ORIGINAL ARTICLE

EVALUATION OF IMMUNO-INFLAMMATORY PARAMETERS AS PREDICTIVE BIOMARKERS IN CRITICAL PATIENTS WITH COVID-19

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Highlights: (1) A decreased lymphocyte-to-total leukocyte ratio indicates mortality in COVID-19. (2) Elevated C-reactive protein levels and platelet-to-lymphocyte ratios indicate mortality in COVID-19. (3) The assessment of inflammatory biomarkers predicts the severity of COVID-19.

PRE-PROOF
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EVALUATION OF IMMUNO-INFLAMMATORY PARAMETERS AS PREDICTIVE BIOMARKERS IN CRITICAL PATIENTS WITH COVID-19

ABSTRACT:

The SARS-CoV-2 virus, the etiological agent of coronavirus disease 2019 (COVID-19), infects host cells and begins its viral replication process. After the viral incubation period, the disease can lead to symptoms that range from flu-like symptoms to severe forms of disease (such as respiratory failure), posing a risk to life. The exacerbated inflammatory response in COVID-19 is associated with changes in leukocyte (global and differential counts), platelet, and C-reactive protein (CRP) levels, which when evaluated in isolation have lower power to provide an accurate clinical picture. However, blood count ratios such as lymphocyte-to-total leukocyte ratio (L/WBC) and platelet-to-lymphocyte ratio (PLR) can assertively infer the immuno-inflammatory clinical status. The objective of this study was to evaluate whether leukocyte parameters can be used as biomarkers of prognosis and outcome in critically ill COVID-19 patients. A total of 236 patients admitted to the COVID-19 ICU in a medium-sized and highly complex hospital located in the northwest of the state of Rio Grande do Sul were included in the study. The clinical and laboratory parameters evaluated were CRP, L/WBC and PLR, collected at patient admission and outcome. Data were expressed as mean and standard deviation and analyzed using the Student's T test, considering a significance level of 5%. We identified the applicability of PCR, L/WBC and PLR as predictive biomarkers in critically ill COVID-19 patients. Serum concentrations of CRP, L/WBC and PLR can predict the outcome and indicate the prognosis of COVID-19 patients with COVID-19.

Keywords: Leukocytes; SARS-CoV-2; Biomarkers; Prognosis.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in China in early December 2019. The infection presents with mild to severe symptoms and may progress to Severe Acute Respiratory Syndrome (SARS), which is more prevalent in COVID-19 intensive care unit (ICU) admissions. SARS-CoV-2 is a positive-sense single-stranded RNA virus belonging to the *Coronaviridae* family and the *Betacoronavirus* subgenus—the same subgenus as the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), both of which have caused potentially fatal infections over the past two decades [1, 2].

EVALUATION OF IMMUNO-INFLAMMATORY PARAMETERS AS PREDICTIVE BIOMARKERS IN CRITICAL PATIENTS WITH COVID-19

Globally, more than 434 million cases of COVID-19 and over 5.9 million deaths have been confirmed. Brazil ranks third in the number of confirmed cases and second in the number of deaths. In the state of Rio Grande do Sul, more than 2.2 million confirmed cases and a total of 38,988 deaths have been reported. Between April and May 2022, there was a decrease in the number of reported cases as well as a reduction of approximately 49% in COVID-19-related deaths, with an average of three deaths per 24 hours. In the municipality of Ijuí, since the beginning of the pandemic, more than 8,700 cases and 165 deaths have been confirmed, according to data collected in May 2022 [3].

SARS-CoV-2 infects human cells by binding of the spike glycoprotein (S protein) to the angiotensin-converting enzyme 2 (ACE2) receptor via endocytosis. This binding process represents a crucial step in the infection and development of COVID-19. Once inside the cell, the viral genetic material is recognized by immune cells, which respond by synthesizing and releasing cytokines responsible for triggering the inflammatory cascade [4]. The viral infection may be asymptomatic or symptomatic, with symptoms that can progress to severe forms of the disease. The most common clinical features include cough, fever, and dyspnea, usually between the second and fourteenth day after exposure to the pathogen. In addition to affecting the respiratory system, COVID-19 can also impact multiple organs, including the cardiovascular system [5]. Severe cases are characterized by dyspnea, pneumonia, and a hyperinflammatory state known as a “cytokine storm,” which is associated with increased morbidity and mortality [6].

The inflammatory “cytokine storm” triggered by SARS-CoV-2 infection, mediated by leukocytes, can lead to a severe form of the disease through hyperactivation of the immune system, resulting in increased tissue production of proinflammatory cytokines such as interleukin-6 (IL-6) and elevated plasma levels of acute-phase proteins such as C-reactive protein (CRP) [2, 7 - 9]. In addition increased cytokine and inflammatory protein levels, SARS-CoV-2 impacts both pulmonary and systemic circulation, promoting platelet activation, aggregation, and the development of a prothrombotic state [10].

The exacerbated inflammatory response observed in critically ill COVID-19 patients is associated with leukocyte abnormalities such as leukocytosis and leukopenia (total count) as well as neutropenia, neutrophilia, lymphopenia (differential count), and platelet dysfunction. When assessed individually, these parameters may have limited predictive value for clinical outcomes; however, when analyzed through cellular ratios - such as the lymphocyte-to-total

leukocyte ratio [L/white blood cell count (WBC)] and the platelet-to-lymphocyte ratio (PLR) they may provide a more accurate picture of the clinical status and disease progression [11].

In this context, there is a pressing need to develop novel biomarkers capable of supporting the prognosis and clinical outcomes of critically ill COVID-19 patients, thereby assisting in clinical decision-making and improving disease management. Furthermore, the use of immunoinflammatory biomarkers such as CRP, L/WBC, and PLR may represent a reliable and cost-effective tool for patient monitoring and clinical decision support.

Therefore, the present study aims to investigate whether circulating concentrations of CRP, L/WBC, and PLR can be used as prognostic biomarkers and predictors of clinical outcomes in critically ill COVID-19 patients.

MATERIALS AND METHODS

Study Design

This was a retrospective and analytical study conducted in the COVID-19 Intensive Care Unit (ICU) of a medium-sized, high-complexity hospital located in the Northwest region of the state of Rio Grande do Sul, Brazil. The study was based on data collected from medical records of patients admitted to the COVID-19 ICU, analyzing laboratory biomarker results (from the first and last day of hospitalization) and the clinical outcomes of the patients.

Ethical Aspects

The study was conducted in accordance with Resolution No. 466/2012 of the Brazilian National Health Council (Brasil, 2012) and was approved by the Hospital Research Evaluation Committee and the Research Ethics Committee of UNIJUÍ University under CAAE No. 51639121.5.0000.5350 and approval report No. 5.073.813.

Population and Sample

Data collection was performed based on the convenience of the researchers hospital administration. Information was extracted from the medical records of patients admitted to the hospital's COVID-19 ICU between January 1 and December 31, 2021.

Inclusion Criteria: All medical records of patients admitted to the COVID-19 ICU during the study period that contained complete clinical and laboratory data were included.

Exclusion Criteria: Medical records outside the defined study period or with incomplete clinical or laboratory data were excluded. Patients with pre-existing autoimmune, oncologic or hematologic diseases were also excluded from the analysis.

Procedures

Data Collection

Clinical and laboratory data were collected between November 2021 and March 2022 in a single phase, directly from the ICU medical records. To ensure standardization of data collection procedures, electronic spreadsheets were created in Microsoft Excel by the research team for data registration and subsequent tabulation.

The following laboratory and clinical parameters were collected: leukogram (from the complete blood count), CRP level, platelet count, length of hospital stay, and clinical outcome (discharge or death).

Laboratory Parameters

After obtaining hospital authorization and approval by the Research Ethics Committee, data were extracted from the hospital's internal database. The collected data were recorded in Microsoft Excel spreadsheets, including the following variables: patient sex, date of birth (age), disease evolution and outcome (discharge or death), leukogram results (from complete blood count), CRP levels, platelet count, length of ICU stay, and clinical outcome.

Determination of Hematologic Ratios

In addition to direct data collection from medical records, hematologic ratios were calculated as follows:

- Lymphocyte-to-Total Leukocyte Ratio (L/WBC): Calculated as the ratio between the absolute lymphocyte count and the total leukocyte count.

- Platelet-to-Lymphocyte Ratio (PLR): Calculated as the ratio between the platelet count and the absolute lymphocyte count.

Statistical Analysis

All data were assessed for normality and expressed as measures of central tendency (mean) and dispersion (standard deviation). Data normality was assessed using the Kolmogorov–Smirnov test. Comparisons were performed using Student's *t*-test, and a significance level of 5% ($p < 0.05$) was adopted for all analyses.

RESULTS

In this study, we evaluated a total of 236 patient medical records: 140 (59.32%) were from male patients and 96 (40.68%) from female patients. The overall mean age of the study population was 58.3 ± 15.12 years; the mean age among male patients was 56.6 ± 14.64 years and among female patients, 60.9 ± 15.54 years.

Patients were evaluated at two time points: upon admission to the COVID-19 ICU and at clinical outcome. They were stratified into two groups according to outcome**:** hospital discharge or death**.** The discharge group comprised 158 patients (66.95%) with an overall mean age of 55.09 ± 14.7 years. In this group, 95 (60.13%) were male patients with a mean age of 54.4 ± 14.85 years and 63 (39.87%) were females with a mean age of 56.1 ± 14.53 years.

The death group consisted of 78 patients (33.05%) with an overall mean age of 56.1 ± 12.5 years. When stratified by sex, 45 (57.69%) were males with a mean age of 61.1 ± 13.22 years and 33 (42.31%) were females with a mean age of 69.9 ± 13.34 years.

Regarding the analysis of CRP) concentrations upon ICU admission, no significant differences were observed between the discharge and death groups, although both presented elevated levels, considering that normal CRP concentrations are up to 6 mg/dL. However, at the time of clinical outcome, the discharge group showed significantly lower CRP values compared to the death group, as illustrated in Figure 1**.**

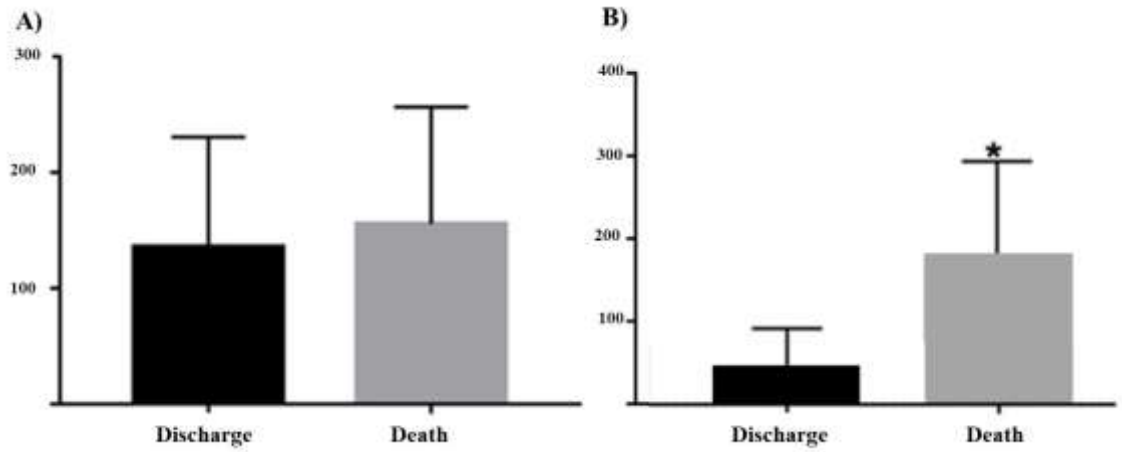

Figure 1. C-reactive protein (CRP) concentration upon ICU admission (A) and at clinical outcome (B). Statistical analysis performed using Student's t-test at admission and outcome (discharge or death) ($p < 0.01$).

With respect to leukocyte parameters, the L/WBC did not differ between groups at ICU admission. However, at clinical outcome, this leukocyte ratio showed a significant reduction in the death group compared to the discharge group, as shown in Figure 2.

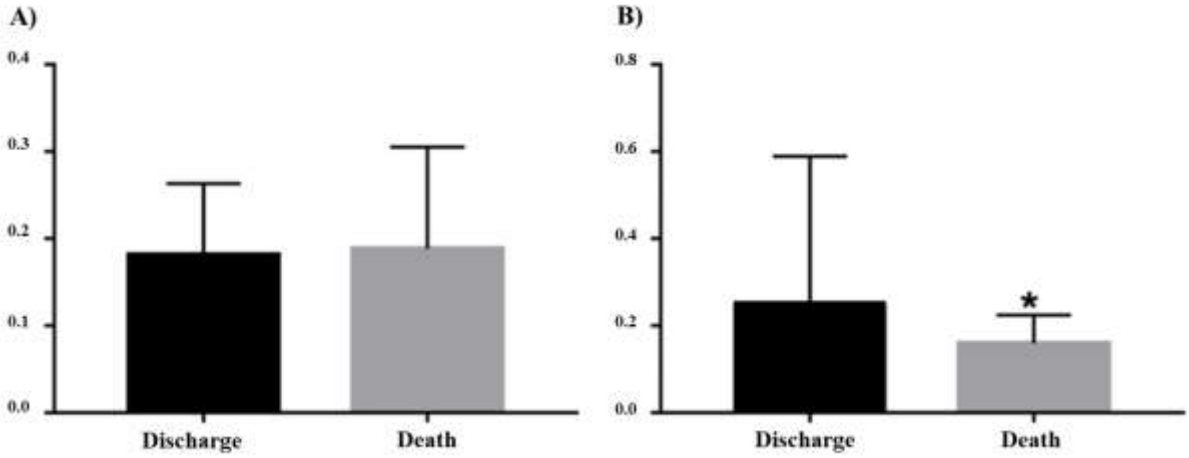

Figure 2. Lymphocyte-to-total leukocyte ratio (L/WBC) upon ICU admission (A) and at clinical outcome (B). Statistical analysis performed using Student's t-test ($p < 0.01$).

The PLR showed no significant differences between the discharge and death groups at the time of ICU admission. However, at clinical outcome, patients who recovered from COVID-19 exhibited a decrease in PLR values, as illustrated in Figure 3**.**

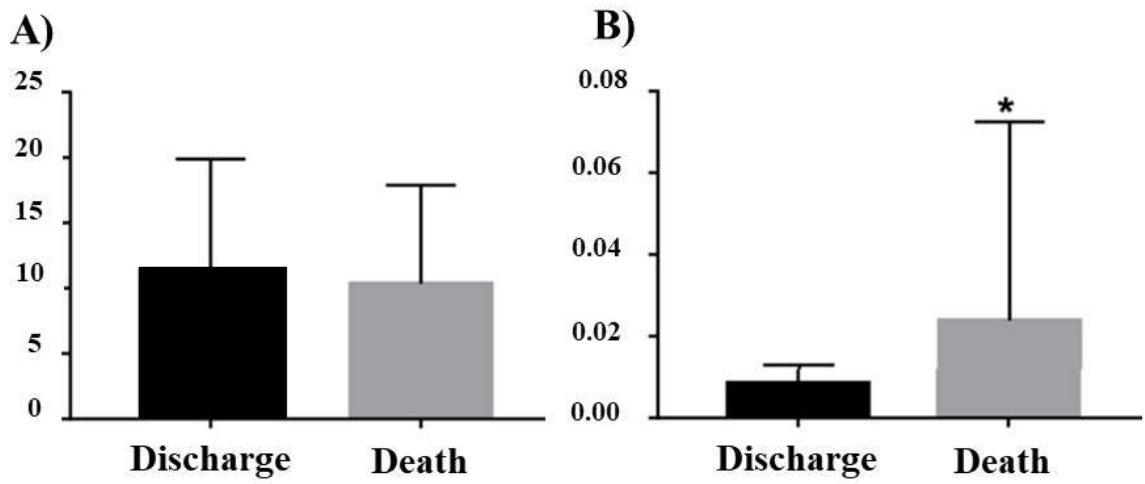

Figure 3. Platelet-to-lymphocyte ratio (PLR) upon ICU admission (A) and at clinical outcome (B). Statistical analysis performed using Student's t-test ($p < 0.01$).

DISCUSSION

Our results demonstrate that CRP concentrations can be used as an outcome biomarker, as the persistence of elevated levels indicates disease progression and a worse prognosis. CRP activates the classical complement pathway, an important component of the host's innate immune response. In this context, CRP is defined as a biomarker of severe and systemic acute-phase inflammation synthesized by the liver in response to IL-6. It is associated with severe diseases and viral and bacterial infections, making it a widely used inflammatory marker. Morevoer, CRP testing is low-cost and easily accessible in most hospitals, allowing faster clinical management of COVID-19 patients.

According to a previous study[13], most COVID-19 hospitalizations are accompanied by abnormal immunological biomarker values, in which higher CRP concentrations indicate greater disease severity. Similarly, it has been shown that the inflammatory response triggered by SARS-CoV-2 infection promotes cardiovascular and respiratory system injury, which is related to elevated circulating CRP levels that can predict cardiovascular complications and mortality[14].

A study involving 298 hospitalized COVID-19 patients reported elevated inflammatory biomarker levels in 84 individuals who subsequently died[15]. Consistent with our findings (Figure 1B), CRP levels were associated with disease severity and correlated with other inflammatory markers in COVID-19 patients.

Regarding hematological parameters, we observed that the L/WBC and PLR (Figures 2 and 3, respectively) acted as predictive biomarkers for the death outcome. The reduction of L/WBC is primarily due to lymphopenia associated with neutrophilic leukocytosis in critically ill COVID-19 patients[17], so that this biomarker could predict clinical worsening and mortality risk (Figure 2B).

During the incubation period of COVID-19, which usually ranges from 1 to 14 days, and in the early phase of the disease—when only nonspecific symptoms are present the leukocyte and lymphocyte counts in peripheral blood are normal or slightly reduced; such reductions already suggest disease progression. In hospitalized patients, Guan et al. (2020) demonstrated that lymphopenia is a cardinal laboratory finding with significant prognostic potential. Throughout the course of the disease, longitudinal assessment of lymphocyte count dynamics and inflammatory markers, such as CRP and interleukin-6 (IL-6) levels, may help identify cases with worse prognosis and indicate the need for early intervention to improve recovery rates[17].

Following the onset of symptoms, clinical manifestations intensify and are accompanied by a marked release of inflammatory mediators and cytokines, characterizing the so-called “cytokine storm”, in which absolute and relative lymphopenia become evident[18]. In this regard, lymphopenia is a common finding in COVID-19 patients and can be explained as a defective immune response to the virus, as observed in our study, where the reduction in L/WBC was mainly driven by decreased lymphocyte counts.

A recent study (2020)[19] showed that monitoring L/WBC may help identify patients who may require ICU care and may be useful as an early indicator for ICU admission. It is associated with reduced antiviral immune responses, increased frequency of bacterial coinfections, thrombocytopenia, and cardiovascular and renal dysfunction. Moreover, Huang et al. (2020) reported that lymphopenia was more pronounced in patients requiring intensive treatment than in those with milder disease courses.

A substantial reduction in total lymphocyte count suggests that SARS-CoV-2 may directly affect immune cells and, to some extent, suppress cellular immune function[21]. It has also been demonstrated that patients with the severe form of the disease exhibit more significant laboratory abnormalities such as lymphopenia and reduced L/WBC compared to those with milder conditions[14]. Furthermore, coronavirus infection induces a sustained cytokine

response the cytokine storm leading to a high frequency of immune-mediated diseases and mortality[22].

Lymphocytes and their subpopulations play a crucial role in maintaining immune system function. As with autoimmune and other infectious diseases, viral infections can dysregulate lymphocyte subpopulations, impair immune responses, and promote the development of coinfections, all of which are associated with poorer outcomes[21],[22].

Critically ill COVID-19 patients with worse prognoses show lower total lymphocyte counts and reduced L/WBC[20], which was also observed in our study. Moreover, patients with fatal outcomes had significantly lower L/WBC values (Figure 2B).

The pro-inflammatory activity of platelets is mediated through their interaction with circulating leukocytes, followed by the release of cytokines and chemokines during the inflammatory process[23]. The PLR serves as an adjunct marker in assessing the extent of inflammation[24]. At the time of peak platelet count, it has emerged as an independent prognostic factor associated with prolonged hospitalization. Previous investigations[25], in agreement with our findings, indicate that high PLR values may reflect a more intense cytokine storm due to greater platelet activation, thereby suggesting a worse prognosis (Figure 3B).

Recognized as a novel inflammatory index, PLR mainly reflects the level of systemic inflammation. Previous studies have confirmed that PLR is closely related to tumors, diabetes, coronary artery disease, and connective tissue disorders. Elevated PLR has also been associated with tumor size, lymph node infiltration, metastasis, and overall prognosis, and may serve as a potential inflammatory indicator for monitoring infectious diseases such as pneumonia[26].

Platelets circulate in an inactive form but can be rapidly activated at sites of vascular injury or in response to pro-inflammatory cytokines or infectious factors. Platelet activation in the absence of vascular damage suggests novel platelet functions, including roles in inflammation and immune regulation. Furthermore, lymphocytes are key immunoactive cells in the human body and their count serves as an early marker of physiological stress and systemic inflammation. Platelet factor 4 release can promote lymphocyte formation, and the presence of activated platelets enhances lymphocyte adhesion to the endothelium, facilitating their migration to inflammation sites. In this context, the advantage of using PLR lies in its association with platelet aggregation and inflammatory response, providing greater accuracy in predicting inflammation compared to platelet or lymphocyte counts alone[26].

Our results demonstrate that PLR is a biomarker capable of reflecting the severity of inflammation during treatment because alterations in platelet and lymphocyte proportions in peripheral blood throughout disease progression may reflect both disease course and prognosis in COVID-19 patients. These findings are consistent with previous studies[27] showing that higher PLR values were proportional to cytokine storm intensity, longer hospital stay, and worse prognosis.

The evaluation of immuno-inflammatory parameters as predictive biomarkers in critically ill patients is advantageous, since PLR can be obtained at no additional cost from platelet and lymphocyte counts. Moreover, the use of these biomarkers may improve clinical decision-making accuracy and serve as an additional tool for predicting disease worsening. However, we acknowledge that the sample used may not fully represent the general population, limiting the generalizability of our results. Future studies, including randomized clinical trials, are necessary to confirm our observations and to assess the clinical applicability and prognostic value of these biomarkers in routine practice.

CONCLUSION

Our study demonstrated the applicability of the biomarkers C-reactive protein (CRP)**,** lymphocyte-to-white blood cell ratio (L/WBC), and platelet-to-lymphocyte ratio (PLR) as predictive biomarkers in critically ill patients with COVID-19. Serum concentrations of CRP, L/WBC, and PLR may serve as predictors of clinical outcomes, as well as indicators of disease prognosis, representing immuno-inflammatory biomarkers with relevant applicability for the evaluation of critically ill patients with COVID-19.

We emphasize that the above parameters should not be used in isolation, but rather in association with the overall clinical and laboratory context, thereby enhancing their predictive capacity.

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