# Prognostic Significance Association of Neutrophil-To-Lymphocyte Ratio and Platelets-To-Lymphocyte Ratio with Mortality in COVID19 Patients

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## Abstract

**Background**: Inflammation is a key factor in COVID-19 progression and is potentially an important predictive factor. The ratios of neutrophils to lymphocytes and platelets to lymphocytes may show significant inflammatory progression, which may contribute to the development of some major complications and mortality problems as observed in COVID-19. Objective: To examine and investigate the correlation of neutrophil lymphocytic ratio (NLR) and platelets to lymphocytes ratio (PLR) with increased mortality risk.

**Methods**: 124 patients admitted to King Abdulaziz hospital with confirmed COVID-19 were enrolled in our study. The blood cell count was used to obtain NLR and PLR. The receiver operating characteristic (ROC) curve was used to determine the sensitivity and specificity of NLR and PLR for severity and mortality of admitted patients with COVID-19. The logistic regression model was used to explore the risk factors associated with mortality and severity.

**Results:** The mortality rate was 23.4%. Among non-survivors' patients' lymphocyte significantly declined with 96.5%, while neutrophil counts increased. The Empirical optimal cut point of NLR correlated with mortality is 4.647, with a sensitivity of 93% and a specificity of 61% (AUC: 0.847, 95% CI 0.774-0.921; P = 0.001). Moreover, the optimal cut point of PLR associated mortality is 17.358, with a sensitivity of 90% and a specificity of 64% (AUC: 0.791, 95% CI 0.703-0.878; P = 0.005).

**Conclusions**: NLR and PLR variables were significantly correlated with severity and mortality. NLR and PLR can be considered independent biomarkers in COVID-19 patients which play a significant role to predict mortality cases.

***Keywords:*** *coronavirus, inflammation, mortality, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio.*

## Introduction

COVID-19 is a disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a virus thought to start in late December 2019 in Wuhan [1]. The number of infected people around the world has been raised significantly now a day. Patients diagnosed with COVID-19 showed different symptoms vary from asymptomatic illnesses to death [2]. Consequently, it is important to define risk factors linked to the poor prognosis of COVID-19 patients.

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Several hematologic anomalies were revealed in COVID-19 patients which were prevalent in lymphopenia and thrombocytopenia [3]. NLR and PLR are available values that correlate and reflect indirectly the inflammation conditions. Their values can be easily obtained from blood routine counts in laboratory. The NLR is determined by dividing the absolute number of neutrophils into the absolute count of lymphocytes, while PLR is calculated by dividing a count of platelets by the absolute count of lymphocytes [4,5]. They are inflammatory markers with low-cost and are replicable to measure, which can be assessed easily with a blood sample [6]. Generally, NLR and PLR are quantitative and convenient suitable factors to assess the susceptibility of death through COVID patients [7].

Immunological research has shown that the severity characteristic in extreme COVID-19 cases is due to elevated levels of proinflammatory cytokines known as a cytokine storm. This intense elevation of cytokines leads to a major proinflammatory reaction occurring in MODS and ARDS, resulting in mortality [8]. From this point of view inflammatory markers can help to evaluate the severity and mortality cases of COVID-19 patients.

Few studies assessed the role of NLR and PLR in severe and non-severe COVID-19 patients. The present study was carried out to determine the association of NLR and PLR to COVID-19 severity and mortality.

## Material and Methods

Our retrospective study on one hundred twenty-four positive COVID-19 cases in patients hospitalized at king Abdulaziz hospital. All patients were confirmed using reverse transcription-polymerase chain reaction (RT-PCR Abbott company, USA). The study was approved by Unit of Biomedical Ethics Research Committee (Reference NO. 301-20). Demographic parameters and laboratory assessments of the complete blood count of the patients were obtained exclusively from the Laboratory Information System (phoneix) in the hospital. Patients with complete data, including 95 survivors and 29 non-survivors' cases, were randomly selected. Whole venous blood samples have been collected on BD EDTA tube and CBC profile analysis has been performed on Sysmex xn-10 and Sysmex xn-20 analyzer (JAPAN).

### Statistical Analysis

The statistical analysis and graphical representation were done using SPSS Statistics 25 (IBM SPSS) and R version 4.0.4. The categorical variables were described as the number/total number (%), and continuous variables were described using the mean, median and interquartile range (IQR) values. The Kolmogorov–Smirnov test was used to test the variables for the normality distribution. Otherwise, the Mann–Whitney test was used to compare the medians for continuous variables. The categorical data were compared by $\chi^2$ test or Fisher's exact test. The receiver operating characteristic (ROC) curve was used to determine the sensitivity and specificity of NLR and PLR for all-cause mortality and severity. The logistic regression model was used to explore the risk factors associated with mortality and severity. p-value $< (\alpha = 0.05)$ was considered statistically significant, where $\alpha$ is a significant to test level.

## Results

The current study enrolled 124 diagnosed patients of COVID-19. The number of male patients was 77(62.1%) while 47(37.9%) were female. The mortality rate was 23.4% as 29 deaths had occurred. The mortality is more likely to present with older age ($\geq 60$) with 62.1%, and more common in male than female (75.8%). At admission time all positive patients underwent blood routine examinations, most of them had peripheral blood system anomalies. Moreover, non-survivors' patients obtained low value of MCH and hemoglobin levels, 75.9% and 100% respectively

regarding the reference range. The increase of neutrophils counts percentage was obvious within 89.6% of non-survivors' patients. More importantly, we found that 96.5% among non-survivor's patients showed significant lymphopenia. Furthermore, 66.1% of all patients exhibited eosinopenia, while this percentage was 75.9.1% of non-survivors' patients. The results revealed normal platelet counts with 98 (79%) among COVID-19 patients. While amongst survivors' patients 26 (27.4%) were in intensive care unit ICU, whereas 28 (96.6%) were in ICU of non-survivors.

A null hypothesis Ho has no significant affiliation between mortality and the categorical variables. It was tested using Chi-squared test. For the continuous variables, the significance differences of median value between the two groups were tested using Man Whitney Test. Results show that the null hypothesis is rejected for all variables except gender, Hb, MCH, platelet, and eosinophils. This indicates a statistically significant difference between the two groups in the median values for age, WBCs, lymphocyte, neutrophils, and monocyte variables.

Table 1 shows the results in comparisons of the values of NLR and PLR between survivors and non-survivors' patients using Man Whitney Test. The results show a significant difference for NLR and PLR variables between the two groups. Moreover, this indicates a statistically significant difference for NLR and PLR variables between ICU and Non-ICU patients. Among the non-survivors' group, NLR and PLR were significantly elevated compared to survivors' group. Moreover, PLR and PLR were considerably raised in severe cases, when compared to non-severe group.

Table 2 shows the logistic regression model analysis. The univariate analysis revealed that several clinical factors were statistically significant risks associated with COVID-19 mortality, which included age, WBCs, monocyte, eosinophils, NLR, and PLR. The forward stepwise logistic regression is used to explore the most important risk factors associated with mortality. According to forward stepwise logistic regression results. The multivariate analysis shows that NLR and monocyte are risk factors associated with mortality with OR 1.081(95%CI :1.013-1.154) and 0.657(95%CI :0.503-0.857), respectively. The results reveled that NLR a valuable biomarker in relation to the mortality in COVID-19. However, PLR was not found to be an independent risk factor for death in multivariate analysis.

According to multivariate analysis, Table 3 shows that NLR and Hb are significantly correlated with severity with OR 1.480 (95%CI:1.266-1.731) and 0.652 (95%CI: 0.520-0.817), respectively. However, PLR was not found to be an independent risk factor for severity in multivariate analysis.

From Fig. 1 and Table 4 based on the ROC curve analysis, NLR, PLR, Monocyte, and the combined effect (NLR and Monocyte together) had diagnostic values for COVID-19 mortality (P-value<0.05), and the AUC from highest to lowest was (combined>NLR>PLR> Monocyte) respectively. The Empirical optimal cut point of NLR correlated with mortality is 4.647, with a sensitivity of 93% and a specificity of 61% (area under the curve (AUC): 0.847, 95% CI 0.774-0.921; P = 0.001). Moreover, the optimal cut point of PLR associated mortality is 17.358, with a sensitivity of 90% and a specificity of 64% (area under the curve (AUC): 0.791, 95% CI 0.703-0.878; P = 0.005). Moreover, Fig.2 showed that NLR, PLR, Hb, and the combined effect (NLR and Hb together) had diagnostic values for COVID-19 severity (P-value<0.05), and the AUC from highest to lowest was (combined >PLR>NLR> Hb) respectively.

**Table 1: The value of NLR and PLR for COVID-19.**

| | Clinical outcome | | | Severity | | |
|---|---|---|---|---|---|---|
| | **Survivors** | **Non-Survivor** | **P-value** | **ICU** | **Non-ICU** | **P-value** |
| NLR | 3.86(7.27) | 14.97(13.89) | 0.000* | 12.597(11.791) | 2.655(3.500) | 0.000* |
| PLR | 10.31(20.34) | 38.40(42.4) | 0.000* | 36.369(38.902) | 8.851(8.515) | 0.000* |

Data are expressed as median (interquartile range).

Symbol (*) denotes to that the difference between the medians is statistically significance at level of significance α=0.05%. Otherwise, are not significant using Man Whitney test.

**Table 2: The Univariate and Multivariate analysis for risk factors associated with death in patients with COVID-19.**

| Clinical characteristics | Univariate analysis | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|
| | | | Variables not in equation | | Variables in equation | |
| | **OR (95%CI)** | **P-value** | **OR** | **P-value** | **OR (95%CI)** | **P-value** |
| Gender | 2.286(0.890-5.869) | 0.086 | 0.214 | 0.644 | | |
| Age | 1.039(1.011-1.069) | 0.006* | 1.057 | 0.304 | | |
| WBCs | 1.171(1.073-1.278) | 0.000* | .186 | 0.682 | | |
| Hb | 0.858(0.731-1.005) | 0.058 | 1.117 | 0.291 | | |
| MCH | 1.052(0.887-1.247) | 0.560 | 0.022 | 0.883 | | |
| Monocyte | 0.579(0.452-0.743) | 0.000* | | | 0.657(0.503-0.857) | 0.002* |
| Eosinophils | 0.557(0.322-0.966) | 0.037* | 2.548 | 0.110 | | |
| NLR | 1.151(1.079-1.228) | 0.000* | | | 1.081(1.013-1.154) | 0.018* |
| PLR | 1.029(1.013-1.045) | 0.000* | 0.866 | 0.438 | | |

(*) denotes to the statistically significance at level of significance α=0.05%.

OR denotes to odds ratio.

**Table 3: The univariate and multivariate analysis for risk factors associated with severity in patients with COVID-19.**

| Clinical characteristics | Univariate analysis | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|
| | | | Variables not in equation | | Variables in equation | |
| | OR (95%CI) | P-value | OR | P-value | OR (95%CI) | P-value |
| Gender | 2.548(1.182-5.496) | 0.017* | 1.011 | 0.315 | | |
| Age | 1.042(1.017-1.067) | 0.001* | 1.344 | 0.246 | | |
| WBCs | 1.445(1.264-1.651) | 0.000* | 2.850 | 0.091 | | |
| Hb | 0.679(0.570-0.809) | 0.000* | | | 0.652(0.520-0.817) | 0.016* |
| MCH | 1.021(0.886-1.177) | 0.773 | 0.050 | 0.824 | | |
| Monocyte | 0.759(0.662-0.871) | 0.000* | 0.347 | 0.556 | | |
| Eosinophils | 0.880(0.635-1.218) | 0.440 | 2.171 | 0.141 | | |
| NLR | 1.416(1.247-1.607) | 0.000* | | | 1.480(1.266-1.731) | 0.000* |
| PLR | 1.119(1.073-1.167) | 0.000* | 3.295 | 0.069 | | |

(*) denotes to the statistically significance at level of significance α=0.05%.

OR denotes to odds ratio.

**Table 4: ROC analysis for COVID-19 mortality and severity.**

| Mortality | | | | Severity | | | |
|---|---|---|---|---|---|---|---|
| **Variables** | **AUC** | **95% CI** | **P-value** | **Variables** | **AUC** | **95% CI** | **P-value** |
| NLR | 0.847 | 0.774-0.921 | 0.001 | NLR | 0.879 | 0.820-0.938 | 0.001 |
| PLR | 0.791 | 0.703-0.878 | 0.005 | PLR | 0.894 | 0.833-0.954 | 0.002 |
| Monocyte | 0.172 | 0.090-0.255 | 0.063 | Hb | 0.218 | 0.135-0.302 | 0.010 |
| Combined* | 0.861 | 0.788-0.933 | 0.000 | Combined** | 0.928 | 0.886-0.969 | 0.001 |

AUC area under the curve, 95% CI confidence interval.

* Combined effect (NLR and Monocyte together).

** Combined effect (NLR and Hb together).

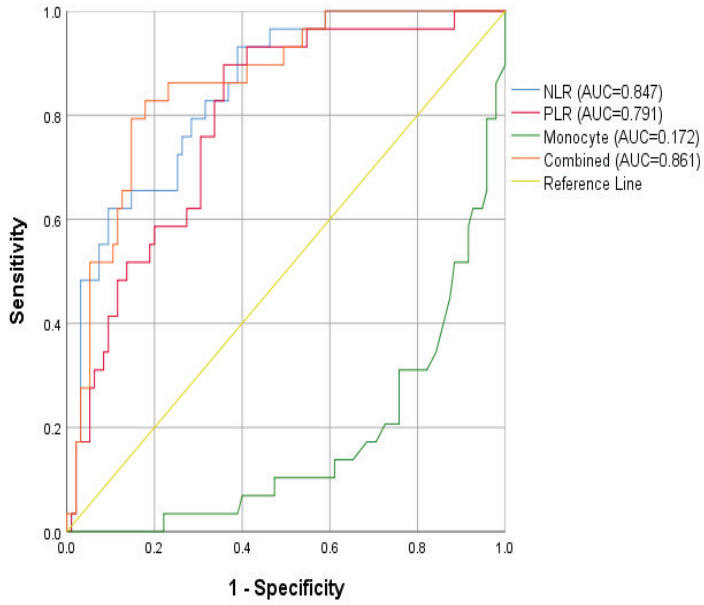


**Fig. 1: ROC analysis of the NLR, PLR, monocyte, and combined effect (NLR and Monocyte together) for prediction of COVID-19 mortality.**

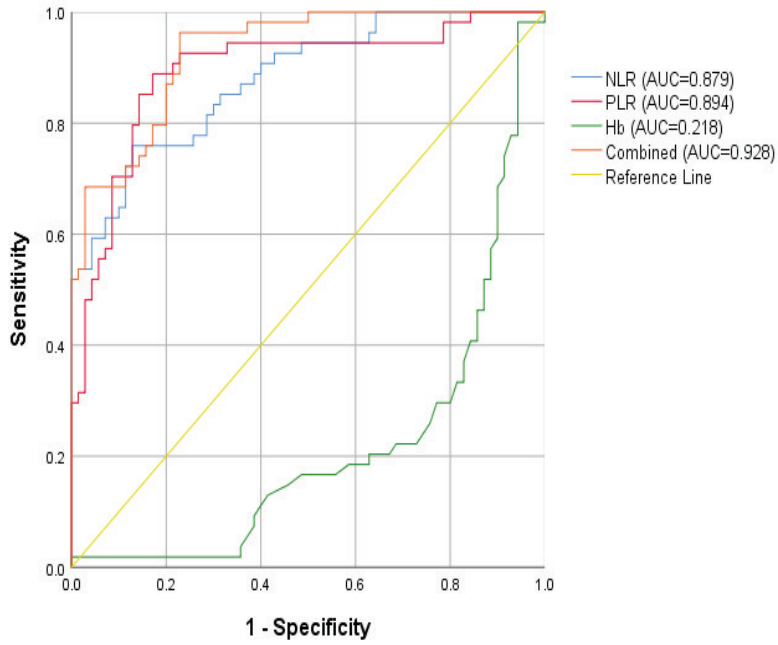


**Fig. 2: ROC analysis of the NLR, PLR, Hb and combined effect (NLR and Hb together) for prediction of COVID-19 severity.**

## Discussion

Several recent reports have described the correlation of age with survivors and non-survivors COVID-19 patients [9,10,11]. Our finding is compatible with the recent study that the older patients had worse health results and higher mortality rate than the young age group. Thus, it can be said that COVID-19 is most found with old age males.

Moreover, the current study found an increase in the neutrophils counts percentage of non-survivors' patients compared with the survivor's patients. Furthermore, we found that 96.5% of non-survivors' patients showed a significant substantial reduction in the number of lymphocyte counts. Additionally, 75.9.1% among non-survivors' patients showed eosinopenia. The findings of our study were aligned with the results of other previous studies [3,12].

The immune response is highly lymphocytic based, and activation of the immune system is mainly due to neutrophils. Moreover, the systemic inflammation will destruct the CD4+ T lymphocytes and induce the suppressor CD8+ T lymphocytes which leads to an increase of the neutrophil-lymphocyte ratio (NLR) [13,14]. Moreover, platelets play an essential role in innate immunity and inflammatory response, and their count reflects the inflammation and infection condition [15,16]. COVID-19 can cause pulmonary endothelial damage, which leads to pulmonary endothelial injury, activation, accumulation, and preservation of platelets in lung, followed by platelet depletion. The cytokine storm induces the inflammation in SARS-CoV-2 patients to worsen, and the platelet- to-lymphocyte (PLR) ratio reflects the level of cytokine inflammation that can be used for evaluation purposes [6,17,18].

The evaluation of inflammatory diseases progression and their changes may be a crucial factor that scientists must take in consideration. In COVID-19 patients, inflammatory biomarkers can be used as potential prognosis predictor factor [19,20]. Most studies show that inflammation plays a central role in the pathogenesis of the disease. More concerning, the severity and mortality characteristic of COVID-19 was identified by several inflammatory factors [21,22,23].

SARS-CoV-2 can lead to various infection conditions, particularly respiratory tract infection diseases [24], which can develop into serious complicated conditions exhibiting pneumonia, pulmonary edema, acute or multiple organ failures leading to patient death [25]. So, it is highly demanded to discover biological markers that can be used to identify COVID 19 at an early stage, helping to save people's life. The early detection will aid to decrease the progression of severity, decrease the mortality, and support the decline of financial expenses of the ministry of health all over the world. Therefore, any parameter that can help for the early diagnosis is crucial.

Recent studies considered NLRs and PLRs as a precursor element for COVID-19 admission condition in the intensive care unit, and they consider it as a useful marker to evaluate the severity [26,27,28] and mortality [29,30]. NLR and PLR are easily calculating from a complete blood count with a differential count.

In this study, we found a higher NLR and PLR values in non-survivors COVID-19 patients compared to survivors' patients. However, univariate analysis identified high NLR and PLR as an independent prognostic factor for survival. After changing the other confounding variables in multivariate Cox analysis, the NLR remained as a risk factor of survival in patients with COVID-19**.** Our findings were consistent with earlier studies [12,31,32]. Whereas other studies reported that PLR not correlated with COVID-19 prognosis at all [17].

Moreover, monocytes are pro-inflammatory cells that can induce inflammation by producing many

cytokines [12,33]. A recent study detected significant decreased in monocytes count within critical COVID-19 patients [34]. Our results demonstrated that monocyte has risk factors associated with mortality with OR 0.657 (95%CI :0.503-0.857).

ROC analysis of our study showed that patients with non-serious symptoms compared to patients with severe COVID-19 signs had higher NLR and PLR values, and they have a diagnostic value for COVID-19 severity and mortality. It was also demonstrated that the empirical optimal cut point of NLR correlated with mortality is 4.647 with a sensitivity of 93% and a specificity of 61%. Moreover, the optimal cut point of PLR associated mortality is 17.358, with a sensitivity of 90%.

Moreover, our results shown that NLR and PLR had diagnostic values for COVID-19 mortality (P-value<0.05). The measurement of their values is a reliable and low-cost test, which can be easily applied in a daily routine blood tests in the lab and may be act as an independent prognostic factor for severity and mortality of COVID-19 patients.

Finally, no universal cutoff value has been found to date for NLR and PLR, especially in patients with COVID-19. Future research should focus on the optimum cutoff value to use it as an important prognostic indicator before medicinal application and patient hospital admission.

## Conclusions

NLR and PLR had diagnostic values for COVID-19 severity and mortality. The daily CBC routine blood test can be used to identify COVID 19 patients at early stage of the infection. This type of detection well saves people life and reducing mortality rates by avoid going through complication stages. Additionally, this is an economical diagnosis tool easily available in cases where logistics and financing are limited.

## Limitation

Our retrospective study was done in a single center and as a result the sample size was limited due to logistic problems and administrative acceptance of many patients that need more processing time, so a multiple centers prospective research is recommended. Also, since this study was conducted on blood laboratory parameters, patients were not constantly tracked for all clinical manifestations.

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