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Prognostic value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio for mortality in patients infected with SARS-CoV-2

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Abstract. The COVID-19 pandemic, which originated in China and spread all over the world, continues to be a significant public health crisis. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are valuable parameters that can be evaluated in routine blood tests and provide information about the inflammation in many diseases.

This study aimed to evaluate the effect of NLR and PLR on mortality.

Methods. Our cross-sectional cohort study included patients who were hospitalized due to COVID-19 with positive polymerase chain reaction test results and patients whose test results were negative at the time of the first admission to the hospital, but whose computed tomography imaging was suspicious for COVID-19 and test results were found to be positive in repeated tests during their hospitalization. Prognosis of the hospitalization outcomes was investigated and discharge, hospital admission, intensive care unit (ICU) admission, and mortality data during the 30 days were recorded and the relationship between these parameters was evaluated.

Results. The mean age of the patients was 57.5 ± 16.7 years. Cough was the most common symptom and was present in over half of patients. Almost one-third of patients (27.1%) had at least three symptoms at presentation. Both increased levels of NLR and PLR were observed to significantly predict the mortality of patients with COVID-19 ($p < 0.001$, $p = 0.001$, respectively). Sensitivity and specificity were 65.2% and 80.4% for NLR (AUC: 0.767, cut-off > 5.49) and 43.5% and 81.9% for PLR, respectively (AUC: 0.622, cut-off > 228.13).

Conclusions. The present study has concluded that NLR and PLR are effective mortality predictors in patients infected with SARS-CoV-2.

Key words: COVID-19, hospital mortality, neutrophil to lymphocyte ratio, prognostic factors, platelet to lymphocyte ratio.

Conflict of interest statement. The authors declare no competing interest.

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Значення співвідношення нейтрофілів до лімфоцитів та співвідношення тромбоцитів до лімфоцитів у прогнозуванні смертності хворих інфікованих SARS-CoV2

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Резюме. Пандемія COVID-19, яка виникла в Китаї та поширилась в усьому світу, залишається значним тягарем в галузі охорони здоров'я. Співвідношення нейтрофілів до лімфоцитів (СНЛ) та співвідношення тромбоцитів до лімфоцитів (СТЛ) – діагностичні маркери, які можна оцінити за допомогою загального аналізу крові та надати інформацію щодо наявності запального процесу.

Наше дослідження мало на меті оцінити значення співвідношення нейтрофілів до лімфоцитів та співвідношення тромбоцитів до лімфоцитів у прогнозуванні смертності хворих інфікованих SARS-CoV2.

Методи. До поперечного когортного дослідження включено пацієнтів, інфікованих SARS-CoV2, які мали позитивний результат ПЛР тесту і пацієнти, результати яких були негативними під час першого звернення до лікарні, але візуалізація комп'ютерної томографії була підозрілою на COVID-19 та мали позитивний ПЛР тест під час повторного звернення або госпіталізації. Оцінювали результати лікування та смертність протягом 30 днів після підтвердження діагнозу COVID-19.

Результати. Середній вік пацієнтів становив $57,5 \pm 16,7$ року. Кашель був найпоширенішим симптомом і був у більш ніж половини пацієнтів. Майже у третини пацієнтів (27,1%) були принаймні три симптоми під час госпіталізації. Визначено, що підвищення як СНЛ, так і СТЛ є маркерами смертності пацієнтів із COVID-19 ($p < 0,001$, $p = 0,001$, відповідно). Чутливість та специфічність тестів становила 65,2% й 80,4% для СНЛ (AUC: 0,767, граничне значення $> 5,49$) та 43,5% й 81,9% для СТЛ (AUC: 0,622, граничне значення $> 228,13$).

Висновки. СНЛ та СТЛ є ефективними маркерами для прогнозування клінічного перебігу та смертності у пацієнтів інфікованих SARS-CoV2.

Ключові слова: COVID-19, госпітальна смертність, співвідношення нейтрофілів до лімфоцитів, прогностичний маркер, співвідношення тромбоцитів до лімфоцитів

Introduction. Coronavirus disease 2019 (COVID-19) was first identified in the Wuhan city of China in December 2019. The COVID-19 pandemic, which originated in China and spread all over the world within a very short period of time, continues to be a significant public health crisis [1]. According to data published by the Republic of Turkey Ministry of Health on September 22, 2020, a total of 306,302 patients were diagnosed with COVID-19 throughout Turkey and 7,639 patients died due to the pandemic [2]. Supportive and empirical treatment is given to the patients, but there is no specific treatment and vaccine yet. Identifying the risk factors affecting the clinical course of the disease is of great im-

portance in determining the treatment approach to be applied and predicting the prognosis of the disease [3].

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are valuable parameters that can be evaluated in routine blood tests and provide information about the inflammation in many diseases including cerebral hemorrhage, acute pulmonary embolism, venous thromboembolism, and subarachnoid hemorrhage [4, 5, 6]. In the study, the mean NLR in healthy people was 1.70 ± 0.70 (Range: 8.38, Min: 0.23, Max: 8.61) and the mean PLR was 117.05 ± 47.73 (Range: 93.60, Min: 19.11, Max: 1598.77) [7]. A recent study on COVID-19 has shown that patients with high NLR have a worse prognosis [8]. In other similar studies, higher PLR values have been shown to be associated with an increase in length of stay in the hospital. Studies have shown that these two parameters have important effects in predicting hospitalization and prognosis [9].

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This study aimed to investigate the prognostic value of NLR and PLR in mortality among patients with COVID-19 infection who applied to the pandemic hospital in the early pandemic period and were hospitalized.

Materials and Methods. This cross-sectional cohort study was approved by the ethics committee of the hospital where the study was conducted (48670771-514.10-209). The study included patients aged 18 years and above, who were diagnosed with COVID-19 between 11.03.2020, the date when the first case was identified in Turkey, and 26.04.2020. According to the national guide published by the Ministry of Health, the diagnoses of the patients were made based on the examination of the swab sample taken from the upper or lower respiratory tract of the patients by PCR. Those whose PCR result was positive were diagnosed with COVID-19. Patients whose test results were negative at the time of the first admission to the hospital, but whose computed tomography imaging was suspicious for COVID-19 and test results were found to be positive in repeated tests during their hospitalization were also included in the study.

The patients with missing information in their files, those who did not apply to the emergency department but were referred by an external center, and those who did not have complete blood count results were excluded from the study. Leukocyte, neutrophil counts, and hemoglobin values in admission day, length of stay in the hospital, the reason for going to the hospital, patients comorbidities (total number of comorbidities), and demographic data of the patients with SARS-CoV-2, which were obtained from the hospital information system, were recorded by emergency physicians in the Case Form created via Google Forms.

Prognosis of the hospitalization outcomes was investigated and discharge, hospital admission, intensive care unit (ICU) admission, and mortality data during the 30-day period were recorded. The patients were divided into two groups as the deceased and surviving patients according to their clinical outcomes. Our primary outcome was the effects of NLR and PLR values

on 30-day mortality, and the secondary outcome was to detect common signs and symptoms in admission day in COVID-19 patients.

Statistical Analysis. The Kolmogorov Smirnov and the Shapiro–Wilk test as well as graphical methods (skewness, kurtosis, histogram, Q-Q plot, and box-plot) were used to check the normality assumptions of the data. Normally distributed variables were presented as mean \pm standard deviation, whereas non-normally distributed variables were given as a median and interquartile range. Categorical variables were presented as numbers and percentages. The Independent Samples t-test was used for normally distributed numerical variables, and the Mann-Whitney U test for non-normally distributed variables when comparing two groups based on the patient outcome, the setting, and NLR levels. To compare the categorical variables, the Chi-square test or Fisher's exact test was used according to the expected values in any of the cells of a contingency table were below 5.

Independent predictors of mortality were investigated with univariate and multivariate logistic regression models. Both clinically important and statistically significant variables in univariate analysis were selected to be included in the multivariate models. However, if the variables showed a strong correlation with each other, only one of them was included in the model. Receiver operating characteristic (ROC) curve analysis was used to examine the relationship between mortality and PLR and NLR. The method proposed by DeLong et al. was used for calculating the area under ROC curves (AUCs) [10].

Jamovi project (Version 1.2.24) and JASP (Version 0.13.1) were used to analyze the data of the study. A p-value <0.05 was accepted as statistically significant.

Results. Baseline characteristics of the whole study group. Overall, 772 patients (48.4% females) whose test was positive during hospitalization, were included in the study. Table 1 shows the patients' demographic data, admission symptoms, clinical outcomes, and some laboratory findings of the patients. The mean age of the patients was 57.5 ± 16.7 years (range 19-98 years).

Table 1

The patients' demographic data, admission symptoms, survival status, and laboratory values of the entire study cohort

	n (%) / Mean \pm SD	Median [IQR]
Age	57.5 \pm 16.7	58.0 [19.0- 98.0]
Sex (%)		
Male	398 (51.6)	
Female	374 (48.4)	
Comorbidities		
Hypertension (%)	276 (35.8)	
Diabetes Mellitus (%)	213 (27.6)	
Malignancy (%)	33 (4.3)	
Asthma (%)	47 (6.1)	

Continuation of Table 1

	n (%) / Mean ± SD	Median [IQR]
Coronary artery disease (%)	93 (12.0)	
Cerebrovascular disease (%)	27 (3.5)	
Chronic kidney disease (%)	56 (7.3)	
Chronic liver disease (%)	8 (1.0)	
Chronic obstructive pulmonary disease (%)	36 (4.7)	
Number of comorbidities		
<3	671 (86.9)	
≥3	101 (13.1)	
Symptoms at admission		
Fever (%)	266 (34.5)	
Cough (%)	459 (59.5)	
Shortness of breath (%)	285 (36.9)	
Myalgia and muscle pain (%)	280 (36.3)	
Loss of appetite (%)	29 (3.8)	
Headache (%)	53 (6.9)	
Diarrhea (%)	36 (4.7)	
Nausea and vomiting (%)	69 (8.9)	
Abdominal pain (%)	13 (1.7)	
Chest pain (%)	13 (1.7)	
Taste-odor loss (%)	10 (1.3)	
Sore throat (%)	17 (2.2)	
Number of symptoms (median [IQR])	2.0 [1.0, 3.0]	
Number of symptoms (%)		
<3	563 (72.9)	
≥3	209 (27.1)	
Survival status (%)		
Survived	680 (88.1)	
Deceased	92 (11.9)	
Hospitalization Setting (%)		
Ward	671 (86.9)	
Ward-to-Intensive care unit	77 (10.0)	
Intensive care unit	24 (3.1)	
Length of Stay in hospital (days)	10.6 ± 7.5	9.0 [0.0- 60.0]
Length of Stay in Intensive care unit (days)	1.4 ± 5.0	0.0 [0.0- 50.0]
Laboratory parameters		
White blood cell count (103/μL)	6.9 ± 3.7	
Hemoglobin (g/dL)	125.7 ± 21.6	127.5 [115.0-139.0]
Neutrophil count (103/μL)	5.1 ± 3.4	4.2 [3.2-6.1]
Lymphocyte count (103/μL)	1.4 ± 1.4	1.2 [0.9- 1.6]
Platelet count (103/μL)	200.0 ± 81.5	188.5 [148.5-236.0]
Neutrophil-to-lymphocyte ratio (NLR)	6.2 ± 5.78	3.4 [2.3-5.5]
Platelet-to-lymphocyte ratio (PLR)	180.8 ± 115.3	153.0 [108.1-209.1]

Min: Minimum, Max: Maximum, SD: Standard Deviation

Cough was the most common symptom and was present in over half of patients. Almost one-third of patients (27.1%) had at least three symptoms at presentation.

Comparison of the patient characteristics according to the hospitalization setting. According to the hospitalization setting, patients' demographic data and some laboratory values of patients are shown in Table 2.

Table 2

Comparison of the patients' demographic data and some laboratory values of the ward, ward-to-ICU, and ICU patients

	Setting		P-value
	Ward (n=671)	Ward-to-ICU and ICU (n=101)	
Age, mean \pm SD	56.3 \pm 16.9	65.6 \pm 12.9	<0.001*
Sex (%)			
Male	337 (50.2)	61 (60.4)	0.072**
Female	334 (49.8)	40 (39.6)	
Comorbidities			
Hypertension (%)	222 (33.1)	54 (53.5)	<0.001**
Diabetes Mellitus (%)	168 (25.0)	45 (44.6)	<0.001**
Malignancy (%)	27 (4.0)	6 (5.9)	0.424**
Asthma (%)	43 (6.4)	4 (4.0)	0.462**
Coronary artery disease (%)	68 (10.1)	25 (24.8)	<0.001**
Cerebrovascular disease (%)	18 (2.7)	9 (8.9)	0.005**
Chronic kidney disease (%)	41 (6.1)	15 (14.9)	0.003**
Chronic liver disease (%)	7 (1.0)	1 (1.0)	0.999**
COPD (%)	24 (3.6)	12 (11.9)	0.001**
Number of comorbidities \geq 3	70 (10.4)	31 (30.7)	<0.001**
Symptoms on admission			
Fever (%)	232 (34.6)	34 (33.7)	0.946**
Cough (%)	414 (61.7)	45 (44.6)	0.002**
Shortness of breath (%)	228 (34.0)	57 (56.4)	<0.001**
Myalgia and muscle pain (%)	257 (38.3)	23 (22.8)	0.004**
Loss of appetite (%)	25 (3.7)	4 (4.0)	0.784**
Headache (%)	52 (7.7)	1 (1.0)	0.022**
Diarrhea (%)	30 (4.5)	6 (5.9)	0.454**
Nausea and vomiting (%)	59 (8.8)	10 (9.9)	0.86**
Abdominal pain (%)	10 (1.5)	3 (3.0)	0.236**
Chest pain (%)	11 (1.6)	2 (2.0)	0.683**
Taste-odor loss (%)	10 (1.5)	0 (0.0)	0.375**
Sore throat (%)	15 (2.2)	2 (2.0)	0.999**
Laboratory parameters			
White blood cell count (103/ μ L), mean \pm SD	6.5 \pm 2.9	9.5 \pm 6.4	<0.001*
Hemoglobin (g/dL), mean \pm SD	126.1 \pm 21.4	123.5 \pm 22.3	0.284*
Neutrophil count (103/ μ L)	4.0 [3.1- 5.7]	5.8 [4.1- 8.6]	<0.001***
Lymphocyte count (103/ μ L)	1.2 [0.9- 1.7]	0.9 [0.7- 1.4]	<0.001***
Platelet count (103/ μ L)	190.0 [151.0- 234.5]	182.0 [132.0- 246.0]	0.469***
NLR	3.2 [2.2-5.0]	6.2 [3.7-9.9]	<0.001***
PLR	151.3 [107.7-200.0]	175.2 [114.5-273.1]	0.008***

COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

* Independent samples t-test was used. Descriptive statistics were presented as mean \pm standard deviation for numerical variables.

** Pearson Chi-squared or Fisher Exact test was used. Descriptive statistics were presented as number (%).

*** Mann-Whitney U test was used. Descriptive statistics were given as median [IQR]. IQR: Interquartile range

Bold p-values were accepted as statistically significant ($p < 0,05$). IQR: Interquartile range, SD: Standard deviation

Ward-ICU and ICU patients were significantly older than ward patients and had more comorbidities. Hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD) and chronic kidney disease (CKD) were significantly more frequent in ward-ICU and ICU patients than in ward patients. While cough, myalgia and muscle pain, and headache were significantly more common in ward patients than in ward-ICU and ICU patients, only shortness of breath was more common in Ward-ICU and ICU patients. In addition, NLR and PLR were significantly higher in Ward-ICU and ICU patients compared with ward patients.

Comparison of patient characteristics according to the survival status. Patients' demographic data and laboratory values of patients who died and survived are exhibited in **table 3**. The deceased patients were older than the discharge patients. Both numbers of comorbidities and frequency of HT, DM, CAD, CVD, CKD, and COPD were higher in deceased patients than in discharge patients. Cough, myalgia and muscle pain, and headache were more common in the survived patients than in the deceased patients, whereas shortness of breath was more common in the deceased group. NLR and PLR were significantly higher in the deceased than in the survived patients (Table 3).

Table 3

Comparison of the patients' demographic data and some laboratory values between the survived and deceased patients

	Outcomes		p-value
	Survived (n=680)	Deceased (n=92)	
Age, mean \pm SD	56.0 \pm 16.7	68.5 \pm 11.6	<0.001*
Sex (%)			
Male	343 (50.4)	55 (59.8)	0.116**
Female	337 (49.6)	37 (40.2)	
Comorbidities			
Hypertension (%)	227 (33.4)	49 (53.3)	<0.001**
Diabetes Mellitus (%)	176 (25.9)	37 (40.2)	0.006**
Malignancy (%)	27 (4.0)	6 (6.5)	0.268**
Asthma (%)	43 (6.3)	4 (4.3)	0.609**
Coronary artery disease (%)	72 (10.6)	21 (22.8)	0.001**
Cerebrovascular disease (%)	17 (2.5)	10 (10.9)	0.001**
Chronic kidney disease (%)	42 (6.2)	14 (15.2)	0.003**
Chronic liver disease (%)	7 (1.0)	1 (1.1)	0.999**
COPD (%)	26 (3.8)	10 (10.9)	0.006**
Number of comorbidities \geq 3	74 (10.9)	27 (29.3)	<0.001**
Symptoms on admission			
Fever (%)	236 (34.7)	30 (32.6)	0.779**
Cough (%)	419 (61.6)	40 (43.5)	0.001**
Shortness of breath (%)	233 (34.3)	52 (56.5)	<0.001**
Myalgia and muscle pain (%)	257 (37.8)	23 (25.0)	0.023**
Loss of appetite (%)	27 (4.0)	2 (2.2)	0.563**
Headache (%)	52 (7.6)	1 (1.1)	0.034**
Diarrhea (%)	30 (4.4)	6 (6.5)	0.424**
Nausea and vomiting (%)	60 (8.8)	9 (9.8)	0.914**
Abdominal pain (%)	11 (1.6)	2 (2.2)	0.661**
Chest pain (%)	11 (1.6)	2 (2.2)	0.661**
Taste-odor loss (%)	10 (1.5)	0 (0.0)	0.618**
Sore throat (%)	16 (2.4)	1 (1.1)	0.709**

Continuation of Table 3

	Outcomes		p-value
	Survived (n=680)	Deceased (n=92)	
Laboratory parameters			
White blood cell count (x103/ μ L) , mean \pm SD	6.5 \pm 3.0	9.6 \pm 6.4	<0.001*
Hemoglobin (g/dL) , mean \pm SD	126.1 \pm 21.3	122.7 \pm 22.9	0.175*
Neutrophil count (x103/ μ L)	4.0 [3.1- 5.7]	6.1 [4.4- 9.2]	<0.001***
Lymphocyte count (x103/ μ L)	1.2 [0.9- 1.7]	0.9 [0.6- 1.3]	<0.001***
Platelet count (x103/ μ L)	189.5 [151.0- 236.2]	181.5 [137.2- 230.0]	0.396***
NLR	3.2 [2.2- 5.0]	6.6 [4.3- 11.4]	<0.001***
PLR	150.7 [106.8- 200.0]	188.9 [129.1- 321.9]	<0.001***

COPD: Chronic obstructive pulmonary disease, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

* Independent samples t-test was used. Descriptive statistics were presented as mean \pm standard deviation for numerical variables.

** Pearson Chi-squared or Fisher Exact test was used. Descriptive statistics were presented as numbers (%).

*** Mann-Whitney U test was used. Descriptive statistics were given as median [IQR]. IQR: Interquartile range

Bold p-values were accepted as statistically significant ($p < 0,05$). IQR: Interquartile range, SD: Standard deviation

Comparison of patient characteristics according to the NLR groups (below and above median). According to the median of the NLR value, the patients were divided into two groups, and these two groups were compared with respect to comorbidities, symptoms, and laboratory findings (Table 4).

Table 4

Comparison of the patient groups according to the NLR groups determined by the median value of NLR in terms of patients demographic data and laboratory values

	NLR Groups		p-value
	Patients with NLR below median value (≤ 3.38) (n=384)	Patients with NLR over median value (> 3.38) (n=383)	
Age, mean \pm SD	54.3 \pm 16.2	60.9 \pm 16.5	<0.001*
Sex (%)			
Male	164 (42.7)	231 (60.3)	<0.001**
Female	220 (57.3)	152 (39.7)	
Comorbidities			
Hypertension (%)	119 (31.0)	157 (41.0)	0.005**
Diabetes Mellitus (%)	99 (25.8)	113 (29.5)	0.284**
Malignancy (%)	12 (3.1)	21 (5.5)	0.152**
Asthma (%)	24 (6.2)	23 (6.0)	0.999**
Coronary artery disease (%)	37 (9.6)	56 (14.6)	0.045**
Cerebrovascular disease (%)	9 (2.3)	18 (4.7)	0.115**
Chronic kidney disease (%)	22 (5.7)	34 (8.9)	0.124**
Chronic liver disease (%)	4 (1.0)	4 (1.0)	0.999**
COPD (%)	9 (2.3)	26 (6.8)	0.005**
Number of comorbidities			
<3	344 (89.6)	322 (84.1)	0.032**
≥ 3	40 (10.4)	61 (15.9)	0.032**

Continuation of Table 4

	NLR Groups		p-value
	Patients with NLR below median value (≤ 3.38) (n=384)	Patients with NLR over median value (> 3.38) (n=383)	
Symptoms on admission			
Fever (%)	139 (36.2)	125 (32.6)	0.336**
Cough (%)	234 (60.9)	222 (58.0)	0.444**
Shortness of breath (%)	123 (32.0)	160 (41.8)	0.006**
Myalgia and muscle pain (%)	144 (37.5)	135 (35.2)	0.567**
Loss of appetite (%)	18 (4.7)	11 (2.9)	0.259**
Headache (%)	37 (9.6)	15 (3.9)	0.003**
Diarrhea (%)	19 (4.9)	17 (4.4)	0.871**
Nausea and vomiting (%)	35 (9.1)	33 (8.6)	0.908**
Abdominal pain (%)	7 (1.8)	6 (1.6)	0.999**
Chest pain (%)	9 (2.3)	3 (0.8)	0.147**
Taste-odor loss (%)	6 (1.6)	4 (1.0)	0.752**
Sore throat (%)	11 (2.9)	6 (1.6)	0.329**
Number of symptoms on admission	2.0 [1.0- 3.0]	2.0 [1.0- 3.0]	0.190***
Number of symptoms (%)			
<3	274 (71.4)	286 (74.7)	0.340**
≥ 3	110 (28.6)	97 (25.3)	
Length of hospital stay (days)	8.0 [5.0- 12.0]	10.0 [6.0- 14.0]	0.004***
Laboratory parameters			
White blood cell count (x103/ μ L), mean \pm SD	5.8 \pm 2.4	8.1 \pm 4.3	<0.001*
Hemoglobin (g/dL), mean \pm SD	127.7 \pm 16.7	125.3 \pm 21.1	0.083*
Neutrophil count (x103/ μ L)	3.4 [2.5, 4.2]	5.7 [4.2, 7.7]	<0.001***
Lymphocyte count (x103/ μ L)	1.5 [1.2- 2.0]	0.9 [0.7- 1.2]	<0.001***
Platelet count (x103/ μ L)	186.0 [152.0- 228.2]	191.0 [147.0- 245.5]	0.295***
PLR	119.3 [94.3- 155.1]	195.9 [150.0- 276.1]	<0.001***

COPD: Chronic obstructive pulmonary disease, ICU: intensive care unit, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

* Independent samples t-test was used. Descriptive statistics were presented as mean \pm standard deviation for numerical variables.

** Pearson Chi-squared or Fisher Exact test was used. Descriptive statistics were presented as numbers (%).

***Mann-Whitney U test was used. Descriptive statistics were given as median [IQR]. IQR: Interquartile range

Bold p-values were accepted as statistically significant ($p < 0.05$). IQR: Interquartile range, SD: Standard deviation

Patients with NLR over the median value were older than patients with NLR below the median value. While male gender was more frequent with patients with NLR over the median value, women were more common in patients with NLR below the median value. Length of hospital stay was longer, and the number of comorbidities, frequency of HT, and CAD were higher in patients with NLR over the median value. While shortness of breath was more frequent in patients with NLR over the median value, the headache was more

frequent in patients with NLR below the median value. Moreover, PLR was significantly higher in patients with NLR over the median value than in patients with NLR below the median value.

ROC analysis to determine performance characteristics of NLR and PLR to predict mortality.

The sensitivity and specificity values for NLR and PLR to predict the mortality of the COVID-19 patients are shown Fig. 1.

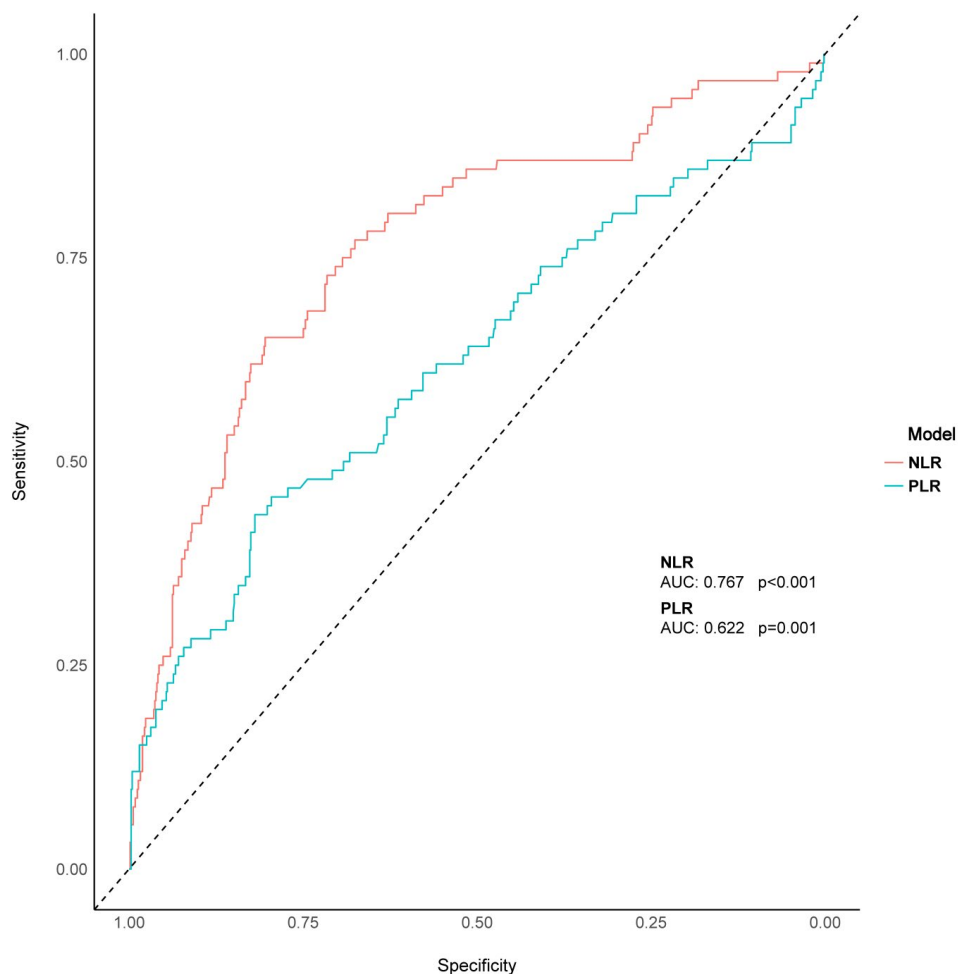


Fig. 1. ROC curves for NLR and PLR in the prediction of the mortality (with the area under the curve for NLR=0.767, and PLR=0.622) in the COVID-19 patients (n=772)

Both NLR and PLR significantly predicted the mortality of the COVID-19 patients ($p < 0.001$, $p = 0.001$, respectively). NLR with a cut-off value > 5.49 predicted the 30-day mortality in hospitalized patients with PCR+ with a sensitivity of 80.44% and

specificity of 65.2% (AUC 0.767, $p < 0.001$). PLR with a cut-off value of > 228.13 predicted the 30-day mortality in hospitalized patients with PCR+ with a specificity of 81.9% and sensitivity of 43.5% (AUC 0.622, $p = 0.001$) (Table 5).

Table 5

ROC analysis showing performance characteristics of NLR and PLR at given cut-off values to predict the mortality

	AUC	Sensitivity	Specificity	Cut-off	%95 CI	P-value
NLR	0.767	65.22	80.44	> 5.49	0.736- 0.797	$< 0,001$
PLR	0.622	43.48	81.93	> 228.13	0.586- 0.656	0,001

AUC: Area Under the Curve, CI: Confidence Interval, NLR: Neutrophil-to-lymphocyte ratio (NLR), PLR: Platelet-to-lymphocyte ratio (PLR)

Univariate and multivariate logistic regression analyses to determine the independent predictors of mortality. To determine the independent predictors of outcomes of COVID-19 patients, logistic regression analysis was performed (Table 6). Variables that statistically significant in univariate logistic regression

were included in the multivariate logistic regression model. In multivariate analysis, age, white blood cell count, and PLR (OR: 1.04, 1.15, and 1.00, respectively) were found as independent associates of mortality.

Table 6

The results of the univariate and multivariate logistic regression analyses

	Univariate LR		Multiple LR	
	Crude OR [95%CI]	Crude P-value	Adj. OR [95%CI]	Adj. P-value
Age	1.05 [1.04-1.07]	< 0.001	1.04 [1.02-1.06]	< 0.001
Hypertension	2.27 [1.47-3.53]	< 0.001	1.19 [0.69-2.04]	0.528
Diabetes mellitus	1.93 [1.23-3.02]	0.004	1.36 [0.80-2.31]	0.253
Coronary artery disease	2.50 [1.45-4.31]	< 0.001	1.31 [0.71-2.44]	0.390
Chronic kidney disease	2.73 [1.42-5.22]	0.002	1.30 [0.62-2.71]	0.485
White blood cell count	1.19 [1.12-1.25]	< 0.001	1.15 [1.08-1.22]	< 0.001
PLR	1.00 [1.00-1.01]	< 0.001	1.00 [1.00-1.00]	0.002
NLR	1.00 [1.00-1.01]	0.337	-	-
Lymphocyte count (x10 ³ /μL)	1.23 [1.16-1.31]	< 0.001	-	-
Platelet count (x10 ³ /μL)	0.96 [0.77-1.18]	0.686	-	-

Dependent variable: Mortality, Adj.: Adjusted, CI: Confidence Interval, NLR: Neutrophil-to-lymphocyte ratio, LR: Logistic Regression, OR: Odds Ratio, PLR: Platelet-to-lymphocyte ratio

Discussion. Neutrophils and lymphocytes have been shown to affect the immune system and the pathogenesis of many diseases. [11] It has been suggested that neutrophil levels reflect the inflammatory state during the progression of the disease, while lymphocyte levels represent the immune responses [12]. It has been observed that SARS-CoV-2 infection can cause a decrease in T lymphocyte counts and worsen the prognosis of the disease [13]. Inflammation caused by lymphocytes in the lungs of patients with SARS-CoV-2 pneumonia was shown in autopsy examinations [14]. In addition, there are studies showing that lymphocytes cause cytokine storm or immune hyperactivation. We think that it may be caused by an inflammatory response in patients with SARS-CoV-2 infection.

Platelets play an important role in coagulation, angiogenesis, immunity, and inflammation [15]. During SARS infection, a decrease in platelet production and an increase in consumption were observed. Endothelial damage during viral infection and mechanical ventilation, thrombocyte aggregation, pulmonary thrombogenesis, and megakaryocyte reduction were thought to be effective causes of this decrease. In addition, thrombocytopenia can be seen as a result of the coronavirus suppressing hematopoietic cells or bone marrow [16].

The NLR, a well-known marker of systemic inflammation and infection, has been studied as a predictor of outcomes in many infections, including pneumonia. In these studies, it was found that lymphopenia was detected in most of the infected patients when laboratory tests were evaluated and that infection-related biomarker levels elevated and as a result, NLR and PLR increased [10, 17-19]. Similar to the present study, these rates were higher in the group of patients who were admitted to the ICU and those who died compared to patients with COVID-19 who were hospitalized in the

service [20, 21]. These results show that both NLR and PLR can be used as prognostic markers.

High NLR and PLR values during hospitalization were found to significantly increase the number of deaths from any cause. In a cohort study of 61 patients, the NLR was reported to be the most beneficial prognostic factor influencing prognosis in severe COVID-19 cases [22]. The neutrophil count may be correlated with inflammation in patients with COVID-19. Increased neutrophil count indicates the severity of the disease. Furthermore, a decrease in lymphocyte count can predict damage to the immune system. Therefore, NLR can be used as a marker to reflect the severity of inflammation or damage to the immune response in patients with COVID-19 [23, 24]. High NLR during hospitalization has also been associated with a longer stay in the ICU and a higher need for respiratory support. A meta-analysis of six studies concluded that an increase in NLR may be associated with the severity of COVID-19 [16]. Early identification of the risk factors for severe COVID-19 cases can facilitate the determination of appropriate supportive care and, if necessary, accelerate access to the ICU.

In a study, when the cut-off point for NLR was accepted as 3.16, its sensitivity and specificity were found to be 76% and 68%, respectively, and it was reported to predict mortality [25]. In the present study, it was concluded that NLR predicted mortality with 65.2% sensitivity and 80.4% specificity when the cut-off point was accepted as 5.49. The results show that the NLR can serve as a powerful factor for predicting the incidence of severe disease among patients with COVID-19 [26]. In studies on PLR, when the cut-off point was accepted as 180, its sensitivity and specificity were found to be 77% and 44%, respectively. Another study reported that its sensitivity and specificity were 72% and 65%, respec-

tively, when the cut-off point was accepted as 153.65 and that it predicted mortality. In the present study, it was concluded that PLR predicted mortality with 43.5% sensitivity and 81.9% specificity when the cut-off point was accepted as 228.13. Another study described PLR as a prognostic marker only when the highest platelet levels were considered during hospitalization [9, 19, 27]. According to the results of the present study, both NLR and PLR predict mortality.

The most common symptom in the present study was found to be cough (59.5%), followed by shortness of breath (36.9%) and myalgia (36.3%). Although fever (34.5%) was found to be the fourth most common symptom in this study, the literature review showed that it was reported to be the most common symptom in other studies. Fever was reported to be followed by cough and shortness of breath, respectively [28, 29]. Cough, myalgia, and headache are more common in patients with a good clinical condition whereas shortness of breath was a more common symptom in patients who were admitted to the ICU and those who died.

Among the patients included in the present study, the most common comorbidities were HT (35.8%), DM (27.6%), and CAD (12%), respectively. There were more than three comorbidities in 101 (13.1%) patients included in the study. Among patients with COVID-19, those who had comorbidities had worse clinical outcomes than those with no comorbidity. The presence of HT, DM, CVD, CAD, CKD, and COPD was found to have a significant effect on ICU admission and mortality. The results of other studies in the literature are compatible with the results of the present study [25, 29]. A more careful assessment of comorbidities at the time of hospitalization can help predict the risk stratification of patients with COVID-19.

Limitations. Recall bias may have occurred because of the retrospective design of the study. Conducting in a single-center is another main limitation. We believe that the limitation of this study is reduced thanks to the fact that the number of patients included in the study is relatively large. There is a need for prospective multi-center studies to clarify the predictive value of NLR and PLR in COVID-19.

Conclusions. The present study has concluded that NLR and PLR are effective parameters in predicting the clinical course and prognosis of the disease. According to the secondary outcomes of the study, the most common symptoms are cough, shortness of breath, myalgia and fever. The presence of HT, DM, CAD, and CKD, and the age of the patients have been found to be correlated with mortality and poor clinical course. There is a need for further investigations as COVID-19 is still considered a global health threat.

Conflicts of interest. The authors declare no conflict of interest.

Authors contribution.

Öner Bozan: writing - original draft, methodology, writing- reviewing and editing;

Bora Çekmen: conceptualization, writing- reviewing and editing, supervision. Şeref Emre Atiş: Conceptualization, Writing- Reviewing and Editing;

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Mustafa Taner Yıldırım: writing- reviewing and editing;

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