E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.01.760

Research Article

Pathophysiological Complications of Persistent Oxidative Stress Following COVID-19

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Received: 13.04.2026, Revised: 09.06.2026, Accepted: 16.06.2026

ABSTRACT

Background: Persistent oxidative stress may contribute substantially to post-COVID-19 complications through sustained inflammation, endothelial dysfunction, mitochondrial impairment, lipid peroxidation and depletion of antioxidant defenses. However, the relationship between persistent redox imbalance and multisystem pathophysiological consequences following recovery from COVID-19 remains incompletely characterized. The present study evaluated oxidative stress biomarkers and their association with pulmonary, cardiovascular, metabolic and functional complications following SARS-CoV-2 infection.

Methods: A comparative cross-sectional study was conducted among 120 adults, comprising 80 individuals with persistent post-COVID-19 symptoms 3–12 months after laboratory-confirmed SARS-CoV-2 infection and 40 age- and sex-matched healthy controls. Serum malondialdehyde (MDA), total oxidant status (TOS), total antioxidant capacity (TAC), superoxide dismutase (SOD), reduced glutathione (GSH), catalase (CAT), C-reactive protein (CRP), interleukin-6 (IL-6), fasting glucose and lipid profile were measured. Oxidative Stress Index (OSI) was calculated as TOS/TAC ×100. Pulmonary function was assessed using spirometry, while persistent fatigue, dyspnea and exercise intolerance were documented using standardized clinical assessment. Comparisons were performed using independent *t*-test or Mann–Whitney U test, and correlations were assessed using Pearson/Spearman correlation analysis.

Results: Post-COVID-19 participants demonstrated significantly greater oxidative stress than healthy controls, with higher MDA (4.82±1.21 vs. 2.91±0.74 nmol/mL), TOS (38.6±9.4 vs. 21.8±5.7 μmol H_2O_2 equivalent/L) and OSI (5.74±1.82 vs. 2.61±0.83; all $p<0.001$). TAC was significantly reduced (0.67±0.16 vs. 1.04±0.21 mmol Trolox equivalent/L), accompanied by lower SOD (71.4±15.8 vs. 96.7±18.3 U/mL), CAT (42.8±9.7 vs. 58.9±11.4 U/mL) and GSH (4.21±1.03 vs. 6.18±1.24 μmol/L; all $p<0.001$). Inflammatory markers were also significantly elevated, including CRP (6.8±3.4 vs. 2.1±1.2 mg/L) and IL-6 (8.7±4.1 vs. 3.2±1.4 pg/mL; $p<0.001$). Among post-COVID participants, 46.3% had persistent dyspnea, 52.5% reported fatigue and 31.3% demonstrated reduced pulmonary function. OSI showed positive correlations with CRP ($r=0.61$), IL-6 ($r=0.57$), MDA ($r=0.68$) and severity of dyspnea ($r=0.49$), while TAC correlated inversely with CRP ($r=-0.52$) and fatigue scores ($r=-0.45$) ($p<0.001$ for all). Participants with high OSI had a 3.42-fold greater likelihood of persistent functional complications than those with lower OSI (95% CI: 1.58–7.39; $p=0.002$).

Conclusion: Persistent oxidative stress following COVID-19 is associated with substantial depletion of antioxidant defenses, increased lipid peroxidation and sustained systemic inflammation. The strong relationship between oxidative imbalance and pulmonary as well as functional complications suggests that persistent redox dysregulation may represent an important pathophysiological mechanism underlying post-COVID-19 morbidity. Oxidative stress biomarkers, particularly OSI, MDA and TAC, may have potential utility for identifying individuals at increased risk of persistent post-COVID complications and may provide targets for future therapeutic interventions.

Keyword: Covid-19, Oxidative Stress Biomarkers, Pulmonary Complications, Cardiovascular Complications, Sars-Cov-2 Infection.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is primarily a respiratory infection but may produce extensive systemic disturbances involving the cardiovascular, metabolic, neurological, renal and immune systems. Although most patients recover from the acute infection, a substantial proportion develop persistent symptoms collectively referred to as post-COVID-19 condition or long COVID. Common manifestations include fatigue, dyspnea, exercise intolerance, cognitive dysfunction, chest discomfort and cardiovascular abnormalities, indicating that the pathological consequences of SARS-CoV-2 infection may persist well beyond viral clearance. Persistent immune activation, endothelial dysfunction, altered cellular metabolism and tissue injury have been proposed as important mechanisms underlying these prolonged manifestations. [1, 2]

Oxidative stress is increasingly recognized as an important component of SARS-CoV-2-induced cellular injury. It develops when the generation of reactive oxygen species (ROS) and reactive nitrogen species exceeds the capacity of endogenous antioxidant systems to neutralize them. Excessive ROS can induce lipid peroxidation, protein oxidation, DNA damage and mitochondrial injury, thereby impairing normal cellular function. Clinical investigations have demonstrated alterations in total oxidant status (TOS), total antioxidant capacity (TAC) and glutathione metabolism in patients with COVID-19, with the magnitude of redox imbalance being associated with disease severity and clinical outcomes.[1] SARS-CoV-2 infection can also directly disturb intracellular glutathione homeostasis, producing depletion of reduced glutathione (GSH), increased oxidized glutathione and protein glutathionylation.[2] These changes may compromise the ability of cells to control oxidative injury and may provide a biochemical basis for prolonged redox dysregulation following recovery.

The interaction between oxidative stress and inflammation is particularly important in determining the persistence of COVID-19-related tissue damage. Excessive ROS can activate inflammatory signalling pathways, while inflammatory cells and cytokines can further stimulate ROS production, establishing a self-perpetuating cycle of oxidative stress and inflammation. A systematic review by Tsermpini et al. emphasized the importance of disrupted antioxidant defenses, including glutathione, superoxide dismutase and catalase systems, in COVID-19 pathogenesis.[3] Persistent immune activation and tissue-specific inflammatory responses have also been implicated in long COVID, with pathological changes extending beyond the respiratory system.[4] Thus, prolonged oxidative stress may not simply represent a consequence of inflammation but may actively participate in maintaining chronic post-infectious pathology.

The respiratory system may be particularly vulnerable to persistent oxidative injury because of its large surface area, high oxygen exposure and intense interaction with inflammatory and immune cells. Pulmonary complications following COVID-19 include persistent interstitial abnormalities, impaired pulmonary function and fibrotic changes. Siekacz et al. demonstrated associations between long-term pulmonary complications after COVID-19 and alterations in mitochondrial regulatory proteins, together with increased inflammatory mediators including interleukin-6 and tumour necrosis factor-α.[5] These observations suggest that mitochondrial dysfunction and oxidative stress may contribute to continuing pulmonary injury after resolution of acute SARS-CoV-2 infection. Oxidative damage to pulmonary epithelial and endothelial cells may further promote abnormal tissue repair, vascular dysfunction and fibrotic remodelling.

Mitochondria represent another important link between persistent oxidative stress and multisystem post-COVID complications. Mitochondria are both major sources and targets of ROS, and excessive oxidative stress can impair mitochondrial respiratory function, mitochondrial DNA integrity, ATP production and cellular energy metabolism. Georgieva et al. described a close relationship between oxidative stress, mitochondrial dysfunction, inflammation and endothelial injury in COVID-19 and its post-acute complications.[6] More recent evidence indicates that mitochondrial dysfunction may persist in individuals with long COVID, potentially contributing to fatigue, exercise intolerance, metabolic abnormalities and impaired tissue function.[7] Structural mitochondrial abnormalities, altered

mitochondrial dynamics, disturbed mitophagy and changes in mitochondrial biomarkers have also been demonstrated in patients with long COVID, supporting the possibility that persistent mitochondrial injury contributes to chronic symptoms.[8]

Oxidative stress may additionally promote endothelial dysfunction and a prothrombotic state. Excess ROS can reduce nitric oxide bioavailability, increase endothelial permeability and activate inflammatory and coagulation pathways. Persistent endothelial injury may therefore contribute to microvascular dysfunction, impaired tissue perfusion, thrombo-inflammatory responses and cardiovascular manifestations after COVID-19. The interaction between mitochondrial ROS production, endothelial dysfunction and inflammatory signalling provides a plausible mechanism through which a predominantly respiratory viral infection can produce prolonged systemic consequences. [6], [7] Furthermore, the persistence of oxidative and inflammatory abnormalities after the acute phase suggests that some patients may remain biologically vulnerable even when conventional markers of active infection have resolved.

Recent clinical evidence has strengthened the association between oxidative stress and post-acute sequelae of COVID-19. Coronel et al. reported persistent alterations in oxidative-stress and inflammatory biomarkers among individuals with post-acute sequelae, including abnormalities in antioxidant enzymes, glutathione-related parameters and protein oxidation, together with increased inflammatory cytokines. [9] These findings support the concept that persistent oxidative imbalance may contribute to the pathophysiology of long COVID rather than being restricted to the acute phase of SARS-CoV-2 infection. However, the relationship between sustained oxidative stress and specific pulmonary, metabolic, inflammatory, mitochondrial and functional complications remains incompletely defined.

Therefore, the present study was designed to investigate the pathophysiological complications of persistent oxidative stress following COVID-19, with particular emphasis on alterations in oxidative and antioxidant biomarkers and their relationship with systemic inflammation, pulmonary dysfunction and persistent post-COVID manifestations. A better understanding of these mechanisms may help identify individuals at increased risk of prolonged complications and may provide a basis for the future development of oxidative-stress-based biomarkers and therapeutic strategies.

MATERIALS AND METHODS

A comparative cross-sectional study was conducted to evaluate the pathophysiological complications associated with persistent oxidative stress following COVID-19. The study included 120 adult participants aged 30–70 years, divided into two groups: 80 patients with a documented history of SARS-CoV-2 infection and persistent post-COVID-19 manifestations for 3–12 months after recovery, and 40 apparently healthy age- and sex-matched controls without a previous history of COVID-19. Previous COVID-19 infection was confirmed through a positive reverse-transcription polymerase chain reaction (RT-PCR) or documented positive SARS-CoV-2 antigen test. Participants with active infection, chronic pulmonary disease, malignancy, chronic kidney or liver disease, autoimmune disorders, uncontrolled diabetes mellitus, or current use of antioxidant supplements were excluded to minimize potential confounding factors. Written informed consent was obtained from all participants, and the study was conducted in accordance with the principles of the Declaration of Helsinki following approval from the institutional ethical review committee.

Clinical and demographic information was collected using a structured questionnaire. Data included age, sex, body mass index, smoking status, history and severity of COVID-19, hospitalization, oxygen requirement, duration since recovery, vaccination status and persistence of post-COVID symptoms. Particular attention was given to fatigue, dyspnea, chest discomfort, exercise intolerance, headache and cognitive difficulties. Dyspnea severity was assessed using the modified Medical Research Council (mMRC) scale, while fatigue was assessed using a standardized fatigue severity questionnaire. Blood pressure, pulse rate, respiratory rate and oxygen saturation were recorded after a period of rest. Pulmonary function was assessed by spirometry according to standardized procedures, including forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1/FVC ratio and peak expiratory flow rate. Values were expressed as absolute measurements and percentages of predicted values.

Following an overnight fast, approximately 5 mL of venous blood was collected from each

participant under aseptic conditions. Blood samples were allowed to clot and subsequently centrifuged at 3000 rpm for 10 minutes. The separated serum was aliquoted and stored at −80°C until biochemical analysis. Serum malondialdehyde (MDA) was measured as a marker of lipid peroxidation, while total oxidant status (TOS) was determined to estimate the overall oxidative burden. Total antioxidant capacity (TAC), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) were assessed to characterize the antioxidant defense system. Oxidative Stress Index (OSI) was calculated as the ratio of TOS to TAC using the formula: OSI = (TOS/TAC) × 100. All biochemical analyses were performed using commercially available standardized assay kits according to the manufacturers' instructions, with appropriate calibrators and quality-control samples.

To assess the inflammatory component of persistent oxidative stress, serum C-reactive protein (CRP) and interleukin-6 (IL-6) concentrations were measured using validated immunoassay methods. Fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were also determined using automated biochemical methods. The relationship between oxidative stress biomarkers and systemic inflammation, pulmonary function and persistent symptoms was subsequently evaluated. Participants were additionally categorized according to the degree of oxidative stress using the median OSI value, allowing comparison of clinical and biochemical characteristics between individuals with relatively higher and lower oxidative stress.

Data were entered and analyzed using IBM SPSS Statistics version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. The normality of continuous variables was assessed using the Shapiro–Wilk test. Independent-samples *t*-test or Mann–Whitney U test was applied for comparison between the post-COVID-19 and control groups, according to data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test. Pearson or Spearman correlation analysis was performed to determine associations between oxidative stress biomarkers, inflammatory markers, pulmonary function parameters and symptom severity. Binary logistic regression was used to determine whether increased oxidative stress was independently associated with persistent post-COVID-19 complications after adjustment for relevant demographic and clinical variables. A two-sided p value <0.05 was considered statistically significant, and 95% confidence intervals were reported where appropriate.

RESULTS

A total of 120 participants were included in the study, comprising 80 patients with persistent post-COVID-19 manifestations and 40 healthy controls. The mean age of the post-COVID-19 group was 49.3±10.7 years compared with 47.6±9.8 years among controls (p=0.394). Males constituted 53.8% of the post-COVID-19 group and 55.0% of the control group. There was no statistically significant difference between the groups with respect to age, sex, BMI or smoking status. Among the post-COVID-19 participants, the median duration since recovery was 7.2 months, while 46.3% reported persistent dyspnea, 52.5% experienced fatigue and 31.3% reported exercise intolerance.

Table 1. Baseline demographic and clinical characteristics of study participants

Variable	Post-COVID-19 (n=80)	Controls (n=40)	*p*-value
Age (years)	49.3±10.7	47.6±9.8	0.394
Male sex, n (%)	43 (53.8)	22 (55.0)	0.897
BMI (kg/m²)	27.1±4.2	26.4±3.8	0.371
Current smokers, n (%)	18 (22.5)	7 (17.5)	0.531
Systolic BP (mmHg)	128.6±14.7	124.8±12.1	0.147
Diastolic BP (mmHg)	79.4±9.2	77.1±8.1	0.184
SpO_2 (%)	95.8±2.1	97.4±1.2	<0.001
Duration after COVID-19 (months)	7.2±2.8	—	—
Persistent dyspnea, n (%)	37 (46.3)	0	<0.001
Persistent fatigue, n (%)	42 (52.5)	4 (10.0)	<0.001
Exercise intolerance, n (%)	25 (31.3)	2 (5.0)	0.001

The baseline characteristics are summarized in Table 1. No significant differences were observed between the two groups in age, sex distribution, BMI, smoking status, systolic blood pressure or diastolic blood pressure, indicating reasonable baseline comparability. However, oxygen saturation was significantly lower in post-COVID-19 participants than in controls (p<0.001). Persistent fatigue was reported by 52.5% of patients, followed by dyspnea in 46.3% and exercise intolerance in 31.3%, demonstrating a considerable burden of persistent functional symptoms after COVID-19.

Table 2. Comparison of oxidative stress and antioxidant biomarkers

Biomarker	Post-COVID-19 (n=80)	Controls (n=40)	Mean difference	*p*-value
MDA (nmol/mL)	4.82±1.21	2.91±0.74	1.91	<0.001
TOS (μmol H_2O_2 Eq/L)	38.6±9.4	21.8±5.7	16.8	<0.001
TAC (mmol Trolox Eq/L)	0.67±0.16	1.04±0.21	−0.37	<0.001
SOD (U/mL)	71.4±15.8	96.7±18.3	−25.3	<0.001
Catalase (U/mL)	42.8±9.7	58.9±11.4	−16.1	<0.001
GSH (μmol/L)	4.21±1.03	6.18±1.24	−1.97	<0.001
OSI	5.74±1.82	2.61±0.83	3.13	<0.001

Table 2 demonstrates a marked imbalance between oxidant production and antioxidant defenses among post-COVID-19 participants. MDA and TOS were significantly elevated, whereas TAC, SOD, catalase and GSH were significantly reduced compared with healthy controls. The mean OSI was more than two-fold higher in the post-COVID-19 group than in controls (5.74±1.82 vs. 2.61±0.83, p<0.001), indicating substantial persistent systemic oxidative stress.

Table 3. Inflammatory, metabolic and pulmonary function parameters

Parameter	Post-COVID-19 (n=80)	Controls (n=40)	*p*-value
CRP (mg/L)	6.8±3.4	2.1±1.2	<0.001
IL-6 (pg/mL)	8.7±4.1	3.2±1.4	<0.001
Fasting glucose (mg/dL)	103.6±18.2	94.8±11.6	0.004
Total cholesterol (mg/dL)	198.4±38.7	184.6±31.2	0.048
Triglycerides (mg/dL)	164.2±57.6	133.8±42.5	0.003
HDL-C (mg/dL)	42.7±8.6	47.9±7.4	0.001
FEV1 (% predicted)	78.6±12.4	91.8±8.7	<0.001
FVC (% predicted)	81.2±11.7	94.1±7.9	<0.001
FEV1/FVC (%)	76.8±6.9	80.4±4.8	0.002
PEFR (% predicted)	74.5±14.2	88.3±10.6	<0.001

As shown in Table 3, post-COVID-19 participants exhibited persistent low-grade systemic inflammation, with significantly higher CRP and IL-6 concentrations than controls. Metabolic abnormalities were also observed, including higher fasting glucose and triglyceride concentrations and lower HDL-C. Pulmonary function was significantly impaired in the post-COVID-19 group, with reductions in FEV1, FVC, FEV1/FVC ratio and PEFR, suggesting persistent ventilatory impairment following SARS-CoV-2 infection.

Table 4. Correlation of oxidative stress index with inflammatory, pulmonary and clinical parameters

Variable	Correlation with OSI (*r*)	*p*-value
MDA	+0.68	<0.001
TOS	+0.74	<0.001
TAC	−0.61	<0.001
CRP	+0.61	<0.001
IL-6	+0.57	<0.001
FEV1 (% predicted)	−0.48	<0.001
FVC (% predicted)	−0.44	<0.001
SpO_2	−0.41	<0.001

Dyspnea score	+0.49	<0.001
Fatigue score	+0.45	<0.001
Exercise intolerance	+0.38	0.001
Duration since COVID-19	+0.29	0.009

Table 4 demonstrates significant relationships between oxidative stress and multiple post-COVID-19 abnormalities. OSI showed a strong positive correlation with MDA and TOS and a significant inverse correlation with TAC. Higher oxidative stress was also associated with increased CRP and IL-6 concentrations. Importantly, increasing OSI was associated with poorer pulmonary function, lower oxygen saturation and greater severity of dyspnea and fatigue. The positive association between OSI and duration since COVID-19 suggests that oxidative imbalance may persist for several months following the acute infection.

Table 5. Comparison of participants according to oxidative stress status

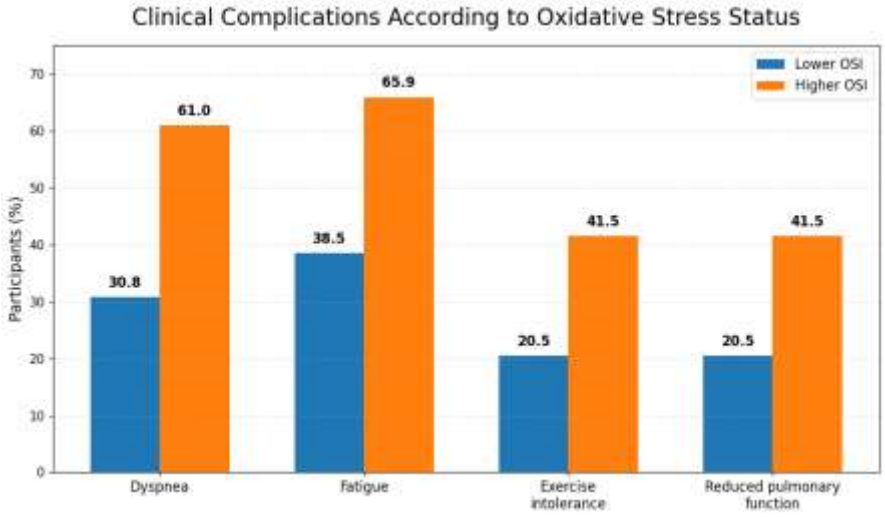
Variable	**Lower OSI (n=39)**	**Higher OSI (n=41)**	***p*-value**
MDA (nmol/mL)	3.91±0.76	5.68±0.91	<0.001
CRP (mg/L)	4.2±1.9	9.3±3.1	<0.001
IL-6 (pg/mL)	6.1±2.6	11.2±3.8	<0.001
FEV1 (% predicted)	84.7±10.3	72.8±11.1	<0.001
FVC (% predicted)	86.7±9.4	76.0±10.2	<0.001
Persistent dyspnea, n (%)	12 (30.8)	25 (61.0)	0.008
Persistent fatigue, n (%)	15 (38.5)	27 (65.9)	0.015
Exercise intolerance, n (%)	8 (20.5)	17 (41.5)	0.049
Reduced pulmonary function, n (%)	8 (20.5)	17 (41.5)	0.049

Table 5 further demonstrates that patients with higher OSI had significantly greater MDA, CRP and IL-6 concentrations and significantly poorer pulmonary function than those with lower OSI. Persistent dyspnea occurred in 61.0% of participants with higher oxidative stress compared with 30.8% among those with lower OSI, while fatigue was observed in 65.9% versus 38.5%, respectively. Reduced pulmonary function was also approximately twice as frequent among participants with higher oxidative stress. These findings indicate that greater oxidative imbalance was associated not only with biochemical abnormalities but also with clinically relevant respiratory and functional complications.

Table 6. Logistic regression analysis of factors associated with persistent post-COVID-19 complications

Variable	**Adjusted OR**	**95% CI**	***p*-value**
High OSI	3.42	1.58–7.39	0.002
Elevated CRP	2.31	1.18–4.53	0.015
Elevated IL-6	2.08	1.07–4.04	0.031
Reduced TAC	2.76	1.31–5.81	0.008
Age >50 years	1.47	0.72–3.01	0.286
Male sex	1.18	0.58–2.40	0.641
BMI ≥30 kg/m²	1.64	0.77–3.49	0.198
Current smoking	1.73	0.76–3.94	0.190

Multivariable logistic regression analysis in Table 6 showed that high oxidative stress remained independently associated with persistent post-COVID-19 complications after adjustment for potential demographic and clinical confounders. Participants with high OSI had 3.42 times greater odds of persistent complications compared with those with lower OSI (95% CI: 1.58–7.39; p=0.002). Reduced TAC was also independently associated with persistent complications (adjusted OR=2.76; 95% CI: 1.31–5.81; p=0.008), while elevated CRP and IL-6 demonstrated significant associations. In contrast, age, sex, obesity and smoking were not independently significant in the adjusted model.



Overall, the results demonstrate a consistent pattern of persistent oxidative imbalance, impaired antioxidant defenses, systemic inflammation and pulmonary dysfunction among individuals recovering from COVID-19. The post-COVID-19 group showed significantly increased MDA, TOS and OSI together with reduced TAC, SOD, catalase and GSH, indicating sustained oxidative injury. These biochemical abnormalities were accompanied by increased CRP and IL-6, impaired spirometric parameters, reduced oxygen saturation, fatigue, dyspnea and exercise intolerance. The significant correlations between OSI and inflammatory as well as pulmonary parameters further support a potential mechanistic relationship between persistent oxidative stress and post-COVID-19 pathophysiology. The regression analysis strengthened this association by demonstrating that high OSI was an independent predictor of persistent complications, suggesting that prolonged redox dysregulation may represent an important biological determinant of long-term morbidity following SARS-CoV-2 infection.

DISCUSSION

The present study demonstrates a consistent pattern of persistent oxidative imbalance among individuals with post-COVID-19 manifestations. Compared with healthy controls, post-COVID-19 participants showed significantly increased MDA, TOS and OSI, together with marked reductions in TAC, SOD, catalase and GSH. These findings suggest that SARS-CoV-2 infection may produce a prolonged disturbance between oxidant generation and antioxidant defense that persists beyond the acute infectious phase. Our findings are in agreement with Al-Hakeim et al., who reported increased oxidative damage, impaired antioxidant defenses and inflammatory abnormalities in individuals with Long COVID, and found that the oxidative/nitrosative stress profile was closely associated with chronic fatigue and other persistent symptoms.[10] The present findings therefore support the concept that oxidative stress is not merely an acute consequence of SARS-CoV-2 infection but may remain biologically active during the post-infectious period.

The significantly elevated MDA observed in our post-COVID-19 group indicates enhanced lipid peroxidation and possible damage to cellular and mitochondrial membranes. Lipid peroxidation can alter membrane permeability, impair membrane-bound enzymes and receptors, and generate secondary reactive aldehydes that further amplify cellular injury. The simultaneous elevation of TOS and reduction in TAC, SOD, catalase and GSH provide additional evidence that antioxidant capacity may be insufficient to neutralize persistent reactive oxygen species. Importantly, our findings are supported by a recent clinical study demonstrating systemic oxidative stress in non-hospitalized COVID-19 survivors. In that study, reduced circulating free sulfhydryl groups during the acute and follow-up periods were longitudinally associated with subsequent development of post-COVID-19 syndrome, suggesting that persistent redox imbalance may have prognostic relevance. [11]

A particularly important observation in our study was the strong relationship between oxidative stress and inflammation. OSI demonstrated significant positive correlations with CRP and IL-6, while participants with higher OSI had substantially greater concentrations of both inflammatory markers.

This relationship is biologically plausible because ROS can activate redox-sensitive inflammatory pathways, while activated immune cells can themselves generate additional ROS, creating a self-perpetuating cycle of oxidative stress and inflammation. Coronel et al. similarly demonstrated persistent oxidative and inflammatory abnormalities in patients with post-acute sequelae of COVID-19, including increased IL-6 and IL-8 and abnormalities in antioxidant enzymes and glutathione-related parameters. [12] These observations strengthen the possibility that persistent inflammation and oxidative stress interact rather than occurring as independent pathological processes.

The pulmonary findings of the present study are particularly relevant to pulmonology and respiratory physiology. Post-COVID-19 participants had significantly lower FEV1, FVC, FEV1/FVC and PEFR than controls, and OSI was inversely correlated with FEV1 and FVC. Participants with higher oxidative stress also had a substantially greater frequency of persistent dyspnea and impaired pulmonary function. These observations are consistent with the study of Siekacz et al., who identified associations between oxidative biomarkers, mitochondrial regulatory proteins and persistent pulmonary complications following COVID-19. Their patients with long-term pulmonary abnormalities demonstrated alterations in PINK1, DNM1L and MFN2 together with increased inflammatory mediators such as IL-6 and TNF-α, supporting an interaction between mitochondrial dysfunction, oxidative stress and pulmonary inflammation. [13]

The relationship between oxidative stress and pulmonary dysfunction may involve several interconnected mechanisms. Excessive ROS can injure alveolar epithelial cells, pulmonary endothelial cells and extracellular matrix components, while persistent inflammatory signalling can promote abnormal tissue repair and fibrotic remodeling. Endothelial dysfunction may additionally impair pulmonary microcirculation and oxygen exchange. Xu et al. emphasized that SARS-CoV-2-associated endothelial injury can extend beyond the pulmonary circulation and contribute to systemic vascular dysfunction and multiorgan injury. [14] Thus, the reduced SpO_2 and impaired spirometric parameters observed in our study may represent the functional consequences of persistent pulmonary and vascular injury rather than simply residual symptoms following an acute respiratory infection.

Mitochondrial dysfunction provides another plausible mechanistic explanation for the observed oxidative abnormalities. Mitochondria are both a major source and target of reactive oxygen species. SARS-CoV-2-related disruption of mitochondrial homeostasis may increase ROS generation while simultaneously impairing ATP production, antioxidant capacity and cellular energy metabolism. Molnar et al. proposed that mitochondrial dysfunction may contribute to fatigue, exercise intolerance, metabolic abnormalities, endothelial dysfunction and oxidative stress in Long COVID. [15] This mechanism is highly relevant to our observation that patients with higher OSI experienced greater fatigue and exercise intolerance. Persistent mitochondrial impairment could therefore provide a common biological pathway connecting biochemical oxidative stress with the functional manifestations of post-COVID-19 syndrome.

Further support for this mechanism comes from Szögi et al., who demonstrated structural mitochondrial abnormalities in Long COVID patients, including mitochondrial swelling and disrupted cristae, together with alterations in mitochondrial regulatory proteins and reduced circulating cell-free mitochondrial DNA. [16] These findings suggest that mitochondrial damage may persist after the resolution of acute SARS-CoV-2 infection. The present study did not directly measure mitochondrial structure or mitochondrial DNA; nevertheless, the marked increase in OSI and MDA together with reduced antioxidant defenses is compatible with a state of continuing mitochondrial redox stress. The association between oxidative stress and fatigue in our cohort may therefore reflect impaired cellular energy production secondary to mitochondrial dysfunction.

Our findings also have potential metabolic and cardiovascular implications. Post-COVID-19 participants demonstrated higher fasting glucose and triglycerides and lower HDL-C compared with controls. Although these differences were less pronounced than the oxidative and inflammatory abnormalities, they may indicate persistent metabolic dysregulation. Oxidative stress can interfere with insulin signalling, mitochondrial metabolism and lipid homeostasis, while chronic inflammation can further promote metabolic dysfunction. At the vascular level, ROS-mediated reduction in nitric oxide

bioavailability can promote endothelial dysfunction, vasoconstriction and a prothrombotic state. Georgieva et al. highlighted the interconnected roles of oxidative stress, mitochondrial dysfunction, inflammation and endothelial injury in COVID-19-related complications. [17]

The regression analysis provides an important finding because high OSI remained independently associated with persistent post-COVID-19 complications after adjustment for age, sex, BMI and smoking. Participants with high OSI had 3.42-fold greater odds of persistent complications, while reduced TAC, elevated CRP and IL-6 were also independently associated with adverse outcomes. This suggests that oxidative stress may have an independent relationship with post-COVID morbidity rather than merely reflecting the presence of inflammation or demographic risk factors. Nevertheless, because the present study used a cross-sectional design, causality cannot be established. High oxidative stress could contribute to persistent symptoms, result from chronic inflammation, or both processes could reinforce each other.

An important strength of the present study is the simultaneous assessment of oxidant biomarkers, antioxidant defenses, inflammatory mediators, pulmonary function and clinical manifestations. The concordance between biochemical and physiological findings strengthens the biological interpretation of the results. In particular, the significant correlations between OSI and CRP, IL-6, FEV1, FVC, SpO_2, dyspnea and fatigue suggest that oxidative stress may represent a common mechanistic pathway linking systemic inflammation with pulmonary and functional abnormalities. Recent clinical evidence further supports the potential value of oxidative-stress measurements for monitoring Long COVID, with OSI and other redox biomarkers showing relationships with inflammatory markers in patients assessed during the Omicron era.[18]

Limitations

The findings should, however, be interpreted in light of several limitations. The relatively modest sample size may limit generalizability, and the cross-sectional design prevents determination of temporal or causal relationships. Oxidative stress was evaluated primarily through circulating biomarkers, which may not completely reflect tissue-specific oxidative injury in the lung, myocardium, skeletal muscle or nervous system. Furthermore, differences in the severity of the original COVID-19 infection, vaccination status, viral variant, treatment received during acute illness and comorbidities may influence long-term oxidative status. Larger longitudinal studies incorporating serial oxidative biomarkers, pulmonary imaging, endothelial markers, mitochondrial parameters and functional assessments are therefore warranted.

CONCLUSION

The present study indicates that persistent oxidative stress is closely associated with systemic inflammation, impaired antioxidant defenses, pulmonary dysfunction, fatigue, dyspnea and exercise intolerance following COVID-19. The strong association of OSI with both biochemical and clinical outcomes, together with its independent relationship with persistent complications, suggests that oxidative stress may be an important component of post-COVID-19 pathophysiology. Future research should determine whether redox biomarkers can be used for risk stratification and whether interventions aimed at restoring antioxidant capacity, mitochondrial function and endothelial health can reduce the burden of persistent post-COVID-19 complications.

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