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Original Article

Assessment of the Pro-oxidant Antioxidant Balance (PAB) in COVID-19 Patients Compared to Healthy Subjects Referred to Masih Hospital

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Abstract

Background: Recent studies have reported that the increase in the pro-oxidant-antioxidant balance (PAB) in patients with COVID-19 is associated with the exacerbation of clinical manifestations of the disease. The underlying risk factors of these patients, including a history of chronic systemic diseases, also may be associated with PAB disorder. It seems that there should be a significant relationship between clinical disorders and laboratory factors with PAB disorder. This issue was evaluated in this study.

Methods: In this cross-sectional study, 105 patients referred to Masih Hospital in Tehran in 2021, including 58 subjects with COVID-19 infection and 47 as a control group, were studied. The subjects in this study were evaluated for PAB by the ELISA method.

Results: The mean value of PAB in individuals with and without COVID-19 was 72.77 ± 17.66 and 66.53 ± 14.30, respectively, which was significantly higher in COVID-19 patients ($P=0.049$). In patients with COVID-19, there was a significant correlation between PAB and plasma triglyceride level ($P=0.011$) and an inverse relationship between PAB level and blood sodium level ($P=0.047$). In the COVID-19 group, there was no significant relationship between PAB level and histories of hypertension, hyperlipidemia, diabetes, and ischemic heart disease.

Conclusion: The increase in PAB is quite evident in patients with COVID-19 compared to healthy individuals. There is a significant relationship between PAB and some laboratory markers in these patients such as blood triglyceride levels as well as decreased serum sodium. Therefore, it still seems that the activity of oxidative stress processes plays a role in the pathogenesis and exacerbation of COVID-19 disease and can be considered one of the therapeutic goals in these patients.

Keywords: COVID-19, Oxidative stress, Severity, Pro-oxidant antioxidant balance, Total antioxidant capacity

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Introduction

COVID-19 infection is caused by a virus called SARS-CoV-2 which belongs to the Coronaviridae family with a single-stranded positive-sense RNA that has spread rapidly around the world due to its remarkable genetic diversity and high recombination rate (1). The COVID-19 epidemic has caused over 545 886 835 cases and approximately 6 343 930 million deaths worldwide as of 22 June 2022 (2). In addition to infecting the respiratory system, COVID-19 can affect a variety of systems, including the cardiovascular, respiratory, gastrointestinal, nervous, and hematopoietic (3). Infected individuals may be asymptomatic or have mild to moderate symptoms, but approximately 15 % of cases with more severe clinical symptoms require hospitalization with a need for supplemental oxygen therapy, and an additional 5% develop acute respiratory distress syndrome (4). The clinical course of the disease can range from asymptomatic conditions to extensive respiratory involvement and even death. In addition, the course of the disease in children and adults appears to be quite different, and therefore it is not yet possible to predict the long-term prognosis of the disease at the time of diagnosis (5). Accordingly, a deep understanding of the pathogenesis of the disease is essential to predict outcomes, such as pneumonia, and thus provide the best treatment options to reduce hospitalization and mortality (6). Evidence suggests that the oxidative stress process may play a key role in the

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pathogenesis of the disease, as it has an important role in responses to infections (7). Numerous studies have shown that oxidative stress regulates the host immune system in a variety of viral diseases, including hepatitis B and C, herpes simplex virus, and influenza (8). Also, oxidative stress plays a major role in the pathogenesis of various lung diseases in children, such as pneumonia, asthma, bronchiolitis, cystic fibrosis, acute respiratory distress, and chronic neonatal lung disease (9). A review of published reports also confirms the strong association between oxidative stress and pathogenesis, severity, and mortality of patients with SARS-CoV (10). However, to date, a comprehensive study on changes in oxidative and antioxidant parameters and their role in the prognosis of COVID-19 disease has not been studied in detail.

Material and Methods

Patients, samples collection, and assays

The present paper is a cross-sectional study performed on 105 subjects referred to Masih Daneshvari hospital in Tehran, the capital of Iran, in 2021. Written informed consent was obtained from each patient. The subjects were divided into two groups consisting of 58 patients with COVID-19 and 47 patients as the healthy control group. Subjects without a history of COVID-19 disease and people who recovered from COVID-19 with a negative PCR test were selected as the control group. People with a history of smoking, alcohol consumption, and antioxidant supplements, including vitamin C, were excluded from the study. This study measured serum PAB levels via a colorimetric technique and enzyme-linked immune sorbent assay (ELISA). In addition to PAB levels, data from routine laboratory tests were also retrieved, such as liver enzyme levels (alanine transaminase [ALT] and aspartate transaminase [AST]), kidney function tests (blood urea nitrogen and creatinine), inflammatory parameters (CRP and ferritin), and D-dimer levels, as well as complete blood count, hemoglobin, white blood count (WBC), neutrophil count, lymphocyte count, and platelet count. Demographic characteristics and clinical information of patients, including age, gender, and underlying diseases (such as hypertension, diabetes, and ischemic heart disease) were extracted from patients' records and registered in a checklist. Serum was isolated from collected blood samples and kept at -80°C until assays.

ELISA test for determinate of serum PAB level

PAB levels were measured in patients' serum samples according to the instructions mentioned in previous studies (11). Standard solutions were prepared by mixing the exact ratio of 250 M H2O2 (0-100%) and 3 M uric acid and adding them to NaOH (10 M). To prepare TMB cation, 60 mg of TMB powder was dissolved in 10 mL of dimethyl sulfoxide (DMSO) and added to 20 mL of acetate buffer (0.05 M, pH 4.5). Then, 70 µL of freshly mixed chloramine T solution (100 mM) was added to the pre-prepared solution, shacked immediately, and incubated for two hours in the dark condition at room temperature (23-27°C). To prepare horseradish peroxidase solution, 25 units of peroxidase enzyme solution was mixed with 20 mL TMB cation, and the prepared mixture was divided into 1 mL microtubes and stored in -20. TMB working solution was prepared by gently mixing 200 µL of TMB/DMSO with 10 mL of acetate buffer (0.05 M, pH 5.8). To measure the level of PAB in the serum of patients' samples, 200 µL of the working solution was added to each well of the ELISA plate, then 10 µL of patient serum, distilled H2O (empty well), and standard solutions were added, and gently mixed, also plates were incubated at 37°C for 15 minutes under dark conditions. Then, 50 µL of 2 N HCl was added to each well as a stop solution, and a wavelength of 450 nm was used to measure PAB, although the reference wavelength was 620 nm or 570 nm. The PAB levels were shown in arbitrary HK (Hamidi-Koliakos) units according to the percentage of hydrogen peroxide assessed in the standard solution. Finally, the PAB values of unknown samples were calculated based on the values obtained from the standard curve.

Statistical analysis

Data analysis was performed using SPSS version 22 (IBM). The normal distribution of the quantitative data was checked using the Kolmogorov–Smirnov test. Due to the abnormality of the data distribution in this study, *t* test or Mann-Whitney nonparametric tests were employed to analyze the results. Spearman's correlation coefficient and chi-square tests were used to determine the relationship between the variables. P value < 0.05 was considered statistically significant.

Results

A total of 105 subjects, 47 healthy subjects and 58 patients with COVID-19, were included in this study. Of 58 patients with COVID-19, 25 (43.1%) were male, and 33 (56.9%) were female, while in the control group, 24 (51.1%) and 23 (48.9%) subjects were male and female, respectively. According to the results of the study, there was no statistically significant difference between the two groups in terms of gender ($P = 0.438$). The mean age in COVID-19 patients was 55.78 ± 15.89 years, while in the control group was 35.64 ± 8.13, which was a statistically significant difference between the two groups ($P < 0.001$). In terms of the prevalence of underlying diseases, frequency of hypertension, diabetes, ischemic heart disease, and hyperlipidemia in the group of patients with COVID-19 were thirteen (22.4%), six (10%), four (3.8%), and eight (7.6%) cases, respectively. In the control group, however, only six (12.8%) cases of hyperlipidemia were reported. In general, the prevalence of underlying diseases

in the group of COVID-19 patients was significantly higher than in healthy individuals ($P<0.05$). There were statistically significant differences between the two groups in terms of laboratory markers such as blood cell count, mean concentration of lipid profile, kidney function tests, liver enzymes, important ions, and inflammatory factors ($P<0.05$). Also, the mean concentration of D-dimer in COVID-19 patients was calculated to be 1449.95 ± 243.95, which has increased significantly but has not been studied in the control group. Tables 1 and 2 summarizes the demographic information, underlying diseases, and laboratory data of the two groups.

The mean serum level of PAB in COVID-19 patients and healthy individuals was 72.77 ± 17.66 and 66.53 ± 14.30, respectively, showing statistically significantly higher levels for COVID-19 patients ($P=0.049$). In patients with COVID-19 infection, the mean PAB in men and women was 71.87 ± 18.23 and 73.41 ± 16.76, respectively, with no significant difference between the two genders ($r=0.045$, $P=0.74$). Also, there was no correlation between patients' age and PAB levels ($r=0.039$, $P=0.788$). In patients with COVID-19, there was a significant direct correlation between the level of PAB and the level of triglycerides in the blood ($r=0.533$, $P=0.011$) and there was an inverse relationship between PAB level and blood sodium level ($r=0.533$, $P=0.011$) (Table 3). Besides, there was no statistically significant relationship between PAB levels in COVID-19 patients and any underlying diseases such as hypertension, hyperlipidemia, diabetes mellitus, and ischemic heart disease ($P>0.05$; Table 4).

Table 1. The demographic information, underlying diseases, and laboratory data of the two groups

Variable	COVID-19 patients	Healthy individuals	*P* value
Gender			0.438
Male	25 (43.1%)	24 (51.1%)	
Female	33 (56.9%)	23 (48.9%)	
Mean age	55.78 ± 15.89	35.64 ± 8.13	<0.001
Underlying disease			
Hypertension	13 (22.3%)	0 (0%)	<0.001
Diabetes mellitus	6 (10.3%)	0 (0%)	<0.001
Hyperlipidemia	2 (3.4%)	6 (12.8%)	0.135
Ischemic heart disease	4 (6.9%)	0 (0%)	<0.001

Table 2. Laboratory markers in patients with and without COVID-19

Variable	COVID-19 patients	Healthy individuals	*P* value
Mean WBC	8.4 ± 0.435	7.27 ± 1.9	0.055
Hemoglobin concentration	13.9 ± 1.93	14.57 ± 1.67	0.017
Mean platelet count	221 ± 79	55 ± 253	0.021
Percentage of neutrophils	78.42 ± 11.64	53.23 ± 9.34	0.001
Absolute number of neutrophils	11.29 ± 2.42	6.27 ± 1.13	0.001
Mean MCV	87.38 ± 6.04	86.31 ± 6.55	0.42
Mean ESR	43.73 ± 22.19	8.71 ± 13.43	0.001
Mean CRP	43.4 ± 31.05	1.20 ± 0.44	0.004
Ferritin concentration	646.51 ± 578.31	56.78 ± 31.69	0.001
Mean concentration of urea	41.64 ± 17.37	28.21 ± 9.02	0.001
Mean creatinine	1.17 ± 0.36	1.03 ± 0.14	0.017
HDL concentration	29.69 ± 8.61	38.63 ± 8.55	0.001
LDL concentration	84.45 ± 68.28	112.98 ± 29.08	0.014
LDH concentration	746.79 ± 368.73	286.00 ± 211.54	0.215
Calcium concentration	9.26 ± 0.55	9.87 ± 0.34	0.007
Phosphorus concentration	3.31 ± 0.06	13.3 ± 0.71	0.461
Sodium concentration	138.54 ± 2.73	140.88 ± 1.35	0.022
Potassium concentration	4.12 ± 0.47	4.06 ± 0.37	0.762
PT	13.54 ± 2.65	12.5 ± 0.5	0.391
PTT	32.04 ± 6.26	29.8 ± 1.48	0.432
INR	1.14 ± 0.25	1.06 ± 0.05	0.427
Serum AST concentration	41.67 ± 23.97	20.92 ± 4.7	0.004
ALT concentration	42.98 ± 37.01	25.21 ± 8.78	0.06
Cholesterol concentration	135.04 ± 39.13	176.07 ± 34.89	0.001
Triglyceride concentration	129.18 ± 78.41	121.76 ± 72.45	0.702
FBS concentration	165.88 ± 68.62	95.91 ± 11.29	0.006
Magnesium concentration	2.26 ± 0.26	2.2 ± 0.42	0.817

Discussion

Prooxidant activation or antioxidant inhibition plays a role in the pathophysiological mechanism of many diseases, including infectious ones (12). With the advent of the COVID-19 pandemic and the revelation of the role of inflammatory and oxidative processes in exacerbating the disease and predicting its adverse consequences, attention was drawn to the PAB imbalance (13). In this regard, recent studies have shown an increase in oxidative stress imbalance in patients with COVID-19 along with exacerbation of clinical manifestations of the disease, and studies are ongoing on this matter (14).

In the present study, it seems that there should be a significant relationship between clinical disorders and laboratory factors with PAB imbalance. The main finding of this study was that the serum level of PAB was higher in patients with COVID-19 compared to healthy individuals, which in line with previous evidence, indicates a significant relationship between the PAB level and COVID-19 disease. Therefore, it seems that the activity of pro-oxidants and the lack of antioxidants play an important role in the incidence, progression, and exacerbation of COVID-19 disease, and accordingly, the use of antioxidant supplements is effective in improving

Table 3. Correlation of PAB in COVID-19 patients with laboratory parameters

Variable	Correlation coefficient	*P* value
Mean WBC	0.084	0.54
Hemoglobin concentration	0.096	0.485
Mean platelet count	0.026	0.853
Percentage of neutrophils	-0.228	0.120
Absolute number of neutrophils	-0.1	0.497
Mean MCV	-0.013	0.931
Mean ESR	0.092	0.566
Mean CRP	0.050	0.717
Ferritin concentration	0.001	0.993
Mean concentration of urea	-0.030	0.826
Mean creatinine	-0.020	0.882
HDL concentration	-0.118	0.519
LDL concentration	0.223	0.228
LDH concentration	-0.158	0.342
Calcium concentration	0.310	0.055
Phosphorus concentration	-0.274	0.106
Sodium concentration	-0.275	0.047
Potassium concentration	-0.126	0.380
PT	-0.009	0.951
PTT	-0.123	0.388
INR	-0.185	0.177
Serum AST concentration	-0.024	0.862
ALT concentration	0.102	0.729
Cholesterol concentration	0.267	0.207
Triglyceride concentration	0.533	0.011
Magnesium concentration	-0.147	0.573

Table 4. Correlation of PAB with underlying diseases in COVID-19 patients

Variables		Mean PAB	*P* value
Gender	Male	71.87±18.23	0.74
	Female	73.41±16.76	
History of hypertension	Yes	74.78±20.83	0.633
	No	72.16±16.32	
History of diabetes mellitus	Yes	76.27±15.62	0.602
	No	72.34±17.54	
History of hyperlipidemia	Yes	58.9±7.21	0.252
	No	73.24±17.34	
History of heart disease	Yes	67.33±15.97	0.52
	No	73.15±17.34	

the symptoms of the disease.

In a study by Aykac et al, reductions in thiol/disulfide levels (which is a potent antioxidant) were confirmed in COVID-19 (15). In a study by Karkhanei et al, an increase in total oxidant status in COVID-19 patients was confirmed, especially in ICU patients. Also, there was a significant relationship between the level of oxidative stress and the percentage of arterial blood oxygen saturation, rate of fever, the length of hospital stay, and the prognosis of the disease (16). In a study by Pincemail et al, levels of vitamin C and antioxidant proteins, including thiol, glutathione, gamma-tocopherol, beta-carotene, and PAOT, were significantly lower in COVID-19 patients than in the healthy control group. In contrast, the copper/zinc ratio (as a representative of oxidative stress factors), as well as inflammatory factors such as CRP and myeloperoxidase in patients, was much higher than in healthy controls (17). In the study by Yaghoubi et al, the level of total antioxidant capacity in patients with COVID-19 was lower than in healthy individuals. On the other hand, a decreasing trend was observed in nitric oxide and superoxide dismutase levels in COVID-19 patients compared to healthy individuals (18). Finally, Muhammad et al reported that the levels of vitamins (A, C, and D), the levels of elements (selenium, zinc, magnesium, and copper), glutathione, superoxide dismutase, and catalase in patients with COVID-19 were much lower than in the control group. Among the oxidative markers, the level of 8-iso-prostaglandin F2α (8-iso-PGF2α) was significantly higher in patients with COVID-19, but the level of malondialdehyde (MDA) in COVID-19 patients was much lower than in healthy individuals (19).

In the present study, elevated PAB levels were associated with some laboratory markers, such as blood triglyceride and sodium levels. According to a study by Dudani et al on plasma levels of triglycerides as primary markers of oxidative stress, there is a significant relationship between plasma levels of triglycerides and GSH (as markers of oxidative stress) (20). A study by Manasa and Chandru demonstrated a significant relationship between plasma levels of triglycerides and MDA in lichen planus patients. In studies that have been done to date, no significant relationship has been found between serum sodium levels and oxidative stress, and the assertion of this relationship needs to be investigated in a larger sample size (21).

In the present study, underlying diseases did not affect PAB levels; it was probably due to the control of underlying diseases, as well as the effect of the drugs used by these patients in reducing oxidative stress. For example, many drugs, such as enalapril and losartan, which are prescribed for hypertension and diabetes patients, also affect oxidative stress and inflammatory markers (22). A study by Aghaei Shahsavari et al, aiming to investigate the effects of enalapril and losartan on acute phase protein and total antioxidant protein in renal transplant recipients with polymorphisms of the renin-angiotensin system (RAS), reported that enalapril and losartan decreased acute phase protein levels and increased total antioxidant levels regardless of the genotypes of the RAS. Also, drugs used to treat hyperlipidemia, including atorvastatin, reduce oxidative stress levels (23). A study by Faghihi et al exhibited that atorvastatin reduces neuropathy associated

with hyperglycemia and oxidative stress (24).

Therefore, it seems that pro-oxidant-oxidant imbalance plays a role in the pathogenesis and exacerbation of COVID-19 disease and can be considered as one of the therapeutic goals in these patients. The present study also encountered limitations, including non-repetition of PAB level tests, inconsistency of control group and patients in terms of underlying diseases, not evaluating the relationship between PAB levels and disease severity, ICU hospitalization, arterial blood oxygen level, length of hospital stay, and disease prognosis.

Conclusion

In conclusion, according to the findings of the present study, an increase in serum PAB levels in COVID-19 patients compared to healthy individuals is evident. There is a significant relationship between the PAB level and some laboratory markers, such as triglyceride level, in addition to serum sodium reduction in COVID-19 patients. Therefore, the activity of the oxidative stress pathway in the pathogenesis of COVID-19 disease is emphasized.

Authors' Contribution

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Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

The study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.MSP.REC.1400.398).

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