# SEVERITY-RELATED DIFFERENCES ON RESPONSE OF ANTIOXIDANT DEFENSE SYSTEM IN COVID-19 PATIENTS

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# РОЛЬ ТЯЖЕСТИ ЗАБОЛЕВАНИЯ НА ОТВЕТ СИСТЕМЫ АНТИОКСИДАНТНОЙ ЗАЩИТЫ У ПАЦИЕНТОВ С COVID-19

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**Abstract**

Background. COVID 19 is a major human infectious disease with devastating economic and public health impacts globally. Oxidative stress plays a pivotal role in the pathogenesis and progression of various viral infections. The aim of the present study was to evaluate oxidative stress biomarkers in COVID-19 patients with different severity to healthy participants.

Materials and methods. This case-control study was conducted on 60 patients with COVID-19 infection (30 moderate and 30 severe) and 30 matched healthy controls referred to Baqiyatallah Hospital, Tehran from March until July 2020. Serum levels of total antioxidant capacity (TAC) and oxidative stress biomarkers such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) activities and levels of glutathione (GSH) and malondialdehyde (MDA) were measured using biochemical methods.

Results. In terms of gender, the healthy control group consisted of 17 males and 13 females, and the group of moderate patients included 20 males and 10 females and severe COVID-19 patients included 14 males and 16 females, which were not statistically significant (P=0.295). Also, the mean age in severe COVID-19 patients (46.6±12.8) was not significantly different from the healthy control (43.8±12; P=0.683) and moderate (45.60±13.30; P=0.953) groups. The results showed that SOD and CAT activities and MDA level in moderate and severe of COVID-19 patients were higher than the healthy individuals, while GPx and GR activities and GSH and TAC levels were significantly lower. SOD and GPx activities and MDA level in severe of COVID-19 patients were significantly different from moderate patients. However, CAT and GR activities and TAC level in severe cases was not significantly different from moderate patients.

Conclusion. Oxidative stress plays an important role in the pathogenesis of COVID 19 infection as indicated by the enhancement of lipid peroxidation,

depletion of GSH and alteration in antioxidant enzymes. The systemic oxidative stress is directly related to the severity of the pathogenesis. Therefore, substances with antioxidant properties may be a potential choice for the treatment of COVID 19 infection.

**Keywords:** COVID-19, Severity of disease Oxidative stress, Antioxidant enzymes, Lipid peroxidation, Serum

**Резюме**

Введение. COVID-19 является серьёзным инфекционным заболеванием, оказывая разрушительное воздействие на экономику и общественное здравоохранение во всем мире. Окислительный стресс играет ключевую роль в патогенезе и прогрессировании различных вирусных инфекций. Целью настоящего исследования была оценка биомаркеров окислительного стресса у пациентов с COVID-19 различной степени тяжести и у волонтеров.

Материалы и методы. Настоящее исследование случай-контроль было проведено с участием 60 пациентов с COVID-19 (по 30 человек со средней и с тяжёлой степенью тяжести) и 30 здоровых лиц контрольной группы, поступивших в больницу «Бакияталлах» в Тегеране с марта по июль 2020 года. Биохимические методы использовались для оценки сывороточных уровней общей антиоксидантной активности (ОАС) и биомаркеров окислительного стресса, таких как супероксиддисмутаза (СОД), каталаза (КАТ), глутатионпероксидаза (ГП) и глутатионредуктаза (ГР), а также уровни глутатиона (GSH) и малонового диальдегида (МДА).

Результаты. В контрольную группу вошли 17 мужчин и 13 женщин, а в группу пациентов средней степени тяжести COVID-19 – 20 мужчин и 10 женщин, с тяжелым течением COVID-19 – 14 мужчин и 16 женщин (P=0,295). Кроме того, средний возраст у пациентов с тяжелым течением COVID-19 (46,6 ± 12,8 лет) существенно не отличался от групп контроля (43,8 ± 12 лет; P=0,683) и средней степени тяжести (45,60 ± 13,30 лет; P=0,953). Результаты показали, что активность СОД и КАТ, а также уровень МДА у пациентов средней и тяжелой степени тяжести COVID-19 были выше, чем у здоровых лиц, в то время как активность ГП и ГР, а также уровни GSH и ОАС были значительно ниже. Активность СОД и ГП, а также уровень МДА у пациентов тяжелой степени тяжести COVID-19 существенно отличались от пациентов средней степени тяжести. Однако активность КАТ и ГР, а также уровень ОАС

у пациентов с тяжелым течением заболевания достоверно не отличались от таковых у пациентов со средней степенью тяжести.

Заключение. Окислительный стресс играет важную роль в патогенезе инфекции COVID-19, о чем свидетельствуют усиление перекисного окисления липидов, истощение GSH и изменение активности антиоксидантных ферментов. Системный окислительный стресс напрямую связан с тяжестью патогенеза COVID-19. Следовательно, вещества с антиоксидантными свойствами могут быть потенциальным выбором для лечения COVID-19.

**Ключевые слова:** COVID-19, Тяжесть заболевания, Окислительный стресс, Антиоксидантные ферменты, Перекисное окисление липидов, Сыворотка крови.

## 1 Introduction

COVID-19 is a major human infectious disease with devastating economic and public health impacts globally [1, 2]. The pathogenic agent of its illness is the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) that was first identified in December 2019 in Wuhan, China [2, 3]. SARS-CoV-2 is enveloped virus with a single positive-stranded RNA genome. There are four subfamilies of coronaviruses, known as alpha, beta, gamma, and delta. However, it is the beta-coronaviruses to which SARS-CoV-2 belongs that cause the most severe morbidity and fatality [1, 4]. COVID-19 has caused more than 241.5 million confirmed cases and more than 4.9 million deaths worldwide [5]. The clinical manifestations of COVID-19 cover a broad range from asymptomatic to severe symptoms (acute lung injury) [2, 3].

Oxidative stress plays a crucial role in the initiation and progression of progression of many diseases such as diabetes mellitus, cancers, hypertension, coronary heart disease, pulmonary disease and various viral infections [6, 7]. Increase in plasma pro-inflammatory cytokines during infectious disease release a great number of reactive oxygen species (ROS) resulting in damage to cellular macromolecules such as such as DNA, lipids, and proteins [1, 8]. Antioxidant defense system includes enzyme antioxidants such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR), and nonenzyme antioxidants such as reduced glutathione (GSH) protect the cells from damage of ROS [6, 9]. Numerous studies have shown that COVID-19 infection is associated with alteration of antioxidant enzyme activities, depletion of GSH and an increase of membrane lipid peroxidation, all of which can lead to oxidative stress and finally cell death [2, 3, 5, 6]. Several investigations have reported that oxidative stress is an essential factor in increasing the severity of COVID-19 in some patients, and it is associated with pulmonary dysfunction, cytokine storm and viral sepsis derived from SARS-CoV-2 infection [6, 10, 11].

Despite the increase in the number of COVID-19 related scientific articles, the pathphysiologic mechanisms underlying the disease are not completely elucidated

[5]. Elucidating the molecular and cellular pathways activated in response to infection is crucial to understanding disease pathogenesis and to developing therapeutic strategies and identify prognostic markers [3, 12, 13]. The ability of oxidant-antioxidant defense system against infection differs in severity of disease [6]. There are few reports on the disease severity effects of COVID-19 infection on induction of oxidative stress. The aim of the present study was to investigate these effects on important biomarkers of oxidative stress including malondialdehyde (MDA) content as an important index of lipid peroxidation and antioxidant defense parameters such as GSH level, activities of SOD, CAT, GPX and GR in serum of COVID-19 patients and assessing their relationship with severity of disease.

## 2 Material and methods

### *Patients and Study design*

This case-control study was conducted at Baqiyatallah Hospital of the Baqiyatallah University of Medical Sciences, Tehran, Iran from March until July 2020. The control group consisted from 30 healthy participants without COVID-19. The case group were selected in two groups, including hospitalised group in non–intensive care units (Non-ICU) (Moderate group) (n = 30) and hospitalised group in intensive care units (ICU) (Severe group) (n=30). The control group was similar in age and sex to the two case groups.

The inclusion criteria for selecting healthy participants as our control group were the people who had no COVID-19 symptoms, or a history of visiting a doctor or being hospitalised due to COVID-19, and for patient groups where patients admitted in hospital due to infection with COVID-19, with a positive COVID-19 RT-PCR test, and identified based on World Health Organization interim guidelines [14]. Subjects with a history of diabetes, hypertension, cancers, autoimmune disorders and using medications with antioxidant properties were excluded from the control and case groups. Prior to the study, all patients were asked to complete a checklist of variables including age and gender by a research physician. Besides that, the participants or

their relatives completed and signed an informed consent form. The ethics committee of the Baqiyatallah University of Medical Sciences approved the study protocol (IR.BMSU.REC.1399.279).

*Serum preparation*

Venous blood samples were taken from all subjects on the first day after admission. After clot forming, the serum was separated from the coagulated blood by centrifugation at 1500×g for 15 min at 4°C. Then, samples were then transferred into 0.5 ml microtubes and stored at –80°C until analysis.

*Biomarkers of oxidative stress*

Serum SOD, CAT, GPx and GR activities and the levels of GSH, total antioxidant capacity (TAC) and MDA were measured using commercially available Eliza kits (ZellBio GmbH, Germany).

*Statistical analysis*

Statistical analysis of the data was conducted using SPSS statistical software version 22 (IBM Corporation, USA). Chi-square test was used for analysis of patients' gender and severity of COVID-19. Data were tested for normal distribution with the Kolmogorov–Smirnov test. Significance was determined by one-way analysis of variance (ANOVA) followed by post hoc analysis using Tukey multiple comparison tests to test within and between subject differences in oxidative stress biomarkers levels. Results were expressed as mean ± SD. Significance level was based on $P< 0.05$.

## 3 Result

*Clinical characteristics of the study population*

Totally 90 participants were enrolled in this study, 30 healthy controls and 60 patients with COVID-19 disease including 30 moderate and 30 severe patients. In terms of gender, the healthy control group consisted of 17 (56.7%) males and 13 (43.3%) females, and the group of moderate patients included 20 (66.7%) males and

10 (33.3%) females and severe COVID-19 patients included 14 (46.7%) males and 16 (53.3%) females, which were not statistically significant (*P*=0.295). Also, the mean age in severe COVID-19 patients (46.6±12.8) was not significantly different from the healthy control (43.8±12; *P*=0.683) and moderate (45.60±13.30; *P*=0.953) groups.

*Parameters of oxidative stress biomarkers*

Serum TAC level in severe of COVID-19 patients was lower than the control group (15.2%, *P*=0.014). However, the decreased TAC level in severe cases was not significantly different from moderate group (*P*=0.062) (Figure 1).

Serum GSH level in moderate (8.06%, *P*=0.042) and severe (12.87%, *P*=0.001) of COVID-19 patients was lower than the control group. However, GSH level in severe cases was not significantly different from moderate group (*P*=0.31). In addition, serum MDA level in moderate (11.16%, *P*=0.007) and severe (24.20%, *P*=0.0001) of COVID-19 patients was higher than the control group. MDA level in severe COVID-19 patients was also significantly higher than moderate covid-19 patients (11.72%, *P*=0.012) (Figure 2).

Serum SOD activity in moderate (10.37%, *P*=0.03) and severe (19.9%, *P*=0.000009) of COVID-19 patients was increased compared to the control group. In addition, SOD activity in severe cases was significantly higher than moderate group (8.64%, *P*=0.049). In addition, serum CAT activity in moderate (32.73%, *P*=0.004) and severe (53.9%, *P*=0.000001) of COVID-19 patients was higher than the control group. However, CAT activity in severe cases was not significantly different from moderate group (*P*=0.086) (Figure 3).

Serum GPx activity in moderate (12.01%, *P*=0.044) and severe (27.23%, *P*=0.000001) of COVID-19 patients was lower than the control group. In addition, GPx activity in severe cases was significantly lower than moderate group (17.3%, *P*=0.008). In addition, serum GR activity in moderate (7.4%, *P*=0.040) and severe (11.57%, *P*=0.001) of COVID-19 patients was lower than the control group.

However, GR activity in severe cases was not significantly different from moderate group ($P$= 0.35) (Figure 4).

## 4 Discussion

Oxidative stress is triggered by a wide variety of viral infections, including HIV, herpes viruses, respiratory viruses, such as corona viruses. During viral infections, ROS are mainly produced by the mitochondrial respiratory chain that activate proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6) and interleukin 8 in macrophages, neutrophils and endothelial cells through NADPH oxidase to produce more superoxide and $H_2O_2$ [1, 6]. The human body has strong endogenous antioxidant mechanisms including SOD and CAT that counteract the harmful effects of ROS. SOD detoxifies superoxide to hydrogen peroxide ($H_2O_2$), while CAT convert $H_2O_2$ into water and oxygen and inhibit the formation of $^{\bullet}OH$ radical [13, 14]. Our results indicated that the activities of SOD and CAT in the serum of moderate and severe patients were significantly higher than the non-patient group. In addition, SOD in the serum of severe COVID-19 patients was significantly higher than the serum of moderate COVID-19 patients. The elevated activities of the antioxidant enzymes are considered as a neutralizing step against increased ROS generation in tissues [15-17]. Overproduction of ROS in COVID-19 patients activates nuclear factor-kappa B, which in turn increases the expression of cytokines genes such as TNF-α and IL-6, leadings to inflammation and depletion of GSH and increased MDA levels [1, 11, 18]. The rise in superoxide anion would have further consequences. It reacts with NO to form peroxynitrite radical and generates hydroxyl radical in conjunction with $H_2O_2$ through the Haber–Weiss and Fenton reactions, all exacerbating lipid peroxidation, DNA damage and cell death [14]. The present results are consistent with a number of studies [2, 17, 19, 20] and in disagreement with a few other ones which reported an otherwise decrease in antioxidant enzymes activities [15, 20]. Yaghoubi et al showed that no significant differences were found between serum activities of SOD and CAT enzymes in COVID-19 infected patients compared with healthy individuals [3].

Also, Golabi et al. reported that there was no significant differences in SOD and GPx activities between COVID-19 patients in the mild and asymptomatic group compared to those with moderate-grade severity [21].

GSH as non-protein thiol source is one of the most important small molecular weight antioxidants in the cell, which acts as a free radical scavenger. Furthermore, it serves as a substrate for several enzymes, including GPx, GR and glutathione S-transferases. Its depletion is considered as an important biomarker of oxidative stress in animals and humans [6, 18]. GPx degrades $H_2O_2$ to water and oxygen in the presence of adequate amount of GSH. GR catalyzes the reduction of glutathione disulfide (GSSG) to GSH and thus it is a key enzyme in the maintenance of GSH [4, 22]. The current study, serum GPx and GR activities and GSH level were significantly lower in COVID-19 patients. In addition, patients with severe injuries showed tendencies for a decreased activity of GPx than patients with moderate injuries. The decline in GSH level could be due to increased utilization of GSH in protecting SH-containing proteins from ROS, which leads to oxidative stress. The decreased GSH leads to the production of oxidized GSH (GSSG) and decrease in GPx activity. Depletion of GPx special in severe patients leads to the accumulation of $H_2O_2$, which may subsequently reacts forming hydroxyl radical ($^{\bullet}OH$) through the Fenton reaction leading lipid peroxidation, DNA damage and cell death [14, 15]. Also, the decrease in GR activity converting GSSG to GSH suggests a decrease in the GSH/GSSG ratio, an index of tissue oxidative stress, which may shift cells through different biological stages, such as proliferation, differentiation, apoptosis and necrosis [4, 22, 23]. Oral administration NAC could potentially be a viable drug to treat COVID-19 infection due to its role in the synthesis of glutathione, improving T cell response, and modulating inflammation and cell death [4, 24]. These findings are in agreement with the results of the previous reports [15, 20, 22, 25]. Several studies indicated high serum level of SOD, CAT and GPx activities in COVID-19 patients [2, 17, 21]. Infection with COVID-19 can stimulate a positive feedback cycle of increased IL-6 and decreased GSH that may explain the cytokine storm that

can accompany this infection [6, 26]. Decreased GSH was associated with increased ROS and more severe clinical manifestation of coronavirus [25, 27]. Studies revealed that COVID-19 patients with critical condition demonstrated lower glutathione levels, with a high concentration of ROS as compared to the patients with mild symptoms [6, 25, 28].

Our results showed a significant increase in serum MDA level in COVID-19 patients. Furthermore, MDA level in the serum of severe COVID-19 patients was significantly higher than the serum of moderate COVID-19 patients. MDA is an end-product of lipid peroxidation, which leads to loss of the cellular membrane integrity via the oxidation of polyunsaturated fatty acids [9, 16]. The increase in lipid peroxidation was associated with a decrease in GSH level in patients, which could severely impair tissue antioxidant function and make the tissue more susceptible to potential oxidative stress [9]. The same results have been obtained by different studies [2, 17, 29].

The cumulative antioxidant efficiency and ability of all antioxidants in the biological fluids to protect is calculated as the serum TAC. In fact, TAC is used as a new clinical biomarker for diagnosis, prognosis and prevention of many diseases [9]. Because TAC is a biochemical parameter, it can be suitable for evaluating the overall antioxidant status of cells against ROS [6]. Our study demonstrated less serum TAC level in patients with severe injuries, suggesting a rising risk of disease progression in COVID-19 patients [6]. The difference in TAC levels over various groups of this study could be attributed to high ROS production, acute inflammatory condition and infiltration of inflammatory cells into the different organs [3]. In addition, the reduced TAC level in COVID-19 patients may be due to the lower plasma vitamins C and E levels, which act as strong antioxidants and help to scavenge the ROS [15, 30].

Moreover, it has been proved that the malnourished individuals have a rising risk of being admitted to the ICU and COVID-19-related mortality [15, 31]. This finding supports a strong relationship between impairment of antioxidant defense in the

pathogenesis of COVID-19. Numerous investigations have also reported the low levels of antioxidant vitamins in COVID-19 patients, and hence suggested that strategies aimed at improving the levels of these vitamins may be useful in these patients [32, 33]. Zhang et al showed that TAC levels at the early stage of COVID-19 tended to increase with disease severity [34]. Golabi et al. showed that there was no significant difference in serum TAC with an increase in COVID-19 disease severity [21]. Several studies have reported that serum TOS (total oxidant status) was significantly increased in COVID-19 patients [2, 17, 29]. The differences observed in the relevant literature may underlie subject age and gender, the sampling time and assay technique employed [34].

## 5 Conclusion

Oxidative stress plays an important role in the pathogenesis of COVID-19 infection as indicated by the enhancement of lipid peroxidation, depletion of GSH and alteration in antioxidant enzymes. The systemic oxidative stress is directly related to the severity of the pathogenesis. Therefore, substances with antioxidant properties may be a potential choice for the treatment of COVID-19 infection. However, further in vitro and in vivo studies are necessary to determine the effectiveness of antioxidants for COVID-19 treatment.

Acknowledgements

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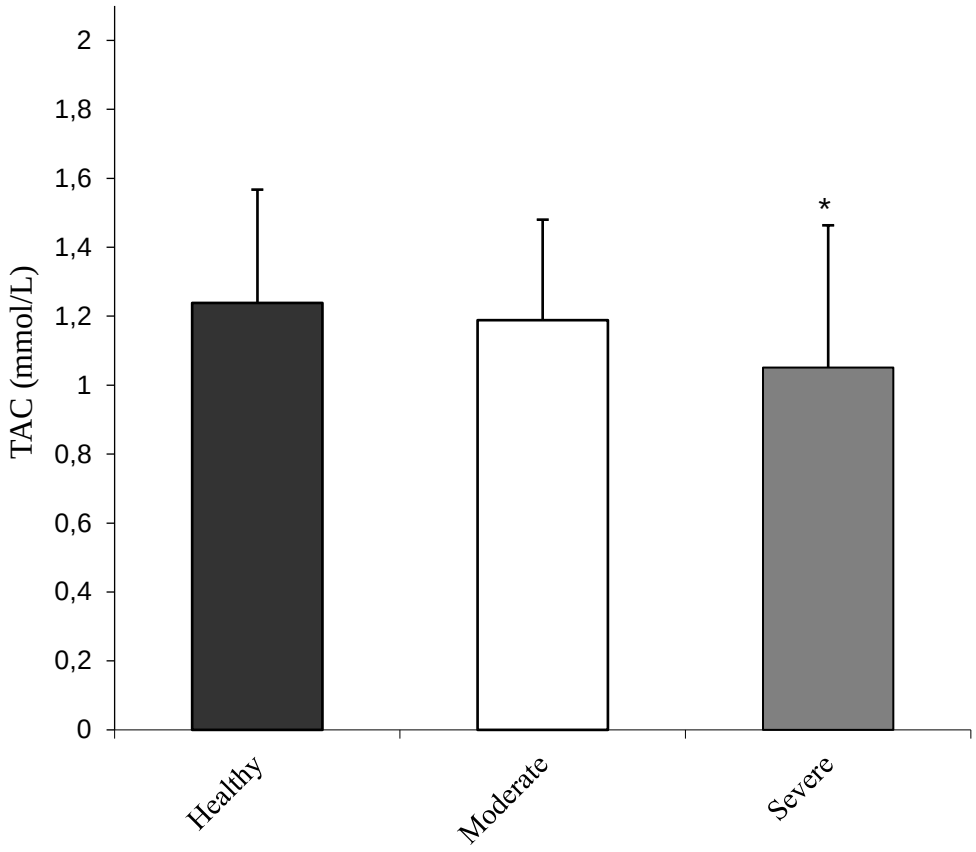
Conflicts of interest

The authors declare that they have no conflict of interest.

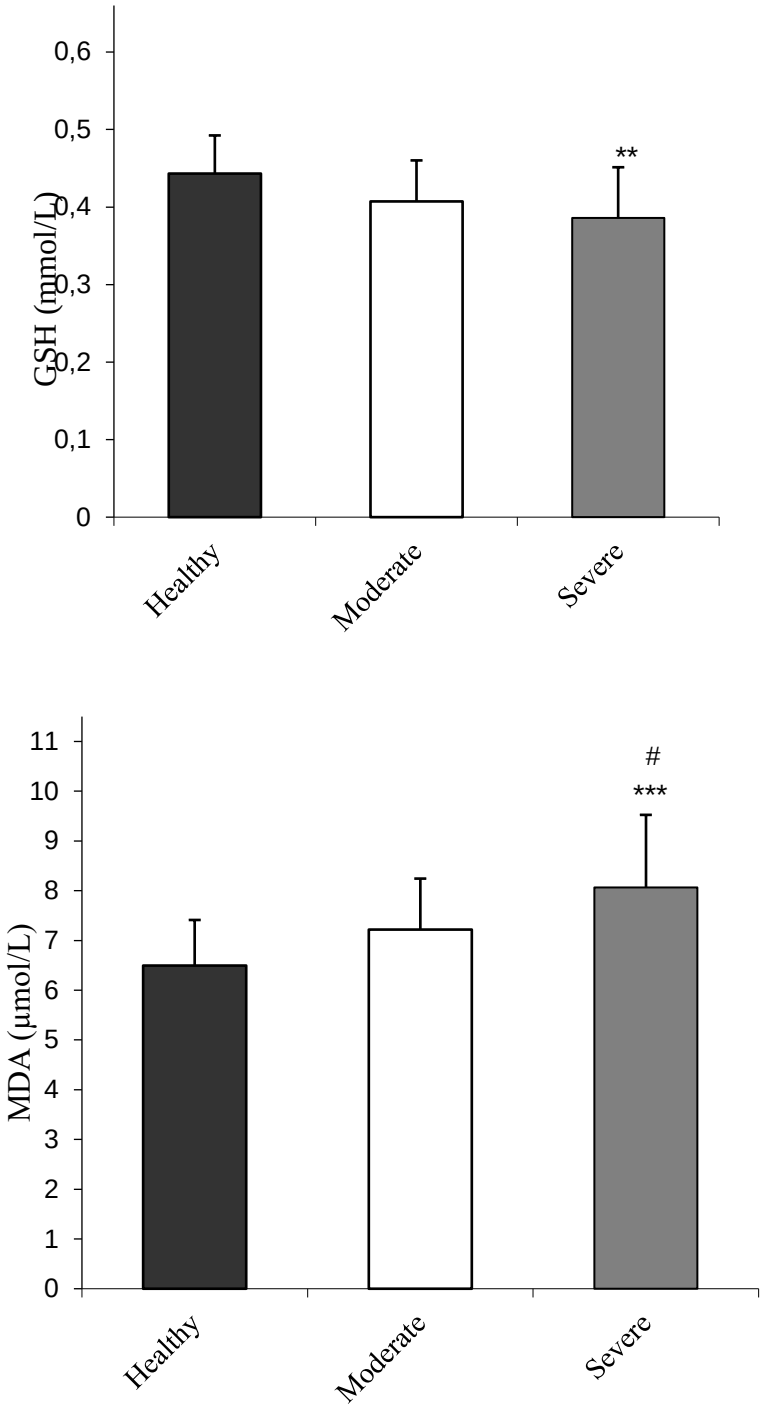
## РИСУНКИ

**Figure 1.** Serum total antioxidant capacity (TAC) level among the healthy, moderate and severe COVID-19 patients. Values are expressed as mean±SD (n=30).



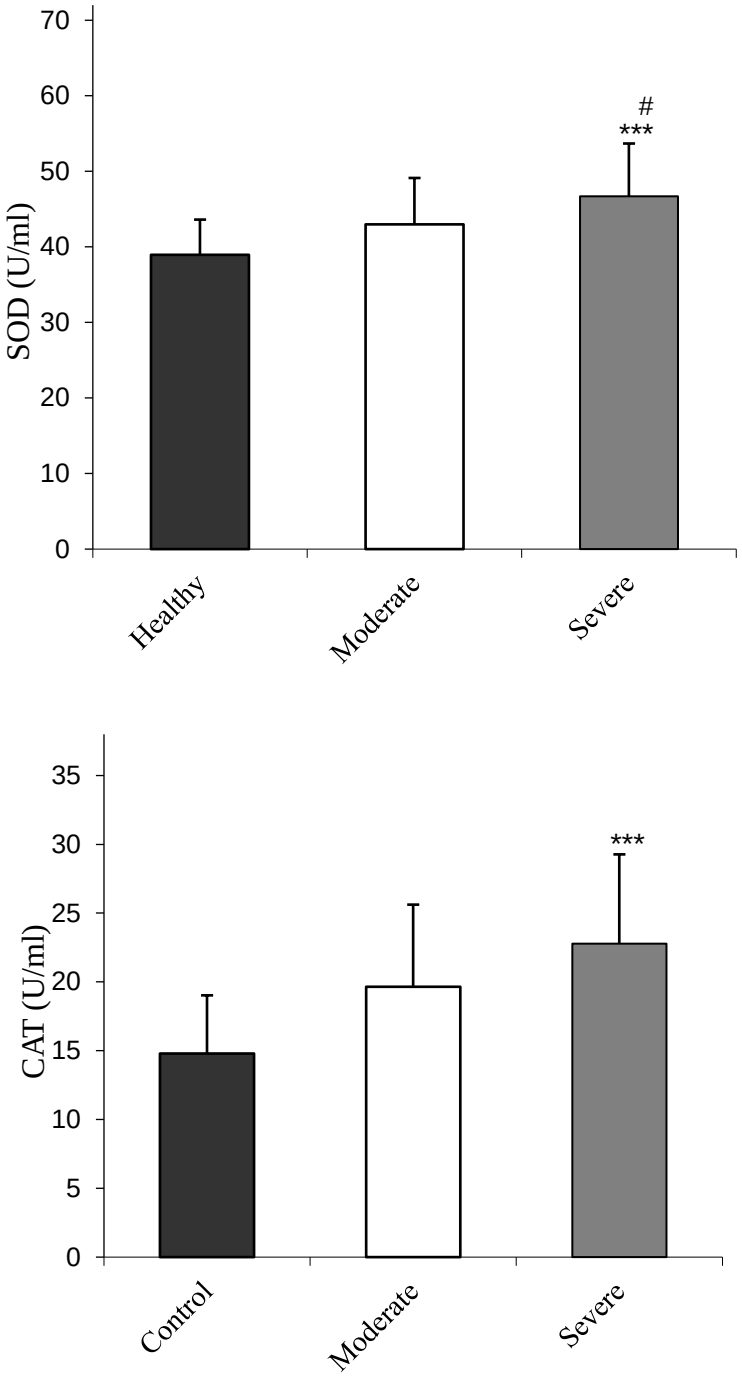

*$P$<0.05 vs. the healthy group.

**Figure 2.** Serum glutathione (GSH) and malondialdehyde (MDA) levels among the healthy, moderate and severe COVID-19 patients. Values are expressed as mean±SD (n=30).



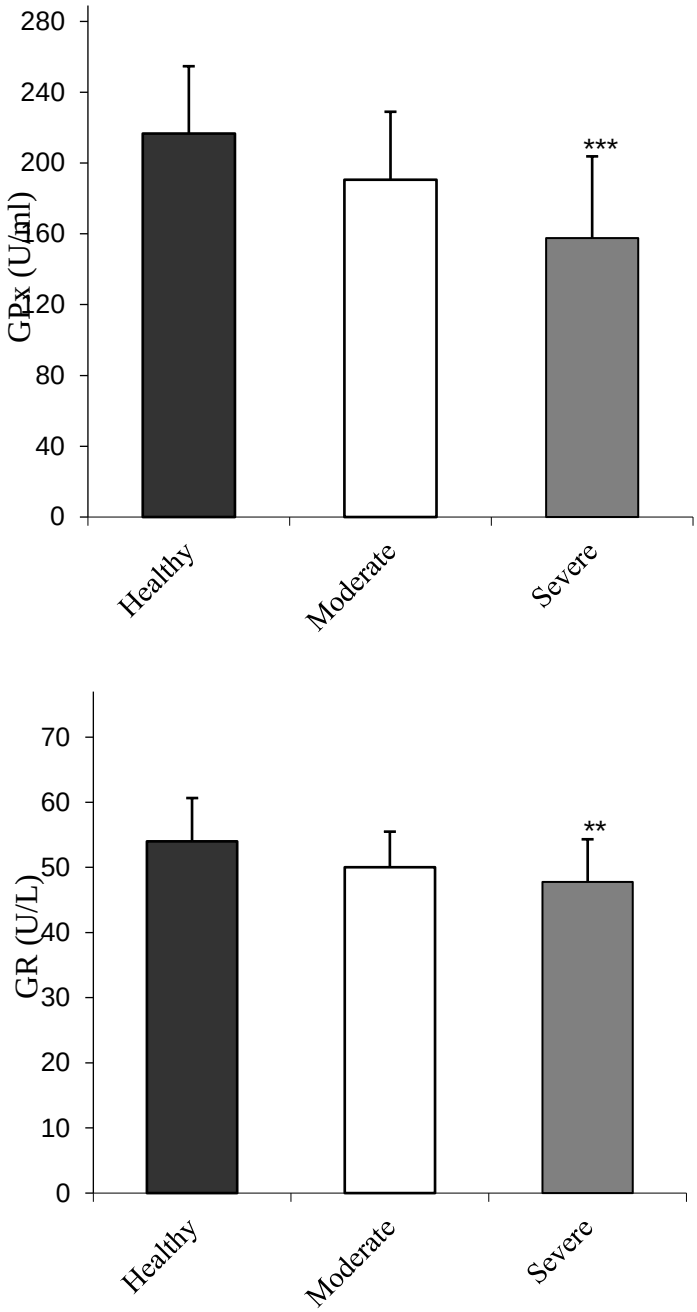

$^{*}P<0.05$, $^{**}P<0.01$ and $^{***}P<0.001$ vs. the healthy group and $^{\#}P<0.05$ vs. moderate COVID-19 patients.

**Figure 3.** Serum superoxide dismutase (SOD) and catalase (CAT) activities among the healthy group, moderate and severe COVID-19 patients. Values are expressed as mean±SD (n=30).




$^{*}P<0.05$, $^{**}P<0.01$ and $^{***}P<0.001$ vs. the healthy and $^{\#}P<0.055$ vs. moderate COVID-19 patients.

**Figure 4.** Serum glutathione peroxidase (GPx) and glutathione reductase (GR) activities among the healthy, moderate and severe COVID-19 patients. Values are expressed as mean±SD (n=30).




*$P$<0.05, **$P$<0.01 and ***$P$<0.001 vs. healthy and ##$P$<0.05 vs. moderate COVID-19 patients.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# ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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**Блок 3. Метаданные статьи**

SEVERITY-RELATED DIFFERENCES ON RESPONSE OF ANTIOXIDANT DEFENSE SYSTEM IN COVID-19 PATIENTS

**Сокращенное название статьи для верхнего колонтитула:**

OXIDATIVE STRESS AND SEVERITY OF COVID 19 INFECTION

**Keywords:** COVID-19, Severity of disease Oxidative stress, Antioxidant enzymes, Lipid peroxidation, Serum.

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**Блок 3. Метаданные статьи**

# РОЛЬ ТЯЖЕСТИ ЗАБОЛЕВАНИЯ НА ОТВЕТ СИСТЕМЫ АНТИОКСИДАНТНОЙ ЗАЩИТЫ У ПАЦИЕНТОВ С COVID-19

**Сокращенное название статьи для верхнего колонтитула:**

ОКИСЛИТЕЛЬНЫЙ СТРЕСС И ТЯЖЕСТЬ COVID-19

**Ключевые слова**: COVID-19, Тяжесть заболевания, Окислительный стресс, Антиоксидантные ферменты, Перекисное окисление липидов, Сыворотка крови

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