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Evaluation of hematological changes and immune response biomarkers as a prognostic factor in critical patients with COVID-19

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Abstract

COVID-19 disease has been a challenge for health systems worldwide due to its high transmissibility, morbidity, and mortality. Severe COVID-19 is associated with an imbalance in the immune response, resulting in a cytokine storm and a hyperinflammation state. While hematological parameters correlate with prognosis in COVID patients, their predictive value has not been evaluated specifically among those severely ill. Therefore, we aim to evaluate the role of hematological and immune response biomarkers as a prognostic factor in critically ill patients with COVID-19 admitted to the intensive care unit. From May 2020 to July 2021, a retrospective cohort study was conducted in a reference hospital in Manaus, which belongs to the Brazilian public health system. This study was carried out as single-center research. Clinical and laboratory parameters were analyzed to evaluate the association with mortality. We also evaluated the role of neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein-to-lymphocyte ratio (CLR). We gathered information from medical records, as well as from prescriptions and forms authorizing the use of antimicrobial medications. During the study period, 177 patients were included, with a mean age of 62.58 ± 14.39 years. The overall mortality rate was 61.6%. Age, mechanical ventilation (MV) requirement, leukocytosis, neutrophilia, high c-reactive protein level, NLR, and CLR showed a statistically significant association with mortality in the univariate analysis. In the multivariate logistic regression analysis, only MV (OR 35.687, 95% CI: 11.084–114.898, p< 0.001) and NLR (OR 1.026, 95% CI: 1.003–1.050, p = 0.028) remained statistically associated with the outcome of death (AUC = 0.8096). While the need for mechanical ventilation is a parameter observed throughout the hospital stay, the initial NLR can be a primary risk stratification tool to establish priorities and timely clinical intervention in patients with severe COVID-19 admitted to the ICU.

Introduction

COVID-19 represented a significant challenge for health systems worldwide due to its high transmissibility. Clinical symptoms show wide heterogeneity, ranging from asymptomatic infection to aggressive life-threatening complications [1]. As the disease progressed, new variants with increased transmissibility and severity emerged, each wave was represented by a new "Variant of Concern (VOC)" [2]. This disease is multisystemic and highly complex since the severity depends on immunological and genetic factors, the tendency to a prothrombotic state, viral load, and comorbidities [3]. Severe cases of COVID-19 are a result of tissue-directed immunopathology, which causes rapid clinical deterioration and multiple organ dysfunction syndrome (MODS). This is due to a hyperinflammatory response rather than the virus itself being the direct cause [4, 5].

Severe COVID-19 is characterized by a cytokine storm, i.e., uncontrolled systemic hyperinflammation with excessive amounts of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α), which can lead to the failure of multiple organs until death. However, the pathogenesis of this condition has not yet been fully elucidated [6, 7].

Innate immunity is the first line of organism defense against intracellular pathogens. Viral infection promotes the expression of pathogen-associated molecular patterns (PAMPs) that activate immune cells and trigger inflammatory responses.

COVID-19, like other cytopathic viruses, also induces the release of diverse endogenous molecules that acts as a danger-associated molecular pattern (DAMPs). PAMPs and DAMPs derived from the host cellular injury are recognized by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), on alveolar macrophages and endothelial cells, promoting the release of pro-inflammatory cytokines and interferon [7]. When inflammation occurs, or the immune system is activated, there are changes in the blood composition. One can assess these changes by conducting different tests, including cytokine dosages, immunoassays, and flow cytometry. However, the routine peripheral blood cell count is a simple, rapid, and cheap test reflecting immune cell subset alterations. The increase in neutrophils and monocyte count represents the inflammatory process and innate immunity. On the other hand, lymphocytes are components of the adaptive immune response [3, 8–10].

Some studies reported that hematological parameters such as white blood cell count (WBC), lymphocyte count, neutrophil count, eosinophil count, platelet count, hemoglobin, neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), platelet-lymphocyte ratio (PLR), Lymphocyte-to-monocyte ratio (LMR) and C-reactive protein-to-lymphocyte ratio (CLR) are helpful in stratifying the severity of patients with COVID-19 [11–14]. However, their predictive value has not been explicitly evaluated among those severely ill.

It is imperative to identify rapid, low-cost, and easily accessible biomarkers to recognize high-risk patients as it enables better allocation of resources and early clinical intervention to prevent the mortality related to COVID-19. Therefore, this work aimed to evaluate the role of the hematological parameters, including NLR, LMR, PLR, and CLR in the prognosis of patients with COVID-19 admitted to a Brazilian intensive care unit.

Materials and methods

Design study and population

We conducted a retrospective cohort study by analyzing the electronic medical records of patients hospitalized with COVID-19 from May 2020 to July 2021. The extended period of the study intended to include the two exponential waves of COVID-19 cases in the city of Manaus.

The cohort was followed up from admission for a maximum period of 180 days, considering the outcomes of discharge or death, whichever occurred first. Data were collected from August to October 2022. The research was carried out at Getúlio Vargas University Hospital - AM's Intensive Care Unit (ICU), part of the Unified Health System and overseen by the Brazilian Hospital Services Company. The ICU capacity is ten adult beds–TYPE II but was later qualified for 30 adult ICU II beds–severe acute respiratory syndrome (SARS), COVID-19, according to the National Register of Health Establishments (CNES). The Federal University of Amazonas Research Ethics Committee approved the research under protocol number CAAE n° 57750422.4.0000.5020. Throughout the study, patients were identified using a growing sequence of alphanumeric codes drawn up by the researchers to ensure the anonymity of the research participants.

Source data and outcomes

Data collection included medical records, prescriptions, and the electronic system AGHU (Application for Management of University Hospitals). For each patient, we gathered the following information: For each patient, we gathered the following information: demographic (age, and sex), clinical (comorbidities, length of stay, needs of mechanical ventilation, and use of antimicrobials), and laboratory (peripheral blood cell count, and C-reactive protein) data. The clinical outcome of the patients in this research was survivor and non-survivor. The length of stay was set from the date of admission to hospital discharge, transfer to other hospitals or death. The associated hematological parameters are described in Table 1.

Statistical analysis

We calculated the mean and standard deviation for the quantitative variables, and the Kolmogorov-Smirnov Normality test was applied. Student's t-test (Normal Distribution) and Mann-Whitney (Non-Normal Distribution) were used to compare two groups (survivors and non-survivors). Categorical variables were shown in percentages or absolute values, and the Chi-Square Test and Fisher's Exact Test were used to verify the association between categorical variables. Finally, we employed the logistic regression model and calculated the receiver operating characteristic (ROC) curve. The pseudo-R2 was calculated to verify the model's explanatory power, and the odds ratio (OR) was calculated. All p values < 0.05 were considered statistically significant. For the analyses, we used the statistical program Stata® version 17.

Results

Demographic and clinical characteristics of COVID-19 patients

Out of 184 COVID-19 patients admitted to the ICU, 177 (96.2%) were included in the study. We excluded seven patients due to incomplete medical records. The average age of the patients was 62.58 ± 14.39 years, with 61,58% being 60 years or older. The mortality rate was 61.58%, with higher rates among elderly patients (77.06%) and male patients (53.21%). The median

Table 1. Description of hematological parameters and their formulas.

Parameter	Acronym	Formula
Neutrophil–to–lymphocyte ratio	NLR	(Absolute neutrophil count) / (absolute lymphocyte count
Lymphocyte-to-monocyte ratio	LMR	(Absolute lymphocyte count) / (absolute monocyte count)
Platelet-to-lymphocyte ratio	PLR	(Platelet count) / (absolute lymphocyte count)
C-reactive protein-to-lymphocyte ratio	CLR	(C-reactive protein count) / (absolute lymphocyte count)

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length of stay in the ICU was 17.00 (1–166) days, ranging from 19.00 (1–166) days for survivors, to 17.00 (1–93) days for non-survivors.

Regarding comorbidities, 66.67% of patients had at least one comorbidity, with hypertension being the most common (44.63%), followed by diabetes (26.55%) and obesity (8.47%). No significant association was found between comorbidities and mortality.

As for supportive procedures, 76.27% of patients required mechanical ventilation, with a significant difference between the survivors (44.12%) and non-survivors (96.33%) groups ($p < 0.001$). Almost all patients admitted to the ICU received antimicrobials (98.31%), with no significant difference between survivor and non-survivor groups ($p = 0.286$). More details about the demographic and clinical characteristics of the cohort can be seen in the supplementary data (S1–S3 Tables).

Changes in hematological parameters in patients with severe COVID-19

The laboratory parameters showed no significant differences in hemoglobin, hematocrit, lymphocytes, monocytes, eosinophils, basophils, and platelet count between the survivor and non-survivor groups. However, non-survivors had significantly higher leukocyte ($p<0.001$) and neutrophil ($p<0.001$) counts, as shown in Table 2. Additionally, the inflammatory marker CRP was also significantly elevated ($p = 0.048$) in non-survivor patients.

To assess the immunological status of the patients, peripheral blood inflammatory parameters and immune cell subset ratios were analyzed. The NLR and CLR were significantly higher in the non-survivor group. However, there were no significant differences in LMR and PLR between survivors and non-survivors, as shown in Table 3. Details of laboratory parameters and peripheral blood immune cell subset ratios are provided in S4 and S5 Tables, respectively.

Parameters associated with COVID-19 mortality

Age, the requirement of MV, leukocytosis, neutrophilia, and an increase in CRP, NLR, and CLR showed a statistically significant association with the mortality of ICU patients with COVID-19 in the univariate analysis. However, in the multivariate logistic regression analysis, only the mechanical ventilation (OR 35.687, 95% CI: 11.084–114.898, $p< 0.001$) and the NLR (OR 1.026, 95% CI: 1.003–1.050, $p = 0.028$) parameters remained statistically associated with the outcome of death. The multivariate logistic regression analysis model used the reverse stepwise approach until all variables were significant (Table 4).

The pseudo R2 of the final model (MV and NLR) was 0.304. The area under the curve was 0.8096, and the sensitivity and specificity were 96.33% and 54.41%, respectively (Fig 1).

Discussion

In this cohort of severely ill COVID patients, we identified the NLR as the most critical hematological parameter to predict in-hospital mortality.

Elderly patients ($\geq$ 60 years old) represented 77.06% of the non-survivor group in this study. In line with the literature, age showed to be significantly associated with mortality from COVID-19 in ICU patients ($p < 0.001$) [15–17]. According to Witkowski et al. (2022), it occurs in aging, a process of immunosenescence that affects the humoral and cellular immune functions, which reduces the effective response to pathogens. These changes could contribute to the increased severity and mortality related to COVID-19 infection in the elderly. In the same way, the immunosenescence process can be aggravated by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection. In addition, inflammatory aging contributes to an exacerbated inflammatory response and pro-inflammatory cytokine storm, promoting tissue damage and organ dysfunction [18, 19].

Table 2. Demographic, clinical, and laboratory characteristics of ICU patients diagnosed with COVID-19.

Variables	Overall	Survivor	Non-survivor	p
Number of patients	177	68 (38.42%)	109 (61.58%)	
Length of Stay, days (median)	17.00 (1–166)	19.50 (1–166)	17.00 (1–93)	0.066
Age, years (mean, SD)	62.58 ± 14.39	55.65 ± 13.24	66.91 ± 13.40	<0.001*
Age, (%)				<0.001*
< 60	38.42	63.24	22.94	
≥ 60	61.58	36.76	77.06	
Sex (%)				0.465
Men	55.37	58.82	53.21	
Woman	44.63	41.18	46.79	
Comorbidities				
Systemic arterial hypertension (%)	44.63	39.71	47.71	0.298
Diabetes mellitus (%)	26.55	23.53	28.44	0.472
Obesity (%)	8.47	4.41	11.01	0.125
Mechanical ventilation (%)	76.27	44,12	96.33	<0.001*
Use of Antimicrobials	98.31	100.00	97.25	0.286
Hematological Parameters				
Hemoglobin (g/dL), median	12.7 (4.60–18.20)	12.7 (5.50–18.20)	12.5 (4.60–17.40)	0.391
Hematocrit (%), median	37.3 (14.3–52.0)	37.90 (16.6–52.6)	36.7 (14.3–52.00)	0.429
Leukocytes (x 10^3/μL), mean (SD)	14.24 ± 7.38	11.83 ± 5.39	15.75 ± 8.06	<0.001*
Neutrophils (x 10^3/μL), mean (SD)	13.33 ± 10.94	10.85 ± 8.05	14.88 ± 12.19	<0.001*
Lymphocytes (x 10^3/μL), mean (SD)	0.97 ± 0.65	1.03 ± 0.72	0.93 ± 0.60	0.353
Monocytes (x 10^3/μL), mean (SD)	0.59 ± 0.39	0.57 ± 0.34	0.60 ± 0.42	0.867
Eosinophils (x 10^3/μL), median	0.008 (0–1.493)	0.007 (0–1.060)	0.008 (0–1.493)	0.835
Platelets (x 10^3/μL), mean (SD)	236.26 ± 106.88	242.08 ± 96.46	232.62 ± 113.18	0.317
CRP (mg/L), mean (SD)	98.57 ± 75.14	82.84 ± 66.65	107.64 ± 75.14	0.049*

CRP: C-reactive protein.

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Regarding the comorbidities, hypertension (p = 0.298), diabetes mellitus (p = 0.472), or obesity (p = 0.125) alone showed no significant difference between the groups of survivors and non-survivors, differing from the results of other studies [15, 20]. However, the role of hypertension on the prognosis of COVID-19, for example, remains controversial in the literature [21].

The requirement for mechanical ventilation is a sign of severe COVID-19 and has been associated with death [3, 22–24]. Our results corroborate the literature data; almost all patients in the non-survival group (96.33%) received MV versus 44.12% in the survivors' group. MV showed a positive association with the outcome of death in both univariate (p< 0.001) and multivariate logistic regression (OR 35.687, 95% CI: 11.084–114.898, p< 0.001). Patients who

Table 3. Inflammatory parameters and immune cell subsets ratios in COVID-19 ICU patients.

Variable	Overall	Survivor	Non-survivor	p
LMR	2.49 ± 3.85	2.21 ± 1.38	2.66 ± 4.79	0.294
PLR	341.89 ± 249.18	331.01 ± 226.91	348.68 ± 262.92	0.648
NLR	19.44 ± 18.64	14.90 ± 16.13	22.28 ± 19.58	0.003*
CLR	0.14 ± 0.17	0.10 ± 0.16	0.16 ± 0.17	0.009*

LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; CLR: C-reactive protein-to-lymphocyte ratio.

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Table 4. Multivariate logistic regression analysis of risk factors for mortality in hospitalized patients with COVID-19 in ICU.

Variable	Odds Ratio	SE	p-value	Confidence Interval (95%)	
				Lower	Upper
MV	35.687	21.280	<0.001	11.084	114.898
NLR	1.026	0.012	0.028	1.003	1.050

SE: standard error; MV: mechanical ventilation; NLR: Neutrophil-to-lymphocyte ratio.

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presented an intense inflammatory response associated with SARS-CoV-2 infection usually develop more severe symptoms and require ICU admission. The mortality rate of COVID-19 patients in the ICU can range from 0 to 84.6% [25]. In the present study, the overall mortality rate was 61.58%. It is essential to highlight that these data represented a period without vaccination or other proven effective treatment for COVID-19. According to epidemiological data, the period of the study comprised two waves of infection, the first with a prevalence of the

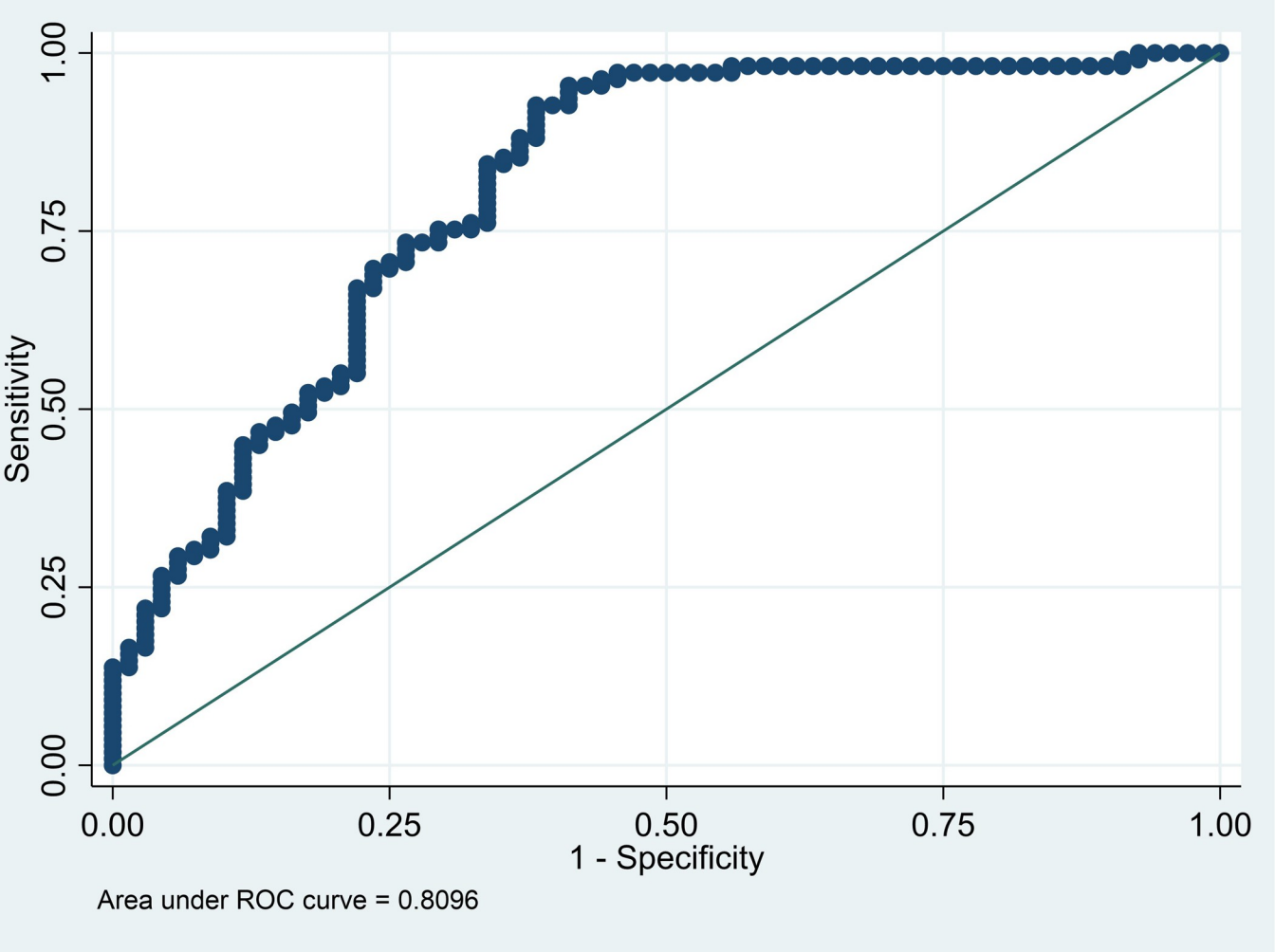

Fig 1. Receiver operating curve (ROC) multivariate logistic regression of the final model (MV and NLR).

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B.1.195 variant (March and May 2020), and the second with a predominance of the variant P.1 (December 2020 and February 2021) [2, 26, 27].

Previous reports have demonstrated a significant increase in the white blood cells (WBC) and neutrophil count in severe COVID-19 patients. In contrast, the number of lymphocytes is reduced in acute infection [4, 28, 29]. Lymphopenia has been an important predictor of severity and mortality related to COVID-19 in patients older than 60 years [30]. In our study, leukocyte ($p< 0.001$) and neutrophil ($p< 0.001$) counts were significantly associated with mortality, being higher in non-survivors than in survivors.

We also observed a reduction in the number of lymphocytes ($p = 0.353$), but the difference was not significant between the groups. It is important to emphasize that these parameters have been used as a marker of severity among patients with mild, moderate, and severe COVID-19. Our study population is composed exclusively of critically ill patients, so some markers may not show a significant difference.

As lymphocytopenia, neutrophilia is a biomarker of acute infection. Neutrophils play a crucial role in the innate immune response, and the increase in their blood count has been associated with adverse outcomes in COVID-19 patients [31]. In the present study, neutrophil counts were statistically higher in the non-survivor group and were positively associated with mortality ($p< 0.001$).

In our data, CRP was another inflammatory biomarker positively correlated with patient mortality ($p = 0.049$). CRP is a non-specific acute-phase inflammation biomarker. Other authors also reported increased CRP in COVID-19 patients [31]. Jemaa et al. (2022) explored the relationship between CRP and the severity of COVID-19 and observed a significant increase associated with ICU admission and ICU mortality. Additionally, CRP levels were correlated to WBC and neutrophil counts in non-ICU and ICU patients [32].

Impaired blood coagulation function is observed in critical COVID-19 patients. Reduction in platelet blood count has been related to withdrawal from circulation by disseminated thrombotic events [33]. In the present study, the mean platelet count was slightly smaller in non-survivor patients ($p = 0.317$), disagreeing with other studies [34, 35]. However, this corroborated the study of Jemaa et al. (2022), which compared platelet count in ICU survivors and non-survivors [32].

In addition to the effects on circulating immune cells, SARS-CoV-2 infection also affects the production of blood cells by impairing hematopoiesis. The expansion of immature and dysfunctional neutrophils, accompanied by increased erythroid precursors in the circulation, is compatible with infection-induced stress hematopoiesis [36, 37].

It is possible to calculate inflammation markers, such as NLR, LMR, PLR, and CLR, that reflect systemic inflammatory response through routine laboratory parameters. The predictive role of these indices in the clinical severity of patients with COVID-19 has been primarily evaluated [38–41].

The predictive role of the LMR is still controversial in the literature, however, our results were consistent with Jemaa, et al. (2022), which showed no correlation between this parameter and severe COVID-19 [32].

Our results demonstrated that increases in NLR ($p = 0.003$) and CLR ($p = 0.009$) are associated with COVID-19 mortality in ICU patients. Still, only NLR remained a risk factor in the multivariate logistic regression model (OR 1.026, 95% CI: 1.003–1.050, $p = 0.028$).

Several studies have verified the role of the NLR in distinguishing non-severe and severe cases of COVID-19, including ICU admission. However, data evaluating the predictive value of the NLR to critically ill patients are extremely scarce in the literature.

Gholinataj Jelodar et al. (2023), in a cross-sectional study, evaluated the NLR parameter of ICU COVID-19 patients and demonstrated a significative difference between the groups of

survivors and non-survivors. NLR was a risk factor in the multivariate logistic regression (OR 1.045, 95% CI: 1.012–1.079, p = 0.007) [42].

Farias et al. (2022) evaluated the association of leukocyte biomarkers, calculated in the emergency department, with the COVID-19 severity and mortality, in a cohort retrospective study, which includes 1,535 patients. They observed that NLR, MLR, and PLR had significant correlations with mortality, but only NLR was independently associated with both outcomes on multivariate analysis [43].

According to a recent meta-analysis conducted by Cheng et al. (2021), which analyzed 17 studies and 7,049 COVID-19 patients, it was found that the NLR (neutrophil-to-lymphocyte ratio) was significantly higher in patients with severe COVID-19 compared to those with non-severe COVID-19 [44]. This study reinforces that the initial NLR can be a reliable predictor of severe COVID-19.

In a study conducted by Asghar et al. (2022), they analyzed data from 1,000 COVID-19 patients who were hospitalized. The study found that both NLR and dNLR (which is calculated by dividing the absolute neutrophil count by the total leucocyte count minus the absolute neutrophil count) are reliable and sensitive markers for predicting the in-hospital outcomes of patients with COVID-19 [13]. Although, the NLR parameter has been more largely evaluated in the literature.

Khalid et al. (2022) compared hematological parameters between patients with COVID-19 and a control group of healthy individuals and observed that the absolute count of lymphocytes, PLR, and NLR was significantly higher in cases of severe disease [35].

Kosidło et al. (2023), in a recent literature review, reinforce the role of NLR as a predictor of the severity of inflammation in the course of COVID-19. On the other hand, it demonstrates the existence of discrepancies in the results involving the role of LMR [45].

As mentioned before, although several studies have addressed inflammatory parameters as predictors of severity and mortality [29, 46, 47], the role of these indices in distinguishing the outcome of death among critically ill ICU patients has rarely been investigated in previous research. Therefore, our results are an important contribution to establishing NLR as a predictor of mortality among critically ill patients admitted to the ICU.

In the current scenario, with a spread vaccination of the world population, the consolidation of hematological prognostic biomarkers remains important for any prospective targeted intervention in vulnerable patients, as the immunocompromised. In addition, the knowledge acquired with COVID-19 will undoubtedly serve as a basis for facing possible new viruses.

The main limitation of the study was the retrospective and unicentric design. Hence, confounding factors may have also affected the outcomes. In addition, the blood parameters assessed were related to the admission period, and changes throughout the hospital stay could have other clinical implications. Further studies, with multicenter and prospective manner, will be important to corroborate the role of leukocyte ratios in discriminating the risk of death in patients with severe COVID-19 admitted to the ICU.

Conclusion

Mechanical ventilation and neutrophil to lymphocyte ratio were shown to be independent predictors of mortality in patients with severe COVID-19 admitted to the ICU. While the need for mechanical ventilation is a parameter observed throughout the hospital stay, the initial NLR can be a prior risk stratification tool to establish priorities and timely clinical intervention. NLR parameter has a potential clinical implication distinguishing the patients who could benefit from pharmacotherapy with anti-inflammatories such as corticoids and tocilizumab, an IL-6 antagonist.

Supporting information

S1 Table. Characteristics of patients admitted to the ICU diagnosed with COVID-19, according to gender.
(DOCX)

S2 Table. Demographic and clinical characteristics of ICU patients with COVID-19.
(DOCX)

S3 Table. Clinical characteristics of ICU patients diagnosed with COVID-19.
(DOCX)

S4 Table. Laboratory characteristics of ICU patients diagnosed with COVID-19.
(DOCX)

S5 Table. Inflammatory parameters and immune cell subsets ratios in COVID-19 ICU patients.
(DOCX)

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