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Physiological Effects of Calprotectin and B Cell Activating Factor in COVID-19 Patients

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Abstract

Objectives: This study set out to determine how Calprotectin and B cell activating factor contributes to early COVID-19 patient severity prediction.

Methods: The study included 25 healthy controls and 52 patients with SARS-COV2 infection who were clinically diagnosed with COVID-19 illness and were between the ages of 23 and 35. The serum levels of CALP and BAFF were measured using the ELISA method. To gauge CRP levels, an immunoturbidometric assay was performed.

Results: Variations in serum levels of CALP and BAFF were found to be statistically insignificant in the study ($P = 0.7109$ & $P = 0.7575$, respectively). When compared to the control group (103.95 ± 36.67 ng/mL; 403.03 ± 1.03), COVID-19 patients had non-significantly raised levels of CALP and BAFF (106.5 ± 4.67 ng/mL; 436.9 ± 12.77 pg/mL, respectively). According to ROC curve analysis, the area under the receiver operating characteristics curve (AUC) for CALP and BAFF was (0.5170) and (0.5259), respectively. ($r = 0.6923$; $P = 0.0001$). There was a significant positive correlation between serum CALP and BAFF levels. The connection between serum CRP levels and CALP ($r = 0.3010$; $P = 0.1271$) and BAFF levels ($r = 0.2912$; $P = 0.1406$) was insignificantly positive.

Conclusion: The current study's findings suggested that serum CALP and BAFF concentrations were increased in COVID-19 patients, suggesting that these inflammatory markers may be helpful indicators of the severity of COVID-19.

Keywords: Calprotectin, B cell activating factor, C-reactive protein, COVID-19

Introduction

A pneumonia outbreak was reported in Wuhan (Hubei Province, China) in December 2019 due to infection with a new coronavirus strain that causes the severe acute respiratory syndrome known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The coronavirus disease 19 (COVID-19) pandemic caused by this virus has affected millions of individuals worldwide.[1] COVID-19 is associated with several clinical signs and symptoms frequently seen in autoimmune illnesses, including arthralgias, myalgias, exhaustion, sicca, and rashes.[2] Patients with COVID-19 have also been noted to exhibit thrombosis, myositis, myocarditis, arthritis, encephalopathy, and vasculitis, in addition to these less typical autoimmune disease symptoms.[3] These clinical data, along with the rising number of "recovered" patients referred to as "long haulers" or "long COVID" who still exhibit post-COVID-19 symptoms, raise the hypothesis that inflammation in response to SARS-CoV-2 infection increases tissue damage during the acute phase and has some long-term consequences.[4]

Furthermore, severe COVID-19 is more likely to occur in persons with underlying conditions such as diabetes, hypertension, cardiovascular disease, and lung disease, and the age-related case fatality rate increases significantly.[5] Since the virus's introduction, it has been of utmost importance to comprehend immunity to the virus, the kinetics and protective function of the immune response in the community, and the level of exposure as measured by serosurveys.[6]

Neutrophil activation signature Calprotectin has become a useful biomarker during the first wave of the pandemic to assess COVID-19 patient risk.[7] The self-aggravating thrombo-inflammatory storm in people with severe COVID-19 may be directly attributed to the neutrophil-related inflammatory marker termed Calprotectin. Silvin et al.[8] revealed the relationship between elevated Calprotectin levels and immature neutrophils and nonclassical monocytes. He also claimed that increased damage-related molecular pattern creation causes this relationship. In light of this, it has been postulated that Calprotectin is a crucial mediator of the hyper-inflammatory host response and the rise in inflammatory monocytes, neutrophils, and platelets that contribute to the particular coagulopathy in severe COVID-19.[1] Additionally, doctors are adopting Calprotectin increasingly frequently to aid in diagnosing and treating a range of different inflammatory illnesses due to its stability, assay repeatability, and inexpensive cost. The molecular functions of CALP in health and unresolved inflammation are poorly understood by most clinicians.[9]

B-cell activating factor (BAFF), a member of the Tumor Necrosis Factor (TNF) class, is expressed by macrophages, monocytes, dendritic cells, activated neutrophils, and stromal cells.[10] First, it has been shown to be necessary for the creation of the humoral response as well as the growth and survival of B lymphocytes.[11] Recent research suggests that BAFF may also regulate innate immune responses, particularly at the level of the respiratory mucosa.[12] The membrane-bound or soluble protein BAFF, which can induce autoimmune disorders in mice and humans,[13] is synthesized excessively. The transmembrane activator and cyclophilin ligand interactor (TACI), the B cell maturation antigen, and the BAFF receptor are the three known BAFF receptors (BMA). All of these receptors are present in B and T lymphocytes as well as antigen-presenting cells, proving that BAFF action goes beyond B cell biology.[14]

Therefore, this case-control study investigates circulating BAFF and Calprotectin levels, function, diagnostic value, and prognostic relevance in COVID-19 infected patients.

Materials and Methods

The 77 participants in the present study included 52 confirmed COVID-19 patients between June 2021 to November 2022 aged (23 to 35 years) and 25 healthy volunteers as the control group. After a COVID-19 clinical diagnosis was made using RT-PCR test, blood samples were taken before the study group's condition was treated. Each participant's blood sample was taken at a volume of 5 mL and centrifuged for 15 minutes at 3500 rpm. After that, the serum was frozen and kept at 70°C. The research purpose ELISA kits were used to measure the levels of Calprotectin (CALP) and B-cell activating factor (BAFF) following the manufacturer's instructions (Sunlong Biotech, China). The CRP levels were measured by immunoturbidometric assay via a fully automated biochemistry analyzer.

Statistical Analysis

Statistical analysis was performed using GraphPad prism version 8 computer program. The Unpaired *t*-test (Man-Whitney U) was used to compare the biochemical parameters between the study groups. ROC curve analysis and Spearman correlation analysis were also performed for biochemical parameters. All comparisons were deemed significant if the *P*-value was less than 0.05.

Results

Serum Level of Calprotectin

Figure 1 and Table 1 revealed a non-significant elevation ($P = 0.7109$) in circulating concentration of serum Calprotectin levels in COVID-19 patients (106.5 ± 4.67 ng/mL) as compared to controls (103.9 ± 5.36 ng/mL).

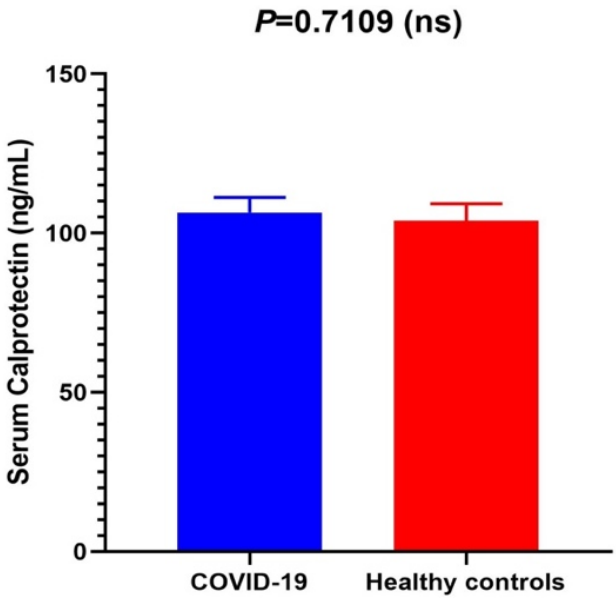

Fig. 1 **Calprotectin levels between the sera of the studied groups.**

Table 1. **Comparison of CALP and BAFF levels among COVID-19 patients and healthy controls**

Parameters	Controls	COVID-19 patients	*P*-value
Calprotectin (ng/mL)	103.9 ± 5.36	106.5 ± 4.67	0.7109
B-cell activating factor (pg/mL)	403.0 ± 31.03	436.9 ± 12.77	0.7575

The value expressed in Mean ± SE.

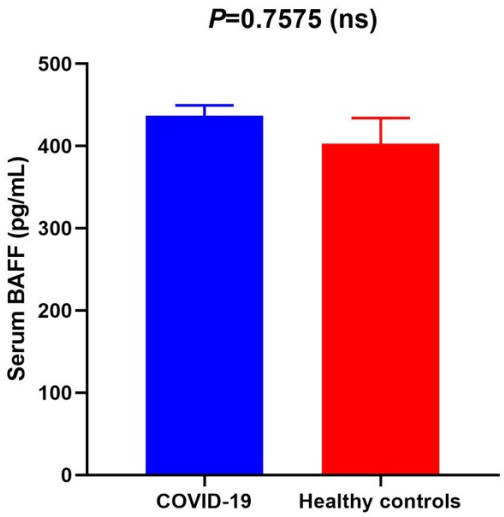

Fig. 2 **B cell-activating factor (BAFF) levels in sera of the two studied groups.**

Serum Level of B Cell Activating Factor

The results in Figure 2 and Table 1 also showed that there were non-remarkable increase ($P = 0.7575$) in circulating levels of BAFF in COVID-19 patients (436.9 ± 12.77 pg/mL) as compared to healthy controls (403.0 ± 31.03 pg/mL).

Relationship Between CALP, BAFF, and CRP in COVID-19 Patients

Correlation analysis assessed the relationships among serum CRP levels, CALP and BAFF levels. BAFF and serum CALP levels were positively correlated ($r = 0.6923$; $P = 0.0001$) (Figure 3). Figure 3 also shows a non-significant correlation between serum CRP levels and CALP ($r = 0.3010$; $P = 0.1271$) and BAFF level ($r = 0.2912$; $P = 0.1406$) (Figure 3). These research results may link BAFF activation and the immuno-inflammatory and pathogenic response, indicating disease activity and tissue damage in various chronic viral infection illness states in COVID-19.

ROC Curve

Based on the (Receiver Operating Characteristic) ROC curve, the area under the curve (AUC) of serum CALP and Serum BAFF were (0.5170) and (0.5259) respectively (Figure 4).

Discussion

Serum Level of Calprotectin

Numerous recent studies have discovered that patients with coronavirus disease-19 illness had higher Calprotectin levels.[1,7]

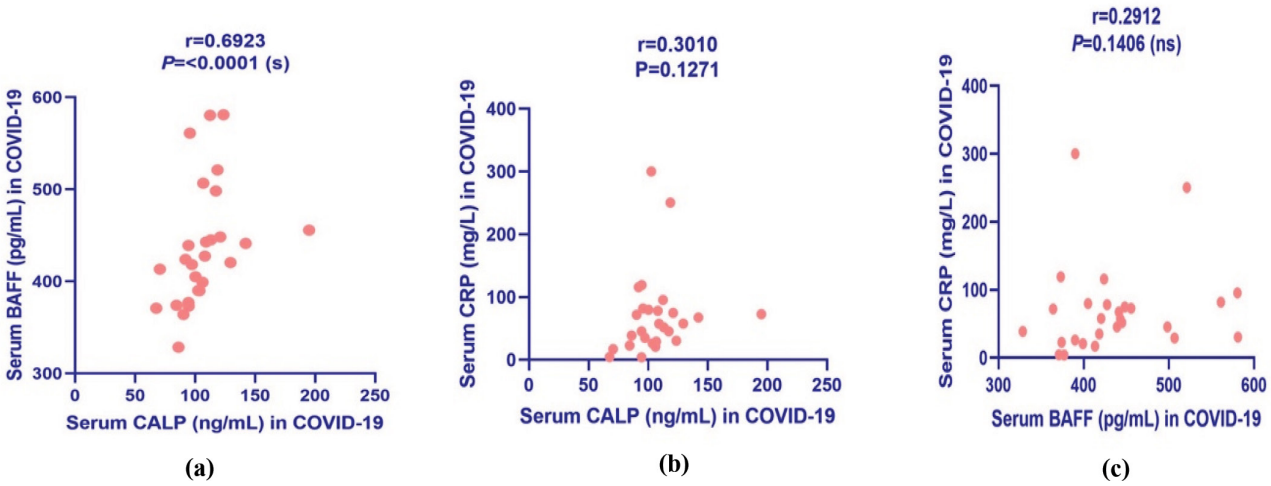

Fig. 3 **Correlation of serum CALP with BAFF (a), serum CRP with CALP (b), serum CRP with BAFF (c).**

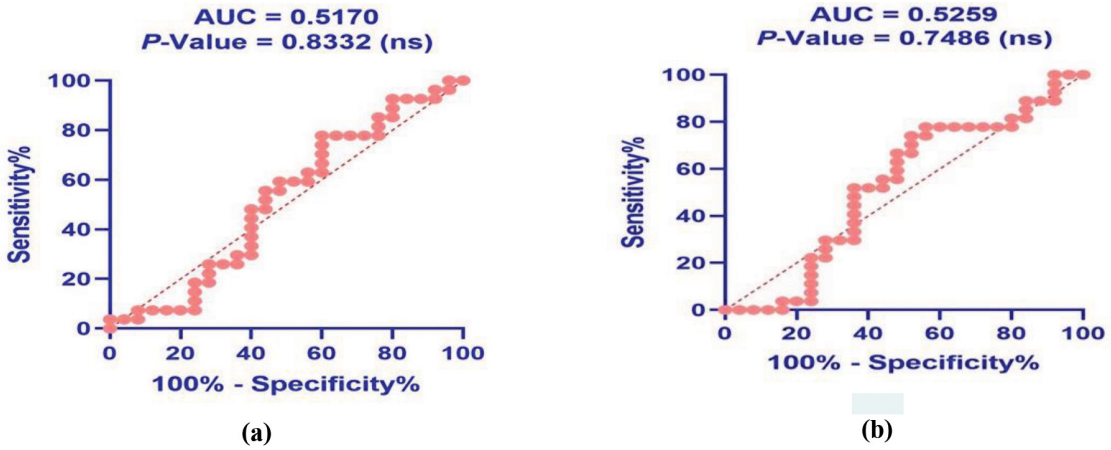

Fig. 4 **Receiver operating characteristic (ROC) curve analysis of serum CALP levels (a) and BAFF levels (b).**

Additionally, these investigations have demonstrated that Calprotectin can predict the need for mechanical breathing, identify death, and differentiate between mild and severe illness states.[8,13] Calprotectin is widely distributed in neutrophils, making up around two-thirds of the cytosol's soluble protein composition. The strong relationship between serum calprotectin levels and coronavirus's present and potential severity indicates that neutrophils are implicated as active promoters of inflammation and respiratory impairment in coronavirus disease. The patients who needed mechanical ventilation while in the hospital also had much greater levels of Calprotectin. This data shows a direct link between the Severe acute respiratory syndrome caused by COVID-19, elevated serum calprotectin levels, and neutrophil activation.[13] Two studies from medical schools in Michigan, Shanghai, and Washington DC, on the role of Calprotectin as an early indicator of neutrophil activation in COVID-19 disease. The levels of Calprotectin were noticeably elevated in hospitalized individuals with coronavirus illness. Calprotectin levels also correlate with the severity of respiratory failure and the demand for mechanical ventilation. This favours using Calprotectin as a biomarker to estimate the severity of a condition and the likelihood that it will result in mortality.

Higher levels of Calprotectin were also associated with an increased risk of dying from thrombotic issues.[13,15] According to recently released research in the academic journal Cell, Calprotectin may be able to differentiate between severe and mild COVID-19 disease. The circulating biomarker most obviously elevated in patients with advanced illness was Calprotectin. This study offers future therapeutic strategies explicitly targeting Calprotectin to treat the severe form of COVID-19 and shows its potential use in the prognosis of severe disease.[8] Similar to the current study, two inflammation-related biomarkers, Growth Differentiation Factor-15 and Calprotectin, have been researched for their potential role in predicting mortality and disease severity in SARS-CoV-2 infected patients. The study results show that Calprotectin levels are markedly higher in people with COVID-19, and they suggest that Calprotectin may help assess the severity of the illness and forecast in-hospital mortality.[1] Calprotectin overexpression may be a direct source of the self-amplifying thrombo-inflammatory storm observed in patients with severe COVID-19. Silvin et al.[8] investigation discovered a connection between elevated Calprotectin levels and immature neutrophils and nonclassical monocytes, supporting their hypothesis that this correlation originates from the excessive production of damage-associated molecular patterns. Due to the host's hyperinflammatory response and the rise in inflammatory monocytes, neutrophils, and platelets, it has been proposed that Calprotectin is a crucial mediator of specific coagulopathy in severe COVID-19 patients.[16] According

to a recent investigation, people with confirmed SARS-CoV-2 infection exhibited increased plasma Calprotectin levels compared to suspected patients with negative RT-PCR.[17] Numerous researchers have confirmed the role of Calprotectin in evaluating illness severity, including studies by Chen et al.,[18] Kaya et al.,[19] Garcia de Guadiana-Romualdo et al.,[1] Mahler et al.,[20] and Bauer et al.[21] Neutrophils are crucial to the immunopathology of COVID-19, according to a recent study by Tomar et al.[22] As a result, it has been discovered that measuring blood Calprotectin levels is a trustworthy indication of COVID-19 severity. Studies proved that neutrophils mainly secrete Calprotectin in response to inflammation. Recently, it was shown that Calprotectin is a biomarker of inflammation that can be used to track the progression of numerous inflammatory diseases.[23–28] Limited research studies look at the connection between the severity and predicator value of serum Calprotectin in COVID-19. Patients brought to the ICU had significantly higher serum levels of Calprotectin than non-ICU patients, and those who died had much higher levels, according to Chen et al.,[18] who conducted a study with 121 COVID-19 patients (41 ICU, 81 non-ICU).

Additionally, that study discovered a correlation between higher mortality in COVID-19 patients with a substantial rise in serum Calprotectin. In their trial with 94 COVID-19 patients, Shi et al. study found that patients needing mechanical breathing had higher serum Calprotectin levels than those not.[13] Based on the available literature and the present study results, we can conclude that serum Calprotectin may be employed as a predictive biomarker for COVID-19 disease severity and prognosis.

Serum Level of B Cell Activating Factor

The greater B-cell activation in COVID-19 patients may be responsible for the many autoantibodies and immune complexes frequently found in these individuals' blood. Our research offered the first conclusive evidence that circulating BAFF levels in COVID-19 patients were higher than in healthy controls. These findings suggest that BAFF participates in persistent viral infection and aids in disease progression. Specifically, BAFF impacts B cell development, maturation, survival, and activation.[29,30] Studies have shown that the process of viral infection caused by COVID-19 and others induces contact between T cells and activated B cells with T cells.[31-33]

Moreover, it has been shown that viral infections, including infections with the respiratory syncytial virus, might cause BAFF release.[34,35] Consequently, even though the fundamental mechanisms may change, it is believed that BAFF is frequently produced by viral infection.[36] According to previous research, our findings provide new evidence that COVID-19 infection may induce the biosynthesis and release of BAFF, which may affect how B cells react to viral infection. The Tumor Necrosis Factor family member B-cell activating factor (BAFF), also known as B lymphocyte stimulator (BLyS) or B cell activating factor, has a unique role in regulating peripheral B-cell survival, homeostasis, and the antibody response.[29,37] Its believed that BAFF could reduce apoptosis and essentially enhances T cell-independent and T cell-dependent humoral immune responses. The study led by Sutherland et al.[38] found that BAFF increased T- and B-cell responses, particularly Th1-type responses. Numerous cells, particularly those connected to the immuno-inflammatory response, such as monocytes, macrophages, neutrophils, dendritic cells (DCs), T lymphocytes, and B lymphocytes, are able to produce BAFF.[39,40] Interleukin-10-producing B cells were enriched and more frequent in chronic hepatitis B patients during hepatic flare-ups, according to a study by Das et al.[32] A different study showed that individuals with chronic hepatitis B have frequently activated B cells, with an abnormally high proportion of these individuals' B cells exhibiting activation markers. This demonstrates that this subset of B cells may control T-cell immunity in chronic hepatitis.[31] The intrinsic B-cell activation molecule Fc receptor like1, as well as the B-cell activation markers CD69 and CD86, were also shown to be present in increased amounts in acute and chronic hepatitis B patients.[33] These results indicate that B cells are essential for the progression of HBV infection, as well as HBV viral antigens and their interactions with T lymphocytes.

Additionally, it was thought that BAFF had a negative impact on the microenvironments of solid and hematological malignancies. So far, it has been demonstrated that BAFF encourages invasive migration in hypoxic breast cancer cell lines.[41] Blood BAFF levels, generated by neutrophils, have been linked to oral cavity cancers.[42] It has been observed that the prognosis and circulating BAFF levels in multiple myeloma are related.[43] According to Koizumi et al. report.[44] It was found that BAFF promoted tumor invasion and dissemination in human pancreatic cancer cases. However, no research has yet been done to determine how BAFF contributes to the growth of hepatocellular carcinoma. Therefore, based on the available literature data and the results of the present study, serum B cell activating factor contributes to early patient severity of COVID-19 and may be a good predictive marker for the disease prognosis.

Diagnostic Performance of Serum CALP and BAFF in COVID-19 Patients

Due to the non-significantly increased blood levels of CALP and BAFF found in COVID-19 patients in the present study, the ability of blood CALP and BAFF to predict COVID-19 was assessed using the ROC curves. According to a presentation by Chen et al.,[18] extremely high levels of Calprotectin were connected to the poor overall survival of COVID-19 patients, supporting the predictability of Calprotectin revealed by earlier investigations. Recent studies by Shi et al.[13] and Zuo et al.,[15] and others[13,15] demonstrated high serum Calprotectin is closely connected to the likelihood of dying in COVID-19, usually from thrombotic problems, which lends credence to the verdicts of the current study. Calprotectin is said to have a higher predictive accuracy when compared to the COVID-GRAM risk score created for prediction by Liang et al.[45] and Chen et al.[18] Calprotectin was thought to have the highest prediction accuracy of all the predictors, according to Chen et al.[18] They examined the receiver operating characteristic curve (ROC) analysis of Calprotectin, HMGB1, COVID-GRAM risk score, and Calprotectin/HMGB1 combo for predicting ICU admission and possible mortality to illustrate results similar to the present investigation.

Conclusion

This study is the first to demonstrate that COVID-19 patients had greater serum levels of the potent inflammatory markers CALP, BAFF, and CRP. The clinical illness condition of

COVID-19 and increased BAFF levels are correlated. The SARS-COV-2 infection risk and severity correlated with serum CALP and BAFF levels. The study results suggest a connection between serum BAFF levels and the manifestation of COVID-19, and assessing serum BAFF levels may be used as an inflammatory biomarker to identify and classify clinical problems related to COVID-19. According to the available evidence, Calprotectin may be a valuable inflammatory biomarker to evaluate the risk and severity of COVID-19. The relationship between Calprotectin and the inflammatory process may present fresh opportunities for managing and improving COVID-19. The combined use of serum CALP, BAFF and CRP levels may be helpful to evaluate and understand how inflammation-related factors such as viral load, SARS-CoV2 antibodies, corticosteroid use, anticoagulants, and pharmaceutical agents would affect neutrophil function. A comprehensive prospective investigation is required to comprehend the progression of the COVID-19 infection, the potential role of blood BAFF levels in determining and monitoring the condition's prognosis, and the treatment response to immunomodulatory medicine. Additional study is also required to completely comprehend the roles played by BAFF in the emergence of COVID-19-associated diseases and the development of the infection.

Conflict of Interest

All authors declare that they have no conflicts of interest.

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