ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ)* 2023, Volume 12, Number 2: 1446-1450
P-ISSN.2089-1180, E-ISSN: 2302-2914

# Diagnostic and predictive value of hematological parameters of COVID-19 patients: a retrospective study

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Received: 2023-03-11
Accepted: 2023-04-22
Published: 2023-05-06

## ABSTRACT

**Background:** Simple, cost-effective, and practical laboratory indicators are required to diagnose and evaluate COVID-19 disease severity. This study assessed the diagnostic value and predictor of severity and outcome parameters of NLR, d-NLR, MLR, PLR, and ALC in COVID-19 patients.

**Methods:** A retrospective study used medical record data from 100 COVID-19 patients from November 2020 to March 2021. SPSS version 22 was used to analyze the data. The severity of COVID-19 was predicted using a ROC curve. Kaplan-Meier analysis was employed to evaluate the ability of various inflammatory markers to predict COVID-19 prognosis. A multivariate analysis with logistic regression was conducted to assess the ability of an independent predictor of COVID-19 severity. A p-value of <0.05 was considered significant.

**Results:** ALC values were lower in the severe-critical COVID-19 group, whereas NLR, d-NLR, MLR, and PLR values were higher. The NLR, d-NLR, and ALC parameters had sufficient accuracy, whereas the MLR and PLR parameters had low accuracy. NLR, d-NLR, MLR, PLR, and ALC had optimal cut-off values of 7.865, 4.82, 0.455, 235.000, and 0.895, respectively. The multivariate odds ratio for ALC was 7.348 (95% CI = 1.914-28.214; p = 0.004). Kaplan-Meier analysis revealed differences in survival time based on the optimal NLR, MLR, d-NLR, and ALC cut-offs obtained.

**Conclusion:** NLR, d-NLR, MLR, PLR, and ALC are all potential predictors of COVID-19 severity and prognosis. ALC is a reliable predictor of COVID-19 severity.

**Keywords:** COVID-19, Infectious disease, ALC, d-NLR, NLR
**Cite This Article:** Kiriwenno, E., Indrasari, Y.N. 2023.Diagnostic and predictive value of hematological parameters of COVID-19 patients: a retrospective study. Bali Medical Journal 12(2): 1446-1450. DOI: 10.15562/bmj.v12i2.4253

## INTRODUCTION

Since the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic in early 2020, it has developed into a global health problem.[1,2] Based on clinical symptoms and laboratory test results, the severity of COVID-19 patients is classified into mild, moderate, severe, and critical. Around 81% of COVID-19 patients have mild-moderate symptoms, 14% severe, and 5% acute symptoms.[3,4] So far, chest X-rays and computerized tomography (CT) scans of the chest have been the primary diagnostic modalities for determining the severity of COVID-19. Due to limited medical resources and relatively high examination costs, the use of CT scan modalities is still low.[5,6] To prevent clinical deterioration and minimize the risk of death in COVID-19 patients, simple, practical, and inexpensive laboratory indicators are necessary for the early stages of the disease to evaluate the severity of the disease and the prognosis.[5,7]

A complete blood count is a routine, inexpensive examination that is simple to perform. It provides information on different cell types and morphology and assesses the degree of inflammation in the early stages of the disease. In recent years, researchers have discovered that the combined ratio of several hematological parameters, such as the neutrophil-to-lymphocyte ratio (NLR), derived NLR (d-NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), can be used as an inflammatory marker to help diagnose, predict outcomes, and assess the severity of COVID-19.[3,5] This study aimed to determine the diagnostic value of hematological inflammatory markers and explore their relation to the seriousness of COVID-19.

## METHODS

This retrospective study involved secondary data from patients diagnosed with COVID-19 from the hospital's medical records from November 2020 to March 2021. Inclusion criteria were patients aged ≥18 years confirmed with a diagnosis of COVID-19, underwent a complete blood count using Sysmex XN-3000 at admission to the Emergency Department and met the criteria for severity of disease according to the Clinical Practice Guidelines. Exclusion criteria were patients with or who had malignancy, aplastic anemia, HIV, autoimmune diseases, pregnant or postpartum patients, and patients with a transfusion history.

Hematological biomarkers measured in this study included absolute lymphocyte count (ALC), neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR), and derived NLR ratio (d-NLR). Diagnosis of COVID-19 patients was based on real-time polymerase chain reaction (PCR).[8,9]

SPSS version 22 was used to analyze the data. The data distribution was determined using the Kolmogorov-Smirnov test. The independent t-test, or the Mann-Whitney test, was conducted to analyze numerical data. The Chi-square or Fisher's exact test was used to analyze categorical data. The severity of COVID-19 was predicted using a receiver operating characteristic (ROC) curve. The ability of each parameter as an independent predictor of COVID-19 severity was assessed using multivariate analysis and logistic regression. The p-value <0.05 was considered significant.

**Table 1. Characteristic of participant**

| Variable | Group COVID-19 | | p |
|---|---|---|---|
| | Severe – Critical | Mild – Moderate | |
| Age (years) (Mean±SD) | 50.45±14.11 | 54.48±12.19 | 0.155 |
| Gender, n (%) | | | |
| Male | 21 (72.41) | 34 (47.89) | 0.044* |
| Female | 8 (28.59) | 37 (52.11) | |
| Hemoglobin (g/dL) (Mean±SD) | 12.90±7.40 | 12.75±2.14 | 0.738 |
| Leukocyte ($10^3$/µL) (Mean±SD) | 11.35±7.32 | 9.58±4.80 | 0.263 |
| Platelet ($10^3$/µL) (Mean±SD) | 240.03±119.93 | 263.00±105.63 | 0.345 |
| Neutrophile (%)(Mean±SD) | 9.95±6.84 | 7.73±4.63 | 0.063 |
| Monocyte (%)(Mean±SD) | 0.57±0.41 | 0.54±0.27 | 0.780 |
| Comorbidities, n (%) | 26 (89.70) | 54 (76.10) | 0.205 |
| Obesity | 7 (24.10) | 8 (11.30) | 0.095 |
| Hypertension | 9 (31.00) | 32 (45.10) | 0.284 |
| Diabetes Mellitus | 18 (62.10) | 39 (54.90) | 0.666 |
| CKD | 1 (3.40) | 5 (7.00) | 0.437 |
| Hepatitis | 4 (13.80) | 1 (1.40) | 0.024* |
| Cardiovascular | 5 (17.20) | 3 (4.20) | 0.043* |

*Statistically significant if p-value less than 0.05.

## RESULTS

### Characteristic participant

Participants in this study did not have significant characteristic differences. There were substantial differences in several variables, including gender and comorbid (hepatitis and cardiovascular). Most participants in the severe-critical group were male (72.41%), and the mild-moderate group were female (52.11%; p = 0.044). Comorbid participants with significant differences were hepatitis in 5 participants and cardiovascular in 8 participants. Comparison of hepatitis between the severe-critical group (13.8%) vs. mild-moderate group (1.4%; p = 0.024) and cardiovascular disease between the severe-critical group (17.2%) vs. mild-moderate group (4.2%; p = 0.043 as seen in Table 1.

There was a significant difference between the severe-critical and mild-moderate groups' hematological markers. ALC values were 0.77 ± 0.33 (severe-critical group) and 1.23 ± 0.52 (mild-moderate group; p <0.001). NLR values were 13.89 ± 7.81 (severe-critical group) and 7.83 ± 6.85 (mild-moderate group; p <0.001). MLR values were 0.81 ± 0.73 (severe-critical group) and 0.52 ± 0.39 (mild-moderate group; p = 0.008). PLR values were 343.69 ± 167.94 (severe-

**Table 2. Differences of hematological biomarkers in COVID-19 groups.**

| Biomarker | Group COVID-19 | | p-value |
|---|---|---|---|
| | Severe – Critical | Mild – Moderate | |
| ALC | 0.77 ± 0.33 | 1.23 ± 0.52 | <0.001** |
| NLR | 13.89 ± 7.81 | 7.83 ± 6.85 | <0.001** |
| MLR | 0.81 ± 0.73 | 0.52 ± 0.39 | 0.008* |
| PLR | 343.69 ± 167.94 | 249.77 ± 144.89 | 0.006* |
| d-NLR | 7.23 ± 3.03 | 4.69 ± 3.65 | 0.001* |

ALC = Absolute Lymphocyte Count; NLR = Neutrophil-To-Lymphocyte Ratio; MLR = Monocyte-To-Lymphocyte Ratio; PLR = Platelet-To-Lymphocyte Ratio; d-NLR = derived NLR ratio; *Statistically significant if p-value less than 0.05; **Statistically significant if p-value less than 0.001.

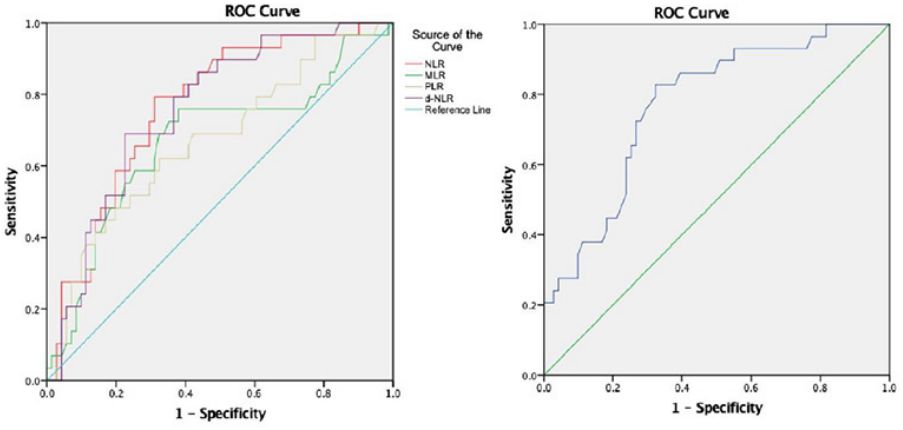


**Figure 1.** Receiver operating characteristics (ROC) curves of NLR, MLR, PLR, and d-NLR (left) and ALC (right) in predicting the severity of COVID-19.

critical group) and 249.77 ± 144.89 (mild-moderate group; p = 0.006). However, d-NLR values were 7.23 ± 3.03 (severe-critical group) and 4.69 ± 3.65 (mild-moderate group; p = 0.001), as seen in Table 2.

An analysis was performed in this study using the curve receiver operating characteristics (ROC) to determine the ability of ALC, NLR, MLR, PLR, and d-NLR to predict the severity of COVID-19, as seen in Figure 1.

The areas under the curve (AUC) and cut-off optimal of each hematological parameter in predicting the severity of COVID-19 as seen in Table 3. The ability of various inflammatory markers to predict prognosis in COVID-19 patients was assessed using Kaplan-Meier curves. The Kaplan-Meier curve analysis revealed differences in the mean survival time based on the optimal cut-off values for NLR, MLR, d-NLR, and ALC, as depicted in Figure 2.

## DISCUSSION

The findings were consistent with previous research, which found that men were at a higher risk of developing severe COVID-19 than women.[10-12] In the case of COVID-19, the severity of the disease, which is more potent in men than in women, is thought to be due to the androgen-driven pathogen mechanism of SARS-CoV-2. In contrast, the female hormone estrogen can increase the activity of the IFN-γ promoter, which is involved in the immune response to pathogens. According to one study, women tend to produce higher IgG antibodies against SARS-CoV-2 than men.[13] The severe-critical COVID-19 group also had higher rates of hepatitis and cardiovascular comorbidities. COVID-19 patients with hepatitis B virus (HBV) co-infection are more susceptible to dysregulated immune responses than COVID-19 patients without HBV co-infection. COVID-19 patients with HBV co-infection also have lower monocyte counts and higher CD8+ T cell counts than COVID-19 patients without HBV co-infection.[14] Cardiovascular disease and its risk factors (hypertension and diabetes) were associated with fatal outcomes in COVID-19 patients of all ages. The study also discovered that, despite the low prevalence of cardiovascular disease in young people, the relative risk of fatal outcomes in young COVID-19 patients with hypertension, diabetes, and cardiovascular disease was higher than in older patients with hypertension, diabetes, and cardiovascular disease.[15]

The severe-critical COVID-19 group had lower ALC values, while the NLR, d-NLR, MLR, and PLR values were higher in the severe-critical COVID-19 group. The SARS-CoV-2 infection will attack cells that express ACE-2 receptors, including lymphocytes, causing lymphocyte

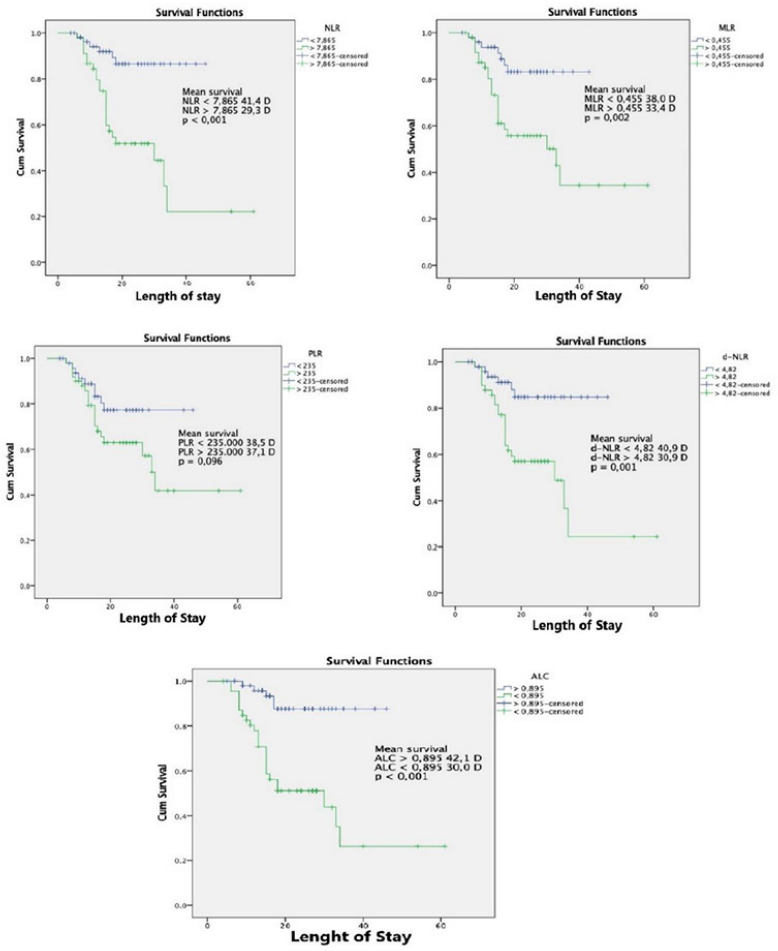


**Figure 2.** Kaplan-Meier curves of NLR, MLR, PLR, d-NLR and ALC predict COVID-19 patient survival time.

**Table 3. Cut-off and Areas Under Curve (AUC) of NLR, d-NLR, MLR, PLR, and ALC in predicting the severity of COVID-19**

| Marker | Cut-off | Sensitivity (%) | Specificity (%) | AUC | 95% CI | p |
|---|---|---|---|---|---|---|
| NLR | 7.865 | 79.3% | 69.0% | 0.765 | 0.666 – 0.863 | <0.001** |
| d-NLR | 4.820 | 79.3% | 63.4% | 0.758 | 0.659 – 0.856 | <0.001** |
| MLR | 0.455 | 75.9% | 62.0% | 0.669 | 0.543 – 0.794 | 0.008* |
| PLR | 235.000 | 69.0% | 57.7% | 0.669 | 0.551 – 0.788 | 0.008* |
| ALC | 0.895 | 82.8% | 67.6% | 0.771 | 0.673 – 0.869 | <0.001** |

Note: ALC = absolute lymphocyte count; NLR = neutrophil to lymphocyte ratio; MLR = monocyte to lymphocyte ratio; PLR = platelet to lymphocyte ratio; d-NLR = derived NLR ratio; CI: Confidence Interval; *Statistically significant if p-value less than 0.05; **Statistically significant if p-value less than 0.001.

damage. Proinflammatory cytokines cause lymphatic organ and lymph node atrophy, which reduces lymphocyte numbers.[16] The degree of lymphopenia was related to the severity of COVID-19.[17]

ALC could be used as a predictor of COVID-19 severity. An increase in the NLR value at the time of admission indicates the severity of the disease and can predict a poor prognosis. The NLR value is related to the seriousness of COVID-19.[18-20] Most studies still concentrate on the predictive ability of NLR and ALC, and the number of studies examining the power of d-NLR, MLR, and PLR in predicting COVID-19 severity still needs to be increased. The MLR had low accuracy in predicting COVID-19 severity, as demonstrated by an AUC of only 0.101 ($p<0.001$), whereas the PLR had good accuracy with an AUC of 0.828 ($p<0.001$). Surprisingly, the AUC value of PLR obtained identical to that obtained by this study.[6] High PLR values in COVID-19 patients were also associated with a longer duration of treatment/hospitalization.[21]

NLR has long been recognized as a marker of systemic inflammation that can predict in-hospital mortality in patients with sepsis, outcomes in cardiovascular disease, and prognosis and ICU admission in patients with acute pancreatitis.[22-24] This current study showed that NLR could accurately predict mortality in COVID-19 patients. However, there has yet to be a widely agreed-upon consensus on the NLR cut-off value to define typical values and increases in NLR values. Along with NLR, ALC is a predictor of mortality in patients with COVID-19. A difference in mean ALC between COVID-19 patients who survived treatment and COVID-19 patients who died during treatment. The study also found that ALC can predict the need for intubation in COVID-19 patients.[17,25-27]

While most experts agree that the NLR can be used as a prognostic indicator for COVID-19, it should be noted that the NLR is a value that is affected by various factors, including age, body mass index, alcohol consumption, smoking, and physical activity.[28,29] This is one of the current study's limitations, as it did not incorporate these factors into the NLR analysis. In addition to NLR, other inflammatory markers such as PLR, LMR, and C-reactive protein are time-sensitive variables, with the dynamics of these inflammatory markers influenced by disease onset.[30,31]

## CONCLUSION

Based on the study results, we can conclude that NLR, d-NLR, MLR, PLR, and ALC are all potential predictors of COVID-19 severity and prognosis. ALC is a reliable predictor of COVID-19 severity.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding this study.

## ETHICAL CONSIDERATION

The study has been reviewed by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital with the number 0030/KEPK/VII/2020.

## FUNDING

None.

## AUTHOR CONTRIBUTIONS

Yulia Nadar Indrasari and Estie Ludi Kiriwenno conceived the study and approved the final draft. Estie Ludi Kiriwenno contributed to collecting data. Yulia Nadar Indrasari Estie Ludi Kiriwenno drafted and critically revised the manuscript for important intellectual content and facilitated all project-related tasks. All authors agree with the content of the manuscript.

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