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Oxidative stress and inflammatory markers in patients with COVID-19: Potential role of RAGE, HMGB1, GFAP and COX-2 in disease severity

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ABSTRACT

Background: SARS-CoV-2 infection can lead to the abnormal induction of cytokines and a dysregulated hyper-inflammatory state that is implicated in disease severity and risk of death. There are several molecules present in blood associated with immune cellular response, inflammation, and oxidative stress that could be used as severity markers in respiratory viral infections such as COVID-19. However, there is a lack of clinical studies evaluating the role of oxidative stress-related molecules including glial fibrillary acidic protein (GFAP), the receptor for advanced glycation end products (RAGE), high mobility group box-1 protein (HMGB1) and cyclooxygenase-2 (COX-2) in COVID-19 pathogenesis.

Aim: To evaluate the role of oxidative stress-related molecules in COVID-19.

Method: An observational study with 93 Brazilian participants from September 2020 to April 2021, comprising 23 patients with COVID-19 admitted to intensive care unit (ICU), 19 outpatients with COVID-19 with mild to moderate symptoms, 17 individuals reporting a COVID-19 history, and 34 healthy controls. Blood samples were taken from all participants and western blot assay was used to determine the RAGE, HMGB1, GFAP, and COX-2 immunocontent.

Results: We found that GFAP levels were higher in patients with severe or critical COVID-19 compared to outpatients ($p = 0.030$) and controls ($p < 0.001$). A significant increase in immunocontents of RAGE ($p < 0.001$) and HMGB1 ($p < 0.001$) were also found among patients admitted to the ICU compared to healthy controls, as well as an overexpression of the inducible COX-2 ($p < 0.001$). In addition, we found a moderate to strong correlation between RAGE, GFAP and HMGB1 proteins.

Conclusion: SARS-CoV-2 infection induces the upregulation of GFAP, RAGE, HMGB1, and COX-2 in patients with the most severe forms of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) is defined primarily as a respiratory disease caused by a single-stranded RNA virus known as SARS-CoV-2. This novel betacoronavirus has a genome size of approximately

29.9 kb [1] packed in an envelope with four associated structural (S, E, M, and N) and sixteen non-structural proteins (nsp1 – 16) [2]. There is evidence that the SARS-CoV-2 S protein is essential for infectivity [3]. The binding between the SARS-CoV-2 S protein and the human angiotensin-converting enzyme 2 (hACE2) [4], which is expressed

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particularly in the kidneys, heart, and respiratory and gastrointestinal tract tissues can lead to the abnormal induction of cytokines and a dysregulated hyperinflammatory state that is implicated in disease severity and risk of death [5,6].

Growing evidence has shown that hACE2 can also be expressed in brain capillary endothelial cells, neurons, astrocytes, oligodendrocytes, and the olfactory bulb [7]. In addition to the possibility of direct viral invasion, it has been proposed that SARS-CoV-2 infection can affect the nervous system through cerebrovascular changes, immune-mediated injury, and peripheral organ dysfunction [8,9]. In a study carried out in Wuhan, China, with hospitalized COVID-19 patients, a prevalence of 36.4% of nervous system manifestations was found, mainly dizziness, headache, and chemosensory disturbances. Moreover, neurological symptoms were significantly more common in severe infections and included acute cerebrovascular disease, impaired consciousness, and skeletal muscle injury [10].

Although studies have suggested a possible direct viral invasion of SARS-CoV-2 into hepatocytes [11], cardiomyocytes [12], alveolar epithelial cells [13] and the nervous system [14], most clinical manifestations of COVID-19 are associated with systemic inflammation and oxidative stress. It has been demonstrated that reduction in ACE2 bioavailability after SARS-CoV-2 binding allows angiotensin II to be available to interact with AT1R, which mediates signals for activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase leading to oxidative stress and inflammatory responses [15]. Therefore, several molecules present in the blood that are associated with immune cellular response, inflammation, and oxidative stress could be used as severity markers in COVID-19 patients. There is evidence that the increased levels of IL-6, C-reactive protein, ferritin, and procalcitonin; increased erythrocyte sedimentation rate; decreased CD4 and CD8 count cells; changes in biochemical indices (albumin, blood urea nitrogen, creatinine, creatine kinase, hypersensitive cardiac troponin I, and lactate dehydrogenase); and coagulation abnormalities, including prolonged prothrombin time, increased d-dimer and thrombocytopenia, are important predictors for mortality in patients with COVID-19 [6]. However, there is a lack of clinical studies evaluating the role of oxidative stress-related molecules including glial fibrillary acidic protein (GFAP), receptor for advanced glycation end products (RAGE), high mobility group box-1 protein (HMGB1) and cyclo-oxygenase-2 (COX-2) in COVID-19 pathogenesis.

GFAP is a cytoskeleton glial protein expressed in astrocytes that regulates the morphology and function of these cells in the central nervous system (CNS). The plasmatic concentration of GFAP is typically not detectable in healthy individuals [16], but increased GFAP levels are considered a nonspecific marker of CNS pathology [17]. Recent studies have shown increased levels of GFAP in patients with COVID-19 and discussed the potential role of this biomarker in SARS-CoV-2 neuro-pathogenesis [18–20].

RAGE is a member of the immunoglobulin superfamily of receptors and can be present in two forms: membrane-bound RAGE (mRAGE) and soluble RAGE (sRAGE). This receptor is expressed in a wide array of cell types including microglia, neurons, endothelial vascular cells, cardiomyocytes and alveolar pneumocytes [21–23], and is involved in inflammatory responses, oxidative stress, and cellular dysfunction in several conditions [24,25]. It was found that RAGE can play an important role as a receptor target for HMGB1, a nonhistone chromosomal protein that mediates late activation of the innate immune response to infection, including the release of chemotactic factors, the upregulation of the COX-2/PGE₂ axis, and the production of proinflammatory cytokines [26–28]. In addition, there is evidence that some respiratory viruses can lead to oxidative stress due to the sequestration of the secretory pathway for the manufacture of viral glycoproteins on infected cells [29], and thus mediate HMGB1 secretion, amplifying the inflammatory response and disease severity [30,31].

This clinical study evaluated the role of RAGE, HMGB1, GFAP (and breakdown products) and COX-2 in patients with COVID-19.

2. Materials and methods

2.1. Study design

This observational study enrolled 93 individuals from Sergipe state, Northeast Brazil, from September 2020 up to April 2021. This group comprised 23 patients with COVID-19 admitted to intensive care unit (ICU), 19 outpatients with COVID-19 with mild to moderate symptoms, 17 individuals reporting a COVID-19 history, and 34 healthy controls. All individuals were tested using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal swab or by serology because of the limited availability of laboratory resources and molecular tests in a resource poor setting. Blood was collected from all individuals to test for oxidative stress-related molecules using western blot assay. Demographic data (age and sex) were collected from all patients. Participants with negative serology without a history of positive RT-PCR for SARS-CoV-2 were included in the control group. All participants received written information about the study and were asked to give written informed consent for participation. This study was approved by the institutional review board of the Federal University of Sergipe (CAAE: 34240620.7.0000.5546).

2.2. Plasma sample preparation

Blood samples were collected with 4 mL EDTA tubes and processed by centrifugation at 2500 g for 15 min at room temperature. Plasma aliquots were frozen at – 80 °C and the samples were thawed only once during the processing. To perform the analysis, total plasma proteins were measured by Bradford assay [32]. The levels of RAGE, HMGB1, GFAP, and COX-2 were measured in plasma samples as described below.

2.3. Western blot assay

Western blot assay was used to determine the RAGE, HMGB1, GFAP, and COX-2 immunocontent. Plasma aliquots from patients and controls were prepared by addition of Laemmli buffer 4x and heated at 95 °C for 5 min. First, measured plasma proteins (total proteins) allowed the equivalent amount of proteins required for each sample to be determined (40 µg of proteins). Samples were separated by SDS-PAGE and transferred to nitrocellulose membranes (BioRad) for 1 h at 25 V in a transfer buffer (48 mM Tris, 39 mM glycine, 20% methanol and 1.3 mM SDS). The nitrocellulose membranes were washed for 5 min in Tris-buffered saline with 0.1% Tween-20 (T-TBS; 0.5 M NaCl, 20 mM Tris, 0.1% Tween-20, pH 7.5), followed by 1 h incubation in blocking solution (T-TBS plus 5% defatted dried milk). The blots were incubated overnight at 4 °C in blocking solution containing the following antibodies at a dilution of 1:1000: anti-COX2 [(clone D5H5) Cell Signaling Technology], anti-RAGE [Cell Signaling Technology, cs 4679], anti-HMGB1 [(D3E5) Cell Signaling Technology, cs 6893] and anti-GFAP [(GA5) Cell Signaling Technology, cs 3670]. Then, the blots were washed three times for 15 min with T-TBS and incubated for 2 h in blocking solution containing peroxidase conjugated anti-rabbit or anti-mouse IgG diluted 1:4000. Finally, the blots were washed twice again for 15 min with T-TBS and twice for 15 min with TBS, and developed using a chemiluminescence substrate. The densitometric band quantification was performed by ImageJ 1.5 k software (National Institute of Health, USA). Normalization of western blots was performed using Ponceau S. Results were expressed as arbitrary units.

2.4. Statistical analysis

Data were expressed as median and quartiles (Q1 and Q3). Differences in biomarker levels between groups were determined using the Kruskal-Wallis test followed by Dunn's post hoc test for multiple comparisons. Correlations between biomarkers were tested using Spearman's correlation coefficients (*rho*). The strength of the correlation was

considered very weak if the ρ was 0–0.19; weak, 0.2–0.39; moderate, 0.4–0.59; strong, 0.6–0.79; and very strong, 0.8–1.0. Two-sided p-values less than 0.05 were considered statistically significant. Analyses were performed using Prism 8.0 software (GraphPad Prism Software Inc., San Diego, CA, USA).

3. Results

3.1. Sample characteristics

The mean age of participants was 44.6 ± 16.4 years (minimum 11, maximum 100), and most of them were female (55.9%; 52/93). All patients with COVID-19 admitted to the ICU had severe or critical COVID-19, whereas all outpatients had mild to moderate symptoms and most individuals with COVID-19 history were asymptomatic

3.2. Immunocontent of GFAP in plasma

Fig. 1 summarizes the levels of GFAP and GFAP breakdown products (GFAP-BDP) among COVID-19 patients admitted to the ICU, outpatients, individuals with COVID-19 history and controls. We found that GFAP and GFAP-BDP levels were higher in patients with severe or critical COVID-19 compared to the outpatients (GFAP: 1.22 [0.97 – 1.66] vs. 1.07 [0.60 – 1.30]; $p = 0.030$ / GFAP-BDP: 1.16 [0.97 – 1.43] vs. 0.74 [0.59 – 1.21]; $p = 0.012$) and controls (GFAP: 1.22 [0.97 – 1.66] vs. 0.86 [0.61 – 1.13]; $p < 0.001$ / GFAP-BDP: 1.16 [0.97 – 1.43] vs. 0.67 [0.51 – 0.82]; $p < 0.001$). Individuals with COVID-19 history had also higher levels of GFAP ($p = 0.018$) and GFAP-BDP ($p = 0.007$) than controls. In addition, our analysis showed that GFAP-BDP was higher in outpatients with COVID-19 compared to the healthy control group ($p = 0.034$).

3.3. Immunocontent of RAGE and HMGB1 in plasma

A significant increase in immunocontents of RAGE were found among patients admitted to the ICU (1.11 [0.96 – 1.43]) compared to those with a COVID-19 history (0.61 [0.46 – 1.05]; $p < 0.001$) and healthy controls (0.71 [0.53 – 1.03]; $p < 0.001$). Outpatients with COVID-19 also had higher levels of RAGE than individuals with a

COVID-19 history ($p = 0.040$) and controls ($p = 0.013$) (Fig. 2A).

HMGB1 levels were higher among patients in ICU group (0.91 [0.61 – 1.29]) compared to outpatients with COVID-19 (0.67 [0.49 – 0.99]; $p = 0.032$) and controls (0.62 [0.42 – 0.71]; $p < 0.001$). In addition, we found differences between HMGB1 levels between patients with COVID-19 history (higher levels) and healthy controls ($p = 0.023$) (Fig. 2B). RAGE and HMGB1 levels, representative blots and Ponceau S stain for each study group are shown in Fig. 2.

3.4. Immunocontent of COX-2

The present study demonstrated that the inducible COX-2 is over-expressed in patients with severe or critical SARS-CoV-2 infection (1.04 [0.60 – 1.33]) compared to patients with mild to moderate COVID-19 (0.47 [0.35 – 0.69]; $p = 0.004$) and healthy controls (0.45 [0.25 – 0.65]; $p < 0.001$). Individuals with COVID-19 history had also higher levels of COX-2 than controls ($p = 0.004$) (Fig. 3).

3.5. Correlations between biomarkers levels

We explored the relationship between (1) RAGE and HMGB1; (2) RAGE and GFAP; (3) RAGE and COX-2; (4) HMGB1 and GFAP; and (5) HMGB1 and COX-2 using the samples from patients admitted to the ICU. There was a strong positive correlation between RAGE and HMGB1 ($p < 0.001$; $\rho = 0.735$) (Fig. 4A) and a moderate positive correlation between RAGE and GFAP ($p = 0.014$; $\rho = 0.532$) (Fig. 4B). In addition, we found a moderate positive correlation between HMGB1 and GFAP ($p = 0.014$; $\rho = 0.518$) (Fig. 4C). No correlation was found between RAGE and GFAP-BDP ($p = 0.434$), RAGE and COX-2 ($p = 0.141$), HMGB1 and GFAP-BDP ($p = 0.360$), and HMGB1 and COX-2 ($p = 0.375$).

4. Discussion

There is evidence that SARS-CoV-2 infection can increase the risk of cardiac, renal, gastrointestinal, and endocrine complications [33,34]. Moreover, patients with COVID-19 can develop a broad spectrum of neurological symptoms including ischemic stroke, meningoencephalitis,

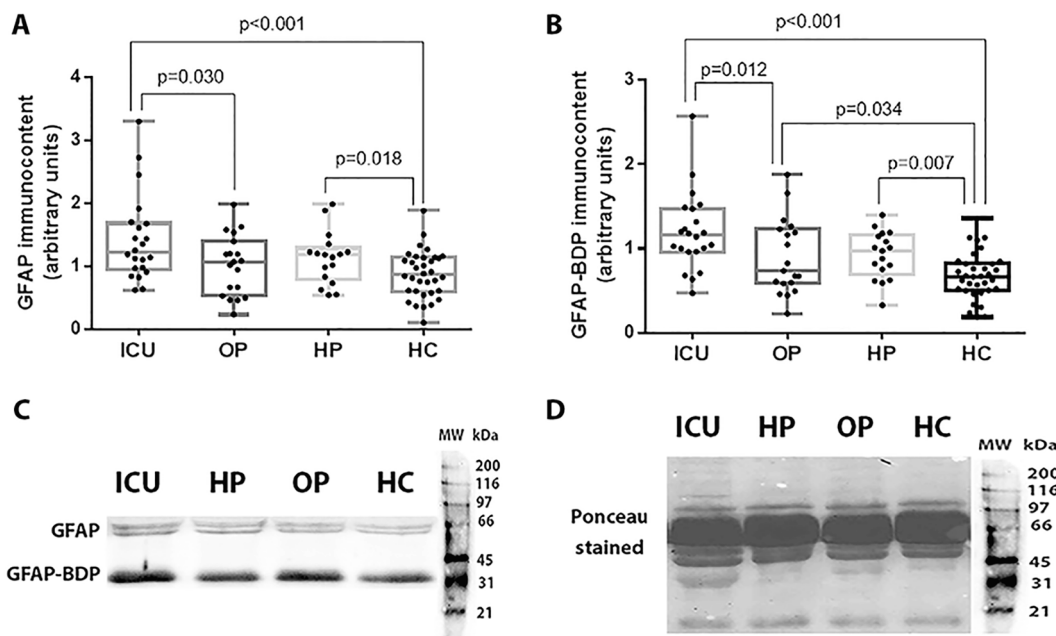


Fig. 1. GFAP (A) and GFAP-BDP (B) levels among COVID-19 patients admitted to the ICU (ICU), outpatients (OP), patients with COVID-19 history (HP), and healthy controls (HC). Representative blots and Ponceau S stain are shown in Fig. 1C and 1D, respectively. Statistically significant differences were determined by Kruskal-Wallis test followed by Dunn's post hoc test for multiple comparisons.

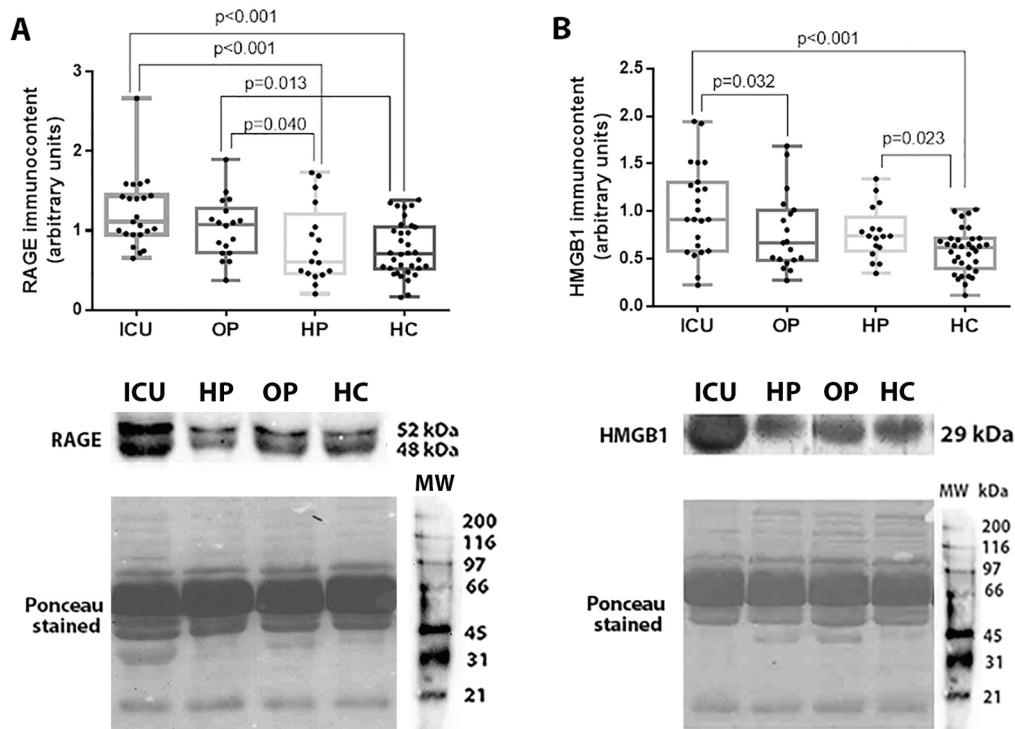


Fig. 2. RAGE (A) and HMGB1 (B) levels among COVID-19 patients admitted to the ICU (ICU), outpatients (OP), patients with COVID-19 history (HC), and healthy controls (HC). Representative blots and Ponceau S stain for RAGE and HMGB1 are shown in Fig. 2C and 2D, respectively. Statistically significant differences were determined by Kruskal-Wallis test followed by Dunn's post hoc test for multiple comparisons.

encephalopathy, acute necrotizing encephalopathy, Guillain-Barré syndrome, and acute disseminated encephalomyelitis [14,35–37]. A wide range of biomolecules associated with the inflammatory and immune cell response, which are used as predictors of organ failure and severity in other diseases, are also being studied in patients with COVID-19 [38,39]. It has been found that several inflammatory and oxidative mediators are misregulated in COVID-19 and are associated with multiorgan damage and poor disease prognosis [40,41].

This study evaluated the role of the inflammatory and oxidative biomolecules GFAP, RAGE, HMGB1 and COX-2 in the COVID-19 pathophysiology. Our findings showed that the levels of these biomarkers were higher in patients with the most severe forms of COVID-19. In addition, we found a moderate to strong correlation between RAGE, GFAP and HMGB1 proteins.

The results obtained from the analysis of GFAP and GFAP-DBP levels may suggest that patients with SARS-CoV-2 infection are at increased risk of astrocytic damage and neural dysfunction, especially among those with severe or critical COVID-19. These findings have also been suggested in other studies [19,42,43] and reinforce the capacity for neural damage caused by the infection. There is growing evidence of the role of astrocytes in the brain response to SARS-CoV-2-triggered neuroinflammation. It has been found that these cells might be targets of SARS-CoV-2 [44] and play a key role in the control of the cytokine microenvironment and brain function in COVID-19 [45,46]. Therefore, elevated serum levels of GFAP may be useful for diagnosis and prognosis of COVID-19 and brain dysfunction.

Furthermore, the disintegration of astrocytes, detected by the GFAP upregulation, can stimulate the overexpression of other inflammatory mediators involved in neurological damage. Necroptotic astrocytes release the HMGB1 protein and stimulate the HMGB1-RAGE axis [47,48] that can induce inflammatory events leading to organ dysfunctions, including the brain. The binding of HMGB1 to RAGE promotes the transcription of inflammatory factors including the NF κ B and MAPK pathways [49], and its sustained activation causes cell death by stimulating the production of reactive oxygen species [50]. It has been

found that the HMGB1-RAGE axis plays a significant role in a wide spectrum of pathological responses such as Alzheimer's disease, brain injury-induced pulmonary dysfunction, chronic inflammatory conditions, cancer, and sepsis [51–55].

Recent studies have suggested the activation of HMGB1-RAGE cascade in COVID-19 pathogenesis [56,57] and an association with disease severity [21,58]. In this respect, our results showed an overexpression of HMGB1 and RAGE proteins in the plasma of patients with COVID-19, confirming that this effect is a common finding in the most severe forms of the disease. In addition, the misregulation of RAGE signaling has been reported as an important factor in sustaining the pathological states in the most common comorbidities of COVID-19 [59]. Therefore, the assessment of the HMGB1-RAGE axis as a predictor of COVID-19 severity may be important in individuals with pre-existing medical conditions.

The cyclooxygenase family has also been found to play an important role in COVID-19 [60]. The inducible COX-2 enzyme has a central role in viral infections and regulates the expression levels of many serum proteins, including proinflammatory cytokines that directly influence the physiological regulation [61]. There is evidence that COX-2 overexpression has been described in patients who have died of H5N1 infection [62], suggesting that this enzyme is associated with poor clinical outcomes in viral infections. Moreover, the production of COX-2 metabolites can lead to coagulopathy and hyperinflammation [63], common findings in patients with severe COVID-19. Recently, it was found that SARS-CoV-2 induced COX-2 upregulation in diverse human cell culture and mouse systems [64], which may be implicated in regulating lung inflammation and disease severity as observed in the present study. In addition, the upregulation of COX-2 could increase the mortality and morbidity rate in COVID-19 patients. The high levels of COX-2 cause a depletion in the endogenous antiviral compound arachidonic acid, making individuals more susceptible to COVID-19 [65].

Finally, the hyperinflammation induced by SARS-CoV-2 infection can potentiate the generation of oxygen reactive species leading to mitochondrial damage, apoptosis, expression of inflammatory

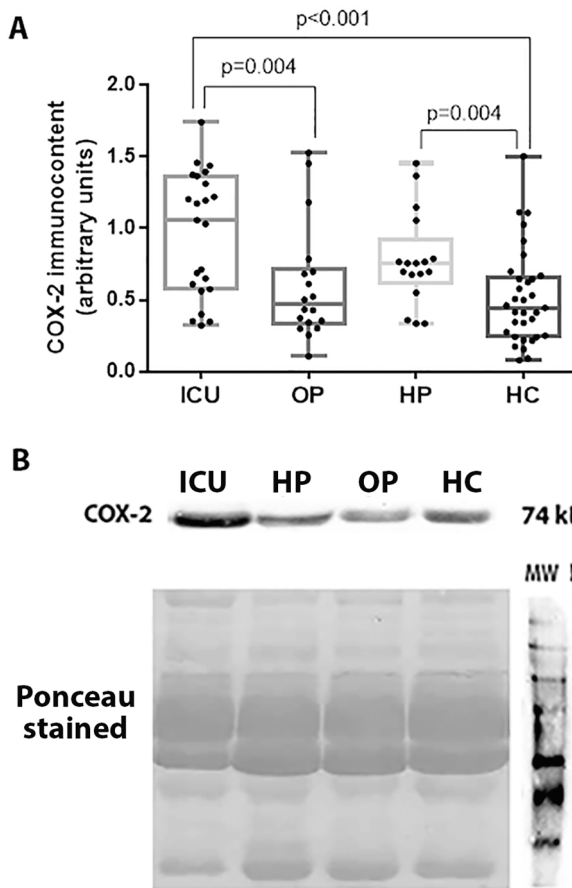


Fig. 3. COX-2 immunocontent in the ICU group (ICU), outpatients (OP), patients with COVID-19 history (HP), and healthy controls (HC) (A). Representative blots and Ponceau S stained are shown in Figure B. Statistically significant differences were determined by Kruskal-Wallis test followed by Dunn's post hoc test for multiple comparisons.

cytokines, vascular endothelial changes, disruption of cellular repair mechanisms, and disease progression [66,67]. In addition, oxidative stress genes were found to be upregulated in the whole blood of COVID-19 patients [68]. Therefore, the imbalance in homeostasis redox contributes to the pathophysiology of COVID-19 [69] and is an important prognostic factor of the disease.

Although the study was the first to assess all these biomarkers together as predictors of severity for COVID-19, it has some limitations which should be noted. First, we used a convenience sample which may increase the risk of selection bias. Second, due to the nature of the study, patients were not followed and outcomes such as death were not evaluated.

5. Conclusion

SARS-CoV-2 infection induces the upregulation of GFAP, RAGE, HMGB1, and COX-2 in patients with the most severe forms of COVID-19 and can be associated with organ dysfunctions including neural structures. The levels of these biomolecules can reflect inflammatory, oxidative, and neurological alterations in patients with SARS-CoV-2 infection and guide future patient-targeted therapies in clinical practice.

CRediT authorship contribution statement

Fabiolla Rocha Santos Passos: Conceptualization, Resources, Data curation, Formal analysis, Software, Investigation, Methodology, Writing-original-draft. **Luana Heimfarth:** Conceptualization, Resources,

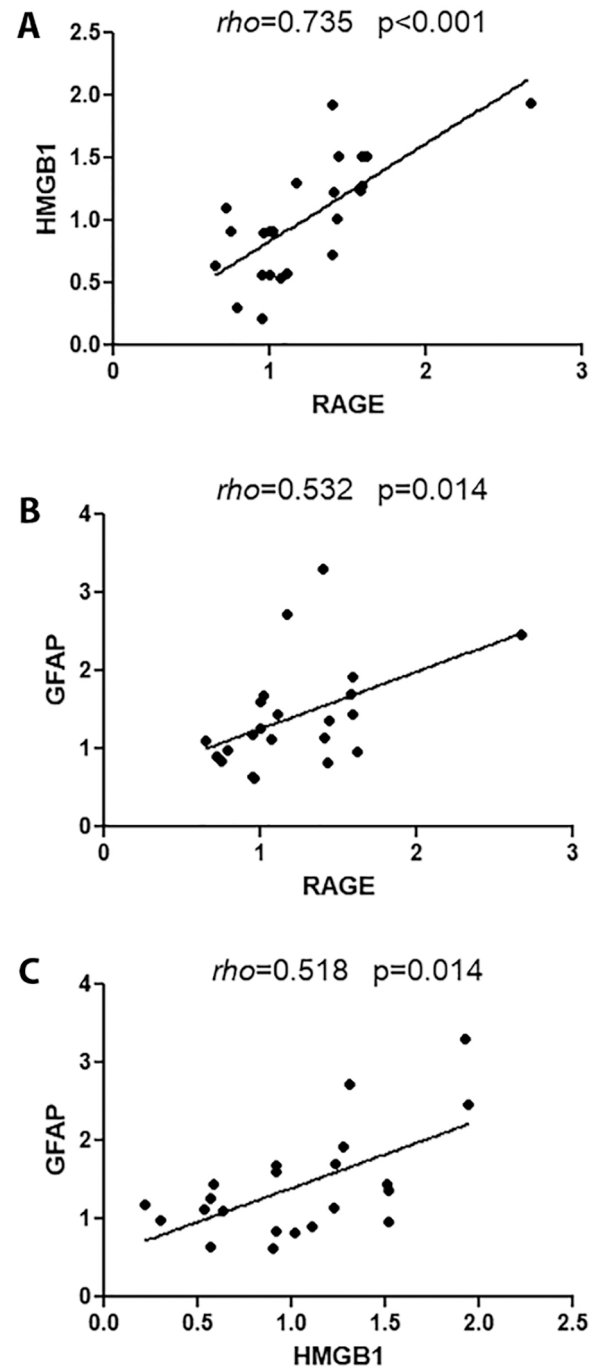


Fig. 4. Correlations between RAGE and HMGB1 (A), RAGE and GFAP (B), and HMGB1 and GFAP (C) in patients admitted to the ICU.

Data curation, Formal analysis, Software, Investigation, Methodology, Writing-original-draft. **Brenda Souza Monteiro:** Data curation, Formal analysis, Software. **Cristiane Bani Corrêa:** Data curation, Formal analysis, Software. **Tatiana Rodrigues de Moura:** Data curation, Formal analysis, Software. **Adriano Antunes de Souza Araújo:** Data curation, Formal analysis, Supervision, Validation, Visualization, Writing-review-editing. **Paulo Ricardo Martins-Filho:** Supervision, Validation, Visualization, Writing-review-editing. **Lucindo Lucindo José José Quintans:** Conceptualization, Resources, Funding acquisition, Project administration. **Jullyana de Souza Siqueira Quintans:** Conceptualization, Resources, Data curation, Formal analysis, Software, Investigation, Methodology, Writing-original-draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.intimp.2021.108502>.

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