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Review Article

Relationship between oxidative stress and COVID-19: a brief systematic review

Relação entre estresse oxidativo e COVID-19: uma breve revisão sistemática

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ABSTRACT: OBJECTIVE: Analyse the possible relationship between Oxidative Stress (OS) and the pathogenesis of COVID-19. METHODS: This brief systematic literature review was conducted based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The search resulted in the selection of 10 papers that met the research theme and were published between January 2020 and March 2021. RESULTS: The results revealed that in the course of the disease, there is a decrease in thiol levels and an increase in disulfide and EO, with a probable depletion of antioxidant elements. They found that the accumulation of Reactive Oxygen Species (ROS), added to the damage to albumin, were related to a worse prognosis and that neutrophils may be responsible for the increased level of oxidative stress associated with the worsening of the clinical condition. In addition, cells transfected with the SARS-CoV-2 spike protein showed around three times the concentration of ROS compared to non-transfected control cells. As for serum O2- levels, they were significantly elevated in critically ill patients, constituting a probable predictor of disease severity. CONCLUSIONS: Thus, from the findings of this study, it is possible to infer that both patients with severe and moderate forms of COVID-19 have high EO index values. However, further studies need to be carried out to confirm these preliminary results.

KEY WORDS: Oxidative Stress; Reactive Oxygen Species; Reactive Nitrogen Species; COVID-19.

RESUMO: OBJETIVO: Analisar a possível relação entre o Estresse Oxidativo (EO) e a patogênese da COVID-19. MÉTODOS: Esta breve revisão sistemática de literatura foi conduzida a partir de recomendações da Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). A busca resultou na seleção de 10 trabalhos que preencheram a temática da pesquisa, publicados entre janeiro 2020 e março de 2021. RESULTADOS: Os resultados revelaram que no curso da doença, ocorre depleção nos níveis de tiol e aumento de dissulfeto e de EO, com provável depleção de elementos antioxidantes. Constataram que o acúmulo de Espécies Reativas de Oxigênio (EROs), somado ao dano à albumina, relacionaram-se a um pior prognóstico e que neutrófilos podem ser responsáveis pelo crescente nível de estresse oxidativo associado ao agravamento do quadro clínico. Além disso, células transfectadas com a proteína spike SARS-CoV-2 apresentaram cerca de o triplo da concentração de EROs em comparação às células controle não transfectadas. Quanto aos níveis séricos de O_2^-, mostraram-se significativamente elevados em pacientes graves, constituindo um provável preditor da gravidade da doença. CONCLUSÕES: Assim, a partir desse trabalho, é possível inferir que tanto pacientes portadores de formas graves quanto moderadas de COVID-19 apresentam elevados valores de índice de EO. Entretanto, novos estudos precisam ser realizados para confirmação destes resultados preliminares.

PALAVRAS-CHAVE: Estresse Oxidativo; Espécies Reativas de Oxigênio; Espécies Reativas de Nitrogênio; COVID-19.

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INTRODUCTION

The balance between oxidizing agents and the antioxidant defense system is essential for the proper functioning of several physiological mechanisms, such as ATP generation and support for the immune system. Oxidative Stress (OS) occurs in the presence of an imbalance in this redox system, with an increased generation of oxidizing compounds and reduced action of enzymatic and non-enzymatic antioxidant mechanisms, which result in oxidative damage to cells[1].

Oxidizing agents, such as free radicals, are reactive molecules that originate mainly from mitochondrial metabolism. The main oxidizing molecules are Reactive Oxygen Species (ROS), such as hydrogen peroxide (H_2O_2), superoxide anion radical (O_2^-), and the hydroxyl radical (OH•). In addition, the reaction between O_2^- and the free radical nitric oxide (NO^-) can generate reactive nitrogen species, such as peroxynitrite ($ONOO^-$), which is potentially reactive[1].

Antioxidant compounds that act to balance and prevent potential damage from ROS and free radicals are divided between endogenous ones, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), catalase and human serum albumin (HSA) and exogenous, such as vitamin E, vitamin C, and carotenoids. These biomolecules and their byproducts involved in the generation or neutralization of free radicals and ROS may be utilized as markers of OS or to assess the antioxidant status[1,2].

HSA is an important endogenous antioxidant agent, being the most abundant protein in plasma. In the redox system, it neutralizes toxins and antioxidants, with its thiol group playing a role in retaining diverse types of ROS. The structural and functional alterations of ASH can be analyzed by identifying changes in its ability to bind strongly and exclusively to fatty acids in the blood, through specific measurements[3].

During viral infections, there is an increase in the production of Reactive Oxygen Species (ROS) intended to contain the infection; however, this process can trigger OS. With a decrease in the effectiveness of the enzyme system and depletion of its first line of defense, the enzyme Superoxide Dismutase (SOD)[4].

Phenomena related to oxidative stress (OS) also occur in the infection caused by the β-coronavirus SARS-CoV-2, in which dysregulated expression of OS marker genes is observed, and this imbalance appears to be associated with the manifestation of the severe form of COVID-19, characterized by Severe Acute Respiratory Syndrome (SARS)[5,6]. Additionally, this hypothesis becomes more relevant when one of the risk groups for developing severe SARS, consisting of the elderly, presents an increase in the OS process triggered by senescence[7].

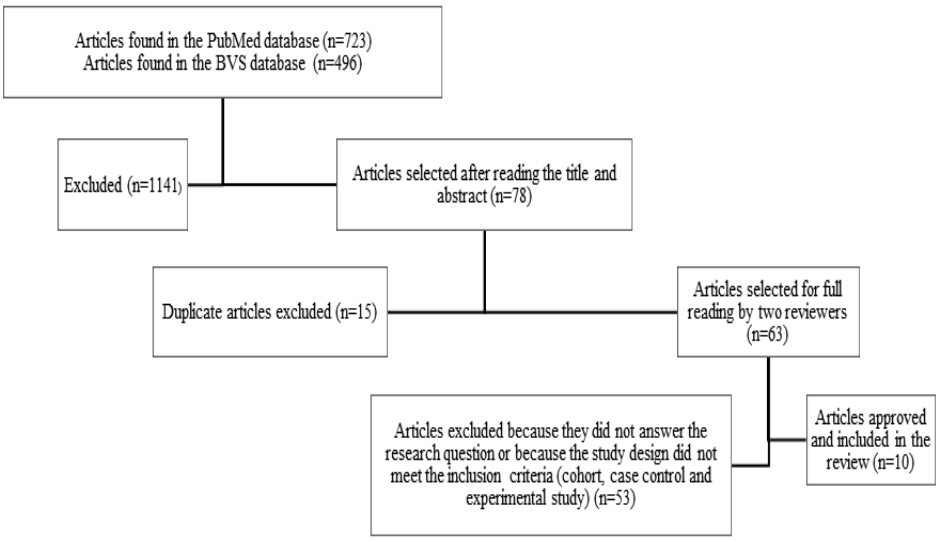
The spread of SARS-CoV-2 occurs mainly through droplets of respiratory fluids, in this way the virus enters the respiratory system, and binds to the Angiotensin Converting Enzyme (ECA2), triggering a high inflammatory immune response with cytokine storm, with a marked presence of phagocytes that also contributes to the imbalance in the redox system, leading to the production of ROS[8,9].

In this context, although vaccination against COVID-19 has been successful, this disease has already caused more than 4 million deaths worldwide. However, in cases where COVID-19 had already become established, a series of empirical therapies were adopted, such as N-acetylcysteine (NAC), indicated for lung diseases, with proven efficacy against OS[10,11]. Thus, the objective of this systematic review is to verify the relationship between the disease caused by SARS-CoV-2 and Oxidative Stress.

METHODOLOGY

This systematic review was conducted in accordance with the Preferred recommendation Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA). Searches were conducted between May 20, 2021 and June 1, 2021, in the United States National Library of Medicine, in its PubMed database , as well as in the Virtual Health Library (VHL). The search was guided by Boolean operators with the keywords: “COVID-19 AND oxidative stress”; “COVID-19 AND reactive oxygen species” and “COVID-19 AND reactive nitrogen species”.

Figure 1 - Depicts the flowchart of the systematic review’s phases



Source: Authors’ data.

The articles collected were published between January 2020 and March 2021, with screening, in the first phase, by title, abstract and methodology, in order to identify whether they were appropriate to the proposed theme and presented adequate methodology, such as cohort and case-control articles. Then, repetitions were excluded; thus, each eligible article was fully analyzed by two reviewers independently.

The inclusion criteria were Articles: (1) with text in English, Portuguese or Spanish; (2) Open access; (3) Published between January 2020 and March 2021; (4) That address the relationship between OS and COVID-19; (5) That were cohort, case-control or experimental studies.

The exclusion criteria adopted were: (1) editorials, case reports, letters, opinion articles, review articles, books; (2) duplications. Therefore, in the third analysis. The works were stratified according to the findings of the relationship between COVID-19 and OS, and their products.

Each included study was analyzed separately and its data were extracted and grouped. After this step, the concordances and discordances between the findings of all articles were verified. The guiding question of this review was: "What is the relationship between oxidative stress and the severity of the clinical picture of COVID-19?"

This work consisted of a brief systematic literature review, thus dispensing with approval by the Research Ethics Committee.

RESULTS

In this research, 723 articles were found in PubMed and 496 in the VHL, of which 78 works were selected in the primary research, of which 15 were repetitions. Thus, for the second screening, 63 articles were selected, and after a second analysis, 10 works were approved to compose this systematic review, as they were in accordance with the research proposal (Figure 1).

Studies conducted in the following countries were included: Turkey (1), United States of America (2), Nigeria (1), North Macedonia (1), Iran (2), Egypt (1), Brazil (1), and Serbia (1). Among the 10 articles, 5 cohort studies were included; 3 case-control studies; and 2 clinical studies. In these studies, data from 732 individuals were evaluated, of which 556 were infected with SARS-CoV-2, and 146 constituted the control groups. The studies used different criteria to classify the groups of patients with coronavirus as: mild, moderate, and severe. However, there was divergence regarding the grouping method; some studies analyzed mild and moderate cases as a single group, while other studies stratified the data from the three groups separately (Table 1).

Table 1 - Detailed characterization of the included studies

Author/year/place	Number of participants/groups	Summary of findings
Kalem et al .[12] 2021 Turkey	Control: 70 Clinical Classification: Mild to moderate COVID-19: 117 Severe COVID-19: 27 Age: 49,6 ± 18,3 Sex male: 94 (65,2%) ≥1 comorbidity: 59 (41%) Hypertension (HAS): 25 (17,3%) Diabetes (DM): 19 (13,1%) Coronary artery disease (CAD): 8 (5,5%) Other 19 (13,1%) ICU: 30 (20,8%) Outcome, death: 9 (6,2%)	The objective of this study was to assess the degree of oxidative stress by means of thiol-disulfide homeostasis in healthy control subjects and patients diagnosed with SARS-CoV-2. The patients were classified according to the WHO guidelines as exhibiting mild to moderate illness or severe illness consistent with the clinical presentation of the virus. Samples were obtained upon admission, revealing that patients with confirmed SARS-CoV-2 infection exhibited significantly elevated leukocyte, neutrophil, C-reactive protein (CRP), ferritin, and interleukin-6 (IL-6) levels compared to the control group ($p < 0.001$). Additionally, lymphocyte values were observed to be significantly reduced in the patient cohort ($p < 0.001$). A progressive decline in native or reduced thiol (NT) values was observed among the control, mild to moderate, and severe coronavirus disease (COVID-19) groups (419.8 ± 55.88 µmol/L; 260.71 ± 83.08 µmol/L; 156.62 ± 69.75 µmol/L), with a statistically significant difference between all groups ($p < 0.001$). A similar trend was observed in the total thiol (TT) values, including both reduced and oxidized forms (459.12 ± 60.05 µmol/L; 305.73 ± 86.40 µmol/L; 192.00 ± 75.20 µmol/L; $p < 0.001$). Furthermore, the metrics of the amount of disulfides (SS) demonstrated a statistically significant difference only between the control and mild to moderate COVD groups ($p = 0.004$) and between the mild and moderate COVD and severe COVD groups ($p < 0.001$). (19.69 ± 4.91 µmol/L; 22.50 ± 6.19 µmol/L; 17.54 ± 5.83 µmol/L). The ROC (Receiver Operating Characteristic)analysis of the variables indicated that IL-6 and NT exhibited the highest capacity for differentiating between healthy individuals and patients with mild to moderate conditions. Conversely, CRP and NT demonstrated the greatest efficacy in differentiating between mild to moderate and severe conditions. Furthermore, a cut-off point for NT values of 328 µmol/L (sensitivity of 97% and specificity of 83%) was identified as a means of discriminating between healthy individuals and patients with mild to moderate coronavirus disease (Covid-19), with an area under the curve (AUC) of 0.95 (95% confidence interval [CI] 0.93-0.99). Furthermore, a cut-off point of 189 µmol/L (sensitivity of 79% and specificity of 72%) was identified for differentiating between mild to moderate and severe cases of the disease (AUC=0.83; CI: 95% 0.75-0.92). Additionally, a significant negative correlation was observed between the duration of symptoms and NT levels.

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Author/year/place	Number of participants/groups	Summary of findings
Dominic et al.[13] 2021 USA	Total: 101 Control: 33 Age: 43,09 (22–68) Sex male:18 (54%) COVID: 68 Age: 58,19 (27–85) Sex male: 35(51,5%) Clinical Classification: Modarate: 46 (67.6%) Severe: 22 (32,3%) Comorbidity: DM: 29 (42.6%) Hypertension: 51 (75%) COPD*: 6 (8,8%) CVDBBB*: 18 (26,4%)	The objective of the study was to analyze the relationship between the availability of NOX and sulfide in healthy controls and patients diagnosed with Coronavirus Disease (COVID-19) who were admitted to the hospital. Following the collection of blood samples, the levels of NOx, free nitrite, and sulfide were quantified. A significant reduction in NO levels was observed in patients affected by SARS-CoV-2 when compared to controls (286.69 ± 140.39 nM; 418.84 ± 153.03 nM; $p < 0.0001$). Similarly, serum free nitrite levels were decreased in patients with SARS-CoV-2 when compared to the control group (179.945 ± 164.0 nM; 292.63 ± 141.67 nM; $p = 0.0017$). The S-nitrosothiol (SNO) fraction also exhibited a reduction in patients affected by SARS-CoV2, when compared to the control group (152.89 ± 85.39; 243.19 ± 91.60 nM; $p < 0.0001$). Sulfide levels, including free sulfide, were found to be significantly reduced in patients diagnosed with SARS-CoV-2 when compared to healthy controls (0.18 ± 0.05 μM; 0.31 ± 0.14 μM, $p < 0.0001$). The determination of oxidizing derivatives revealed that nitrotyrosine was obtained from the plasma of patients with coronavirus disease 2019 (COVID-19) and the control group, respectively. There was a significant increase in patients with confirmed cases of the disease (107.049 ± 7.907 nM vs 44.7606 ± 12.85 nM; $p < 0.0001$). A patient who was primarily in the control group developed symptoms of coronavirus disease 2019 (COVID-19). Total nitric oxide (NO) and sulfide levels were significantly reduced during the infection (280 nM and 0.8523 μM, respectively), compared to the pre-infection baseline (400 nM and 1.11039 μM). Additionally, the C-reactive protein (CRP) level was elevated (1.35 mg/dL), exceeding the normal range of 0.3-1.0 mg.
Muhammad et al. [14] 2021 Nigéria	Total: 71 Control: 21 Age: 35,8 ± 6,8 Sex male: 11 (52,4%) Sex fem..: 10 (47,6%) COVID: 50 Age: 43,8 ± 13,8 Sexo male 35 (70%) Sexo fem.: 15 (30%) Clinical Classification Mild: 32 (64%) Moderate: 10 (20%) Severe: 8 (16%) Comorbidity: DM: 4 (8%) Hypertension: 6 (12%) Malária: 9 (18%)	The research quantified the presence of antioxidant trace elements, 8-isoprostaglandin F2 alpha (8-iso-PGF2α), malondialdehyde (MDA), as well as erythrocyte activity of glutathione (GSH), glutathione peroxidase (GPx), SOD, and catalase. It was observed that the levels of vitamins A, C, and E were significantly reduced in patients affected by SARS-CoV-2 when compared to the control group. The respective levels of vitamins A, C, and E in the control group were as follows: vitamin A, μg/dL (26. The mean values for vitamins A, C, and E were 5±2.3, 0.33±0.43, and 0.63±0.05 mg/dL, respectively, in the control group, and 28.0±1.1, 0.44±0.32, and 0.87±0.06 mg/dL, respectively, in the patient group. These differences were statistically significant ($p<0.001$). Additionally, the antioxidant enzymes were observed to decrease in patients with SARS-CoV-2 infection and the control group. The mean ± SD of GSH was 2.1 ± 0.39 in the patient group and 2.7 ± 0.24 in the control group ($p < 0.001$). The mean ± SD of GPx was 32.5 ± 2.3 in the patient group and 38.5 ± 2.8 in the control group ($p < 0.001$). The mean ± SD of SOD was 1.73 ± 0.39 in the patient group and 2.84 ± 0.38 in the control group ($p < 0.001$). Notably, catalase exhibited a marked increase in patients with SARS-CoV-2 infection, with a mean value of 112.5 ± 3.0 units per milliliter (UM/L) in the patient group and 109.0 ± 4.3 UM/L in the control group ($p < 0.001$). With regard to antioxidant elements, a significant reduction was observed in patients affected by SARS-CoV-2 when compared to the control group. The levels of manganese (1.64 ± 0.36 and 2.10 ± 0.35, $p < 0.001$), selenium (25.3 ± 2.4 and 29.1 ± 1.9, $p = 0.000$), and copper (128.3 ± 7.7 and 136.5 ± 5.3, $p < 0.0001$) were significantly reduced in patients affected by SARS-CoV-2 when compared to the control group. While the markers of free radical production in the control group and the group of patients with SARS-CoV-2 infection were increased in the latter group, Malondialdehyde (MDA) levels were significantly elevated in patients with SARS-CoV-2 infection (4.9 ± 0.5 mmol/L) compared to the control group (3.4 ± 0.21 mmol/L, $p < 0.001$). Similarly, 8-iso-PGF2α levels were markedly higher in patients with SARS-CoV-2 infection (83.2 ± 7.2 pg/mL) compared to the control group (54.6 ± 5.9 pg/mL, $p = 0.049$).
Cekerevac et al.[15] 2021 Serbia	Clinical Classification: Total: 127 Mild (M/F): 11/6 Moderate (M/F): 27/13 Severe ((M/F): 49/21 Leve - Mod. - Grave Age 59,2 49,6 61,9 Comorbidity. (M/F) Smoking: Hipertensio: DM: Obesit: COPD: Malignant disease: 13/4 - 34/6 - 63/7 8/9 - 29/11 - 23/47 11/6 - 34/6 - 51/19 12/5 - 36/4 - 58/12 16/1 - 38/2 - 67/3 16/1 - 39/1 - 68/2	The study assessed patients who tested positive for the SARS-CoV-2 virus, categorizing them into three groups based on the World Health Organization (WHO) classification: mild, moderate, and severe. The objective was to identify predictors of severity and the final outcome. With regard to the differences between the groups, it was observed that the group with severe covid exhibited a greater prevalence of comorbidities. With regard to the pro-oxidant factors under consideration, the serum superoxide (O2-) levels observed in the mild (3.5 nmol/ml), moderate (4.84 nmol/ml) and severe (11.3 nmol/ml) groups were statistically different between the three groups ($p < 0.001$). Furthermore, there was a notable discrepancy in nitric oxide (NO-) concentrations (3.03; 3.2 and 2.66 nmol/ml; $p < 0.001$) between the mild and severe COVD groups, as well as between the moderate and severe COVD groups. No significant differences were observed in the levels of H2O and the degree of lipid peroxidation in the plasma between the groups. Among the antioxidant parameters evaluated, only the enzyme catalase (CAT) demonstrated a statistically significant difference when comparing all the groups (mild= 0.79; moderate= 0.68; and severe= 1.15 U/Hb*103; p=0.001). Conversely, no significance was observed in the measurements of superoxide dismutase (SOD) and glutathione reductase (GSH). Pearson's correlation test revealed a negative correlation between NO levels and both ICU and hospital stay lengths. Specifically, NO levels were negatively associated with ICU stay length ($R = -0.243$, $p = 0.01$) and hospital stay length ($R = -0.185$, $p = 0.05$). Ultimately, the evaluation of predictors of clinical condition severity via linear regression revealed that oxygen was positively correlated with the independent variable of clinical condition severity (standardized beta coefficient of 0.565; $p < 0.001$).

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Author/year/place	Number of participants/groups	Summary of findings
Meyer et al..[16] 2021 USA		The objective of the experimental study was to assess the impact of the SARS-CoV-2 virus infection on cultures of human epithelial liver cells (Huh7.5) and transformed epithelial lung cells (A549). The infected group consisted of cells that had been transfected with the virus, while the control group consisted of cells that had not been infected. In addition, the study examined the impact of the infected cells on hepatic sinusoidal endothelial cells (TMNK-1) and human umbilical vein endothelial cells (EAhy926). The authors conducted an analysis of cell signaling, indications of cellular senescence, production of reactive oxygen species (ROS), and endothelial adhesion molecules. Additionally, they investigated the influence of signaling pathway inhibitors on the aforementioned variables. The results demonstrated a threefold increase in intracellular ROS levels in the transfected lung cells (A549) when compared to the non-transfected cells ($p < 0.005$). Additionally, ROS levels were 1.8 to 2 times higher in the endothelial cells (TMNK-1 and EAhy926) exposed to the transfected culture when compared to those exposed to the control culture medium ($p < 0.05$). Moreover, when endothelial cells were treated with IL-6 inhibitors (tocilizumab) or Bruton's tyrosine kinase inhibitors (zanubrutinib), which affect B lymphocyte development and activation, the authors observed ROS levels within the endothelial cells that were comparable to those observed in the control group cultures.
Mortaz et al.[17] 2020 Iran	Total: 18 Control: 4 Hypoxic non-COVID-19: 2 Age: 41-42 Sex male: 2 COVID: 14 Age: 21-80b Sex male: 8 MV*: 7	The study analyzed the role of NO in the pathophysiology of COVID-19, by determining intracellular NO levels in patients with COVID-19, and in healthy patients, with and without hypoxia. Patients with COVID-19 had higher DHL, CRP peaks, and reduced lymphocyte counts compared to the control group. Intracellular NO was determined from erythrocytes and stained with 4-amino-5-methylamino-2', 7'-difluorofluorescein (DAF-FM DA); intracellular NO levels were elevated in COVID-19 patients compared to the control group with and without hypoxia.
Arcanjo et al.[18] 2020 Brazil	Total: 20 COVID: 20 Age: 18-83 Sex male:12 Sex fem.:8 Clinical Classification: Moderate: Severe:20 Comorbidity: DM: 10 Hypertension:12 COPD:1 Obesity:7	The study examined serum samples from 20 patients with confirmed SARS-CoV-2 infection in the acute phase of the disease to ascertain whether the virus stimulates the formation of reactive oxygen species (ROS) and neutrophil extracellular traps (NETs) through the process of netosis. The criteria for confirming acute infection were based on a positive result from a real-time reverse transcription polymerase chain reaction (RT-PCR) test of nasopharyngeal swab samples. Fluorescence readings were conducted to analyze ROS and neutrophil activity, employing specific methodologies. The study revealed that samples containing SARS-CoV-2 exhibited a statistically significant induction of the neurosis process in comparison to the control group ($p \leq 0.0001$). Additionally, the production and release of ROS by neutrophils were observed to be significantly elevated in the presence of SARS-CoV-2 ($p \leq 0.05$).
Karkhanei et all.[19] 2021 Republic of North Macedonia	Total: Control: 19 Age ≤60: 10 (55,56%) Sex male: 11 (61,11%) COVID: 96 Clinical Classification: n-ICU*: 35 Age ≤60: 12 (34,29%) Sex male: 13 (37,14) Outcome, death: 0 (0%) ICU without IE*: 24 Age ≤60: 11 (45,83%) Sex male: 16 (66,67) Outcome, death: 6 (25,00%) ICU with EI*: 19 Age ≤60: 4 (21,05%) Sex male: 9 (47,37) Outcome, death: 15 (78,95%)	The study examined the levels of glutathione, total antioxidant capacity (TAC), and total oxidant status (TOS) among hospitalized patients diagnosed with coronavirus disease 2019 (COVID-19). These patients were stratified according to the severity of their clinical condition, including those who were not admitted to the intensive care unit (ICU), those who were admitted to the ICUs without endotracheal intubation (ICU without EI), and those who were admitted to the ICUs with endotracheal intubation (ICU with EI). Additionally, the study compared the levels of these biomarkers in healthy patients without the disease. The total oxidant status (TOS) levels were found to be significantly elevated in the groups of patients with confirmed cases of SARS-CoV-2 infection, including those who were not admitted to the intensive care unit (n-ICU). The mean GSH measurement was significantly reduced compared to the healthy control group (n-ICU: 227.03 ± 36.91; ICU without EI: 134.54 ± 38.11; ICU with EI: 102.11 ± 36.86; control: 374.94 ± 41.15; p-value: ($p < 0.001$). A comparison of the TAC measurements between the CG and non-ICU groups revealed no statistically significant difference (control: 66.72 µmol/dL vs. non-ICU: 50.26 µmol/dL). However, a statistically significant difference was observed between the control and the other groups (ICU without EI: 519.26 µmol/dL and ICU with EI: 310.00 µmol/dL) ($p < 0.001$). The TOS/GHS ratios were measured and found to be as follows: n-ICU (0.070 ± 0.018), ICU without EI (0.224 ± 0.069), ICU with EI (0.907 ± 0.331), and control (0.003 ± 0.002). The p-value was less than 0.001. Furthermore, the TOS/TAC ratio was higher in patients with a diagnosis of SARS-CoV-2 infection (n-ICU: 0.323 ± 0.106; ICU without EI: 0.061 ± 0.025; ICU with EI: 0.306 ± 0.129; control: 0.019 ± 0.011; $p < 0.001$).

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Author/year/place	Number of participants/groups	Summary of findings
Badawy et al e col.[20] 2021 Egipt	Total: 35 Control: 10 COVID: 25 Clinical Classification: Severe Deaths (SD): 14 Age: 68.9 Male: 53.14% Comorbidities: Diabetes: 50% Hypertension: 42.8% Severe Survivors (SS): Age: 62.6 Male: 54.54% Comorbidities: Diabetes: 58.18% Hypertension: 27.27%	The study analyzed blood samples from hospitalized patients with severe COVID-19 in order to assess the degree of injury and the state of configuration of serum albumin by means of electron paramagnetic resonance (EPR), markers of oxidative stress and compare them to those of the control group without the disease. The measurement of serum albumin (mg/ml) was not statistically significant between the groups with severe disease that survived and those that died, respectively (31.8; 26.9; p-value: 0.067); CRP (mg/L) was high in the group with severe disease that had a fatal outcome, compared to the group that survived (90.6; 39.9; p=0.05). As for the neutrophil count, it was significantly higher in the groups with severe illness that had a fatal outcome and in the group that survived, compared to the healthy control group (76.4 ± 6.8, n = 11); (64.0 ± 20.0, n=10); (40.78 ± 14.0, n=9); (p<0.001). H2O2 levels were significantly higher in the group with severe disease that progressed to a fatal outcome and in the group that survived, compared to the healthy control group (Control: n=7: 2.57±0.57, SS: n=6: 5.37±1.0; SD: n=7: 8.8 ± 1.7; ANOVA p-value = 1.15 × 10 -7). As for albumin (mg/mL), the patients who died had mild hypoalbuminemia compared to the other groups (Control: n=8: 40.45±10.93, SS: n=8: 30.66± 10.99; SD: n=10: 24.71±5.88; p-value = 0.006). The authors also found that oxidative stress markers were related to the structural damage found in albumin by EPR spectroscopy, and that the biophysical changes in the structural alterations of albumin, the ratio between protein bonds (S/W), showed a significant association with the lethality of the patients (p = 0.008), the lower the S/W the greater the lethality. Based on the results, they established a ratio between the S/W of albumin and H2O2 which gave rise to a risk score, which enabled 100% of deaths to be predicted, compared to using S/W alone.
Zendelovska et al e col.[21] 2021 Republic of North Macedonia	Total: 70 Controle: 20 COVID: 50 Age: 56 (18-79) Clinical Classification: Moderate: 20 Severe:30	The study evaluated oxidative stress markers in the blood of patients hospitalized with COVID-19, stratified into moderate (signs of pneumonia, SpO 2 > 90% on room air) and severe disease (SpO2 < 90%, tachypnea; 30 breaths/minute or presence of severe respiratory distress), and compared them with the healthy control group; it also compared intragroup and intergroup, the level values of these markers measured at admission and at discharge of the patients. In the moderate group, at admission: (PAT: 2887±102.1; p=0.0004; d-ROM: 431.2±25.25 p=0.0001); (OSI: 94.2±13.9 p=0.0001). At discharge from the group with moderate disease: (PAT: 2673±160.6; p=0.1325); (d-ROM: 334.3±13.87; p=0.0002); (OSI: 52.25±5.60; p=0.0001). The severe group, at admission: (PAT: 2801±85.86 p=0.0008); (d-ROM: 413±17.28 p=0.0001); (OSI: 84.03±8.86 p=0.0001), at discharge (PAT: 2652±148.8; p=0.0043); (d-ROM: 325.3±22.46; p=0.0019); (OSI: 43.40±10.87 p=0.005). In the severe group, patients who died after the 2nd blood draw: (PAT: 2186±233.2; p=0.2497); (d-ROM: 462.4±28.04; p=0.0001); (OSI: 107.8±18.20; p=0.0001). These groups were compared with healthy individuals (PAT: 2406±71.5; d-ROM: 271±5.590; OSI: 21±2.527). Other parameters predictive of the course of the disease were assessed in the moderate and severe COVID-19 groups, and compared with the healthy control group. On admission, C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR) and lactate dehydrogenase (LDH) were found to be higher in the disease groups than in the control group. Moderate group (CRP: 44.1 ± 6.46; NLR: 6.47 ± 1.64; LDH: 280.3 ± 25.27; p<0.05); severe group (CRP: 113 ± 17.85; NLR: 20.23 ± 2.06; LDH: 800 ± 60. 27; p < 0.0001); severe group that died (CRP: 127 ± 33.49; NLR: 44.72 ± 10.49; LDH: 827.2 ± 130.6; p<0.05); reference values (CRP: 0-10; NLR: 120-246; LDH: < 3.0;).

Source**:** Authors' data

Legend:* COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DM = Diabetes Mellitus ; ICU with EI group: hospitalised group in intensive care units with endotracheal intubation; ICU without EI group: hospitalised group in intensive care units without endotracheal intubation; ICU: intensive care units; MV = Mechanical Ventilation.

Levels of elements linked to oxidative stress

Kalem et al.[12] found that serum levels of Native Thiol (NT), Total Thiol (TT) and disulfides (SS), oxidized forms of thiol, were significantly related to infection and/or severity of the clinical picture of COVID-19. These authors measured statistically decreased TT and NT levels in patients with mild to moderate and severe COVID-19 compared to the control group (p value <0.001). As for SS levels, they were elevated in the mild to moderate COVID-19 group (22.50 ± 6.19 µmol/L) compared to the control group (19.69 ± 4.91 µmol/L; p=0.004) and the group with COVID-19. severe (17.54 ± 5.83 µmol/L; p<0.001)[12].

Dominic et al.[13] demonstrated that nitrotyrosine, a marker of cell injury and inflammation, was present at high levels in the plasma of patients affected by COVID-19 (107.049 nM), compared to the control group (44.7606 nM), (p value < 0.0001), which indicates an increase in the degree of OS associated with the increase in the process of tyrosine nitration by reactive nitrogen species (RNS) in these patients[13].

Muhammad et al.[14] found that the oxidative marker 8-isoprostaglandin F2 alpha (8-iso-PGF2α) showed high levels in patients with COVID-19 (83.2 pg/mL), and lower in the control group (54.6 pg/mL), (p value = 0.049). Likewise, another oxidative marker, Malondialdehyde (MDA), was increased (4.9 mmol/L) in patients with COVID-19, when compared to the control group (3.4 mmol/L)[14].

Levels of reactive oxygen species and other markers

of oxidative stress

Cekerevac et al.[15] in a study carried out in patients with mild (n=17), moderate (n=40) or severe (n=70) forms of COVID-19, enzymatic antioxidant factors (catalase - CAT, superoxide dismutase - SOD, reduced glutathione - GHS) and lipid peroxidation index and measurement of the concentration of ROS ($O_2^{-\cdot}$ H_2O_2 and NO^-). The results revealed that serum levels of O_2^- (mild: 3.5; moderate: 4.84; severe: 11.3 [nM/mL]); were higher in severe patients ($p \leq 0.001$), constituting a probable predictor of the severity of COVID-19. As for the levels of NO^- (mild: 3.03; moderate: 3.2; severe: 2.66 [nM/mL]) were higher in patients with moderate clinical condition ($p \leq 0.001$) and were inversely associated with the length of hospitalization and ICU stay ($p = 0.01$)[15].

In experimental research, transformed human lung epithelial cells (A549), liver epithelial cells (Huh7.5), liver sinusoidal endothelial cells (TMNK-1) and human umbilical vein endothelial cells (EAhy926) were analyzed. The results demonstrated an increase in the amount of intracellular ROS, with A549 cells transfected with the SARS-CoV-2 spike protein presenting approximately three times the value measured in non- transfected control cells ($p<0.005$) and also resulting in an increase of approximately twofold ROS in transfected endothelial cells (TMNK-1 and EAhy926) compared to the control culture medium ($p<0.05$)[16].

The case-control study, carried out by Mortaz et al.[17], with 14 patients diagnosed with COVID-19 and pulmonary involvement, 2 with hypoxia without COVID-19 and 2 healthy individuals, found an increase in the amount of nitric oxide in the red blood cells of patients with COVID-19 ($p \leq 0.05$) compared to the control group with and without hypoxia without COVID-19[17].

Arcanjo et al.[18] carried out a comparative study of donors without COVID-19 with 20 patients with COVID-19 in the severe phase of the disease, in which the identification of ROS was detected by dichlorodihydrofluorescein diacetate probe (Invitrogen). The results demonstrated that SARS-CoV-2 induced neutrophils to produce ROS, a production related to the neutrophil netosis process[18].

Antioxidant factor levels

Muhammad et al.[14] studied the serum levels of vitamins and other antioxidant factors among COVID-19 patients and control group. They found that vitamin A (26.5 µg/dL and 28.0 µg/dL, $p<0.001$), vitamin E (0.63 mg/dL and 0.87 mg/dL, $p<0.001$), vitamin C (0.33 mg/dL and 0.44 mg/dL, $p<0.001$) GSH (2.1 mg/gHb and 2.7 mg/gHb, $p<0.001$), Glutathione Peroxidase (GPx) (32.5 U/gHb and 38.5 U/gHb, $p<0.001$) and SOD (1.73 U/mL and 2.84 U/mL) Manganese (1.64 mg/dL and 2.10 mg/dL, $p<0.001$), Selenium (25.3 ng/dL and 29.1 ng/dL, $p=0.000$) and Copper (128.3 µg/dL and 136.5 µg/dL, $p<0.0001$) showed significantly decreased serum levels in patients with COVID-19 compared to the control group. However, regarding the chromium levels, there were no statistically significant differences between the two groups (2.2mg/L and 2.2 mg/L, $p=0.605$).

Karkhanei et al.[19] carried out a comparative study that evaluated 96 patients hospitalized and diagnosed with COVID-19, stratified into: non-Intensive Care Unit (ICU) patients, ICU without endotracheal intubation (ICU without IE) and with endotracheal intubation (ICU with IE). These patients were compared to a control group (CG) for the analysis of GHS levels, Total Antioxidant Power (TAP) and Total Oxidant Status (TOS), markers which were calculated using commercially available ELISA kits according to the company's instructions. Significantly decreasing levels of GHS (CG: 374.94; Non-ICU: 227.03; ICU without EI: 134.54 and ICU with EI: 102.11 [mmol/mL]) ($p < 0.001$) and increasing levels of total oxidation status (CG: 1.28; Non-ICU: 15.4; ICU without EI: 28.13 and ICU with EI: 82.89 [mmol/mL]) ($p < 0.001$) were observed according to the severity of the clinical picture. Regarding PAT, the comparison between CG and non-ICU did not show a statistically significant difference (CG: 66.72 µmol/dL, non-ICU: 50.26 µmol/dL, and p-value = 0.09). However, there was a statistically significant difference when comparing the CG and the other groups (ICU without EI: 519.26 µmol/dL and ICU with EI: 310.00 µmol/dL) ($p < 0.001$)[19].

Oxidative stress as a predictor of risk of death/clinical outcome

Karkhanei et al.[19] also measured the SOT/PAT ratios (CG:0.019; Non-ICU:0.323; ICU without EI:0.061; ICU with EI:0.306; ep < 0.001) and the ratio between SOT and GHS, (CG:0.003; Non-ICU: 0.07; ICU without EI:0.224; ICU with EI:0.907; ep < 0.001), from which it can be inferred that there may be a positive relationship between the severity of the disease and the increase in reasons, as in the Non-ICU and ICU with EI groups. There was an increase in oxidizing factors and a decrease in antioxidants. However, this positive relationship did not show linear growth between all groups, since the ICU without EI group presented a low value, and with greater proximity to the CG, than the high values of the non-ICU and ICU with EI groups. Furthermore, the relationship between both variables and the clinical outcome also demonstrates relevant results, among deceased and discharged patients, with SOT/PAT ratios of 0.318 and 0.063 and SOT/GHS of 0.59 and 0.031, respectively. ($p < 0.001$)[19].

Changes in the structure and functionality of albumin were evaluated in the form of a ratio between the availability of strong and weak bond possibilities (S/W, Strong/Weak), respectively. It was found that the decrease in the S/W ratio was significantly related to lethality (COVID-19: 18.2%; CG: 81.8%; p=0.008). It was also verified that the ratio between S/W and the quantification of H_2O_2 ([S/W]/[H_2O_2]), allowed predict 100% of deaths in patients with COVID-19. Likewise, patients affected by COVID-19 and high levels of H_2O_2 showed changes in the structure and functionality of albumin of around 83.3% when compared to controls (16.7%, $p = 0.049$) [20]. Therefore, there is evidence that the accumulation of ROS, combined with structural damage to albumin, appears to be associated with a worse prognosis and greater lethality[20].

The cohort study carried out by Zendelovska et al.[21] analyzed data from patients with COVID-19, classified as moderate (signs of pneumonia, SpO2 > 90% on room air) and severe (SpO2 < 90%, tachypnea: 30 IRPM or presence of severe respiratory impairment) and compared them to those of a healthy control group. Among the participants with moderate and severe COVID-19, the following values were measured, respectively, upon admission: Plasma Peroxides (PP) (PP = 431.2 p = 0.000 and PP = 413 p = 0.0001). Additionally, the Oxidative Stress Index (OSI), automatically calculated by the spectrophotometer with reference values and the values obtained from PP and PAT, (OSI = 94.2 p = 0.0001) and (OSI = 84.03 p = 0.0001) were evaluated. Like this, the results demonstrated statistically significant differences between the two groups. It was also found that both moderate cases and serious presented levels significantly elevated PP and IEO, when compared to the values of the healthy control group, (PP= 271, IEO= 21, p=0.0001)[21]. Although the moderate COVID group had higher OE markers than the severe COVID group, both on admission and at discharge, among the severe cases that progressed to death, the OE markers were significantly higher than in the moderate group (d-ROM: 462,4 p=0.0001, t-test; OSI: 107.8; p=0.0001, t-test).

Other relevant findings linked to the natural history of the disease

Zendelovska et al.[21] also evaluated serum markers of oxidative stress considered predictors of the course of the disease, such as C-reactive protein (LDH), neutrophil-lymphocyte ratio (NLR) and lactate dehydrogenase (LDH) among COVID-19 patients and healthy individuals. On admission of patients with moderate disease, characterized by clinical signs of pneumonia, but not severe and SpO2 > 90% in room air, serum levels of CRP= 44.1 (mg/L), NLR= 6.47 and DHL= 280.3 (IU/mL) were found. Among the patients with severe disease, with SpO2 <90% in room air, respiratory rate >30 breaths/min or presence of severe respiratory discomfort, they found levels of CRP= 113 (mg/L), NLR= 20.23 and LDH= 800 (p<0.05, between the moderate and severe groups). As for the measurements taken among patients who died, the authors observed an increase in these parameters compared to the group of healthy individuals (CRP= 127 (mg/L); NLR= 44.72; DHL= 827.2 (IU/mL); p<0.05)[21].

DISCUSSION

Deleterious effects of the accumulation of ROS on the body and their relationship withCOVID-19

The OS resulting from the excessive generation of ROS is present in COVID-19 and is associated with processes developed during infection, possibly influencing the pathogenesis of the disease and causing deleterious effects on infected cells and tissues. In this way, it becomes possible to consider that the increase in OS increases the degree of severity of COVID-19[1,22].

In addition, the exacerbation of ROS can lead to the impairment of cellular components, as well as the dysregulation of the functionality of red blood cells, stimulating the oxidation of fatty acids in the membrane of these cells and consequent changes in the diffusion of O2 and CO2 and deformability in the capillaries. In this way, the excess of ROS increases the risk of thrombocytosis and compromises the release of ATP and NO-, which interferes with metabolic reactions, as well as destabilizing iron homeostasis[23].

NO^- and its role in the pathophysiology of COVID-19

NO- is a highly unstable and reactive free radical with the potential to trigger structural damage to proteins, DNA and the plasma membrane, actions which result in OS23. However, NO^- also has relevant physiological functions in the immune system. Several studies have demonstrated the activity of this molecule against viruses (e.g. HIV, herpes simplex-1, influenza). Interaction with these occurs through the nitrosylation of viral cysteinyl proteases,an activity that also seems to occur against SARS-CoV-2[25].

Although NO- is related to vascular complications in viral infections, such as dengue, its physiological function as a vasodilator is more relevant. Exogenous NO- has therefore been proposed as a therapy for COVID-19 patients with pulmonary hypertension and high intrapulmonary shunts, which are detrimental to the hematosis process. This therapeutic proposal proved to be effective in reducing systolic pulmonary artery pressure and increasing peripheral oxygen saturation in a study of severe COVID-19 patients treated with inhaled NO^-[26].

Relationship between neutrophils, lymphocytes and ROS

In the event of an infection, neutrophils are the body's first line of defense. In SARS- CoV-2 infection, neutrophilic leukocytosis occurs with maximum infiltration in the pulmonary capillaries[1,21]. The activation of these neutrophils against the virus includes an increase in the production of ROS, such as the superoxide radical O_2^-, which although not as reactive, can give rise to highly reactive species, such as hydrogen peroxide (H2O2), which when bound to iron has increased toxicity, and the hydroxyl radical (OH-), which is more unstable 1, 27. In addition, the occurrence of lymphopenia during the course of the disease has been noted, which, together with neutrophilia, constitute relevant hematological alterations in the estimation of hospital mortality[23,28].

The relationship between a high neutrophil-lymphocyte ratio (NLR) and a higher risk at the onset of infection has been identified in COVID-19 patients. The presence of lymphopenia is associated with an inadequate immune response, while neutrophilia may reflect an exacerbated inflammatory response. Thus, early identification of these characteristics is important for early intervention and prevention of a more serious clinical condition[22,23].

Studies that monitored NLR showed that the more pronounced the neutrophilia and lymphopenia, the more likely the patient was to develop an unfavorable outcome. Therefore, NLR can be used as a predictor of fatal outcome among patients

with COVID-19 12, 27, 28. They also found that the elderly and individuals with comorbidities such as obesity, diabetes, cancer and atherosclerosis have high serum levels of pro-inflammatory cytokines. These individuals are more likely to have an increase in NLR and therefore a worse prognosis, due to the likelihood of an increase in the severity of the disease. The higher the NLR, the higher the levels of inflammatory cytokines (IL-1, IL-6, IL-10), which trigger an inflammatory response, with an increase in neutrophils, which, in response to the virulence of SARS-CoV-2, increase the production of free radicals[1,21,23].

Reduced glutathione and glutathione peroxidase: their roles as antioxidant factors and relationship with COVID-19

GSH and Gpx are the constituents of the enzymatic antioxidant system that have the largest share of the thiol group in the intracellular environment. When Gpx encounters an oxidizing element, its function is to reduce it, so GSH is oxidized to glutathione disulphide (GSSG). This reaction can be reversed by other components of the redox system, such as glutathione reductase (Grd)[1,30,31,32].

Therefore, it is inferred that if there is an increase in the amount of oxidizing substances, the GSH index will decrease and the disulfide index (SS) will increase, making the cell more susceptible to oxidative damage. During SARS-CoV-2 infection, they found that GSH and Gpx were lower in patients infected with SARS-CoV-2 when compared to the levels measured in healthy individuals (non-ICU: 227.03; ICU without EI: 134.54; ICU with EI: 102.11; CG: 374.94; $p < 0.001$), demonstrating the occurrence of possible oxidative damage during the disease[12,14,19,32,33].

Thus, low levels of thiol and high levels of SS may be related to the severity of the infection. Therefore, these results corroborate the assumption that OS is relevant in the pathophysiology of COVID-19[12,14,19].

Superoxide dismutase and catalase: actions as antioxidant factors and relationship withCOVID-19

SOD and CAT are some of the main enzymatic antioxidants in the body and are responsible for slowing down or stopping the oxidation of oxidizable substrates. SOD reduces ROS by removing superoxide radicals; CAT acts by fighting excess methemoglobin and degrading H_2O_2. However, in general, serum levels of these enzymes are lower in COVID-19 patients than in control cases[12,34]. It is worth mentioning that in some studies CAT showeda slight increase in patients with the disease compared to the control group or no statistically significant difference, thus representing a counterpoint to other studies evaluated[14,15].

Mineral elements and vitamins: antioxidant functions

Deficiency of vitamins and minerals, such as vitamin D (Vit D) and Mg, can negativelyaffect the modulation of the immune system. Likewise, insufficiency of vitamin E (Vit E), a lipophilic antioxidant, compromises the non-enzymatic antioxidant system, which protects cells against lipid peroxidation. However, COVID-19 infection can trigger depletion of both micromineral elements (Zn and Cu) and macrominerals (Mg), as well as vitamins. Zn deficiency was related to the most unfavorable outcomes; they also showed that severe patientswere more likely to be depleted of these elements when compared to healthy individuals[12,35,36]. In this way, the replacement of vitamins and minerals contributes to the homeostasis of theredox system through the action of these substances in attenuating the inflammatory response because they have antioxidant properties and contribute to more favorable clinical outcomes[37,38].

Structural alteration of albumin and oxidative stress

Albumin has antioxidant and antithrombotic functions, with the ability to sequester ROS, Fe ions2+ and other oxidizing elements present in the bloodstream, and in pathological conditions, it becomes essential for the favorable clinical evolution of the patient[39]. However, the biological functions of albumin are compromised in severe inflammatory processes, in which there is an increase in vessel permeability with extravasation of albumin into the extracellular medium and a consequent decrease in half-life. This mechanism results in hypoalbuminemia, which can contribute to a worsening of the patient's clinical condition and potential death, regardless of the pathology in question[40].

Although albumin has antioxidant actions on ROS, ROS also influence albumin, oxidizing it and modifying its structure, especially in conditions of OS, where CAT and SOD do not neutralize the excess of ROS41. In addition to inflammation and OS triggering hypoalbuminemia, albumin oxidation stimulates the release of cytokines such as IL-6 and leukocyte adhesion molecules, which generates a pro-inflammatory effect on tissues, triggering a cycle of worsening disease42. This phenomenon also manifests itself among patients hospitalized with COVID-19, as they are at greater risk of developing severe symptoms, thrombotic events and death[43,44].

Total antioxidant power, total oxidant status and plasma peroxides in oxidative stress

Hydrogen peroxide (H_2O_2) is formed from the dismutation of the superoxide radical $O2^-$, by SOD, and is subsequently eliminated by the action of other antioxidants, such as CAT and GSH. Although H_2O_2 is not a free radical, as it has no free electrons in the last electronic layer, it is highly reactive, especially with transition metals such as iron, which reacts to form a highly reactive radical, HO·. Thus, critically ill patients with a fatal outcome had high PP compared to mild patients; the Oxidative stress index(OSI), measured in the spectrophotometer by comparing the reference values of d-ROM and PAT to those presented by the patients, was shown to quadruple during the illness, signifying the exacerbated action of oxidizing agents with depletion of antioxidant substrates. PAT was also found to be increased in ICU patients. This result shows that the body has reduced its capacity for synergistic action of antioxidant

elements, due to the increase in oxidizing activity related to OS, which compromises homeostasis and leads to a fatal outcome[19,21,45].

Heterogeneity of the methods used to measure oxidative stress levels

Different methods of analysis have been used by the researches to monitor the data relating to the OS, the component proteins of the enzymatic system and the elements of the non-enzymatic system. Some of the methods used were the ELISA kit, the rapid REDOX kit, cytometry and the automated spectrophotometric method. In addition to these, new studies are using different methodologies to identify and quantify the OS that occurs during the COVID- 19 disease triggered by the new coronavirus. Thus, the use of different methodologies made it difficult to compare the results between the articles; however, despite this caveat, there was an association between the level of OS and the severity of the clinical condition associated with COVID-19.

Limitations of the studies

The studies carried out had quantitative limitations regarding sample size, given the emergency situation during the COVID-19 pandemic. Studies were carried out with a small number of patients because they were carried out over a short period of time and some did not have the possibility of comparing the results with control groups. It is therefore essential that these studies are continued, in the different locations where they were carried out post- pandemic, retrospectively and prospectively, with larger sample sizes, so that it is possible to confirm or not the results found during the pandemic.

CONCLUSION

Therefore, OS plays a relevant role in the pathophysiology of COVID-19 and high levels of markers related to it, such as changes in ROS concentrations, enzymes and antioxidant substrates which, together with the individual inflammatory response (IER), may be related to the severity of the patients' clinical condition. Thus, individuals with a disproportionately aggressive immune response to the virus produce excess ROS, which requires greater activity from the antioxidant systems. As a result of this exacerbated activity, damage is caused to proteins, lipids and genetic material and the inflammatory condition worsens. This creates a cycle of imbalance between ES and RII which results in a progressive deterioration in the clinical condition of individuals with severe forms of COVIDB-19.

REFERENCES

1. Velloso JCR, Biavatti M, Françóia PCO, Mello BJ de, Almeida AC de, Bueno GE. Estresse oxidativo: uma introdução ao estado da arte / oxidative stress: an introduction to the state of art. Braz J Dev. 2021;7(1):10152-68. Doi: https://doi.org/10.34117/bjdv7n1-688.
2. Almeida, LT. Avaliação do estresse oxidativo e defesas antioxidantes na infecção pelo zika virus (Flaviviridae) [Tese - Doutorado]. Ouro Preto(MG): Universidade Federal de Ouro Preto, 2020.
3. Souto MD, Xavier DE de F, Dourado KF, de Moura MWS, de Aguiar GB, de Andrade MIS, et al. Níveis de albumina sérica e o desfecho de pacientes internados com COVID-19 no estado de Pernambuco. Braz J Develop. 2022;8(9):64929-47. Doi: https://doi.org/10.34117/bjdv8n9-300.
4. Barreiros ALBS, David JM, David JP. Estresse oxidativo: relação entre geração de espécies reativas e defesa do organismo. Química Nova [Internet]. 2006. 29(1):113–23. DOI: https://doi.org/10.1590/S0100-40422006000100021.
5. Sharif-Askari NS, Sharif-Askari FS, Mdkhana B, Hussain Alsayed HA, Alsafar H, Alrais ZF, et al. Upregulation of oxidative stress gene markers during SARS-COV-2 viral infection. Free Radic Biol Med. agosto de 2021;172:688–98. DOI: 10.1016/j.freeradbiomed.2021.06.018.
6. Delgado-Roche L, Mesta F. Oxidative Stress as Key Player in Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection. Arch. Med. Res. julho de 2020;51(5):384–7. DOI: 10.1016/j.arcmed.2020.04.019.
7. Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? Aging. 29 de maio de 2020;12(10):9959–81. DOI: 10.18632/aging.103344.
8. Scholz JR, Lopes MACQ, Saraiva JFK, Colombo FC. COVID-19, Renin-Angiotensin System, Angiotensin-Converting Enzyme 2, and Nicotine: What is the Interrelation? Arq. Bras. Cardiol. 13 de outubro de 2020;115(4):708–11. DOI: 10.36660/abc.20200653.
9. Oliveira YPA. O papel de ros (espécies reativas de oxigênio) na exacerbação da resposta inflamatória na sepse [Dissertação - Mestrado]. Salvador(BA): Fundação Oswaldo Cruz, Centro de Pesquisas Gonçalo Moniz, 2011.
10. WORLD HEALTH ORGANIZATION (WHO). Health Emergency Dashboard. 2021.
11. Hecke, OV, Lee J. N-acetylcysteine: A rapid review of the evidence for effectiveness in treating COVID-19. Oxford COVID-19 Evidence Service. 2020. https://www.cebm.
12. Kalem AK, Kayaaslan B, Neselioglu S, Eser F, Hasanoglu İ, Aypak A, et al. A useful and sensitive marker in the prediction of COVID-19 and disease severity: Thiol Free Radic Biol Med. 2021;166:11-7. Doi: 10.1016/j.freeradbiomed.2021.02.009.
13. Dominic P, Ahmad J, Bhandari R, Pardue S, Solorzano J, Jaisingh K, et al. A diminuição da disponibilidade de óxido nítrico e sulfeto de hidrogênio é uma marca registrada da COVID-19. Redox Biol [Internet]. 2021;43:101982. Doi: http://dx.doi.org/10.1016/j.redox.2021.101982
14. Muhammad Y, Kani YA, Iliya S, Muhammad JB, Binji A, El-Fulaty Ahmad A, et al. Deficiency of antioxidants and increased oxidative stress in COVID-19 patients: A cross-sectional comparative study in Jigawa, Northwestern Nigeria. SAGE Open Med. 2021;9:205031212199124. Doi: 10.1177/2050312121991246.

15. Cekerevac I, Turnic TN, Draginic N, Andjic M, Zivkovic V, Simovic S, et al. Predicting Severity and Intrahospital Mortality in COVID-19: The Place and Role of Oxidative Stress. Kocic G, organizador. Oxidative Med Cel Longev. 2021:1-15. Doi: 10.1155/2021/6615787.

16. Meyer K, Patra T, Mahantesh V, Ray R. SARS-CoV-2 spike protein expressing epithelial cells promotes senescence associated secretory phenotype in endothelial cells and increased inflammatory response. Immunology. 202195(17):1-12. Doi: 10.1128/JVI.00794-21.

17. Mortaz E, Malkmohammad M, Jamaati H, Naghan PA, Hashemian SM, Tabarsi P, et al. Silent hypoxia: higher NO in red blood cells of COVID-19 patients. BMC Pulm Med. 2020;20(1):269. Doi: 10.1186/s12890-020-01310-8.

18. Arcanjo A, Logullo J, Menezes CCB, Giangiarulo TCSC, dos Reis MC, de Castro GMM, et al. The emerging role of neutrophil extracellular traps in severe acute respiratory syndrome coronavirus 2 (COVID-19). Scient Rep. 2020;10(1). Doi: https://doi.org/10.1038/s41598-020-76781-0.

19. Karkhanei B, Talebi Ghane E, Mehri F. Evaluation of oxidative stress level: total antioxidant capacity, total oxidant status and glutathione activity in patients with COVID-19. New Microbes New Infect. 2021;42:100897. Doi: 10.1016/j.nmni.2021.100897.

20. Badawy MA, Yasseen BA, El-Messiery RM, Abdel-Rahman EA, Elkhodiry AA, Kamel AG, et al. Neutrophil-mediated Oxidative Stress and Albumin Structural Damage Predict COVID-19-associated Mortality. Infectious Diseases (except HIV/AIDS); 2021;10:e69417: 1-22. Doi: https://doi.org/10.1101/2021.04.01.21254767.

21. Zendelovska, D, Atanasovska E, Petrushevska M, Spasovska K, Stevanovikj M, Demiri I, Labachevski N. Evaluation of oxidative stress markers in hospitalized patients with moderate and severe COVID-19. Rom J Intern Med. 2021;59(4):375-83. Doi: 10.2478/rjim-2021-0014.

22. Gadotti AC, Lipinski AL, Vasconcellos FT, Marqueze LF, Cunha EB, Campos AC, et al. Susceptibility of the patients infected with Sars-Cov2 to oxidative stress and possible interplay with severity of the disease. Free Radic Biol Med. 2021;165:184-90. Doi: 10.1016/j.freeradbiomed.2021.01.044.

23. Laforge M, Elbim C, Frère C, Hémadi M, Massaad C, Nuss P, et al. Tissue damage from neutrophil-induced oxidative stress in COVID-19. Nat Rev Immunol. 2020;20(9):515-6. Doi: 10.1038/s41577-020-0407-1.

24. Wu J. "Tackle the free radicals damage in COVID-19." Nitric oxide: Biol Chemist. 2020;102:39-41. Doi:10.1016/j.niox.2020.06.002

25. Lisi F, Zelikin AN, Chandrawati R. Nitric Oxide to Fight Viral Infections. Adv Sci (Weinh). 2021;9;8(7):2003895. PMID: 33850691; PMCID: PMC7995026. DOI: 10.1002/advs.202003895.

26. Feng WX, Yang Y, Wen J, Liu YX, Liu L, Feng C. Implication of inhaled nitric oxide for the treatment of critically ill COVID-19 patients with pulmonary hypertension. ESC Heart Fail. 2021;8(1):714-8. Doi:10.1002/ehf2.13023.

27. Martelli F, Nunes FMF. Radicais livres: em busca do equilíbrio. Cienc Cult. 2014;66(3):54-7. Doi: http://dx.doi.org/10.21800/S0009-67252014000300017.

28. Zhang B, Zhou X, Zhu C, Song Y, Feng F, Qiu Y, et al. Immune phenotyping based on the neutrophil-to-lymphocyte ratio and IgG level predicts disease severity and outcome for patients with COVID-19. Front Mol Biosci. 2020;7:157. Doi: 10.3389/fmolb.2020.00157.

29. Alves JMR. Relação neutrófilo-linfócito e resposta imune como fatores de prognóstico para COVID-19. Rev Bras Anal Clin. 2020;52(2). Doi: 10.21877/2448-3877.20200014.

30. Souza LF. Modulação redox de peroxirredoxinas e a participação dos sistemas da GSH e da Trx na proteção/função celular [Tese - Doutorado]. Florianópolis(SC): Universidade Federal de Santa Catarina - Centro de Ciências Biológicas, 2017.

31. Rover Júnior L, Höehr NF, Vellasco AP, Kubota LT. Sistema antioxidante envolvendo o ciclo metabólico da glutationa associado a métodos eletroanalíticos na avaliação do estresse oxidativo. Quím Nova. 2001;24(1). Doi: https://doi.org/10.1590/S0100-40422001000100019.

32. Barbosa KBF, Costa NMB, Alfenas RCG, De Paula SO, Minim VPR, Bressan J. Estresse oxidativo: conceito, implicações e fatores modulatórios. Rev Nutr. 2010;23(4):629-43. Doi: https://doi.org/10.1590/S1415-52732010000400013.

33. Cecchini R, Cecchini AL. SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. Med Hypotheses. 2020;143:110102. Doi: 10.1016/j.mehy.2020.110102.

34. Carvalho LBV. Avaliação dos níveis de estresse oxidativo induzido por exposição ao mercúrio em população ribeirinha infantojuvenil do rio Madeira (RO) [Dissertação - Mestrado]. Rio de Janeiro(RJ): Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz, 2016.

35. Silva AA, Gonçalves RC. Espécies reativas do oxigênio e as doenças respiratórias em grandes animais. Cienc Rural. 2010;40(4):994-1002. Doi: https://doi.org/10.1590/S0103-84782010005000037.

36. Sethuram R, Bai D, Abu-Soud HM. Potential role of zinc in the COVID-19 disease process and its probable impact on reproduction. Reprod Sci. 2022;29(1):1-6. Doi: 10.1007/s43032-020-00400-6.

37. DiNicolantonio JJ, O'Keefe JH. Magnesium and vitamin D deficiency as a potential cause of immune dysfunction, cytokine storm and disseminated intravascular coagulation in covid-19 patients. Mo Med. 2021;118(1):68-73. PMCID: PMC7861592 PMID: 33551489.

38. Lima WL, Batista MCC, Silvino VO, Moura RC de, Mendes IL, Moura MSB de. et al. Importância nutricional das vitaminas e minerais na infecção da COVID-19. Res Soc Dev. 2020;9(8). Doi: http://dx.doi.org/10.33448/rsd-v9i8.610.

39. Chavarría AP, Vázquez RRV, Cherit JGD, Bello HH, Suastegui HC, Moreno-Castañeda L, et al. Antioxidants and pentoxifylline as coadjuvant measures to standard therapy to improve prognosis of patients with pneumonia by COVID-19. Comput Struct Biotechnol J. 2021;19:1379-90. Doi: 10.1016/j.csbj.2021.02.009.

40. Deng S, Liu S, Jin P, Feng S, Tian M, Wei P, Zhu H, Tan J, Zhao F, Gong Y. Albumin Reduces Oxidative Stress and Neuronal Apoptosis via the ERK/Nrf2/HO-1 Pathway after Intracerebral Hemorrhage in Rats. Oxid Med Cell Longev. 2021;1:1-14. Doi: 10.1155/2021/8891373.

41. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. J Parenter Enter Nutr. 2019;43(2):181-93. Doi: 10.1002/jpen.1451.

42. Roy D. Role of reactive oxygen species on the formation of the novel diagnostic marker ischaemia modified albumin. Heart. 2006;92(1):113-4. Doi: 10.1136/hrt.2004.049643.

43. Magzal F, Sela S, Szuchman-Sapir A, Tamir S, Michelis R, Kristal B. In-vivo oxidized albumin– a pro-inflammatory agent in hypoalbuminemia. PLoS One. 2017;12(5):e0177799. Doi: 10.1371/journal.pone.0177799.

44. Kheir M, Saleem F, Wang C, Mann A, Chua J. Higher albumin levels on admission predict better prognosis in patients with confirmed COVID-19. PLoS One. 2021;16(3):e0248358. PMID: 33725003; PMCID: PMC7963065. Doi: 10.1371/journal.pone.0248358.

45. Acharya R, Poudel D, Bowers R, Patel A, Schultz E, Bourgeois M, et al. Low Serum Albumin Predicts Severe Outcomes in COVID-19 Infection: A Single-Center Retrospective Case-Control Study. J Clin Med Res. 2021;13(5):258-67. Doi: 10.14740/jocmr4507.

46. Costa JO. Capacidade antioxidantes total do plasma: associações com componentes do risco cardiometabólico e consumo alimentar em jovens não obesos e clinicamente saudáveis [Dissertação - Mestrado]. Aracaju (SE):Universidade Federal de Sergipe, 2015.

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