation status deterioration, antioxidant levels have been shown to decrease not only with COVID-19 but also with other respiratory viruses such as Respiratory Syncytial Virus (RSV), human metapneumovirus (hMPV), and influenza [14]. Ischemia-modified albumin (IMA) levels increase in response to oxidative stress in conditions of perfusion disruption and ischemia of different tissues in the body. It is well known that serum IMA levels increase in pregnancy, pregnancy-related complications, and terminal cancers, especially in the early period of ischemic heart disease [15,16]. Badawy et al. [17] reported that there may be a relation between the change in serum albumin by increased oxidative stress and mortality in patients with COVID-19.

The first aim of our study was to demonstrate the oxidative stress through the detection of native thiol, total thiol, disulfide, IMA, and MPO levels in hospitalized COVID-19 patients and to examine the relationship of these parameters with lung involvement and time of hospital stay.

Materials and Methods

The study protocol was approved by Biruni University Faculty of Medicine Ethics Committee and the Ministry of Health (Authorization Number: 2021/47-42). The study was completed in accordance with the requirements of the Helsinki Declaration.

Study Design and Participants

The study was conducted with individuals who applied to the internal medicine and chest diseases outpatient clinics with the suspicion of COVID-19 between September 31, 2021, and February 28, 2022.

The study included a total of 45 patients hospitalized for lung involvement in COVID-19 disease after the diagnosis was confirmed by positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test in oro-nasopharyngeal swab and radiological changes in chest computed tomography (CT). In addition, 38 healthy participants of similar age and sex were included as a control group.

Patients with chronic diseases such as diabetes mellitus and other endocrinopathies, hypertension, chronic heart, liver, and kidney diseases, rheumatological diseases, malignancies, neurologic problems, those using steroids or immunosuppressive drugs, individuals with immunosuppressive illnesses, alcohol and smoking users, pregnant women, and those younger than 18 years old were excluded.

During hospitalization, oropharyngeal and nasal swab samples for the COVID-19 RT-PCR nucleic acid test developed with the virus sequence specified in the Ministry of Health guidelines and blood samples for laboratory tests (biochemical analyses such as complete blood count) were taken from all patients. Demographic characteristics, symptoms, physical examination findings, laboratory and radiological findings at the onset of the disease, and length of hospital stay were recorded.

In our study, thoracic CT images taken with a Siemens Somatom Scope (Germany) 16-slice CT device with section thickness 1.5 mm, obtaining images without gaps between slices (gapless) using low-dose radiation (mAs: 50, Kvp: 120), were assessed. CT positivity was defined by findings consistent with COVID-19 pneumonia (peripheral, bilateral ground-glass appearance, multifocal rounded ground-glass areas, reverse halo) and findings consistent with viral pneumonia, including COVID-19 (peripheral and non-rounded multifocal, diffuse, perihilar or unilateral ground-glass opacity, low numbers, and very

small peripheral and non-rounded ground-glass areas). The severity of pulmonary involvement was obtained by dividing both lungs into three sections—upper, middle, and lower zones—for a total of 6 regions [18]. The volume involvement in each region was graded with 1 point for 0-25%, 2 points for 25-50%, 3 points for 50-75%, and 4 points for 75-100%.

After an overnight fast, in the morning (08–09 a.m.), blood and urine samples were taken simultaneously. Blood samples were collected in EDTA-containing tubes and anticoagulant-free tubes. After centrifugation at 2500xg for 5 min, the plasma and serum were separated for at least 30 min. Each sample (serum, plasma, and urine) was divided into four aliquots, and samples were stored at -80°C until biochemical analysis.

Total/native thiol and disulfide levels were measured using the method developed by Özcan Erel and Salim Neşelioğlu in 2014 [13], and IMA levels were measured using the method developed by Bar-Or et al. [19]. These were studied with reagents prepared by us, as stated in the reference articles, in our automatic spectrophotometry device in our laboratory [20]. MPO activity was also studied in our spectrophotometer device with the reagents prepared by us using the method specified in the reference articles [13,19,20]. IL-6 levels were measured using an ELISA (enzyme-linked immunosorbent assay) kit.

Statistical Analysis

The normal distribution of the data was tested using the one-sample Kolmogorov-Smirnov test. Continuous variables are presented as mean±standard deviation. Categorical variables are presented as numbers. The statistical comparisons were performed using the two-sided Student's t-test. Categorical variables were compared using the Chi-square test or Fisher's exact test for small samples. Pearson's correlation was used for the numerical data, and Spearman's correlation was used for the nominal data. $p<0.05$ values were considered statistically significant. The statistical analyses were performed using SPSS 20.0 software (SPSS, Chicago, IL, USA) for Windows.

Results

A total of 83 people, including 45 patients with COVID-19 disease and 38 healthy participants, were included in the study. Age and gender distribution were similar in both groups. The most common symptoms in COVID-19 patients were fatigue, fever, and cough. In the patient group, the oxygen saturation was significantly lower, while respiratory rate and heart rate were significantly higher than in the control group ($p<0.001$) (Table 1).

In the patient group, leukocyte and neutrophil numbers from blood count tests, and levels of CRP, ferritin, LDH, D-dimer, and IL-6 were significantly higher compared to the control group (Table 2).

Table 1. Demographic characteristics, symptoms and clinical-radiological findings of the study groups.

	Control (n=38)	COVID patients (n=45)	p
Gender (F/M)	11/27	19/26	0.255
Age (years)	53.8±14.3	55.5±19.2	0.317
Symptoms			
Fatigue		42 (93.3)	
Fever		37 (82.2)	
Cough		30 (66.6)	
Chest pain		14 (31.1)	
Dyspnea		8 (17.7)	
Taste/smell abnormalities		6 (13.3)	
Diarrhea		5 (11.1)	
Clinical Findings			
Systolic blood pressure (mmHg)	118.1±14.4	119.4±21.2	0.474
Diastolic blood pressure (mmHg)	69.9±6.6	69.1±8.8	0.691
Heart beat (/minute)	83.9±10.8	94.1±15.2	**<0.001**
Oxygen saturation (%)	97.4±1.4	94.4±5.1	**<0.001**
Respiratory rate (/minute)	14.1±2.2	19.6±4.1	**<0.001**
Duration of hospitalization		5.8±4.1	
Total score of radiological findings		6.5±4.8	

Table 2. Laboratory findings of the study population.

	Control (n=38)	COVID patients (n=45)	p
Leukocyte (10^3/mL)	6.99±2.71	9.74±5.36	**<0.001**
Neutrophil (10^3/mL)	4.60±2.44	7.58±5.05	**<0.001**
Lymphocyte (10^3/mL)	1.58±0.75	1.38±1.08	0.080
Monocyte (10^3/mL)	0.67±0.28	0.72±0.39	0.298
Eosinophil (10^3/mL)	1.14±1.26	0.84±0.94	0.081
Haemoglobin (g/dL)	13.40±1.78	13.17±2.21	0.199
Haematocrite	39.76±4.62	38.34±5.70	0.401
Platelet (10^3/mL)	227±79	229±16	0.814
CRP (mg/L)	3.5±2.1	86.6±88.1	**<0.001**
Ferritin (ng/mL)	76.3±58.2	266±275	**<0.001**
Creatinine (mg/dL)	0.7±0.1	0.8±0.2	0.709
AST (U/L)	19.9±11.2	20.4±8.6	0.798
ALT (U/L)	23.7±15.8	22.4±13.9	0.626
LDH (U/L)	170.6±37.6	305±294	**0.005**
D-dimer (ng/mL)	95.7±45.3	679±945	**<0.001**
Native thiol (µmol/L)	581±137	390±109	**<0.001**
Total thiol (µmol/L)	625±142	461±140	**<0.001**
Disulphide (µmol/L)	22.1±5.5	35.5±37.4	**0.021**
Disulphide/native thiol (%)	3.9±0.9	9.2±9.9	**0.001**
Disulphide/total thiol (%)	3.6±0.8	6.9±5.2	**<0.001**
Native thiol/total thiol (%)	92.8±1.7	86.1±10.3	**<0.001**
IMA (ABSU)	0.72±0.15	0.86±0.14	**<0.001**
IL-6 (pg/mL)	63.3±44.9	172.8±104.9	**<0.001**
MPO (U/L)	34.4±26.3	58.2±37.7	**0.002**

ABSU: absorbance units; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; IMA: ischemia modified albümin; LDH: lactate dehydrogenase; MPO: Myeloperoxidase.

Native thiol level, one of the protective antioxidants against oxidative stress, was significantly higher in the control group (581±137 µmol/L) than in the COVID-19 patient group (390±109 µmol/L) (p<0.001). In the control group, the levels of total thiol (625±142 µmol/L) were also significantly higher than in the patient group (461±140 µmol/L) (p<0.001). The levels of disulfides, as the degradation products of oxidative stress, were significantly higher in the patient group (35.5±37.4 µmol/L) than in the control group (22.1±5.5 µmol/L) (p=0.021). Disulfide/native

Table 3. Relationship of total score of radiological findings and duration of hospitalization with other parametres.

	Total score of radiological findings		Duration of hospitalization	
	r	p	r	p
Age	0.328	**0.028**	0.473	**0.001**
Leukocyte	0.476	**0.002**	0.379	**0.015**
CRP	0.486	**0.001**	0.314	**0.038**
Native thiol	-0.450	**0.002**	-0.312	**0.043**
Total thiol	-0.436	**0.003**	-0.309	**0.049**
Disulphide	-0.216	0.155	-0.054	0.725
IMA	0.146	0.337	-0.010	0.948
IL-6	0.227	0.134	0.241	0.110
MPO	0.252	0.095	0.317	**0.034**

CRP: C-reactive protein; IMA: ischemia modified albümin; LDH: lactate dehydrogenase; MPO: Myeloperoxidase.

thiol (%) and disulfide/total thiol (%), which are indicators of disulfide-thiol homeostasis, were statistically higher in the patient group than in the controls (p=0.001, p<0.001, respectively). IMA (0.86±0.14 ABSU) and MPO (58.2±37.7 U/L) levels in the patient group were significantly higher than IMA (0.72±0.15 ABSU) and MPO (34.4±26.3 U/L) levels in the control group (p<0.001, p=0.002, respectively).

The total score of thoracic CT findings in the patient group was positively correlated with acute phase reactants such as leukocytes and CRP, and was negatively correlated with native thiol and total thiol levels (r=-0.450, p=0.002; r=-0.436, p=0.003, respectively).

The duration of hospitalization was significantly negatively correlated with native thiol and total thiol levels (r=-0.312, p=0.043; r=-0.309, p=0.049). MPO levels were significantly positively correlated with the duration of hospitalization, but there was no correlation between the total score of thoracic CT findings and MPO levels (r=0.252, p=0.095) (Table 3).

Discussion

In our study, it was shown that native thiol, total thiol, disulfide, and myeloperoxidase levels decreased in COVID-19 patients, and thiol levels decreased with increasing lung involvement and duration of hospitalization associated with disease severity.

Oxidative stress, which occurs when the balance between antioxidant defense and ROS and reactive nitrogen products is disrupted in the body, damages deoxyribonucleic acid, lipids, and proteins [21]. Transcription factors activated by oxidative stress affect the expression of genes in the inflammatory pathway [22]. It is known that chronic inflammation caused by oxidative stress may lead to cancer, diabetes, cardiovascular, neurological, and pulmonary diseases [23]. Oxidative stress plays an essential role in COVID-19. Oxidative stress biomarkers were found to be associated with COVID-19 pneumonia severity, the decision to admit the patient to an intensive care unit, and COVID mortality [24-26].

Thiols are compounds containing a sulfhydryl group, which are important in the detoxification process through antioxidant protection, signal transduction, and apoptosis mechanisms [27]. Antioxidant levels can be determined by measuring total thiol, and oxidant levels can be determined by measuring oxidized protein products and IMA [2]. Duran et al. [28], in their study of 25 COVID-19 patients followed up in the intensive care unit, found that disulfide and total thiol levels increased in 9 discharged patients due to immune response, in contrast to 16 patients who were deceased. Similar to our study, Aykac et al. [29] found decreased native thiol and total thiol levels in 40 adult COVID-19 patients in a study conducted with 153 patients, including 79 children and 74 adults. Disulfides, formed as a result of the reaction of oxidized proteins with thiols, show the defense mechanism and also occur in the presence of pathological conditions [2]. Erel et al. [30], in their study with 517 COVID-19 patients and 70 healthy control groups, found that the total thiol level was low in the COVID-19 patient group and was at the lowest level, especially in intensive care patients. In a study by Ducastel et al. [2] in 160 COVID-19 patients, and in a study by Çakırca et al. [11] in 86 patients, it was reported that low total thiol levels may predict intensive care unit hospitalization. In our study, there was a negative correlation between the duration of hospitalization and native thiol and total thiol levels in hospitalized patients who did not require intensive care admission, and native thiol and total thiol levels decreased in COVID-19 patients. Typical tomographic findings for COVID-19 are bilateral multifocal ground-glass or consolidated opacities, and it is known that the prognosis worsens with increasing radiological involvement [31]. In our study, unlike other studies, a negative correlation was found between the radiological score showing the amount of radiological involvement and native thiol and total thiol levels. These findings suggest that the decrease in protective antioxidants such as thiols against ROS and thiols transformed into disulfide bond structures plays an important role in the development of diffuse lung involvement seen in the course of COVID-19 and thus in the formation of the immune process.

Shrivastava et al. [32] found that MPO levels increased in 63 patients with COVID-19, similar to our study. MPO is an antimicrobial enzyme found in the azurophilic granules of neutrophils, and it is stated that its release during inflammation and decrease in levels may play a role in COVID-19-related coagulopathy [33]. In our study, while MPO levels were increasing in COVID-19 patients, a significant relationship was found between MPO levels and the duration of hospitalization. Although these findings support the formation of lung damage by vasoconstriction in the pulmonary vessels caused by NO consumption and MPO-related ROS and lung damage in COVID-19 patients, no correlation was found between the amount of lung involvement and MPO levels.

The current study has some limitations. First, the results cannot be generalized to the whole population because the study was conducted in a single center, included only patients over 18 years of age, and excluded those

with comorbid diseases. Second, the experimental data are limited. It would also be interesting to compare these groups with other populations that develop ARDS.

Conclusion

Disruption of thiol-disulfide homeostasis and inflammation triggered by increased oxidative stress may cause severe disease that may progress to acute respiratory distress syndrome in COVID-19 patients. We think that the measurement of thiol and oxidative biomarkers in COVID-19 patients may be useful in determining the duration of hospitalization and radiological involvement, indicating the severity of pneumonia.

Ethics Committee Approval: The study was approved by Biruni University Faculty of Medicine Ethics Committee (No: 2021/47-42, Date: 29/01/2021).

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Conflict of Interest: The authors declare that there is no conflict of interest.

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References

1. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance, 13 March 2020. Available at: https://apps.who.int/iris/handle/10665/331446. Accessed Aug 4, 2023.
2. Ducastel M, Chenevier-Gobeaux C, Ballaa Y, Meritet JF, Brack M, Chapuis N, et al. Oxidative stress and inflammatory biomarkers for the prediction of severity and ICU admission in unselected patients hospitalized with COVID-19. Int J Mol Sci 2021;22:7462.
3. Montazersaheb S, Hosseiniyan Khatibi SM, Hejazi MS, Tarhriz V, Farjami A, Ghasemian Sorbeni F, et al. COVID-19 infection: An overview on cytokine storm and related interventions. Virol J 2022;19:92.
4. Fara A, Mitrev Z, Rosalia RA, Assas BM. Cytokine storm and COVID-19: A chronicle of pro-inflammatory cytokines. Open Biol 2020;10:200160.
5. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846–8.
6. Pedersen SF, Ho YC. SARS-CoV-2: A storm is raging. J Clin Invest 2020;130:2202–5.
7. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically Ill patients with coronavirus disease 2019. Clin Infect Dis 2020;71:1937–42.
8. Goud PT, Bai D, Abu-Soud HM. A multiple-hit hypothesis involving reactive oxygen species and myeloperoxidase explains clinical deterioration and fatality in COVID-19. Int J Biol Sci 2021;17:62–72.
9. Maitra D, Byun J, Andreana PR, Abdulhamid I, Diamond MP, Saed GM, et al. Reaction of hemoglobin with HOCl: Mechanism of heme destruction and free iron release. Free Radic Biol Med 2011;51:374–86.
10. Laforge M, Elbim C, Frère C, Hémadi M, Massaad C, Nuss P, et al. Tissue damage from neutrophil-induced oxidative stress in COVID-19. Nat Rev Immunol 2020;20:515–6. Erratum in: Nat Rev Immunol 2020;20:579.
11. Çakırca G, Damar Çakırca T, Üstünel M, Torun A, Koyuncu İ. Thiol level and total oxidant/antioxidant status in patients with COVID-19 infection. Ir J Med Sci 2022;191:1925–30.
12. Hanikoglu F, Hanikoglu A, Kucuksayan E, Alisik M, Gocener AA, Erel O, et al. Dynamic thiol/disulphide homeostasis before and after radical prostatectomy in patients with prostate cancer. Free Radic Res 2016;50(Suppl 1):S79–S84.
13. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem 2014;47:326–32.
14. Komaravelli N, Casola A. Respiratory viral infections and subversion of cellular antioxidant defenses. J Pharmacogenomics Pharmacoproteomics 2014;5:1000141.
15. Erol SA, Anuk AT, Tanaçan A, Semiz H, Keskin HL, Neşelioğlu S, et al. An evaluation of maternal serum dynamic thiol-disulfide homeostasis and ischemia modified albumin changes in pregnant women with COVID-19. Turk J Obstet Gynecol 2022;19:21–7.
16. Bahinipati J, Mohapatra PC. Ischemia modified albumin as a marker of oxidative stress in normal pregnancy. J Clin Diagn Res 2016;10:BC15–7.
17. Badawy MA, Yasseen BA, El-Messiery RM, Abdel-Rahman EA, Elkhodiry AA, Kamel AG, et al. Neutrophil-mediated oxidative stress and albumin structural damage predict COVID-19-associated mortality. Elife 2021;10:e69417.
18. Ooi GC, Khong PL, Müller NL, Yiu WC, Zhou LJ, Ho JC, et al. Severe acute respiratory syndrome: Temporal lung changes at thin-section CT in 30 patients. Radiology 2004;230:836–44.
19. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med 2000;19:311–5.
20. Gaze DC. Ischemia modified albumin: A novel biomarker for the detection of cardiac ischemia. Drug Metab Pharmacokinet 2009;24:333–41.
21. Krueger AJ, Yang JJ, Roy TA, Robbins DJ, Mackerer CR. An

automated myeloperoxidase assay. Clin Chem 1990;36:158.
22. Yıldırım E, İpek E, Bavunoğlu I, Yıldırım N, Cengiz M, Yavuzer S, et al. The impact of protein oxidation on sustained and white coat hypertension. Anatol J Cardiol 2017;17:210–6.
23. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative stress and inflammation: What polyphenols can do for us? Oxid Med Cell Longev 2016;2016:7432797.
24. Uysal P, Yüksel A, Durmus S, Cuhadaroglu Ç, Gelisgen R, Uzun H. Can circulating oxidative stress-related biomarkers be used as an early prognostic marker for COVID-19? Front Med (Lausanne) 2023;10:1041115.
25. Mehri F, Rahbar AH, Ghane ET, Souri B, Esfahani M. Changes in oxidative markers in COVID-19 patients. Arch Med Res 2021;52:843–9.
26. Avila-Nava A, Pech-Aguilar AG, Lugo R, Medina-Vera I, Guevara-Cruz M, Gutiérrez-Solis AL. Oxidative stress biomarkers and their association with mortality among patients infected with SARS-CoV-2 in Mexico. Oxid Med Cell Longev 2022;2022:1058813.
27. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: How are they linked? Free Radic Biol Med 2010;49:1603–16.
28. Duran E, Taşkın A, Pehlivan B, Çelik H, Pehlivan VF, Taşkın S. Dynamic thiol disulphide homeostasis in the follow-up of the prognosis of patients treated for COVID-19 in the intensive care unit. Cureus 2022;14:e27542.
29. Aykac K, Ozsurekci Y, Yayla BCC, Gurlevik SL, Oygar PD, Bolu NB, et al. Oxidant and antioxidant balance in patients with COVID-19. Pediatr Pulmonol 2021;56:2803–10.
30. Erel Ö, Neşelioğlu S, Ergin Tunçay M, Fırat Oğuz E, Eren F, Akkuş MS, et al. A sensitive indicator for the severity of COVID-19: Thiol. Turk J Med Sci 2021;51:921–8.
31. Garavaglia ML, Giustarini D, Colombo G, Reggiani F, Finazzi S, Calatroni M, et al. Blood thiol redox state in chronic kidney disease. Int J Mol Sci 2022;23:2853.
32. Shrivastava S, Chelluboina S, Jedge P, Doke P, Palkar S, Mishra AC, et al. Elevated levels of neutrophil activated proteins, Alpha-Defensins (DEFA1), Calprotectin (S100A8/A9) and Myeloperoxidase (MPO) are associated with disease severity in COVID-19 patients. Front Cell Infect Microbiol 2021;11:751232.
33. Toussie D, Voutsinas N, Chung M, Bernheim A. Imaging of COVID-19. Semin Roentgenol 2022;57:40–52.