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ARAŞTIRMA / RESEARCH

Serum oxidant, antioxidant, and paraoxonase levels in COVID-19 patients

COVID-19 hastalarında serum oksidan, antioksidan ve paraoksonaz düzeyleri

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Abstract

Purpose: The aim of his study was to determine serum oxidant status (TOS), antioxidant status (TAS), and paraoxonase (PON1) levels and to determine their diagnostic values in patients diagnosed with COVID-19.
Materials and Methods: The research was carried out on patients diagnosed with COVID-19. Within the scope of the study, a total of 87 patients with a diagnosis of COVID-19, 48 (55.1%) male and 39 (44.9%) were evaluated. Total antioxidant determination was performed using a microplate reader according to the Erel method. To calculate the Oxidative stress index (OSI), TOS and TAS levels were determined.
Results: Male gender was associated with high PON1, smoking with high TOS, the presence of hypertension and Diabetes mellitus (DM) diseases with low OSI, and the presence of asthma with low PON1. High PON1 was found to be associated with shorter hospitalization duration and high TOS was associated with longer hospitalization duration. TAS and TOS levels increased significantly due to the increase in CRP, TOS levels due to the increase in neutrophil level, OSI levels due to the increase in leukocyte level, PON1 levels increased due to the increase in LDH level TAS, TOS, OSI, and PON1 cut-off values were 1.41 (AUC: 0.647), 4.56 (AUC: 0.493), 0.421 (AUC: 0.505) and 340 (AUC: 0.536), sensitivity values were 65.5, 55.2, 48.3 and 51.7; specificity values were calculated respectively as 62.1, 46.6, 34.5 and 53.4.
Conclusion: Although it is seen that oxidative stress types have diagnostic value, there is a need for more comprehensive studies with larger samples on the subject.

Keywords:. Oxidant, Antioxidant, Paraoxonase, Covid-19

Öz

Amaç: Bu çalışmada, COVID-19 tanısı konan hastalarda serum oksidan, antioksidan ve paraoksonaz düzeylerinin belirlenmesi ve tanısal değerlerinin belirlenmesi amaçlanmıştır.
Gereç ve Yöntem: Araştırma, COVID-19 tanısı konulan hastalar üzerinde gerçekleştirilmiştir. Çalışma kapsamında COVID-19 tanılı 48 (%55,1) erkek ve 39 (%44,9) olmak üzere toplam 87 hasta değerlendirildi. Toplam antioksidan tayini, Erel yöntemine göre bir mikroplaka okuyucu kullanılarak yapıldı. Toplam oksidan tayini, Erel yöntemine göre bir mikroplaka okuyucu kullanılarak yapıldı. OSI hesaplamak için TOS ve TAS seviyeleri belirlendi.
Bulgular: Erkek cinsiyetin yüksek PON1 ile yüksek TOS ile sigara kullanımı, hipertansiyon ve DM hastalıkları varlığı ile düşük OSİ ve düşük PON1 ile astım varlığı ile ilişkili olduğu bulundu. Ayrıca yüksek PON1 daha kısa hastanede kalış süresi ve yüksek TOS daha uzun hastanede kalış süresi ile ilişkili bulunmuştur. CRP'deki artışa bağlı olarak TAS ve TOS seviyeleri, nötrofil seviyesindeki artışa bağlı olarak TOS seviyesi ve OSI seviyesi nedeniyle anlamlı olarak arttı. lökosit seviyesindeki artışa bağlı olarak PON1 seviyesi LDH seviyesindeki artışa bağlı olarak yükselmiştir TAS, TOS, OSI ve PON1 cut-off değerleri 1.41 (AUC: 0.647), 4.56 (AUC: 0.493) olmuştur. 0.421 (AUC: 0.505) ve 340 (AUC: 0.536), hassasiyet değerleri 65.5, 55.2, 48.3 ve 51.7; özgüllük değerleri sırasıyla 62.1, 46.6, 34.5 ve 53.4 olarak hesaplanmıştır.
Sonuç: Çalışmamız sonucunda oksidatif stres türlerinin tanısal değeri olduğu görülmekle birlikte konu ile ilgili daha geniş örneklemli daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Oksidan, Antioksidan, Paraoksonaz, Covid-19.

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INTRODUCTION

In the city of Wuhan, Hubei province of China, in December 2019, a series of pneumonia cases of unknown cause emerged with clinical manifestations significantly similar to viral pneumonia. As a result of the sequence analyses performed on the lower respiratory tract samples taken from these cases, a new coronavirus named 2019 novel coronavirus disease (COVID-19) was detected. In studies conducted on the subject, the incubation period was found to be 1-4 days, usually 3-7 days, and the most common symptoms were reported to be fever, dry cough, and fatigue [1]. Due to the increase in the number of cases, new cases have started to be seen in other cities in China and various countries abroad. The sources of infection seen so far are generally respiratory droplets and COVID-19 patients transmitted by close contact[2].

It has been reported that COVID-19-positive patients have an increase in CRP levels and liver function tests. However, D-Dimer and prothrombin time levels are higher in severe patients who need intensive care [3]. In particular, the detection of a D-dimer value above 1g/mL is one of the independent indicators of mortality in hospitalized patients. Procalcitonin level is mostly high in those with secondary infection. It has been reported that the level of troponin-1 is high in those with cardiac damage due to the virus, and the mortality rate is significantly higher, especially in those with troponin levels of 28 pg/ml and above [4,5].

Lymphopenia, elevated liver enzyme levels, increased lactate dehydrogenase, elevated inflammatory markers (CRP, Ferritin, etc.), elevated D-Dimer, prolonged prothrombin time, elevated troponin, creatine phosphokinase, and acute kidney injury can be listed as poor prognosis criteria [3,6,7]. The response of the immune system affected by SARS-CoV-2 infection has two stages, the first of which is the specific adaptive immune system necessary to eliminate the virus and prevent the progression of the disease. The second is to increase the determinant and important immune responses [8]. From a topical perspective, most respiratory viral COVID-19 infections may be strongly associated with inflammation, cytokine production, cell death, and other pathophysiological processes induced by oxidative stress [9-11].

Aggressive molecules that occur during the use and metabolism of oxygen taken into the body are called free radicals. Normally, these radicals are kept under control by the body and there is a balance. If this balance is disturbed, a large number of reactive oxygen species (ROS) emerge. These molecules are molecules with extremely high reactivity. They are also produced as a result of normal metabolism in organelles, especially in mitochondria, or due to ischemia-perfusion, aging, exposure to radiation, high oxygen pressure, inflammation, and exposure to chemicals [12-14]. Oxidative stress is responsible for the pathogenesis of many diseases, including cancer, cardiovascular diseases, diabetes, neurological disorders, and inflammatory disorders [12-14].

Oxidative stress is a condition that can occur due to numerous viral infections, including respiratory tract, viral hepatitis, herpes viruses, and coronaviruses. It has been shown that the majority of viral, bacterial, and paralytic infections are effective in the production of ROS and reactive nitrogen species (NOS) associated with lung tissue damage and barrier dysfunction, and it has become a need to determine whether such a situation is also effective in COVID-19 patients. A limited number of studies on the subject have partially revealed the relationship between COVID-19 and oxidative stress [9,15].

Processes such as increased cytokine release and inflammation are frequently seen in COVID-19 patients. Considering this situation, it can be said that it may be related to oxidative stress. As a result of studies, it has been shown that increased ROS and lack of antioxidant defense mechanisms have an important role in the pathogenesis of SARS-CoV infection [9,16,17]. The relationship between the severity of viral infections and oxidative stress parameters has been demonstrated by studies. Studies on patients diagnosed with COVID-19 are not yet at a sufficient level. Although there are various findings related to the overproduction of reactive oxygen species (ROS) and depletion of antioxidants, the development, and severity of respiratory diseases and their functions in the pathogenesis of SARS-CoV infections are extremely important. As a result of animal studies on the subject, it has been reported that antioxidant levels decrease and ROS levels increase during SARS-CoV infection [17].

Research on parameters that can be used in the diagnosis of COVID-19 disease continues at full speed. In the study conducted by Rodríguez-Tomàs

et al. [18], it was reported that the level of PON1 enzyme activity can be used in the diagnosis of COVID-19. In the related study, the sensitivity and specificity of PON1 were very high in patients with COVID-19. In this study, we aimed to determine the total oxidants, total antioxidants, and paraoxonase levels and oxidative stress status after COVID-19 infection and whether these are effective in diagnosis.

MATERIAL AND METHODS

Study protocol and collection of samples

Approval was obtained from the Gaziantep University Clinical Research and Ethics Committee (Date: 23/03/2022, Decision No: 2022/74) for this study. Male and female patients between the ages of 40-70 were carried out on patients hospitalized with the diagnosis of COVID-19 at Gaziantep University Şahinbey Research and Practice Hospital.

All participants were informed about the aim of the study and the results that could be obtained. Written informed consent was obtained from the patients for participation in the study. Of the participants, those who have any acute illness (flu infection, sore throat, inflammation in the muscles, etc.) that may affect the results of the study, those who regularly use antioxidant or vitamin supplements, patients with chronic kidney failure, chronic liver failure, cerebrovascular disease, malignancy, hematological disorders, and rheumatic disease were excluded from the study. Patients who did not accept the study were excluded from the study. A total of 87 COVID-19 patients, 48 (55.1%) male, and 39 (44.9%) female were included in the study.

Determination of Total Antioxidant Capacity (TAS)

TAS level was determined using the method described by Erel[19]. In this method, the Fe2+-o-dianisidine complex forms a Fenton-type reaction with hydrogen peroxide to form the OH radical. This extremely potent reactive oxygen species react with the colorless o-dianisidine molecule at low pH values to form yellow-brown dianicidyl radicals. they also increase color formation by participating in further oxidation reactions. However, the antioxidants in the samples stop the color formation by suppressing these oxidation reactions. This reaction is measured spectrophotometrically by an automated analyzer.

Determination of Total Oxidant Capacity (TOS)

TOS level was determined using the method developed by Erel [20]. While measuring the TOS levels of the samples, the color change caused by the oxidation of the ferrous ion to the ferric ion by the oxidant molecules they contain was evaluated. Results were expressed as μmol H2O2 equivalent/gr protein.

Calculation of Oxidative Stress Index (OSI)

After determining TAS and TOS levels, OSI was calculated using the following formula [21]:

OSI (AU) = TOS [(μmol H2O2 equivalent/L) /TAS (μmol H2O2 equivalent/L)] × 100

Paraoxonase enzyme activity measurement

Paraoxonase is a lipophilic, hydrophobic antioxidant enzyme linked to HDL-Cholesterol. The activity of this enzyme was measured using the Rel Assay kit. Briefly, in this method, paraoxon (O, O-diethyl-O-p-nitrophenyl-phosphate) by reacting with its substrate. As a result of this hydrolysis process, a colored p-nitrophenol product is formed. The absorbance of the formed product is monitored in the kinetic mode at 412 nm, and the enzyme activity is expressed as U/g protein [22]. All parameters were analyzed by authorized persons in the laboratory of Gaziantep University Faculty of Medicine, Department of Biochemistry.

Statistical analysis

Before the study, "Power Analysis" was performed to ensure that the data to be obtained from the study could be used and evaluated, and the total number of participants was determined as 86 to determine a statistically significant difference (α=0.05 1-β=0.80 f=0.3). Analyzes were made in G Power version 3.1. SPSS 24.0 (Chicago, IL, USA) package program was used for data analysis. Mean, standard deviation (±), and percentage values were given as descriptive statistics. Whether the data fit the normal distribution was tested with the Kolmogorov-Smirnov test. Whether there was a relationship between the variables was analyzed with Pearson's correlation analysis. ROC analysis was used to determine the diagnostic efficacy of TAS, TOS, OSI, and PON1. Obtained results were evaluated at a 95% ($p<0.05$) significance level.

RESULTS

55.1% of the patients included in the study were male. The mean age of the patients was 54.46±8.06. 57.7% of the patients were smokers. Of the patients, 50.5% had hypertension, 41.3% had DM, 20.6% had asthma, and 2.29% had COPD. The hospitalization duration of the patients was 6.96±8.14 days (Table 1).

Table 1. Demographic properties of the patients

Variable	
Gender (n/%)	
Male	48/55.1
Female	39/44.9
Age (mean±Std.D)	54.46±8.06
Cigarette (n/%)	
Yes	52/57.7
No	35/42.3
Hypertension (n/%)	
Yes	44/50.5
No	43/49.5
Diabetes Mellitus (n/%)	
Yes	36/41.3
No	51/58.7
Asthma	
Yes	18/20.6
No	69/79.4
COPD (n/%)	
Yes	2/2.29
No	85/97.71
Hospitalization Duration (mean±Std.D)	6.96±8.14

*COPD: Chronic obstructive pulmonary disease

The mean TAS, TOS, OSI, and PON1 levels of the COVID-19 patients included in the study are presented in Table 2. The mean TAS value of the patients was 131±46, TOS value was 632.7±427.3 μmol Trolox quiv/L, OSI value was 519.3±354.3 AU, and PON1 value was 285±174.2 U/L.

Table 2. Mean TAS, TOS, OSI, and PON1 values of the COVID-19 patients

Parameters	**Mean±Std.D**
TAS (mmol Trolox quiv/L)	**131±46**
TOS (μmol Trolox quiv/L)	632.7±427.3
OSI (AU)	519.3±354.3
PON1 (U/L)	285±174.2

TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, PON1: Paraoxonase

In our study, it was found that the male gender was associated with high PON1, smoking with high TOS, the presence of hypertension and DM diseases with low OSI, and the presence of asthma with low PON1. In addition, high PON1 was found to be associated with shorter hospitalization duration ($p = 0.04$) and high TOS was associated with longer hospitalization duration ($p = 0.02$) (Table 3). TAS ($p = .04$) and TOS ($p = .05$) levels increased significantly due to the increase in CRP, TOS level ($p = .08$) due to the increase in neutrophil level, and OSI level ($p = .08$) due to the increase in leukocyte level, PON1 level ($p = .06$) increased due to the increase in LDH level (Table 4). TAS, TOS, OSI and PON1 cut-off values were 1.41 (AUC: 0.647), 4.56 (AUC: 0.493), 0.421 (AUC: 0.505) and 340 (AUC: 0.536), sensitivity values were 65.5, 55.2, 48.3 and 51.7; specificity values were calculated respectively as 62.1, 46.6, 34.5 and 53.4 (Table 5; Figure 1).

Table 3. Relationship between demographic properties and TAS, TOS, OSI and PON1 values

	TAS (mmol/L)	**TOS (µmol/L)**	**OSI**	**PON1 (U/L)**
Parameters	p	p	p	p
Male	0.2	0.2	0.1	0.04
Female	0.3	0.3	0.1	0.3
Age	0.8	0.9	0.4	0.6
Cigarette (+)	0.1	0.09	0.3	0.2
Cigarette (-)	0.3	0.2	0.4	0.3
Hypertension	0.4	0.6	0.04	0.4
Diabetes Mellitus	0.6	0.5	0.05	0.5
Asthma	0.4	0.4	0.1	0.04
COPD	0.1	0.8	0.2	0.5
Hospitalization Duration	0.04 (>12 days)	0.02 (>16 days)	0.08 (>14 days)	0.04 (>5 days)

*COPD: Chronic obstructive pulmonary disease

Table 4. The relationship between various biochemical parameters and TAS, TOS, OSI and PON1

	TAS (mmol/L)	**TOS (µmol/L)**	**OSI**	**PON1 (U/L)**
Parameters	p	p	p	p
CRP	0.04	0.05	0.7	0.5
Ferritin	0.5	0.1	0.3	0.8
D-Dimer	0.4	0.2	0.2	0.3
Lymphocyte	0.3	0.3	0.4	0.6
Neutrophil	0.5	0.08	0.5	0.1
Leukocyte	0.2	0.5	0.04	0.4
Procalcitonin	0.6	0.8	0.5	0.9
Fibrinogen	0.2	0.1	0.6	0.8
LDH	0.6	0.2	0.8	0.06

TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, PON1: Paraoxonase, CRP: C-reactive protein, LDH: Laktat dehidrogenase

Table 5. Diagnostic performance of TAS, TOS, OSl and PON1 in COVID-19 patients

Parameters	AUC (95% CI)	Cut-off level	Sensitivity	Specificity	p
TAS (mmol Trolox quiv/L)	0.647 (0.12)	1.41	65.5	62.1	0.02
TOS (µmol Trolox quiv/L)	0.493 (0.88)	4.56	55.2	46.6	0.07
OSI (AU)	0.505 (0.72)	0.421	48.3	34.5	0.01
PON1 (U/L)	0.536 (0.35)	340	51.7	53.4	0.06

TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, PON1: Paraoxonase

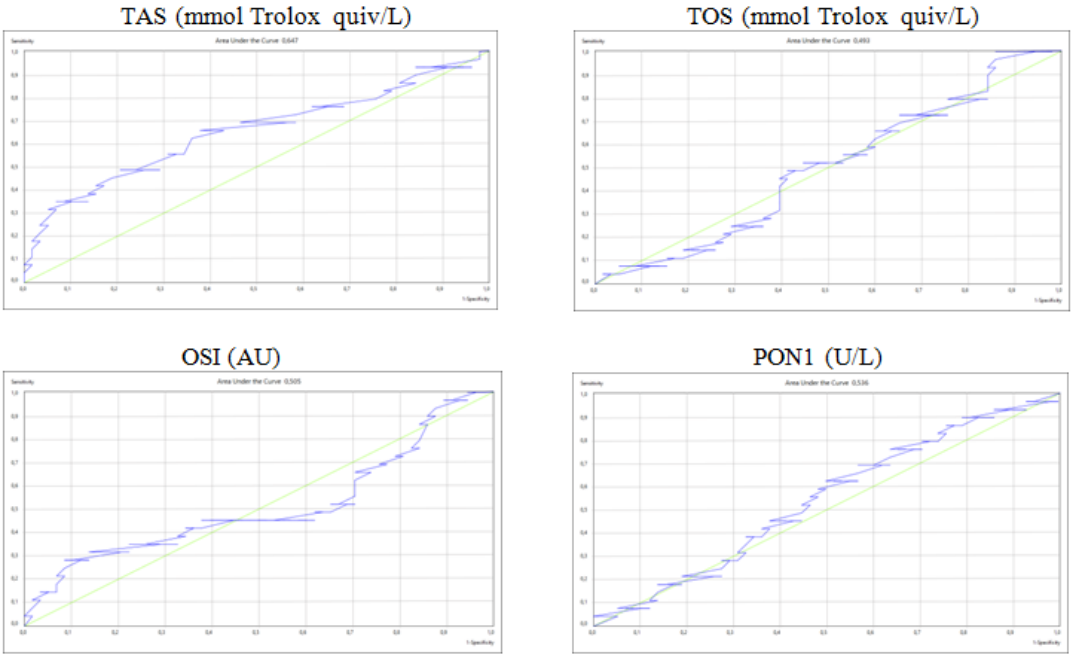

Figure 1. Diagnostic performance of TAS, TOS, OSI and PON1 in COVID-19 patients based on ROC Analysis
TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, PON1: Paraoxonase

DISCUSSION

COVID-19 is a disease that causes mitochondrial dysfunction, resulting in a relative decrease in oxygen and energy production and an increase in ROS production. As a result of all these, oxidative damage occurs in patients. Studies have reported that oxidative damage is associated with many different factors such as demographic, physical, nutrition, etc.[23]. Our findings were similar to these results, and TAS, TOS, OSI, and values were found to be high and PON1 was lower. The Paraoxonase enzyme family includes three antioxidant isoenzymes, PON-1, PON-2, and PON-3. In recent studies, it has been reported that PON1 concentration decreases in diseases associated with increased oxidative stress, including COVID-19[24,25].

PON1 enzyme is an enzyme that is synthesized in the liver and enters the circulation connected with HDLs. In addition to being internalized in peripheral cells, protein expression is found in almost all tissues. It has been shown that the paraoxonase (PON1) enzyme purified from human serum is a glycoprotein with a minimum molecular mass of 43-45 kDa and 354 amino acids, it needs calcium ions for its catalytic activity, can be inhibited by agents with sulfhydryl, and cysteines are included in its structure[26,27]. PON1 is a lipoperoxide hydrolase that breaks down lipoperoxides in lipoproteins and cells, participating in the individual's innate immune system and defense against oxidative stress[26,27]. Decreased PON1 activity has been reported in bacterial infections[28–30] and viral infections such as COVID-19[25]. When routine laboratory findings of COVID-19 are examined, an increase in inflammatory biomarkers such as CRP, procalcitonin, ferritin, and LDH, lymphocytopenia in complete blood count, leukocytopenia and thrombocytosis are observed[31,32].

In a study comparing COVID-19 patients and healthy people, the TOS value was found to be higher in cases, and a significant increase in TAS value was observed in severe cases[33]. In our study, a positive correlation was found between TAS and TOS levels and CRP levels, and a positive correlation between TOS and neutrophil levels. As a result, oxidant and antioxidant molecules, which increase with immune system activation, may be as elevated in COVID-19 cases as in symptomatic people. Therefore, TAS and

TOS measurements may not distinguish COVID-19 cases from symptomatic individuals.

In the current study, the diagnostic value (AUC: 0.647), sensitivity (65.5), and specificity (62.1) of TAS for COVID-19 were found to be higher than TOS, OSI, and PON1. Studies have reported that the change in oxidative stress parameters in COVID-19 patients is related to the severity of the disease, and it has been stated that oxidative stress parameters can be used in the diagnosis in these studies[34,35]. Oxidative species have been reported to be strongly altered in critically ill COVID-19 patients, as evidenced by increased lipid peroxidation as well as deficiencies in some antioxidants such as vitamin C, glutathione and thiol proteins, and trace elements such as selenium[34,35]. As a result of our study, although it is seen that oxidative stress types have diagnostic value, there is a need for more comprehensive studies with larger samples on the subject. In a study, TOS, TAS, and OSI levels were investigated among COVID-19 patients. In the same study, it was determined that thiol and TAS levels were lower in intensive care patients than in patients not in intensive care units. Also in the study, they stated that their data can be used to differentiate thiol, TAS, TOS, and OSI markers for COVID-19 patients[36].

Our study has some limitations that should be considered. As this is a small-scale cross-sectional study, our results should be confirmed by prospective studies. However, since this disease is a pandemic situation, it may not be possible to reach patients with the same characteristics again. On the other hand, there may be other oxidative stress source factors that we could not detect, apart from COVID-19, in the patients included in this study. The homogeneity of our study group is low, as conditions such as age, nutrition, and psychosocial status are also factors that affect oxidative stress. As a result, oxidative stress and ROS formation are observed in COVID-19 patients. However, the balance or imbalance between the patient's ROS-antioxidant status is predicted to determine the prognosis of the disease. Therefore, more studies are needed in the literature to assess whether changes in oxidation state are truly relevant to worsening outcomes in COVID-19 patients.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ; Veri toplama: , NÖM; Veri analizi ve yorumlama: ; Yazı taslağı: ; İçeriğin eleştirel incelenmesi: ; Son onay ve sorumluluk: ; Teknik ve malzeme desteği: -; Süpervizyon: ; Fon sağlama (mevcut ise): yok.
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Yazarın Notu:
Author Contributions: Concept/Design : ; Data acquisition: ; Data analysis and interpretation: ; Drafting manuscript: ; Critical revision of manuscript: ; Final approval and accountability: ; Technical or material support: -; Supervision: ; Securing funding (if available): n/a.
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