

# The relationship between Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), and Monocyte to Lymphocyte Ratio (MLR) with the clinical severity level of COVID-19 patients at Udayana University Hospital

A relação entre a razão Neutrófilo para Linfócito (NLR), Razão Plaquetas para Linfócito (PLR) e Razão Monócito para Linfócito (MLR) com o nível de gravidade clínica dos pacientes com COVID-19 no Hospital da Universidade Udayana

La relación entre la Razón Neutrófilo a Linfocito (NLR), Razón Plaquetas a Linfocito (PLR) y Razón Monocito a Linfocito (MLR) con el nivel de severidad clínica de los pacientes con COVID-19 en el Hospital de la Universidad de Udayana

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## Abstract

Background: COVID-19 is an pandemic with a high transmission rate. Due to its widespread availability, complete blood count has the potential to be used as an initial screening for clinical severity. Objective: This study aims to determine the relationship between NLR, PLR, and MLR with the clinical severity level of patients with COVID-19.

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**Method:** A cross-sectional study was conducted at Udayana University Hospital on COVID-19 patients hospitalized from March 2020 to March 2021. Subjects were divided into critical and non-critical groups and analyzed for their relationship with the components of the complete blood count on the first day of hospitalization. **Result:** The analysis found that the study subjects had a mean ( $\pm$  standard deviation) age of 54.20 ( $\pm$  15.57) years. The mean ( $\pm$  SD) hemoglobin level was found to be 13.44 ( $\pm$  4.05) g/dL, and the platelet count was 245.75 ( $\pm$  107.36)  $\times 10^3/\mu\text{L}$ . The median (interquartile range) leukocyte count was found to be 7.78 (4.91)  $\times 10^3/\mu\text{L}$ , neutrophils 5.72 (4.91)  $\times 10^3/\mu\text{L}$ , basophils 0.01 (0.01)  $\times 10^3/\mu\text{L}$ , eosinophils 0.01 (0.01)  $\times 10^3/\mu\text{L}$ , monocytes 0.53 (0.41)  $\times 10^3/\mu\text{L}$ , lymphocytes 1.10 (0.89)  $\times 10^3/\mu\text{L}$ , NLR 5.21 (7.77), PLR 193.34 (153.54), and MLR 0.51 (0.42). **Conclusion:** NLR, PLR, and MLR are significantly associated with the clinical severity level in COVID-19 patients at Udayana University Hospital. These findings can assist clinicians in assessing the potential for worsening clinical severity from mild to severe or critical levels in COVID-19 patients.

**Keywords:** Clinical severity level; COVID-19; Monocyte to lymphocyte ratio; Neutrophil to lymphocyte ratio; Platelet to lymphocyte ratio.

### Resumo

**Contexto:** A COVID-19 é uma pandemia com uma alta taxa de transmissão. Devido à sua ampla disponibilidade, o hemograma completo tem o potencial de ser usado como uma triagem inicial para a gravidade clínica. **Objetivo:** Este estudo tem como objetivo determinar a relação entre NLR, PLR e MLR com o nível de gravidade clínica de pacientes com COVID-19. **Método:** Um estudo transversal foi conduzido no Hospital Universitário Udayana com pacientes de COVID-19 hospitalizados de março de 2020 a março de 2021. Os sujeitos foram divididos em grupos críticos e não críticos e analisados quanto à sua relação com os componentes do hemograma completo no primeiro dia de hospitalização. **Resultado:** A análise encontrou que os sujeitos do estudo tinham uma idade média ( $\pm$  desvio padrão) de 54,20 ( $\pm$  15,57) anos. O nível médio ( $\pm$  DP) de hemoglobina foi encontrado em 13,44 ( $\pm$  4,05) g/dL, e a contagem de plaquetas foi de 245,75 ( $\pm$  107,36)  $\times 10^3/\mu\text{L}$ . A mediana (intervalo interquartil) da contagem de leucócitos foi encontrada em 7,78 (4,91)  $\times 10^3/\mu\text{L}$ , neutrófilos 5,72 (4,91)  $\times 10^3/\mu\text{L}$ , basófilos 0,01 (0,01)  $\times 10^3/\mu\text{L}$ , eosinófilos 0,01 (0,01)  $\times 10^3/\mu\text{L}$ , monócitos 0,53 (0,41)  $\times 10^3/\mu\text{L}$ , linfócitos 1,10 (0,89)  $\times 10^3/\mu\text{L}$ , NLR 5,21 (7,77), PLR 193,34 (153,54) e MLR 0,51 (0,42). **Conclusão:** NLR, PLR e MLR estão significativamente associados ao nível de gravidade clínica em pacientes com COVID-19 no Hospital Universitário Udayana. Esses achados podem auxiliar os clínicos na avaliação do potencial de piora da gravidade clínica, de níveis leves para graves ou críticos em pacientes com COVID-19.

**Palavras-chave:** COVID-19; Nível de gravidade clínica; Relação neutrófilo-linfócito; Relação monócito-linfócito; Relação plaqueta-linfócito.

### Resumen

**Contexto:** COVID-19 es una pandemia con una alta tasa de transmisión. Debido a su amplia disponibilidad, el hemograma completo tiene el potencial de ser utilizado como una evaluación inicial de la gravedad clínica. **Objetivo:** Este estudio tiene como objetivo determinar la relación entre NLR, PLR y MLR con el nivel de gravedad clínica de los pacientes con COVID-19. **Método:** Se realizó un estudio transversal en el Hospital Universitario Udayana con pacientes con COVID-19 hospitalizados desde marzo de 2020 hasta marzo de 2021. Los sujetos fueron divididos en grupos críticos y no críticos y se analizaron en relación con los componentes del hemograma completo en el primer día de hospitalización. **Resultado:** El análisis encontró que los sujetos del estudio tenían una edad media ( $\pm$  desviación estándar) de 54,20 ( $\pm$  15,57) años. El nivel medio ( $\pm$  DE) de hemoglobina fue de 13,44 ( $\pm$  4,05) g/dL, y el recuento de plaquetas fue de 245,75 ( $\pm$  107,36)  $\times 10^3/\mu\text{L}$ . La mediana (rango intercuartílico) del recuento de leucocitos fue de 7,78 (4,91)  $\times 10^3/\mu\text{L}$ , neutrófilos 5,72 (4,91)  $\times 10^3/\mu\text{L}$ , basófilos 0,01 (0,01)  $\times 10^3/\mu\text{L}$ , eosinófilos 0,01 (0,01)  $\times 10^3/\mu\text{L}$ , monócitos 0,53 (0,41)  $\times 10^3/\mu\text{L}$ , linfocitos 1,10 (0,89)  $\times 10^3/\mu\text{L}$ , NLR 5,21 (7,77), PLR 193,34 (153,54) y MLR 0,51 (0,42). **Conclusión:** NLR, PLR y MLR están significativamente asociados con el nivel de gravedad clínica en pacientes con COVID-19 en el Hospital Universitario Udayana. Estos hallazgos pueden ayudar a los clínicos a evaluar el potencial de empeoramiento de la gravedad clínica de niveles leves a graves o críticos en pacientes con COVID-19.

**Palabras clave:** Nivel de gravedad clínica; COVID-19; Relación monocito-linfocito; Relación neutrófilo-linfocito; Relación plaqueta-linfocito.

## 1. Introduction

COVID-19 is a pandemic with a relatively high rate of transmission which was initially very difficult to diagnose due to limited equipment, especially in developing countries (Park et al., 2020; Purnamasidhi et al., 2021; *COVID-19 Traveler Policy in Migrant Worker: How It Helped Shape Distinct Clusters During the Early Phases of the Pandemic*, n.d.). Since the outbreak of this pandemic, efforts have continued to be made to address and reduce its broad impact on global society (Wang et al., 2020). With the rapid rate of spread, especially in countries with dense populations, appropriate care and treatment are

crucial to minimize mortality and reduce the burden on health systems and medical education systems (Gallo Marin et al., 2021a; R. Suteja et al., 2020; Nahian et al., 2022).

One of the challenges in dealing with this pandemic is how to early identify COVID-19 patients who are at risk of experiencing complications and more severe disease progression (Gallo Marin et al., 2021a). Several previous studies have shown that changes in complete blood count can provide early clues to the clinical severity of COVID-19 patients. Although several clinical guidelines can be used to assess severity, laboratory parameters are more objective in determining the patient's immune response (Weisnawa et al., 2022). This has a significant impact on the provision of therapy and priority triage so that the best drug and vaccine resources become more effective (Sumardika et al., 2021; Putu Kintan Wulandari et al., 2022; Harkitasari et al., 2023; Purnamasidhi et al., 2023). Therefore, a simple analysis of these hematological parameters can be a useful tool in evaluating the clinical severity of COVID-19 patients at an early stage (Rahman et al., 2021; R. C. Suteja et al., 2023).

Complete blood count (CBC) is one of the common laboratory tests performed to obtain an overview of the components of human blood cells. HDL includes several major components, including leukocytes, erythrocytes, platelets, and other blood cells (Bellan et al., 2021). In the context of COVID-19, several studies have highlighted the important role of certain blood cells, such as lymphocytes, neutrophils, monocytes, and platelets, in responding to this viral infection and contributing to disease pathogenesis (Rahman et al., 2021).

In recent medical research, attention has been drawn to the ratios of certain blood cells, namely the Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), and Monocyte to Lymphocyte Ratio (MLR). These ratios are obtained by dividing the number of certain blood cells by the number of lymphocytes in HDL (Fors et al., 2022; R. C. Suteja et al., 2023). NLR reflects the level of inflammation and activation of the immune system, PLR can indicate the inflammatory response and the balance status between clotting blood cells and lymphocyte blood cells, while MLR can reflect the role of monocytes in the immune response (Seyit et al., 2021a; Simadibrata et al., 2022a; Vafadar Moradi et al., 2021a).

Previous studies have shown that NLR, PLR, and MLR may be associated with clinical severity in several medical conditions, including acute respiratory diseases, infections, and inflammatory diseases (Seyit et al., 2021b). However, the relationship between these ratios and clinical severity in COVID-19 patients is still controversial and requires further research to confirm.

Given the importance of this information in identifying and assessing the risk of COVID-19 patients, this study aims to explore the relationship between NLR, PLR, and MLR with clinical severity in COVID-19 patients at Udayana University Hospital.

## **2. Methodology**

The research method used in this study was a cross-sectional study conducted at Udayana University Hospital and was done under the guidance of a methodology book (Sastroasmoro & Ismael, 1995). The population studied were COVID-19 patients aged between 18 and 59 years, who had been confirmed by Reverse Transcription Polymerase Chain Reaction (RT-PCR) tests and were hospitalized from March 2020 to March 2021. The selection of the age group of 18 to 59 years was based on the consideration that this age range is a group that is often exposed to COVID-19 and is at risk of experiencing various levels of clinical severity.

The selection process of the research subjects was carried out carefully to ensure the validity and representativeness of the data. Patients who had incomplete medical records, who did not undergo a complete blood count examination on the first day of hospitalization, had a history of hematological disease, were infected with HIV, or had autoimmune comorbidities, were

excluded from the subjects to be analyzed in this study. This was done to ensure that the data used in the analysis were consistent and reliable data.

After subjects who met the inclusion and exclusion criteria were determined, they were then grouped into two groups, namely critical and non-critical groups, based on the criteria of the Indonesian Ministry of Health which describes the level of clinical severity in COVID-19 patients. This severity classification is based on clinical manifestations, signs and symptoms, and relevant supporting examination results.

Data for analysis were obtained from the results of a complete blood count examination performed on the patient's first day of hospitalization. At that time, researchers will collect data on the number of certain blood cells, including leukocytes, neutrophils, monocytes, and platelets, as well as the number of lymphocytes. This data will be used to calculate the desired ratios, namely Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), and Monocyte to Lymphocyte Ratio (MLR).

After the data is collected, statistical analysis will be performed to evaluate the relationship between NLR, PLR, and MLR with clinical severity in COVID-19 patients. The analysis method used is bivariate analysis, taking into account other factors that may affect the results of the study, such as patient age, history of comorbidities, and other health conditions. The use of this analysis method is expected to produce accurate and reliable findings in identifying the relationship between blood cell ratios and clinical severity in COVID-19 patients.

All data and information obtained from this research will be managed and processed with strict confidentiality and will only be used for research purposes. The research process will be closely monitored and evaluated to ensure the integrity and validity of the research results. The study respected the Helsinki declaration and has gained ethical approval from the Ethical Committee of Faculty of Medicine, Udayana University.

### 3. Results

This study involved 176 subjects with an average age of 54.20 ( $\pm$  15.57) years. Of the total samples, 61.4% were male, while 38.6% were female. The results of the analysis showed that the average value ( $\pm$  standard deviation) of hemoglobin levels in the study subjects was 13.44 ( $\pm$  4.05) g/dL, and the platelet count was 245.75 ( $\pm$  107.36)  $\times 10^3/\mu\text{L}$ . In addition, the median (interquartile range) of leukocyte count was 7.78 (4.91)  $\times 10^3/\mu\text{L}$ , neutrophil count was 5.72 (4.91)  $\times 10^3/\mu\text{L}$ , basophil count was 0.01 (0.01)  $\times 10^3/\mu\text{L}$ , eosinophil count was 0.01 (0.01)  $\times 10^3/\mu\text{L}$ , monocyte count was 0.53 (0.41)  $\times 10^3/\mu\text{L}$ , and lymphocyte count was 1.10 (0.89)  $\times 10^3/\mu\text{L}$ . In addition, NLR was 5.21 (7.77), PLR was 193.34 (153.54), and MLR was 0.51 (0.42). Complete epidemiological and laboratory characteristics of research subjects can be seen in Table 1.

**Table 1 - Epidemiological and Laboratory Characteristics of Research Subjects.**

Variable		Mean ( $\pm$ Standard Deviation) / Median (Interquartile Range) / N (%) (N = 176)
Age (year)		54.20 ( $\pm$ 15.57)
Gender	Men	108 (61.4%)
	Woman	68 (38.6%)
Hemoglobin (g/dL)		13.44 ( $\pm$ 4.05)
Leukocytes ( $\times 10^3/\mu\text{L}$ )		7.78 (4.91)
Neutrophil ( $\times 10^3/\mu\text{L}$ )		5.72 (4.91)
Basophil ( $\times 10^3/\mu\text{L}$ )		0.01 (0.01)
Eosinophil ( $\times 10^3/\mu\text{L}$ )		0.01 (0.01)
Monocytes ( $\times 10^3/\mu\text{L}$ )		0.53 (0.41)
Lymphocytes ( $\times 10^3/\mu\text{L}$ )		1.10 (0.89)
Platelets ( $\times 10^3/\mu\text{L}$ )		245.75 ( $\pm$ 107.36)
NLR		5.21 (7.77)
PLR		193.34 (153.54)
MLR		0.51 (0.42)

Source: Author's own work.

Table 1 displays the epidemiological and laboratory characteristics of the study subjects, including means ( $\pm$  standard deviation) or medians (interquartile range) for numeric variables and percentages for categorical variables such as age, sex, and clinical severity. Bivariate analysis of numerical variables can be seen in Table 2.

**Table 2 - Bivariate Analysis of Numerical Variables.**

Variable	Clinical Severity Level		R value	P Value
	Critical	Non Critical		
NLR	9,46 (9,77)	2,70 (2,41)	0,68	0,00*
PLR	268,01 (185,67)	163,32 (88,57)	0,44	0,00*
MLR	0,64 (0,47)	0,38 (0,31)	0,39	0,00*

Source: Author's own work.

Table 2 shows the results of bivariate analysis of numerical variables related to clinical severity. The correlation value (R) indicates the relationship between each numerical variable and clinical severity, while the P value assesses the statistical significance of the relationship. The results of the analysis show that NLR, PLR, and MLR have P values  $<0.01$ , indicating that these three variables are significantly related to clinical severity in COVID-19 patients at Udayana University Hospital.

#### 4. Discussion

In this study, we aimed to evaluate the relationship between NLR, PLR, and MLR with the clinical severity of COVID-19 patients at Udayana University Hospital. Based on the results of the analysis, we can conclude several important things that are relevant to this study.

The results showed that COVID-19 patients in this study had a wide age range, with an average age of around 54.20 years. More than half of the patients were male (61.4%), and the rest were female (38.6%). These data reflect a good representation of COVID-19 patients in our hospital.

In laboratory analysis, we found that COVID-19 patients in this study had a mean hemoglobin value of around 13.44 g/dL, and leukocyte and platelet counts within the normal range with a mean of  $7.78 \times 10^3/\mu\text{L}$  and  $245.75 \times 10^3/\mu\text{L}$ , respectively. However, we also observed significant variations in NLR, PLR, and MLR values among patients.

Previous studies have shown that increased NLR, PLR, and MLR can be used as indicators of inflammation and immune system response in COVID-19 patients (Seyit et al., 2021b). A high NLR ratio reflects a higher level of inflammation and can be used to predict the clinical severity of a patient (Vafadar Moradi et al., 2021b). Previous studies have also found that high NLR levels are associated with an increased risk of developing more severe disease and can be used as a predictor for the prognosis of COVID-19 patients (Seyit et al., 2021b; Vafadar Moradi et al., 2021b; Suteja et al., 2023).

On the other hand, PLR and MLR are also important inflammatory biomarkers. High PLR ratio indicates an increased platelet response, which may lead to hypercoagulability in COVID-19 patients (Simadibrata et al., 2022b). This has serious clinical implications as it may increase the risk of thrombotic complications in patients with COVID-19 (Ahmed et al., 2020). In addition, high MLR reflects an unbalanced monocyte response, which may contribute to systemic inflammation and higher clinical severity in COVID-19 patients (Seyit et al., 2021b).

Various theories have been proposed to explain the relationship between the NLR, PLR, and MLR ratios with clinical severity in COVID-19 patients (Seyit et al., 2021b). One of them is the theory that the SARS-CoV-2 virus can cause severe inflammation in the lungs and cause an increase in the number of neutrophils and monocytes in the blood (Junqueira et al., 2022). In addition, viruses can also damage endothelial cells and trigger platelet activation, which causes an increase in the number of platelets in the blood (Kumar et al., 2020). In this condition of excessive inflammation, there is an imbalance between the white blood cells that play a role in the immune response, which is reflected in high NLR, PLR, and MLR ratios (Seyit et al., 2021b).

However, this study has several limitations. The cross-sectional design does not allow for causal conclusions to be drawn, and further studies with prospective study designs are needed to validate these findings. In addition, the relatively small sample size may also affect the generalizability of the results of this study. Although we have controlled for several potential factors that may affect the results of this study, other factors not measured in this study may affect the relationship between the NLR, PLR, and MLR ratios and the clinical severity of COVID-19 patients.

## 5. Conclusion

NLR, PLR, and MLR were significantly associated with clinical severity in COVID-19 patients at Udayana University Hospital. These findings may assist clinicians in assessing the potential for increased clinical severity from mild to severe or critical in COVID-19 patients. We suggest further studies to perform a more stratified approach especially on age to know whether these relations are significant in patients excluded from this study (pediatrics, advanced-age patients).

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