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Experimental Biomedical Research **Original article**

The prognostic value of neutrophil–to-lymphocyte ratio and platelet–to-lymphocyte ratio in the severe COVID-19 cases

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ABSTRACT

Aim: COVID-19 is a cause of high-mortality pandemic with the RNA virus in its etiology and has an effect all over the world. In the present study, the relationship between in-hospital prognosis and mortality was investigated by comparing neutrophil-to-lymphocyte ratio (NLR), platelet –to-lymphocyte ratio (PLR) values with C-reactive protein (CRP) and with a detailed analysis of complete blood count and biochemical parameters in mild and severe COVID-19 cases.

Method: A total of 271 patients who were diagnosed with pneumonia because of COVID-19 and 278 healthy control groups were included in the study. In our study, COVID-19 cases were divided into 2 groups as mild and severe, and the data were compared with healthy people without COVID-19. Lung tomography results of the cases that were diagnosed with COVID-19 were examined. Those with positive RT-PCR (Real-Time Polymerized Chain Reaction) test results were recorded from the system. Biochemical tests and complete blood count parameters of the patients, NLR/ lymphocyte- to- monocyte ratio (LMR)/PLR N/L, and CRP levels were compared with the control group. The results were evaluated and analyzed in statistical terms.

Results: When all the data were analyzed, NLR/PLR and CRP levels were found to be higher at statistically significant levels in the severe patient group than in the control group, and LMR was lower (p<0.01). In ROC analysis, NLR/PLR and CRP had a high AUC (area under the curve) (0.844/0.719/0.501) and LMR had a low AUC (0.225).

Conclusion: NLR and PLR might be useful in demonstrating the prognosis in severe COVID-19 cases.

Key words: SARS-CoV-2, neutrophil-to-lymphocyte ratio, platelet–to-lymphocyte ratio, C-reactive protein, lymphocyte-to-monocyte ratio.

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Introduction

The SARS-CoV-2 disease pandemic started in China/Wuhan at the end of 2019 (COVID-19). Many people have died since then [1]. Because of its high contagiousness, people have had to be hospitalized and live under long-term quarantine. It still maintains its disease-causing effects by undergoing various mutations. Also, it was shown in many studies that COVID-19 and its variants cause high morbidity and mortality [2-4].

Some parameters in serum in COVID-19 cases were investigated as a prognostic indicator before. white blood cell (WBC), neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) levels, which are acute phase reactants,

guide in showing the severity of the disease [5-7].

In the present study, the relationship between in-hospital prognosis and mortality was investigated by comparing NLR, platelet–to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) values with CRP and with a detailed analysis of complete blood count and biochemical parameters in mild and severe COVID-19 cases.

Materials and methods

After the approval of the Ethics Committee of Ankara City Hospital with the 2021/2043 the blood samples taken from 271 patients and 278 healthy volunteers from the diagnosed COVID-19 cases were examined in the laboratory, and the data were analyzed.

In our study, COVID-19 cases were divided into 2 groups as mild and severe, and the data were compared with healthy people without COVID-19. Computed lung tomography results of the cases that were diagnosed with COVID-19 were examined. Those with positive RT-PCR (Real-Time Polymerized Chain Reaction) results were also included. Biochemical values, complete blood count parameters, WBC, NLR, PLR, LMR, and CRP values of all subjects included in the study were entered into a separate statistical program.

Admission criteria for severe cases:

1- Those whose blood oxygen saturation does not exceed 90 despite oxygen therapy

2- Those who need respiratory support

3- Those with hypotension

4- Those with tachypnea

Admission criteria for mild cases:

1- Those with lung involvement and oxygen saturation above 90

2- Those who do not need respiratory support

3- Normotensives

4- Those without tachypnea

Those who were under the age of 18, trauma patients, and pregnant women were excluded from the study.

Statistical analysis

The Statistical Package for Social Sciences for Windows, Version 22 (IBM, Armonk, NY, USA) was used for statistical analyses. The Kolmogorov-Smirnov Test was used for the normality of the variables. Non-normal distribution data were represented by the median (interquartile range). The Mann-Whitney U Test was used to compare the mean values between the groups. The categorical variables were summarized as numbers and percentages in each category. The Chi-Square and Fisher's Exact Test were used for categorical variables. Optimal threshold values of continuous age, CRP, NLR, PLR, and LMR were calculated by applying the Receiver Operating Curve (ROC) analysis. The Binary Logistic Regression Analysis was performed to determine the effect of age, gender, and all other important factors. The Hosmer-Lemeshow Goodness-Of-Fit statistics were used to evaluate the model fit and $p< 0.05$ was considered statistically significant.

Results

No significant differences were detected between the control and patient group in terms of age, neutrophils, NLR, LMR, and PLR and although WBC, lymphocyte, monocyte, hemoglobin, and platelet were lower in the patient group than in the control group, CRP was found to be higher (Table 1).

Table 1 presents routine blood parameters in mild and severe groups. Routine blood examinations were performed at admission to 128 mild and 143 severe patients in total. WBC, neutrophil, NLR, and PLR were significantly higher in the severe group than in the mild case group. Lymphocytes and LMR were lower in the severe group than in the non-severe group (Table 2). No significant

Table 1. Blood routine parameters characteristics of control and COVID-19 patients group.

Parameters	**Control (*n* = 278)**	**COVID-19 patients (*n* = 271)**	***p* Value**
Age (years)	58 (44-72), 21-93	60.5, (42-74), 20-91	0.245
Gender, male/female	145/133	160/111	0.048
Leucocytes, ($\times10^9$ / L)	7.49 (6.75-10.53)	6.69 (5.44-9.01)	<0.001
Neutrophils, ($\times10^9$ / L)	4.75 (3.24-7.66)	4.39 (3.08-7.01)	0.262
Lymphocytes, ($\times10^9$ / L)	2.05 (1.26-2.53)	1.56 (0.94-2.25)	0.003
Monocytes, ($\times10^9$ / L)	0.47 (0.36-0.69)	0.42 (0.31-0.59)	0.002
Hemoglobin (g/L)	13.6 (12.6-14.5)	13.3 (11.2-14.7)	0.028
Platelet, ($\times10^9$ / L)	247.5 (198.75-303.5)	188.8 (139.2-236.8)	<0.001
NLR	2.46 (1.5-5.44)	2.67 (1.58-6.14)	0.290
LMR	4.65 (2.19-5.97)	3.77 (2.03-5.99)	0.409
PLR	131.38 (100.3-184.16)	116.04 (69.72-193.1)	0.083
hsCRP, g/L	0.004 (0.001-0.005)	0.08 (0.01-0.21)	<0.001

Values: median (IQR); NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PLR: platelet–to-lymphocyte ratio; hs-CRP: high-sensitivity C-reactive protein.

Table 2. Blood routine parameters of severe and non-severe group of COVID-19.

Parameters	**Non-severe (*n* = 128)**	**Severe (*n* = 143)**	***p* Value**
Age (years)	50 (33-67), 18-93	60.5, (42-74), 20-91	0.004
Gender, male/female	80/48	80/63	0.038
Leucocytes, ($\times10^9$ / L)	6.32 (5.30-7.80)	8.21 (5.65-11.31)	<0.001
Neutrophils, ($\times10^9$ / L)	3.6 (2.87-4.77)	6.19 (3.85-9.65)	<0.001
Lymphocytes, ($\times10^9$ / L)	2.03 (1.53-2.49)	0.99 (0.62-1.51)	<0.001
Monocytes, ($\times10^9$ / L)	0.42 (0.30-0.55)	0.45 (0.31-0.64)	0.276
Hemoglobin (g/L)	14 (12.8-15)	11.7 (9.8-14.1)	<0.001
Platelet, ($\times10^9$ / L)	188.8 (140-236.8)	184 (129-239.2)	0.946
NLR	1.77 (1.32-2.7)	5.81 (3.24-12.64)	<0.001
LMR	5.3 (3.32-7.23)	2.55 (1.53-4.03)	<0.001
PLR	88.9 (59.5-136)	165 (98.5-289.4)	<0.001
hsCRP, g/L	0.082 (0.03-0.26)	0.09 (0.03-018)	0.960
ESR, mm/hour	16 (10-36)	44 (30-79)	<0.001
Ferritin, µg/L	55 (30-166)	198 (97.75-421)	<0.001
Ferritin/ESR	3.86 (1.5-8.66)	4.5 (2.2-12.2)	0.044

Values: Median (IQR); NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet–to-lymphocyte ratio; hs-CRP: High-sensitivity C-reactive protein; ESR: Erythrocyte sedimentation rate.

differences were detected between the severe and mild case groups in terms of CRP, monocyte count, and platelet counts. When compared with the mild case group, severe patients were significantly older (median age, 60.5 years [IQR, 42.0-74.0] and 50.0 years [33.0-67.0]; p= 0.004).

ROC curve results

Figure 1 shows that the severe group was

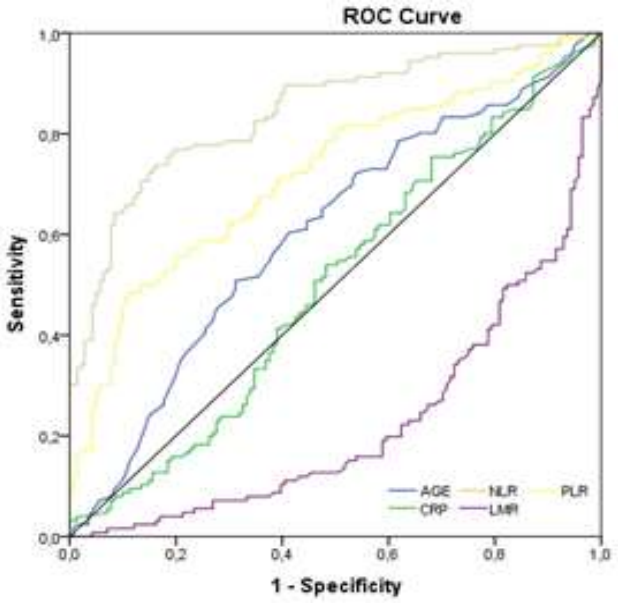

Figure 1. ROC curve was applied to evaluate patients with severe and non-severe COVID-19. NLR: Neutrophils-to-lymphocytes ratio; MLR: Monocyte-to- lymphocytes ratio; PLR: Platelet-to-lymphocytes ratio.

determined as the positive group and the non-severe group as the negative group. The ROC curve was created to analyze the effectiveness of various parameters of blood routine in the diagnosis of severe COVID-19 at admission. The optimal threshold values calculated by ROC analysis and the ROC curves are given in Figure 1. LMR and CRP could not be used as potential diagnostic biomarkers for further analysis because the AUC values of these parameters were less than or close to 0.50. The optimal cut-off values for NLR, PLR, and age were 0.844, 0.719, and 0.603, respectively. The highest specificity and sensitivity values are given in Table3.

Odds ratio results

After the Binary Logistic Regression Analysis, the odds ratios were obtained to identify the risk factors that might influence COVID-19

Table 3. AUC values of NLR, PLR, LMR and CRP.

Parameters	AUC	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Age	0.603	0.035	0.004	0.535	0.671
CRP	0.501	0.035	0.972	0.432	0.571
NLR	0.844	0.024	<0.001	0.796	0.891
LMR	0.225	0.028	<0.001	0.169	0.280
PLR	0.719	0.032	<0.001	0.657	0.781

AUC: area under the curve; CRP: C-reactive protein; NLR: Neutrophils-to-lymphocytes ratio; MLR: Monocyte-to-lymphocytes ratio; PLR: Platelet-to- lymphocytes ratio. Asymptotic significance less than 0.05 were considered significant.

Table 4. The odds ratio results.

Parameters	Unadjusted ORs		Adjusted ORs	
	OR (95%CI)	*p* value	OR*(95%CI)	*p* value
WBC	0.972 (0.854-1.107)	0.668	0.983 (0.861-1.123)	0.804
CRP	0.613 (0.152-2.474)	0.492	0.510 (0.121-2.153)	0.359
NLR	1.481 (1.220-1.798)	<0.001	1.438 (1.184-1.748)	<0.001
LMR	0.889 (0.774-1.021)	0.095	0.883 (0.770-1.012)	0.073
PLR	1.001 (0.997-1.005)	0.609	1.001 (0.997-1.005)	0.541

WBC: White blood cell; CRP: C-reactive protein; NLR: Neutrophils-to-lymphocytes ratio; MLR: Monocyte-to-lymphocytes ratio; PLR: Platelet-to- lymphocytes ratio.

progression. The possible effects of age and gender were excluded and the adjusted OR was obtained after adjusting for gender and age, as CBC parameters are affected by age and gender. The results showed that NLR was significantly correlated with the risk of COVID-19 (adjusted OR: 1438, $p<0.001$) (Table 4). However, the risks of WBC, CRP, PLR, and LMR were not clear.

Discussion

Some changes in the blood values help clinicians in the diagnosis of patients with COVID-19. Lymphopenia, leukocytosis, neutrophilia, and an increase in N/L Ratios are frequently observed changes. Lymphopenia is a common finding and is considered to occur because of an inadequate immune response to the virus. Studies are arguing that hypercytokinemia might be the cause of lymphopenia. In this case, the clinical course of the disease becomes severe, and acute respiratory failure called ARDS, which can result in mortality, might occur [8].

CRP is among the inflammatory markers and is an acute-phase protein synthesized by hepatocytes. In the present study, it was found that CRP levels increased in COVID-19 patients in response to proinflammatory cytokines, which were reported to be increased in most of the previous studies [9, 10]. CRP, a biomarker indicating systemic inflammation, was found to be high in our study.

Many studies have shown in recent years that some ratios of complete blood count parameters are significant in showing the severity of the disease. Some of these rates are NLR, LMR, and PLR, and these rates were used in the diagnosis and prognosis of many inflammatory conditions. Yang et al. reported that age, WBC count, NLR, LMR, PLR, and CRP were significantly elevated in severe patients when compared to other patients, and the lymphocyte count was significantly lower [11]. In the present study, contrary to the study of Yang et al., LMR was low in severe cases, and WBC, NLR, PLR, and CRP were high. In the study of Lissoni et al. and Zhang et al., the LMR value was found to be similar to our results and lower in cases with a severe course [12, 13].

High NLR is an increased risk factor for in-hospital mortality. Although neutrophils increase in COVID-19 cases, the decrease in lymphocytes ends with an increase in NLR. There are publications associated with the severity of the disease with high NLR (14, 15). In the present study, although NLR and PLR increased, LMR decreased.

Qu et al. He argued that high PLR levels in the blood parameters of 30 patients with a diagnosis of COVID-19 were associated with the prognosis of the disease [16]. Although the rate of PLR did not differ significantly between severe and mild patients, they found that it was significantly higher when high platelet count was achieved. In this study, the PLR value was found to be significantly higher in severe cases, suggesting that it can give an idea to clinicians in showing the severity of the disease. There are some publications in which the optimum cut-off value for some serum biochemical parameters was determined by using the severe disease ROC curve as a prognosis indicator in COVID-19 [17]. The %LUC levels can be used as independent prognostic indicators. In the present study, NLR had the highest AUC in the PLR analysis. According to ROC analysis, NLR and PLR AUC values, which are considered acute phase reactants in COVID-19 infection, are significant in showing disease prognosis. The highest specificity and sensitivity were in NLR, PLR. According to these results, NLR and PLR can be used to predict the severity of the disease.

The study had some limitations. Serial reviews could not be performed on the patients because

of financial and logistical constraints. The sample size was small and more extensive studies are needed.

In conclusion, our study revealed that NLR is an independent risk factor in determining the severity of COVID-19 disease. In addition, patients with high platelets and longer mean hospital stays may be associated with cytokine storm. We believe that further research is needed to compare and confirm our results, as comprehensive analysis of clinical and admission laboratory parameters to identify patients with a severe prognosis is important not only for the follow-up of patients, but also for determining the pathophysiology of the disease.

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