**ORIGINAL ARTICLE**

# C-REACTIVE PROTEIN, PLATELET-TO-LYMPHOCYTE RATIO, AND D-DIMER AS PROGNOSTIC BIOMARKERS IN COVID-19 PATIENTS

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**Highlights:**

1. Prognostic biomarkers and outcome predictors in COVID-19 patients.
2. Evaluation of the interaction between immune and platelet responses in severe acute respiratory syndrome.
3. Inflammatory and coagulation biomarkers indicate severity in COVID-19 patients.

PRE-PROOF
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**C-REACTIVE PROTEIN, PLATELET-TO-LYMPHOCYTE RATIO, AND D-DIMER AS PROGNOSTIC BIOMARKERS IN COVID-19 PATIENTS**


## ABSTRACT

**Objective:** To evaluate the biomarkers platelet-to-lymphocyte ratio (PLR), D-dimer, and C-reactive protein (CRP) as indicators of prognosis and outcome in patients with coronavirus disease 2019 (COVID-19). **Methodology:** A retrospective, descriptive, and analytical study was conducted using clinical and laboratory data from patients hospitalized in a hospital located in the northwestern region of the state of Rio Grande do Sul, Brazil. The clinical and laboratory parameters evaluated were C-reactive protein (CRP), D-dimer, and absolute lymphocyte and platelet counts (used to calculate the PLR), recorded at the patient admission and at the outcome. Data were expressed as mean ± standard deviation and analyzed using the Student's t-test, with a significance level of 5% ($P<0.05$). **Results:** CRP (174.82 ± 116.8 mg/dL, $P = 0.001$) and D-dimer (1.25 ± 1.1 µg/mL, $P < 0.0001$) levels were elevated, while PLR (92.83 ± 61.73/mm³, $P = 0.01$) was decreased at the admission in patients who progressed to death compared to those who were discharged. **Conclusion:** The biomarkers CRP, D-dimer, and PLR demonstrated potential for use in COVID-19 patient care protocols as prognostic and outcome parameters.


**Keywords:** SARS-CoV-2; Biomarkers; Platelets; Lymphocytes; Fibrin Degradation Products; Prognosis.

## INTRODUCTION

The novel coronavirus, responsible for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease known as coronavirus disease 2019 (COVID-19), has been recognized as a global public health concern due to its high transmissibility and elevated morbidity and mortality rates. According to recent data from the Brazilian Ministry of Health, over 38 million confirmed COVID-19 cases have been reported in Brazil, with approximately 712,000 resulting in death. In the state of Rio Grande do Sul, more than 3.1 million cases have been confirmed, with 42,936 deaths. The COVID-19 mortality rate in the state is 377.4 cases per 100,000 inhabitants, and the incidence rate is 27,577.8 cases per 100,000 inhabitants – figures considered high for a viral respiratory infection[1].

SARS-CoV-2 exhibits a strong affinity for binding to cells like those of the pulmonary epithelium, intestines, kidneys, central nervous system, and human vascular endothelium. The

virus contains a spike (S) protein in its structure, which binds to the angiotensin-converting enzyme 2 (ACE2) receptor, predominantly found on the surface of type II pneumocytes in the alveoli[2]. Once the virus infects the host cells, it begins a cycle of viral replication followed by the release of new viral particles, infecting additional cells[3]. The virus's pathological mechanism is based on triggering an inflammatory response in the body, which can progress to severe disease forms through a "cytokine storm," primarily mediated by the pro-inflammatory cytokine interleukin-6 (IL-6)[4]. IL-6 stimulates hepatic synthesis of the acute-phase protein C-reactive protein (CRP), a sensitive inflammatory biomarker[5].

Elevated CRP levels are associated with increased expression of procoagulant factors in endothelial cells damaged by viral replication, promoting platelet adhesion and aggregation, leading to microthrombosis. As a result, a degradation product of these blood clots – D-dimer – is formed. Platelet consumption during intravascular coagulation can also be evaluated through the platelet-to-lymphocyte ratio (PLR), which is associated with the development of complications and worsening of COVID-19[6]. Such complications often include thrombotic events resulting from hypercoagulability[7]. The pathophysiological mechanism of the coronavirus is illustrated in Figure 1.

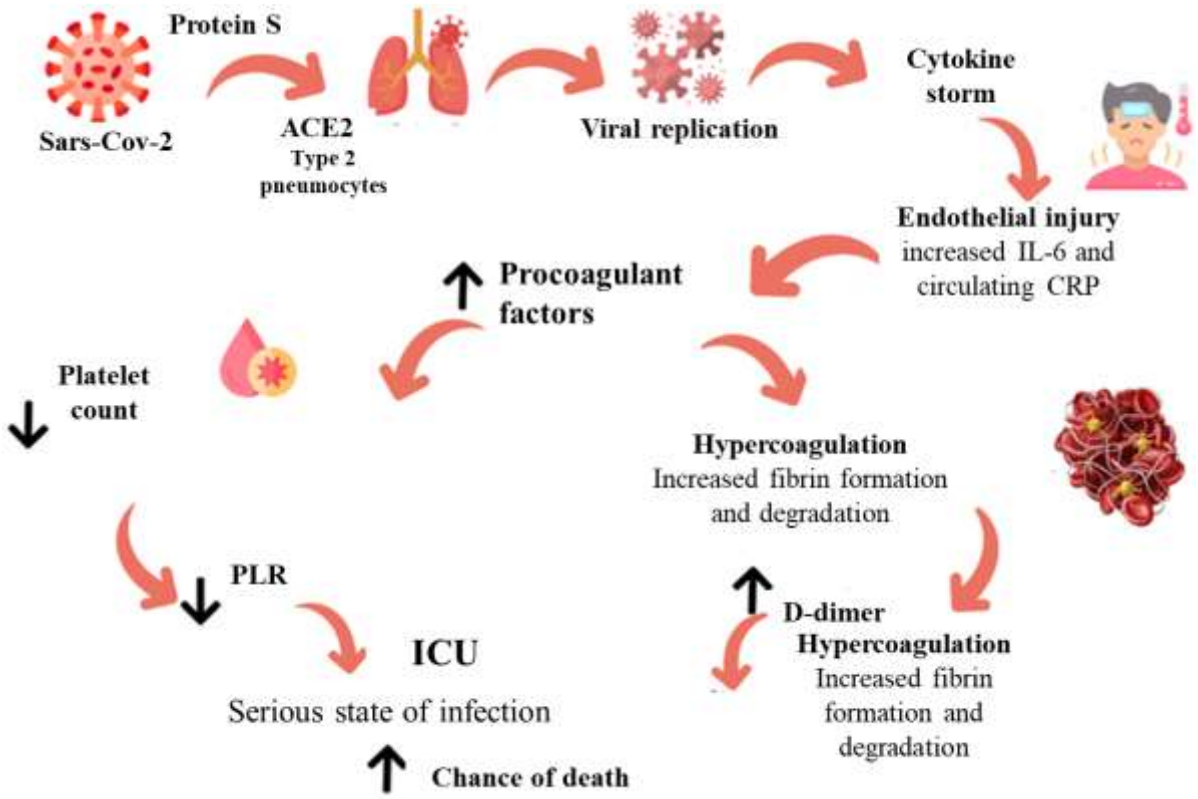


**Figure 1 –** Interaction of the SARS-CoV-2 virus with Angiotensin-Converting Enzyme 2 (ACE2) and the pathophysiological mechanisms associated with the inflammatory processes triggered by COVID-19. SARS-CoV-2 has a high affinity for ACE2 present in pneumocytes, initiating an intense local and systemic inflammatory response. This process may lead to vascular complications, activation of procoagulant factors, hypercoagulability, and thrombus formation, thereby worsening the clinical course of COVID-19 and increasing the risk of death.

In this context, SARS-CoV-2 infection is associated with changes in laboratory biomarkers related to hemostasis and pro-inflammatory responses, including elevated C-reactive protein (CRP) levels and fibrin degradation products like D-dimer, both of which are positively correlated with increased mortality rates[8–9]. Additionally, the platelet-to-lymphocyte ratio (PLR) tends to decrease in hypercoagulability cases due to platelet consumption and lymphocyte migration resulting from excessive inflammation and tissue injury. This ratio has shown prognostic potential for predicting complications and mortality in COVID-19.

As COVID-19 is a relatively new disease, there is still a strong need for studies that identify potential laboratory biomarkers to evaluate patient prognosis and outcomes. A better understanding of the disease's pathophysiological mechanisms and its impact on hemostatic

parameters is crucial at the global level, as these laboratory markers may assist in predicting disease severity and serve as monitoring tools and prognostic indicators in moderate to severe cases. In this context, the present study aims to evaluate platelet count, PLR, D-dimer, and CRP as prognostic and outcome biomarkers in COVID-19 patients, both at the admission and upon disease outcome.

## METHODOLOGY

### Study Design

This research is a retrospective, descriptive, and analytical study based on the collection of data from medical records of patients hospitalized due to COVID-19 in a hospital located in the northwestern region of the state of Rio Grande do Sul, Brazil, during the year 2021.

### Sample

Medical records of patients diagnosed with COVID-19 and admitted to the hospital's intensive care unit (ICU) were evaluated at the time of admission and at the outcome (discharge or death). The following laboratory test results were collected:

- Sociodemographic data (age and sex);
- C-reactive protein (CRP);
- D-dimer;
- Absolute platelet and lymphocyte counts.

**Inclusion criteria:** Patients admitted to the hospital ICU between January 1 and November 30, 2021, diagnosed with COVID-19 confirmed through prior testing, and whose records contained all study variables – clinical and laboratory data, disease progression, and outcome – were included.

**Exclusion criteria:** Patients hospitalized for conditions other than COVID-19, as well as those with incomplete clinical or laboratory data in their medical records, were excluded from the study.

### Data Collection Procedures

The collected data were organized in a Microsoft Excel spreadsheet, considering disease progression, outcome (discharge or death), and laboratory test results: C-reactive protein, D-dimer, platelet count, and lymphocyte count. In addition to data extracted from the medical records, the platelet-to-lymphocyte ratio (PLR) was calculated by dividing the total platelet count by the absolute lymphocyte count per $mm^3$.

### Ethical Considerations

The study followed all the recommendations of Resolution No. 466/2012 of the Brazilian National Health Council (CONEP, as per its Portuguese acronym)[10] and was approved by the Research Ethics Committee of UNIJUÍ under approval number 5.073.813.

### Statistical Analysis

Data were expressed as mean ± standard deviation, and a descriptive statistical analysis was performed using the Student's *t*-test, with a significance level of 5% ($P < 0.05$).

## RESULTS

PLR, CRP, and D-dimer levels at the patient admission and at the outcome were evaluated to compare the discharge and death groups and thereby determine whether these parameters can be used as prognostic and outcome biomarkers in COVID-19 patients. Of the 108 patients evaluated, 86 (79.6%) were discharged, and 22 (20.4%) progressed to death. The mean age of male patients was 54.4 ± 15.6 years, and for female patients, it was 55.8 ± 16.7 years. Among the 86 patients who were discharged, the mean age was 52.4 ± 15.3 years; 54

(62%) were male and 32 (38%) were female. In contrast, the 22 patients who died had a mean age of 64.9 ± 15.2 years, with 11 (50%) male and 11 (50%) female patients.

It was found that at the hospital admission, the platelet-to-lymphocyte ratio (92.83/mm³ ± 61.73/mm³) was significantly lower (P = 0.01) in patients who progressed to death compared to those who were discharged (174.05 ± 143.21) (Figure 2A). It was also observed that CRP levels were significantly higher (P = 0.001) in patients whose outcome was death (174.82 ± 116.8 mg/dL) compared to those discharged (101.4 ± 83.93 mg/dL) (Figure 2B). Additionally, D-dimer concentrations were significantly increased (P < 0.0001) in patients who died (1.25 ± 1.1 µg/mL) when compared to those who were discharged (0.48 ± 0.35 µg/mL) (Figure 2C). Regarding the absolute platelet count, no significant difference was observed between the groups at the admission (P = 0.06), as shown in Figure 2D.

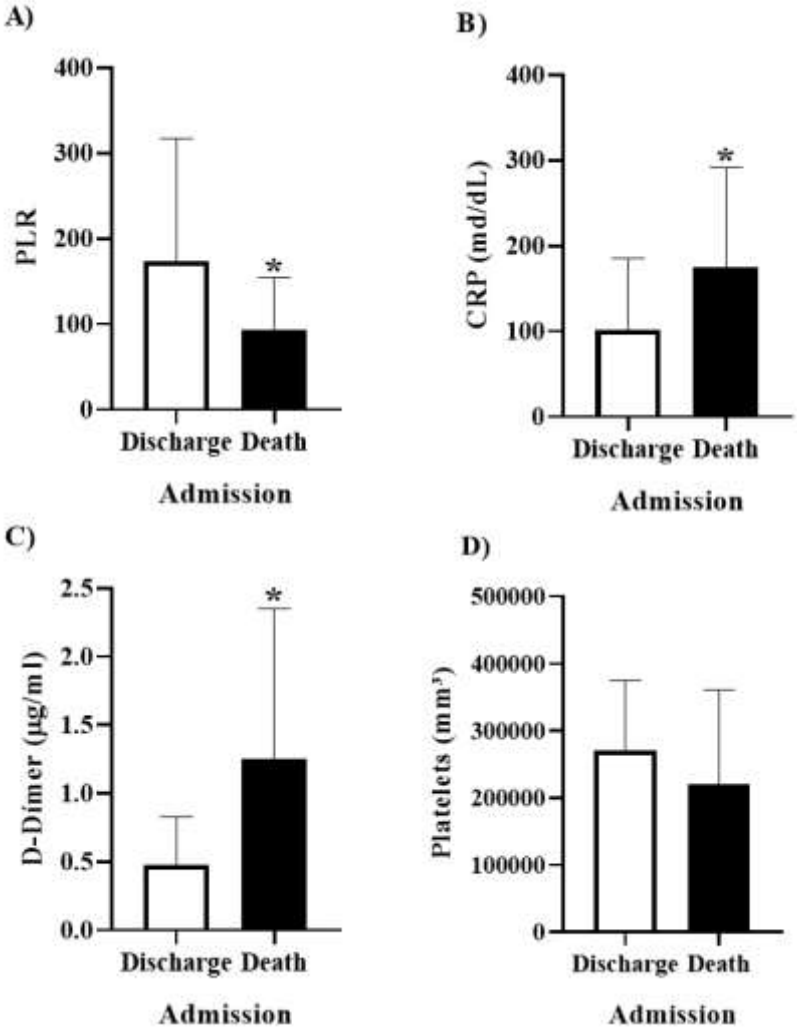


**Figure 2 –** Evaluation of biomarkers at the hospital admission in COVID-19 patients, with outcomes of discharge or death: platelet-to-lymphocyte ratio (PLR) (A), C-reactive protein (CRP) (B), D-dimer (C), and absolute platelet count (D) in COVID-19 patients who were discharged or died. Statistical analysis was performed using an unpaired *t*-test ($P < 0.05$).

When evaluating the PLR at the time of outcome, COVID-19 did not show significant changes (P = 0.15) when comparing the discharge group (133 ± 79/mm³) to the death group (104.6 ± 95/mm³) (Figure 3A). The systemic inflammatory process of COVID-19 sustained elevated CRP levels (186.8 ± 128 mg/dL) in patients who died throughout hospitalization, compared to survivors (47.1 ± 28.8 mg/dL) (Figure 3B). Meanwhile, the absolute platelet count was lower at the outcome in patients who died (P = 0.01), likely due to more severe hypercoagulability observed in these cases. The death group had a platelet count of 225 ± 143 × 10³/mm³, while patients who were discharged had 294 ± 105 × 10³/mm³ (Figure 3C).

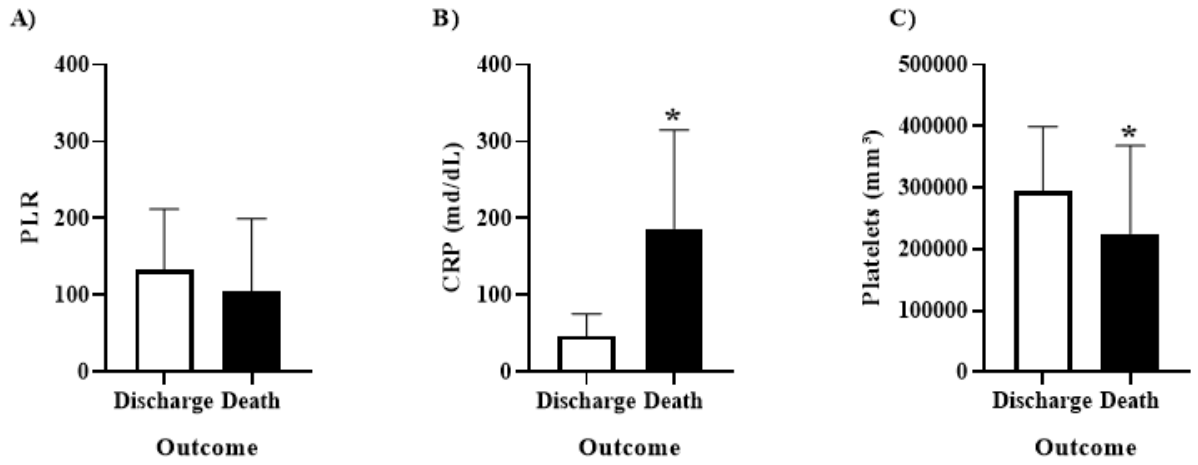


**Figure 3 –** Evaluation at the time of discharge or death in COVID-19 patients: platelet-to-lymphocyte ratio (PLR) (A), C-reactive protein (CRP) (B), and absolute platelet count (C). Statistical analysis was performed using an unpaired *t*-test ($P < 0.05$).

## DISCUSSION

Leukogram measurement is a routine laboratory test with high sensitivity and accuracy for monitoring the patient's response throughout disease progression, making it a reliable tool for establishing prognosis. Platelet count testing is also essential to monitor the hematologic response to the infectious challenge posed by SARS-CoV-2 and COVID-19. Our results demonstrate that CRP, D-dimer, and PLR play important roles as biomarkers for the clinical outcome of COVID-19 patients at the hospital admission.

COVID-19 is a systemic infection that impacts both the inflammatory and hemostatic responses, requiring thorough evaluation of hematological variables that have the potential to indicate and monitor the clinical status of affected patients[11]. A previous systematic review of the literature[12] showed that many current studies investigate hematological variables, such as leukogram and platelet count, in COVID-19 patients. These studies highlight the pathophysiological alterations of SARS-CoV-2 infection in the hematopoietic system, including hypercoagulability and lymphopenia. They also report enhanced inflammatory responses due to elevated cytokine levels, such as TNF-α, IL-1β, and IL-6, as well as typical findings, such as thrombocytosis, thrombocytopenia, morphological platelet changes, and

variations in neutrophil counts. Given these alterations, it is essential to analyze the relationship between hematological variables. In our study, a decrease in PLR at the hospital admission among patients was observed (Figure 2A), even though there was no proportional difference in platelet count between the discharge and death groups (Figure 2D).

PLR was lower in patients who progressed to death compared to survivors at the time of admission, suggesting platelet consumption associated with disseminated intravascular coagulation (DIC), and a concurrent increase in D-dimer levels (Figure 2C). This reduction was also linked to lymphocyte recruitment to damaged tissues as a result of the cytokine storm[13]. PLR is therefore associated with inflammation, hypercoagulability, and platelet consumption. However, studies by Qu et al. (2020) and Akan & Bilgir (2021) reported differing results, in which PLR was higher in patients with worse outcomes. In those studies, the PLR increase was attributed not to higher platelet counts but rather to intense lymphopenia[13,14].

Chan and Rout (2020) defined PLR as an independent biomarker for determining the severity of COVID-19, emphasizing that early identification of severe cases allows for timely therapeutic intervention[15]. Furthermore, PLR is associated with the length of hospital stay and the extent of the cytokine storm. In a study involving 415 patients, Huang et al. (2020) emphasized the importance of calculating PLR at the admission, as it serves as an excellent prognostic biomarker for COVID-19 severity[16].

In our study, PLR was not elevated at the time of outcome when comparing survivors to those who died (Figure 3A). The hypercoagulable state secondary to platelet aggregation in COVID-19, along with severe lymphopenia[12], may explain the similar PLR values at the outcome. This underscores the importance of early monitoring of PLR to evaluate the severity of the immune-inflammatory response in COVID-19.

Among biomarkers associated with acute-phase inflammatory response, CRP is the most sensitive[13]. Laboratory analyses showed that patients who died had already presented elevated CRP levels at the admission, which persisted until their outcome, compared to those who were discharged (Figures 2B and 3B). In COVID-19, severely ill patients who do not survive tend to present elevated CRP levels during hospitalization, which is associated with

increased IL-6 production[5]. Torun et al. (2021), in a study with 188 patients, and Ergenç et al. (2021), in a study with 635 patients, concluded that CRP elevation is related to the intensity of the cytokine storm and worsening prognosis[17,18]. This CRP increase is associated with death, as excessive inflammation may trigger multiple organ damage[19]. Goulart et al. (2021) also reported that approximately 97% of patients with SARS-CoV-2 respiratory infection had already elevated CRP levels at the hospital admission. In their study, most of these patients died, highlighting CRP as a valuable early biomarker for disease severity and mortality[20].

Elevated CRP levels are associated with a decrease in platelet count due to excessive recruitment resulting from the hypercoagulable state caused by acute inflammation. COVID-19 patients who die typically experience a drop in platelet count during the course of the disease, with counts falling below 100,000/mm$^3$. Fleury (2020) noted that this reduction is a common finding in critically ill patients and generally indicates severe physiological decompensation and the possible development of intravascular coagulopathy[9].

The high levels of systemic inflammation, which drive CRP elevation, also promote a hypercoagulable state. According to Robba et al. (2021), this is due to endothelial injury that leads to dysregulation of coagulation systems, with increased expression of procoagulant factors, greater fibrin formation, platelet consumption, and production of fibrin degradation products – especially D-dimer[21]– as observed in our study (Figure 2C). Similarly, Wang et al. (2020) reported that 71% of patients who died from COVID-19 had elevated D-dimer levels[22], and this association with mortality has been confirmed in other studies[8,19]. In this regard, Poudel et al. (2021), in a study with 182 patients, concluded that D-dimer is an accurate biomarker, with an optimal cutoff value of 1.5 µg/mL to predict poor prognosis at the admission[23].

It is worth emphasizing that CRP, D-dimer, and PLR are accessible and widely available biomarkers in clinical laboratories. These parameters should be further investigated for their potential to monitor disease progression, severity, and outcomes in COVID-19.

## CONCLUSION

C-reactive protein (CRP), D-dimer, and the platelet-to-lymphocyte ratio (PLR) demonstrated potential as prognostic biomarkers at the time of hospital admission in COVID-19 patients. The implementation of these laboratory parameters into clinical protocols for hospitalized COVID-19 patients may play a key role in risk stratification, guiding therapeutic decisions, and preventing complications and mortality associated with the disease. Complications arising from inflammation triggered by SARS-CoV-2 infection are frequently associated with elevated CRP levels, while a reduction in absolute platelet count indicates a worse prognosis. Early measurement of the PLR may serve as an early indicator of more severe cases of the disease.

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| **Authors' contributions** | |
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| Catrini Fiori: | Conceptualization; Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing. |
| Maria Andreatta: | Methodology; Data curation; Investigation. |
| Gabriela Cabrera: | Methodology; Data curation; Investigation. |
| Maicon Machado Sulzbacher: | Data curation; Formal analysis; Writing – original draft; Writing – review & editing. |
| Vitor Antunes de Oliveira: | Data curation; Methodology; Writing – original draft; Writing – review & editing. |
| Matias Nunes Frizzo: | Conceptualization; Data curation; Methodology; Supervision; Writing – original draft; Writing – review & editing. |
| **All the authors have approved the final version of the text.** | |
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# C-REACTIVE PROTEIN, PLATELET-TO-LYMPHOCYTE RATIO, AND D-DIMER AS PROGNOSTIC BIOMARKERS IN COVID-19 PATIENTS

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