IJKD KIDNEY DISEASES

Examining the Association between Oxidative Stress Markers and the Severity of Symptoms in Individuals with COVID-19 and Healthy Individuals

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Introduction. The association between inflammation and oxidative stress in COVID-19 patients is well documented. The primary objective of the present study was to evaluate the levels of oxidative stress markers in COVID-19 patients compared to the healthy individuals.

Methods. In this case-control study, a comprehensive evaluation was conducted on 45 individuals, comprising 30 patients diagnosed with COVID-19 and 15 in a healthy control. COVID-19 patients were divided into two groups: mild and severe, based on clinical severity. In addition to standard laboratory tests like ESR, serum levels of oxidative stress markers were measured, including total protein, total antioxidant capacity, total oxidant status, carbonylated protein content, glutathione reductase enzyme, and catalase activity.

Results. ESR levels were significantly elevated in the severe group compared to the mild group. However, no significant differences were observed in the levels of oxidative stress markers between mild and severe COVID-19 patients. Compared to healthy controls, COVID-19 patients exhibited a significant decrease in total protein levels ($P < .0001$), and significant increases were observed in serum total antioxidant capacity (TAC) ($P < .0001$) and total oxidant status (TOS) ($P = .002$).

Conclusion. Oxidative stress markers exhibit a substantial rise in patients with COVID-19, suggesting a potential role in the progression of the disease. Implementing strategies to prevent oxidative stress may offer clinical advantageous in managing COVID-19 patients.

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INTRODUCTION

Coronavirus disease (COVID-19) is a multifaceted condition caused by the SARS-CoV-2 virus. It arises from the intricate interplay between the virus and host cells, triggering the activation of the immune response. In December 2019, medical professionals working at hospitals in Wuhan, China, observed a sequence of atypical pneumonia cases caused by a new beta coronavirus. On January 12, 2020, the World Health Organization (WHO) designated the initial name for this virus as 2019. Within a day of its confirmation, Chinese scientists shared the viral genome sequence, facilitating a rapid global research response.[1] Common clinical manifestations of SARS-CoV-2 infection include fever, fatigue, and an unproductive or dry cough.[2] Some individuals may experience symptoms such as nasal congestion, rhinorrhea, throat discomfort, or gastrointestinal disturbances, including diarrhea. In severe cases, the infection can progress to acute respiratory distress syndrome (ARDS), renal dysfunction, metabolic acidosis, septic shock, coagulopathy, and death, approximately one week after the symptom onset.[3,4]

The role of oxidative stress in inflammatory processes is significant.[5] A hypothesis suggests a correlation between oxidative stress and the pathogenesis of SARS-CoV-2 infection.[6] Key mechanisms linking oxidative stress to disease include elevated redox signaling, activation of inflammatory factors, and DNA damage.[7] Immune cells employ a substantial respiratory burst, generating reactive oxygen species (ROS) to eliminate invading pathogens. Studies have demonstrated that excessive production of ROS can directly harm host cells, resulting in direct lung injury during COVID-19.[8] Consequently, pulmonary impairment and multiple organ dysfunction syndromes (MODS) following the cytokine storm in COVID-19 could potentially be attributed to heightened oxidative stress and subsequent activation of the innate immune system. The interplay between the proinflammatory cytokines and oxidative stress is an area of investigation. Several viruses induce oxidative stress to facilitate their replication within the host cell.[9] In contrast to other coronaviruses, SARS-CoV-2 exhibits several unique characteristics such as higher infectivity than MERS-CoV and elevated inflammatory factors in severely ill patients.[10] In high-risk individuals, including the elderly and those with obesity or diabetes mellitus, the virus can initiate a series of rapid biological reactions driven by elevated ROS levels, ultimately resulting in respiratory failure requiring ventilatory support or, in severe cases, increased mortality.[11]

The presence of oxidative stress has been linked to the severity of various diseases. Oxidative stress contributes to the aging process and is observed in certain chronic conditions like diabetes mellitus, cancers, hypertension, coronary artery disease, and specific infections, especially those caused by RNA viruses like coronavirus.[12] Recent research indicates that oxidative stress plays a crucial role in exacerbating the severity of COVID-19 among specific individuals. It is closely linked to pulmonary impairment, cytokine storms, and the development of viral sepsis resulting from SARS-CoV-2 infection.[13] The detrimental effect of ROS on the performance of pulmonary and red blood cells is considered as the primary contributor to hypoxic respiratory failure in the most critical cases of COVID-19.[11] It was demonstrated by Yaghoubi *et al.* that individuals with COVID-19 may exhibit a reduction in their total antioxidant capacity (TAC).[14] Furthermore, they suggested that these alterations in the laboratory results of infected individuals could serve as a predictive factor for the severity of COVID-19. According to a separate investigation by Ivan Cekerevac *et al.*, it was found that in severe cases of COVID-19, the concentration of superoxide anion radicals was significantly elevated compared to those with moderate severity.[15] The evident role of oxidative stress in the pathogenesis of respiratory syncytial virus and potentially other viruses involving pulmonary system suggest that antioxidant interventions present a logical strategy for managing lower respiratory tract infections caused by diverse respiratory viral pathogens.[16] Given the significance of the subject matter, the current research was conducted to investigate the correlation between markers of oxidative stress and clinical status experienced by individuals with coronavirus and healthy individuals.

MATERIALS AND METHODS

This case-control study aimed to investigate oxidative stress markers in 30 patients with COVID-19 and 15 healthy controls who attended to Dr. Labbafinejad Hospital, Tehran, Iran, in 2021.

The case group included patients with mild or severe COVID-19 while the control group consisted of healthy individuals.

Inclusion criteria for the case group involved individuals over 18 years, with a positive polymerase chain reaction (PCR) test for SARS-CoV-2 from a nasal/ pharyngeal sample and evidence of lung involvement consistent with COVID-19. Exclusion criteria were failure to provide informed consent and recent usage of antioxidant supplements (e.g., vitamin C, vitamin E, coenzyme Q10). A total of 45 participants were recruited and divided into three equal groups (n = 15 per group), based on the convenience sampling method, consisted of: 1) Mild COVID-19 group: admitted to the ward. 2) Severe COVID-19 group: admitted to the intensive care unit (ICU). 3) Control group: healthy individuals over the age of 18 with no history of COVID-19 and matched to the patients' groups.

Sampling and Data Collection

Sampling was performed on patients who were experiencing acute phases of illness and individuals who did not display respiratory symptoms.. Patients selection was based on the diagnostic criteria for COVID-19. Moreover, the control group consisted of individuals who tested negative for SARS-CoV-2 PCR. These individuals had no history of respiratory ailments or other underlying medical conditions.

After evaluating the clinical conditions based on WHO ordinal scale for COVID-19,[17] and observing the laboratory and paraclinical findings, including CT scan results, a decision was made to admit the patients with mild disease to ward and those with severe disease to ICU.

Measurement of oxidative stress indicators

The Enzyme-linked immunosorbent assay (ELISA) method was utilized to measure the oxidative stress markers. These measurements were conducted across various groups and compared to the control group. The ELISA technique was employed to quantify the levels of target proteins, while a spectrophotometer was utilized to determine the protein concentration. The following sections outline the procedural steps involved in this analysis.

The blood levels of total protein, total oxidant capacity (TAC), total oxidant status (TOS), carbonyl protein concentration, glutathione reductase enzyme, and catalase activity were assessed using commercially available ELISA kits according to the manufacturer's instructions. (Zell Bio GmbH, Veltlinerweg42, and 89072 Ulm, Germany).

Data collection tools

A checklist was employed as the data collection tool for this project. The checklist was designed to collect the necessary information, including demographic characteristics, clinical observations, and laboratory findings.

Ethical considerations

The primary focus of this study was to prioritize the health and safety of the participants throughout the research process and beyond. The research was designed and implemented by individuals possessing the essential clinical expertise and skills, with a strong emphasis on safeguarding the health and welfare of the participants. Informed and voluntary consent was obtained from all participants, and the study findings were published with utmost honesty, precision, and comprehensiveness. This research received ethical approval from the ethics committee of Shahid Beheshti University of Medical Sciences, with the assigned ethics code (IR.SBMU.12543) and clinical trial code (NCT04375137).

Data analysis

Data were analyzed using SPSS software version 23. Continuous data were described using the median and interquartile range (IQR). The non-parametric Mann-Whitney U test was employed to compare the laboratory findings and oxidative stress markers between mild and severe COVID-19 groups. Furthermore, the non-parametric Kruskal-Wallis test was utilized to compare the oxidative stress markers between individuals with COVID-19 and healthy subjects. A significance level of $P < .05$ was considered statistical significance for all tests.

RESULTS

The current study involved 45 individuals (26 males and 19 females) with a mean age of 42 ± 11 years (range: 20 to 85 years). Table 1, compares the laboratory findings of patients with mild and severe COVID-19. Among the analyzed parameters, a significant difference was observed in the erythrocyte sedimentation rate (ESR)

Table 1. Comparison of laboratory results in individuals diagnosed with COVID-19

Variable	Non-severe (n=15)	Sever (n=15)	*P*
WBC (per/μL)	5300 (3600-10300)	6900 (5400-12000)	.089
PMN (per/μL)	75 (68-88)	80 (70-85)	.838
Lymph (per/μL)	18 (10-28)	15 (10-27)	.806
Hb (g/dL)	11.90 (10.50-14.4)	13.10 (11.50-13.7)	.624
PLT (per/μL)	157000 (8700-193000)	145000 (129000-209000)	.567
AST (U/L)	31 (16-40)	36 (31-41)	.116
ALT (U/L)	31 (18-37)	41 (22-45)	.305
Bilirubin Total (mg/dL)	0.7 (0.5-1.20)	0.75 (0.69-0.93)	.847
Bilirubin Direct (mg/dL)	0.2 (0.2-0.3)	0.3 (0.2-0.4)	.290
ESR (mm/h)	40.5 (29.7-47)	58 (41-67)	.012
CRP (mg/dL)	66 (45-89)	98 (57-120)	.126
LDH (U/L)	412 (302-539.75)	460 (431-689)	.102
Urea (mg/dL)	41 (36-163)	100 (68-124)	.050
Cr (mg/dL)	1.23 (1.05-2.5)	2.30 (1.4-2.6)	.106
Alb (g/dL)	3.6 (3.4-4)	3.4 (3.1-3.7)	.161

values between the two groups of patients (mild vs. severe) ($P = .012$). Specifically, patients with severe disease exhibited significantly higher ESR levels than those with the mild disease (58 vs. 40.5 mm/h). However, no significant differences were observed in the other parameters between the two COVID-19 groups.

As shown in Table 2, the levels of oxidative stress markers including, TAC, TOS, carbonylated protein content, glutathione reductase enzyme, catalase activity, and total protein, did not differ significantly between the mild and severe COVID-19 patient groups ($P < .05$).

A comparison of oxidative stress markers among two groups of patients and a control group is detailed in Table 3. It was observed that individuals with COVID-19 exhibited significantly lower levels of total protein ($P < .001$) and carbonylated protein content ($P = .045$) compared to healthy subjects. Conversely, TAC ($P < .001$), TOS ($P = .002$), and catalase activity ($P < .001$) were significantly higher in patients with COVID-19. However, there were

Table 2. Comparison of the markers of oxidative stress in COVID-19 patients

Variable	Infected people		*P*
	Mild (n=15)	Severe (n=15)	
Total protein (g/dL)	5.95 (5.56-6.31)	5.88 (5.10-6.62)	.935
Total antioxidant capacity (TAC) (unit)	258 (177-363)	306 (228-444)	.148
Total oxidant status (TOS) (unit)	13 (8-19.2)	8.8 (8.60-13.4)	.250
Carbonylated protein content (nmol/mg)	151 (112-176)	151 (138-176)	.902
glutathione-disulfide reductase (GSR) enzyme (IU)	2.20 (1.60-3.20)	2.30 (1.90-2.60)	.683
Catalase activity (MU/L)	651 (477-1089)	822 (696-996)	.305

Table 3. Post- hoc Kruskal-Wallis analysis of oxidative stress markers in the studied groups

Variable	Infected patients		Healthy individuals (n=15)	*P*
	Mild (n=15)	Severe (n=15)		
Total protein	5.95 (5.56-6.31)	5.88 (5.10-6.62)	7.41 (6.94-7.72)	< .0001
Total antioxidant capacity (TAC)	258 (177-363)	306 (228-444)	150 (99-177)	< .0001
Total oxidant status (TOS)	13 (8-19.2)	8.8 (8.60-13.4)	6.10 (4.30-8.10)	.002
Carbonylated protein content	151 (112-176)	151 (138-176)	117 (98-127)	.045
glutathione-disulfide reductase (GSR) enzyme	2.20 (1.60-3.20)	2.30 (1.90-2.60)	1.90 (1.50-2.10)	.127
Catalase activity	651 (477-1089)	822 (696-996)	2598 (2412-3300)	< .0001

no notable differences in the levels of glutathione reductase enzyme among the three groups (P = .127) (Table 3).

DISCUSSION

The findings of the present study revealed a correlation between inflammatory factors and severity of COVID-19. Patients with severe disease exhibited a notable increase in ESR levels compared to those in the mild disease (58 mm/h versus 40.5 mm/h). Although C-reactive protein (CRP) levels displayed higher in the severe group (98 mg/l versus 66 mg/l), this difference was not statistically significant. These findings align with previous research, witch reported elevated inflammatory indicators, such as ESR and CRP, in individuals with more severe disease.[18] In the present study, it was noted that there was no significant difference in the levels of oxidative stress markers between patients with mild and severe COVID-19. However, compared to the control group, there was a substantial increase in TAC, TOS, and catalase activity. These inherent antioxidant mechanisms protect cells effectively against oxidative damage resulting from free radical generation due to diverse conditions, including viral infections.[19,20] ROS are produced during cellular metabolism and play crucial roles in multiple pathways, including signal transduction, metabolism, cell differentiation, proliferation, and apoptosis. Furthermore, ROS actively controls infection, serving as a protective mechanism for host cells.[21] However, excessive ROS production during viral infection, disrupts redox homeostasis and overwhelm host defense mechanisms, which can influence cellular responses and the pathogenesis of the viral infection.[22] In this regard, incrementing total antioxidant capacity (TAC) is a defensive mechanism for combatting oxidative damage induced by excessive ROS. This increase primarily stems from non-enzymatic antioxidants, including albumin, glutathione, ascorbic acid, alpha-tocopherol, and uric acid.[20,23] Furthermore, the regulation of oxidative damage also encompasses the antioxidant activity of catalase, superoxide dismutase, and glutathione-dependent enzymes in the serum.[23]

Endogenous production of oxidant molecules occurs naturally within organisms, while external sources also contribute to their presence. The electron transport chain and various oxidase enzymes, such as xanthine oxidase, glycolate oxidase, and monoamine oxidases, serve as primary origins of endogenous ROS.[24] Our findings revealed that COVID-19 patients exhibited elevated levels of total antioxidant capacity (TAC), although a trend suggested that the increase might be greater in severe cases, the difference between severity groups was not statistically significant. These findings align with previous research on patients with severe COVID-19;[20,25] and support the notion that TAC and TOS may serve as prognostic indicators of disease severity and outcome in affected patients.[26] A decrease in total protein levels was observed notably in patients categorized as severe or critical COVID-19 compared to healthy controls.

Hospitalized COVID-19 patients exhibit diminished total protein and albumin levels and elevated blood urea nitrogen levels.[27] Protein carbonylation, an oxidation process, is an irreversible mechanism that tags proteins for degradation through the proteasomal pathway. This process is of significant importance as a biological marker for assessing oxidative stress.[28] Consistent with our study's findings, Aryal *et al.* reported a significantly elevated protein carbonylation in plasma samples obtained from both acute and convalescent COVID-19 patients compared to the healthy controls. The primary focus of their study centered on investigating oxidative stress caused by metal catalysts and its effect on protein oxidation.[28] The generation of ROS and subsequent protein oxidation are well-known consequences of metal-catalyzed oxidation (MCO) reactions. Redox-active metals, notably copper and iron, exhibit proficient mechanisms in facilitating metal-catalyzed protein oxidation.[29] MCO triggers protein carbonylation and the formation of dihydroxyphenylalanine in recombinant proteins. Consequently, the presence of redox-active free metal ions in plasma samples of COVID-19 patients may play a crucial role in augmenting protein carbonylation.[27] Through molecular docking analysis, it has been demonstrated that specific surface proteins of SARS-CoV-2 interact with heme on hemoglobin, leading to the extraction of iron from porphyrin and subsequent inhibition of heme metabolism.[30]

Concurrently, studies have documented elevated serum iron levels following SARS-CoV-2. This rise is hypothesized to result from hemoglobin degradation and subsequent iron release, processes

that can induce oxidative stress and promote proteins oxidation. Furthermore, the surface-expressed E protein of SARS-CoV-2 can bind with iron or heme, and it contains conserved regions resembling cytochrome C oxidase, Fe-SOD, catalase, and peroxidase domains. Upon binding to Heme, the E protein can produce damaging ROS such as superoxide, hydrogen peroxide, and hydroxyl radicals, that can injure host cells or tissues near the viral surface.[31] Superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase are the primary antioxidant enzymes defense against ROS and reactive nitrogen species.[32] As indicated in our investigation, COVID-19 patients exhibited a substantial rise in catalase activity compared to healthy individuals. Although there was an elevation in the levels of the glutathione reductase enzyme among patients with COVID-19, this difference was not statistically significant compared to the levels observed in healthy individuals, which may be influenced by sample size. Consistent with our findings, other studies have reported similar observations; for instance, Lage *et al.* documented increased activity of catalase and superoxide dismutase in the plasma of COVID-19 patients across all severity, compared to healthy individuals.[33] Similarly, Cekerevac *et al.*, found that catalase activity was significantly higher in patients with severe COVID-19 than in those with mild and moderate disease.[34]

CONCLUSION

The findings of our study demonstrated the significant association between oxidative stress and COVID-19. The distinct levels of total protein biomarkers, TAC, TOS, carbonylated protein content, and catalase activity observed in patients with COVID-19, compared to healthy individuals, support this conclusion. Consequently, COVID-19 is associated with increased oxidative damage. Different approaches aimed at mitigating or averting oxidative stress could be beneficial in managing COVID-19.

DECLARATION OF INTEREST

There is no conflict of interest to declare.

CONSENT

Consent form was taken from all patients to participate in the study and publication.

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DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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