Prognostic role of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in critically ill COVID-19 patients: A retrospective study

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ABSTRACT

Introduction: Critical coronavirus disease (COVID-19) patients have a high mortality rate. To identify high-risk patients, first-level healthcare facilities can use the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) as prognostic markers. We aimed to assess the NLR and the PLR profile in critically ill COVID-19 patients to predict disease severity.

Materials and methods: This descriptive retrospective study featured 221 patients diagnosed with clinically critical COVID-19 from August 2021 to March 2022 in the Intensive Care Unit (ICU) of RSUP Dr. M. Djamil, Padang, Indonesia. The study employed a total sampling technique to collect data from medical records in the hospital. Patients aged 18 years or older who underwent testing for leukocytes, platelets, neutrophils, and lymphocytes were included in the study. We analysed the data using descriptive univariate analysis. Then, the NLR and PLR of the patients were statistically compared based on comorbidities and coincidence.

Results: According to the study, most patients with critically ill COVID-19 exhibited high levels of NLR (88.2%) and PLR (71.1%). The severe COVID-19 patients with comorbidity of kidney disease had the highest NLR (Mean ± SD) of 31.74 ± 27.95 (p-value <0.001) and the highest mean PLR (Mean ± SD) of 469.33 ± 362.95 (p-value 0.001).

Conclusion: Our findings showed a significantly higher NLR and PLR in patients with critically ill COVID-19, particularly in patients with comorbidity of kidney disease. Thus, elevated levels of NLR and PLR were identified as potential prognostic markers for predicting disease severity in COVID-19 patients, especially those with kidney comorbidity.

KEYWORDS:
Blood test, critical illnesses, hematologic tests, prognostic marker, SARS-CoV-2

INTRODUCTION

Coronavirus disease (COVID-19) is highly contagious and can cause multiple organ failure.[1,2] It has various severity levels, with critical cases requiring life-sustaining therapies.[3] Mortality rates for critically ill COVID-19 patients range from 40 to 67.6%.[4,5] High mortality rates have been observed in critical COVID-19 cases in Indonesia.[6,7] Studies have identified inflammatory biomarkers as predictors of mortality, but unfortunately, lab tests for these biomarkers are not widely available in Indonesia and are only performed in tertiary hospitals.[1,8]

Research has found that Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) levels may impact patients with various conditions, including COVID-19.[9-11] Patients with severe COVID-19 symptoms tend to have higher NLR and PLR levels, indicating a link to mortality.[12-13] Both can be easily measured and are effective predictors of early death in COVID-19 patients.[14]

Research suggests that using a combination of NLR and PLR can improve the accuracy of predicting severity of disease in patients. However, the optimal values for NLR and PLR in predicting disease severity, particularly for patients with comorbidities, require further investigation. Given these considerations, the aim of our study was to determine the profile of NLR and PLR in critically ill COVID-19 patients in the ICU of Dr. M. Djamil Hospital Padang during the delta and omicron eras to predict the disease severity. The data gathered from this study can provide a scientific basis to improve optimal service for critical clinical COVID-19 patients, utilizing minimal infrastructure and preparing for future outbreaks.

MATERIALS AND METHODS

This retrospective study was conducted at a tertiary hospital in Indonesia, specifically at the Dr. M. Djamil Hospital in Padang. We evaluated data from 221 patients who were diagnosed with clinically critical COVID-19 and admitted to

This article was accepted: 19 October 2024
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the COVID ICU during the delta and omicron eras, which were from August 2021 to March 2022. Patient data were collected from electronic medical records at the hospital, and the study was conducted in compliance with the Declaration of Helsinki. The ethical and research committee from the Dr. M. Djamil Hospital, Padang, approved this study with registration number LB.02.02/5.7/273/2023.

Given the retrospective nature of the research, informed consent was waived. The patients included in this study were 18 years or older and tested for leukocytes, platelets, neutrophils, and lymphocytes. We recorded patient characteristics such as age, gender, comorbidities, coincidences, leukocytes, platelets, neutrophils, and lymphocytes while excluding those with incomplete medical records.

Diagnoses were made according to interim guidance from the World Health Organization (WHO). The COVID-19 patients with acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions requiring life-sustaining treatments like mechanical ventilation or vasopressor therapy were considered clinically critical.[3] Age was recorded in years and categorized based on the Ministry of Health of the Republic of Indonesia.[15] Gender was categorized as male or female. Comorbidities were pre-existing conditions that exacerbated the patient's condition, while coincidences were unrelated conditions or events that occurred alongside the COVID-19 infection. These details were recorded in medical records by ICU doctors. The leukocyte, platelet, neutrophil, and lymphocyte count of clinically critical COVID-19 patients were determined by laboratory results from Dr. M. Djamil Padang Hospital during ICU admission. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated as follows: NLR = absolute neutrophil count/ absolute lymphocyte count; PLR = platelet counts/absolute lymphocyte count.

The leukocyte count was classified into three groups: normal ($5x10^3$-$10x10^3/mm^3$), leukopenia ($<5x10^3/mm^3$), and leucocytosis ($>10x10^3/mm^3$). Similarly, platelet count was divided into three categories: normal ($150x10^3$ - $400x10^3/mm^3$), thrombocytopenia ($<150x10^3/mm^3$), and thrombocytosis ($>400x10^3/mm^3$). The neutrophil count was classified into normal ($2.5x10^3$ - $7x10^3/mm^3$), neutropenia ($<2.5x10^3/mm^3$), and neutrophilia ($>7x10^3$ mm^3), while lymphocyte count was categorized into normal ($1x10^3$ - $4x10^3/mm^3$), lymphopenia ($<1x10^3/mm^3$), and lymphocytosis ($>4x10^3/mm^3$). These categorizations align with the clinical data interpretation guidelines of the Ministry of Health of the Republic of Indonesia.[16] The NLR values were grouped into normal (<3.13), high (3.13-5), and very high (>5), and PLR values were categorized into normal (≤180) and high (>180), based on previous research.[17] Finally, the NLR and PLR values were described according to comorbidities based on the affected organ system and the coincidence of critical clinical COVID-19 patients in the ICU Dr. M. Djamil Hospital Padang.

In order to mitigate potential biases and ensure the accuracy of our findings, we have taken steps to standardise our sampling procedures and thoroughly review our data for any anomalies or errors. The descriptive univariate analysis will be conducted to identify the frequency distribution characteristics of our research subjects, while the comparison of NLR and PLR values will be analysed using appropriate statistical analysis, i.e., the Anova oneway or Wilcoxon rank-sum test.

RESULTS

In this study conducted from August 2021 to March 2022, 223 patients with clinically critical COVID-19 were initially involved. However, 2 samples (0.9%) had to be excluded due to incomplete medical record data, including age, gender, and comorbidities or coincidences. As a result, the study ultimately included 221 samples. Table I provides detailed information on the characteristics of the participants. The ICU DR. M. Djamil Hospital Padang obtained data for patients with clinically critical COVID-19 in the Delta and Omicron eras. The table showed that 66 patients (29.7%) were aged over 65 years, 112 patients (50.7%) were male, 52 patients (18.7%) had comorbidity of diabetes mellitus, 19 patients (90.5%) were pregnant, 172 patients (77.8%) had leucocytosis, 158 patients (71.5%) had normal platelets, 187 patients (84.6%) had neutrophilia, and 128 patients (57.9%) had lymphopenia (Table I).

According to the NLR and PLR results, most patients with critically ill COVID-19 exhibited high levels of NLR (88.2%) and PLR (71.1%) (Figure 1). The severe COVID-19 patients with comorbidity of kidney disease had the highest NLR (Mean ± SD) of 31.74 ± 27.95, p-value <0.001, and the highest PLR (Mean ± SD) of 469.33 ± 362.95, p-value 0.001 (Table II). In addition, the patients with a coincidence of pregnancy had higher NLR and PLR than those with a coincidence of operation procedures (NLR of 11.63 ± 6.82 vs 3.71 ± 0.50; PLR of 11.63 ± 6.82 and 3.71 ± 0.50 263.20 ± 205.71 vs 220.04 ± 28.70) (Table II).

DISCUSSION

Efficient biomarker tests such as NLR and PLR are known to accurately predict mortality rates in COVID-19 patients. These assessments can be easily administered at primary healthcare centers and have been successfully implemented to diagnose various ailments, including COVID-19.[18] They play a crucial role in managing COVID-19 cases.19 In this retrospective analysis, we evaluated 221 critically ill COVID-19 patients in the ICU at DR. M. Djamil Hospital Padang during the Delta and Omicron periods.

Our findings show that the majority of critically ill COVID-19 patients had significantly elevated NLR levels (>5) and high PLR levels (>180). Interestingly, even those without underlying conditions displayed similarly elevated levels of NLR and PLR when critically ill. Previous research has suggested that NLR could be a potential biomarker for predicting COVID-19 mortality, as evidenced by Violetta et al.[20] In addition, Soumya et al.'s meta-analysis found that PLR was associated with disease severity and mortality in COVID-19 patients, further supported by the findings of Asghar et al., Ok et al., and Wang et al.[21]

In particular, our study identified that a significant proportion of patients with severe COVID-19 were male, over

Table I: Characteristics of Critically Ill COVID-19 Patients in the ICU at DR. M. Djamil Hospital, Padang. The table summarizes the main characteristics of critically ill COVID-19 patients, showing that most were over 65 years old, male, and had diabetes mellitus, leucocytosis, normal platelet counts, neutrophilia, and lymphopenia. Pregnancy was also noted among female patients

PatientçCharacteristics	N (%)
Age	
17-25 years	11 (4,9%)
26-35 years	23 (10,4%)
36-45 years	24 (10,9%)
46-55 years	33 (14,9%)
56-65 years	64 (28,9%)
> 65 years	66 (29,7%)
Gender	
Male	112 (50,7%)
Female	109 (49,3%)
Comorbidities	
Hypertension	31 (11,2%)
Diabetes mellitus	52 (18,7%)
Community pneumonia	17 (6,1%)
Chronic renal failure	28 (10,1%)
Acute renal impairment	24 (8,6%)
Stroke	19 (6,8)
Malignancy	13 (4,6%)
Other cardiovascular disease	26 (9,3%)
Other pulmonary disease	18 (6,5%)
Other neurological diseases	7 (2,5%)
Liver disease	10 (3,6%)
Other diseases	4 (1,4%)
No comorbidities	29 (10,4%)
Coincidences	
Pregnant	19 (90,5%)
Surgery	2 (9,5%)
Leukocytes	
Normal	41 (18,6%)
Leukopenia	8 (3,6%)
Leucocytosis	172 (77,8%)
Platelets	
Normal	158 (71,5%)
Thrombocytopenia	43 (19,5%)
Thrombocytosis	20 (9%)
Neutrophil	
Normal	30 (13,6%)
Neutropenia	4 (1,8%)
Neutrophilia	187 (84,6%)
Lymphocyte	
Normal	92 (41,6%)
Lymphopenia	128 (57,9%)
Lymphocytosis	1 (0,5%)

the age of 65, and had comorbid diabetes mellitus. As shown in Table I, advanced age was closely associated with compromised immunity, reduced physiological function, and a higher prevalence of comorbidities, making elderly patients particularly vulnerable to severe clinical manifestations of COVID-19, which can ultimately lead to increased mortality.[22] Notably, Table I illustrated that males face a disproportionately higher risk of severe COVID-19 compared to females, in agreement with a previous study, mentioning that males are three times more likely to require intensive care unit (ICU) admission and have a 15% greater chance of mortality, as indicated by higher vasopressor levels, prolonged ICU stays, and extended intubation.[23-24] Additionally, a former study found that COVID-19 patients with diabetes mellitus often present with heightened levels of IL-6 and CRP, leading to cytokine storms and systemic inflammation, including acute respiratory distress syndrome (ARDS).[25] Consequently, our findings emphasize that male patients, those over the age of 65, and individuals with comorbid diabetes mellitus are more frequently observed within this critical subset of COVID-19 patients, highlighting the need for targeted interventions in these high-risk groups. Additionally, the majority of patients in this study exhibited leucocytosis, normal platelet counts, neutrophilia, and lymphopenia. Patients with leucocytosis were found to be more likely to have chronic illnesses, experience critical conditions, require ICU admission, receive mechanical ventilation, and face a higher risk of mortality compared to those without leucocytosis.[26] Tessa et al.'s study on platelet index analysis in COVID-19 patients revealed that 73% had normal platelet counts while 20% had thrombocytopenia.[27] Iba et al. also found that patients with severe COVID-19

Table II: Comparison of Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) in Severe COVID-19 Patients by Comorbidities and Coincidences. This table shows that patients with kidney disease had the highest NLR and PLR. Furthermore, pregnant patients exhibited higher NLR and PLR compared to those who underwent surgical procedures

Organ-based comorbodities	Neutrophil - Lymphocyte Ratio (NLR)			p-value	Platelet - Lymphocyte Ratio (PLR)			p-value
	Mean	±	SD		Mean	±	SD	
Kidney	31.74	±	27.95	<0.001*	469.33	±	362.95	0.001*
Respiration	21.95	±	20.40		339.28	±	309.85	
Endocrine	20.95	±	14.10		375.25	±	282.55	
Multisystem	20.27	±	18.12		336.70	±	267.28	
Cardiovascular	19.94	±	17.28		289.48	±	195.88	
Malignancy	19.28	±	9.41		314.90	±	131.36	
None	15.17	±	7.06		315.27	±	205.71	
Neurology	11.77	±	8.06		213.21	±	131.72	
Gastrointestinal - Hepatobiliary	10.54	±	8.76		224.51	±	138.79	
Hematology	4.55	±	1.30		149.52	±	60.21	
Coincidences	**Neutrophil - Lymphocyte Ratio (NLR)**			**p-value**	**Platelet - Lymphocyte Ratio (PLR)**			**p-value**
	Mean	**±**	**SD**		**Mean**	**±**	**SD**	
Pregnancy	11.63	±	6.82	0.02**	263.20	±	205.71	0.63**
Operative Procedures	3.71	±	0.50		220.04	±	28.70	

*p-value of Anova oneway test
**p-value of Wilcoxon ranksum test

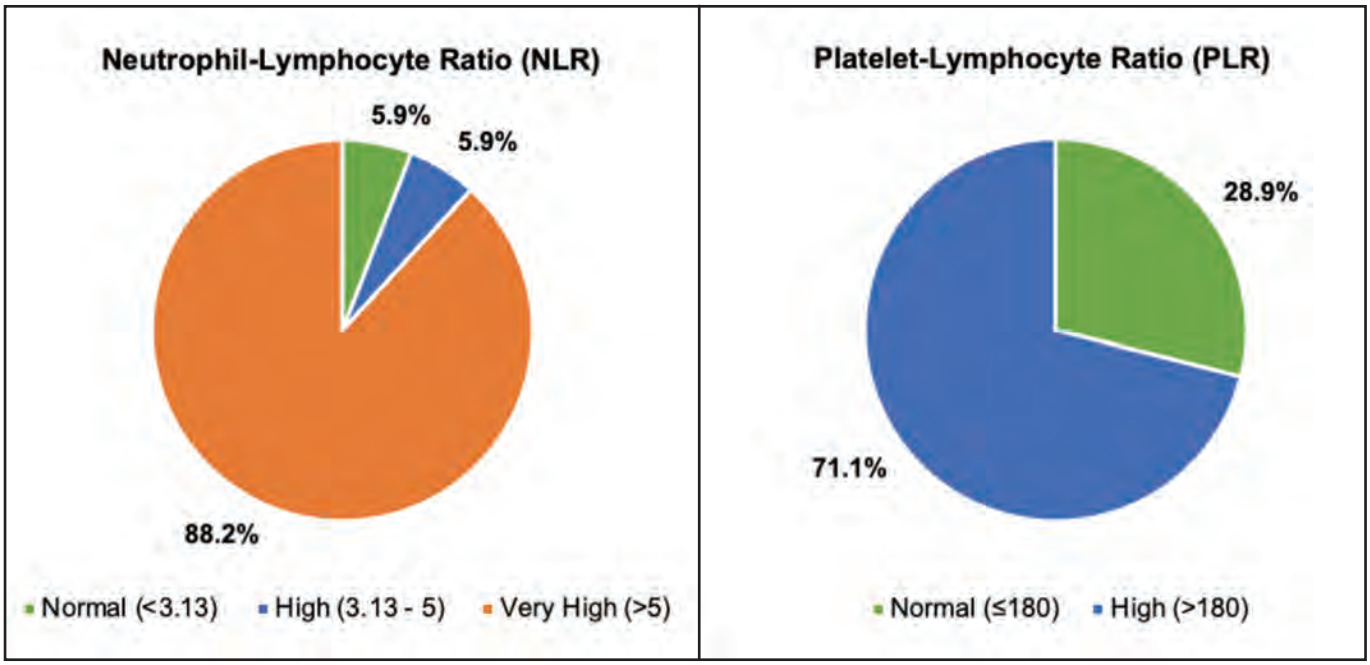

Fig. 1: Proportions of Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) Categories (Normal, High, Very High) in Critically Ill COVID-19 Patients. This figure illustrates the distribution of NLR and PLR categories among critically ill COVID-19 patients, indicating that the majority exhibited very high NLR levels and high PLR levels

symptoms often had low platelet and lymphocyte counts.[28] While this study primarily focused on critically ill COVID-19 patients, heterogeneity in the results may have arisen due to differences in patient comorbidities. Platelet counts in COVID-19 patients can be either normal or abnormal, and while no specific theory directly explains normal platelet counts in critically ill COVID-19 patients, it is possible that age, immune response, and the blood clotting process work together to maintain stable platelet levels. Regarding neutrophil counts, Enas et al.'s research demonstrated that neutrophilia and lymphopenia are common hematological changes in critically ill COVID-19 patients, particularly those with cytokine storms.[29]

Our study also explored NLR and PLR values in COVID-19 patients with comorbidities. Notably, patients with kidney disease had the highest NLR and PLR levels among severe COVID-19 cases. According to Arzu et al., COVID-19 patients with chronic renal failure are at a higher risk of severe disease and death. These patients tended to exhibit higher NLR

levels, and those who succumbed to the disease had significantly higher NLR and PLR values than those who recovered.[30] COVID-19 can alter immune responses through various factors such as iron deposition, uraemia, vitamin D deficiency, or haemodialysis, leading to particularly high NLR levels in critically ill patients with kidney disease.[31-32]

In addition, our research identified pregnancy as a common factor among severe COVID-19 cases. Pregnant women had higher NLR and PLR levels compared to those undergoing other medical procedures. Previous studies have suggested that pregnant women are at a greater risk of contracting and experiencing severe symptoms of COVID-19, particularly during the Delta period.[33] Critically ill pregnant patients with COVID-19 are more likely to experience poor prognoses. Recent findings indicate that pregnant women are more susceptible to severe cases of COVID-19 than their non-pregnant counterparts.[34]

However, several limitations must be acknowledged in this study. First, due to the relatively small sample size, NLR and PLR values could not be described in detail based on comorbidities related to specific organ systems, as samples were collected only during a specific time period. Second, this study did not comprehensively review platelet counts in critically ill COVID-19 patients, irrespective of previous therapies. Additionally, limited resources, study scope, and access to patient medical records may have constrained data collection from a larger pool of patients, potentially affecting our understanding of the condition. Future studies with larger patient populations are necessary to establish NLR and PLR cut-off values with optimal sensitivity and specificity before these biomarkers can be implemented in clinical practice.

Nevertheless, this study has notable strengths. The sample was drawn from an Indonesian tertiary hospital population, and the data collection process followed standardized protocols. However, whether the findings from this study can be generalized to other regions remains uncertain, as NLR and PLR values may vary depending on the population being studied. Future research should include multi-centre prospective studies to validate the efficacy of NLR and PLR in predicting disease progression in critically ill COVID-19 patients.

Despite limitations like small sample size and regional focus, our findings provide valuable insights into the prognostic utility of NLR and PLR, warranting further research to validate these results and establish optimal clinical cut-off values.

CONCLUSION

In conclusion, our study underscores the potential of the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) as effective biomarkers for predicting mortality in critically ill COVID-19 patients. A significant proportion of our cohort, particularly males over 65 and individuals with comorbid diabetes mellitus, exhibited elevated NLR and PLR levels. Common findings of leucocytosis, normal platelet counts, neutrophilia, and lymphopenia further indicate markers of disease severity. Patients with comorbid conditions, such as kidney disease, showed even higher values, emphasizing the need for heightened monitoring.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

DATA AVAILABILITY

All relevant data related to the manuscript are available upon request from the author.

ACKNOWLEDGMENT

The authors would like to express their appreciation for the ICU and Medical Record team in Dr. M. Djamil Hospital, Padang, Indonesia, who provided data for this research.

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