



The importance of neutrophil-to-lymphocyte, platelet-to-lymphocyte, and neutrophil-to-platelet ratios as predictive indicators of severity in COVID-19 Patients

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Abstract

Background: COVID-19 is a global pandemic caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). Various clinical and hematological findings have been identified that can predict disease severity. This study aims to investigate the roles of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-platelet ratio (NPR) in predicting the severity of COVID-19 infection.

Methods: In this analytical cross-sectional single-center study, after obtaining Ethics Committee clearance, patients with laboratory-confirmed COVID-19 infection admitted during their first two weeks of illness were included. NLR, PLR, and NPR were derived from the CBC reports. These ratios were compared in each clinical category group to assess the severity.

Results: The total number of cases was 160, with a mean age at diagnosis of 56 years. The proportion of males was slightly higher (54.4%) than that of females (45.6%). The proportion of Category C patients (66.9%) was higher than that of Category B (25%) and Category A (8.1%) patients. It was found that NLR, PLR, and NPR ratios had a statistically significant association with severe COVID-19 infection, suggesting they can be used to differentiate between Category C and Category A or B. NLR is a better predictor of the severity of COVID-19 disease than PLR and NPR.

Conclusion: NLR, PLR, and NPR ratios can serve as predictive markers of disease severity in COVID-19 infections. Among these ratios, NLR has the highest predictive value for disease deterioration.

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Introduction

The SARS-CoV-2 virus, a highly contagious enveloped single-stranded RNA virus that belongs to the family of Beta coronaviruses, is the causative agent of the infectious disease COVID-19. Most individuals infected with the virus will experience mild to severe respiratory disease but will recover without requiring special care. However, some individuals may develop severe diseases (1). From asymptomatic carriers to moderate respiratory symptoms and fatal acute respiratory distress syndrome, SARS-CoV-2 infections can affect virtually anyone. Severe forms of the disease are more likely to affect elderly persons and people with severe co-morbidities, such as cancer, diabetes, cardiovascular disease, or chronic respiratory diseases. Fever, cough, anorexia, dyspnea, sputum production, and myalgia are some of the most prevalent symptoms of the illness, according to the CDC (Centers for Disease Control). There is ongoing uncertainty regarding the actual infection fatality rate of SARS-CoV-2, which has been reported to range globally from 0.3% to 8.4%. COVID-19 can cause severe illness or death in individuals of any age (2).

Several biomarkers have been identified in COVID-19. Many studies have reported on the predictors of disease severity in COVID-19 patients, particularly in light of the global rise in COVID-19 cases, which is attributed to its highly contagious nature. It has been shown that, compared to milder non-fatal cases, severe or fatal cases of COVID-19 disease are associated with an elevated white blood cell count, a lower lymphocyte count (1000/L), and a lower platelet count (100x10⁹/L) (3-6). Anemia, polycythemia, leukopenia, leukocytosis with neutrophil predominance, and leukocytosis with decreasing platelet count have all been linked to severe illness and a worse prognosis in hospitalized patients. In the immunocompromised phase, the virus can cause T-cell dysregulation, resulting in the activation of monocytes and macrophages, uncontrolled cytokine release, and catastrophic multi-organ failure (7-10). There are close connections between the related hematological, coagulation, inflammatory, and immune pathways.

Different biomarkers are produced based on the organ or system of origin. The most critical biomarkers that are elevated in COVID-19 are CRP, LDH, D-dimer, and ferritin (11). This study investigated the roles of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-platelet ratio (NPR) in predicting the severity of COVID-19 infection.

Methods

This analytical cross-sectional single-center study was conducted after obtaining approval from the Institutional Ethics Committee at MES Medical College in Perinthalmanna, Kerala. A total of 160 cases diagnosed as COVID-19 positive by antigen test or RT PCR test and admitted during the period from August 1, 2020, to January 31, 2022, at MES Covid Hospital during their first two weeks of illness were included in this study. Antigen or RT-PCR test-positive patients were admitted after 2 weeks of symptom onset, and patients with pre-existing hematological malignancies were excluded.

The enrolled patients were assessed upon admission and classified into three categories according to the World Health Organization (WHO) criteria. Category A represented mild disease and included patients exhibiting symptoms such as fever, malaise, cough, and upper respiratory issues, along with less common manifestations of COVID-19, including headache and loss of taste or smell. Category B included moderate disease, characterized by the presence of lower respiratory symptoms, which could be accompanied by infiltrates visible on chest X-rays. Patients in this category were capable of maintaining adequate oxygenation while breathing room air.

Category C included patients with severe disease and major complications. Key indicators of severe illness included hypoxia, defined as an oxygen saturation (SpO₂) of 93% or lower on atmospheric air or a PaO₂/FiO₂ ratio of 300 mmHg or lower. Additionally, tachypnea was present, indicated by a respiratory rate exceeding 30 breaths per minute, and more than 50% lung involvement was observed on chest imaging.

After obtaining informed consent, the demographic details were collected from the study subjects. The clinical features, including vitals and comorbidities, were recorded. The chest X-ray findings and the clinical diagnosis were recorded.

Blood samples were collected from patients by venipuncture. A complete blood count (CBC) was performed using the Mindray BC-6200, an automated 5-part differential hematology analyzer. The ratios of neutrophil-to-lymphocyte count, platelet-to-lymphocyte count, and neutrophil-to-platelet count were derived from the CBC report and evaluated.

NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count, PLR as the ratio of the platelet count to the absolute lymphocyte count, and NPR as the ratio of the absolute neutrophil count to the absolute platelet count. The optimal cut-off values for the continuous NLR, PLR, and NPR were calculated using receiver operating characteristic (ROC) analysis. The area under the curve (AUC), sensitivity, and specificity of hematological parameters in predicting the severity were analyzed.

Statistical analysis

The data was entered in Microsoft Excel 2019. The proportions of various hematological parameters and cellular characteristics were analyzed and compared within each clinical category group. Descriptive statistics included frequency analysis (Percentages) for categorical variables and mean $\pm$ SD for continuous variables. Comparisons were done using the chi-square test for categorical variables and the ANOVA test for continuous variables. Univariate logistic regression was performed to explore the association of clinical characteristics and laboratory parameters.

The ratios of neutrophils to lymphocytes, platelets to lymphocytes, and neutrophils to platelets were calculated. The optimal cut-off values for the continuous NLR, PLR, and NPR were determined using ROC analysis. The AUC, sensitivity, and specificity of hematological parameters in predicting the severity were analyzed. Statistical analysis was performed using SPSS version 26. All the tests with a p-value < 0.05 was considered statistically significant.

Results

This study included a total of 160 confirmed cases of COVID-19. The patients were divided into two groups: severe (Category C) and non-severe (Categories A and B), based on their initial clinical presentation at the time of admission. The non-severe group consisted of 53 cases (Category A: 13 cases and Category B: 40 cases), while the severe group comprised 107 cases (Table 1).

The age distribution in the current study was 56.91 ± 15.75 , with a minimum age of 20 and a maximum age of 88 years. The proportion of male patients (54.4%) was slightly higher than that of females (45.6%). Table 2 shows the distribution of vital signs among the study population. The mean systolic and diastolic BP were found to be higher than the normal reference range.

Table 1. Distribution of COVID-19 categories among the study population. The majority (66.9%) of the study population were in COVID-19 Category C, followed by Category B (25%)

Category	Frequency	Percentage (%)
A	13	8.1
B	40	25
C	107	66.9
Total	160	100

Table 2. Distribution of vital signs among the study population

Parameter (Unit)	Minimum	Maximum	Mean	Standard deviation
SBP (mmHg)	110	200	141.89	16.353
DBP (mmHg)	70	144	93.22	15.129
PR (beats/min)	56	122	74.15	7.465
RR (per min)	16	28	21.65	2.419
SpO ₂ (%)	80	100	91.44	4.239

Severe disease was more common in patients with comorbidities such as diabetes or hypertension. In this study, 35.63% (n = 57) had no comorbidities. The most common co-morbidities identified in this study population were type 2 diabetes mellitus, hypertension, coronary artery disease, and bronchial asthma (Table 3).

Table 3. Comparison of comorbidity with COVID-19 severity categories

Comorbidity	COVID category			Total	P-value
	A	B	C		
Yes	7	17	79	103	0.001
No	6	23	28	57	
Total	13	40	107	160	

The present study investigated the mean differences of various hematological parameters among participants with different severities of COVID-19. The mean total count and mean neutrophil count were found to be significantly higher among Category C patients. The mean lymphocyte count was significantly lower among participants in Category C. Platelet count showed no statistically significant difference among the three categories of COVID-19 (Table 4).

Upon analyzing the ROC curve, the areas under the curve for NLR, PLR, and NPR were found to be above the reference line, indicating that NLR, PLR, or NPR can statistically differentiate between the different severities of the disease (Figure 1).

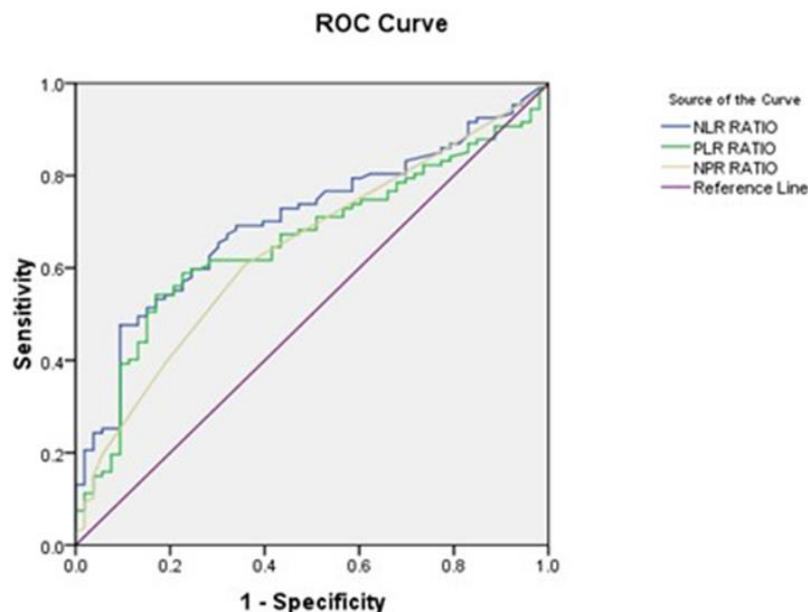
Since the area under the curve for the NLR ratio was higher than that of the PLR and NPR ratios, it can be considered a better test to differentiate between Category C Covid-19 and Categories A and B. The cut-off value observed from the ROC curve for NLR was 3.680 with a sensitivity of 70.1% and a specificity of 60.4%. The cut-off value for PLR was with a sensitivity of 70.1% and a specificity of 49.1%. The NPR cutoff was 0.0250, with a sensitivity of 60.7% and a specificity of 64.2% (Table 5).

Table 4. Comparison of various parameters as quantitative variables

Parameter	Category	Number	Mean	Standard deviation	P-value
Total count	A	13	6.839231	2.1800553	0.027
	B	40	7.277750	3.2426584	
	C	107	9.318318	5.3708543	
	Total	160	8.606750	4.8175744	
Neutrophil count	A	13	5.176923	2.3931165	0.005
	B	40	5.194500	2.9694159	
	C	107	7.822430	5.4454838	
	Total	160	6.950500	4.8896213	
Lymphocyte count	A	13	1.326154	0.6388993	0.001
	B	40	1.688000	0.8247772	
	C	107	1.137196	0.6646120	
	Total	160	1.290250	0.7401385	
Platelet count	A	13	260.92	72.131	0.559
	B	40	221.55	84.737	
	C	107	241.08	143.098	
	Total	160	237.81	126.185	

Table 5. Prediction of the severity category of COVID-19 using NLR, PLR, and NPR ratios

Test result variable	Cut off value	Area under the curve	Sensitivity (%)	Specificity (%)	P-value
NLR	3.680	0.702	70.1	60.4	< 0.001
PLR	146.50	0.658	70.1	49.1	0.001
NPR	0.0250	0.641	60.7	64.2	0.004

**Figure 1.** ROC Curve depicting NLR, PLR, and NPR ratio

Discussion

This study aimed to determine the role of NLR, PLR, and NPR ratios in predicting the disease severity and outcomes among COVID-19 patients. The study population consisted of patients diagnosed as COVID-19 positive by antigen test or RT-PCR test who were admitted to MES Medical College, Perinthalmanna, during the period from August 2020 to January 2022, within their first two weeks of illness. A total of 160 participants who met the inclusion and exclusion criteria were included in the study.

The mean age of the study population was 56.91 ± 15.75 years, with a range of 20 to 88 years. In this study, the proportion of males (54.4%) was slightly higher than that of females (45.6%). A similar age distribution was observed in a study by Nazarullah A et al, where the mean age was 55 years, ranging from a minimum of 25 years to a maximum of 100 years. Among the COVID-19-positive patients in the study by Nazarullah et al., 58.33% were males, and the remaining patients were females. This finding is similar to the present study (12).

The mean differences in various hematological parameters among the three COVID categories were analyzed in the current study. The results demonstrated that Category C patients had significantly higher mean total counts and mean neutrophil counts. Category C had the lowest mean lymphocyte count, which was also statistically significant. There was no statistically significant difference among the three categories of COVID-19 patients in terms of platelet count. A study by Dubey et al. reported that patients with severe illness had significantly higher total leukocyte counts (TLCs) than patients with only mild or moderate symptoms. They found a significant difference in the mean total leukocyte count, neutrophil percentage, lymphocyte percentage, and monocyte percentage between cases with mild and moderate symptoms (13).

This study investigated whether the NLR, PLR, and NPR ratios can predict the severity of COVID-19. In the ROC curve, the areas under the curve for NLR, PLR, and NPR were found to be statistically significant, which implied that NLR, PLR, and NPR can differentiate between Category C patients and those in Categories A and B. The area under the curve for the NLR ratio was higher than that of the PLR and the NPR ratio. Therefore, NLR can be a more reliable parameter for distinguishing between Category C COVID patients and those in Categories A and B. The cut-off values observed for NLR, PLR, and

NPR ratios were 3.680 (Sensitivity, 70.1%; specificity, 60.4%), 146.50 (Sensitivity, 70.1%; specificity, 49.1%), and 0.0250 (Sensitivity, 60.7%; specificity, 64.2%), respectively. Yang A-P et al. observed a higher area under the ROC curve of 0.841 for NLR. For PLR, the area under the curve was 0.784. The highest specificity and sensitivity were 0.636 and 0.88 for NLR at a cut-off of 3.3, and 0.44 and 0.77 for PLR at a cut-off of 180 in their study (14).

Another study by Asaduzzaman MD et al. reported that in hospitalized COVID-19 patients, neutrophil-to-lymphocyte ratios (NLR), derived NLRs (d-NLR), and neutrophil-to-platelet ratios (NPR) were significant predictors of mortality. To predict in-hospital mortality for COVID-19 patients, the optimal cut-off points for NLR, d-NLR, and NPR were 7.57, 5.52, and 3.87, respectively (15).

In another study of 3508 COVID-19 patients, Chan A S et al. observed that NLR and PLR ratios were statistically higher in the severe categories of COVID-19, compared to this study. The NLR value showed a standard mean difference of 2.80, a 95% confidence interval of 2.12-3.48, and a p-value of less than 0.00001 when compared with patients in the non-severe category. Similarly, PLR also showed a statistically significant association with predicting the severity of COVID-19, with a Standard mean difference of 1.82, a 95% Confidence interval of 1.03-2.61, and a p-value of less than 0.00001 (16).

A study on "the effects of NLR, NMR, NPR and CRP values on the patient's transmission to the intensive care unit and mortality," conducted by Akan O Y et al in a total of 160 COVID-19 positive cases, showed that NLR and NPR ratios had a statistically significant association in COVID-19 patients. The cut-off value of NLR in patients admitted to the intensive care unit was 2.9, while the mortality cut-off value of NLR was 3.7. The cut-off values for NMR, NPR, and CRP in relation to the mortality rate were 9.5, 0.022, and 79.2, respectively (17).

Conclusion

In this study, we found that the NLR, PLR, and NPR ratios were associated with a statistically significant increase in the risk of severe COVID-19 infection. Therefore, these ratios can be used to differentiate between patients with different severities of the disease. The NLR ratio had a larger area under the ROC curve. It can therefore be considered a superior parameter for differentiating between Category C and Categories A and B of COVID-19 infection.

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Ethical statement

The Institutional Ethics Committee of MES Medical College, Perinthalmanna (Reference No. IEC/MES/10/2020, Dated 22/12/2020) approved the study.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the publication of this article.

Author contributions

All authors contributed essential feedback and played a significant role in shaping the research, analysis, and manuscript.

Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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