

RESEARCH ARTICLE

Evaluation of the prognostic role of NLR, LMR, PLR, and LCR ratio in COVID-19 patients

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Abstract

We aimed to find the most useful biomarker by examining the prognostic effect of neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and lymphocyte-C reactive protein ratio (LCR) in patients with coronavirus disease 2019 (COVID-19). Three hundred and four patients diagnosed with COVID-19 infection in our hospital within 5 months (April–August 2020) were examined. Laboratory values and demographic findings of the patients were analyzed retrospectively. Thirty-six patients were diagnosed with severe cases. The ratio of NLR, LMR, PLR, and LCR of patients with severe and those with nonsevere clinical symptoms were statistically analyzed. The NLR and PLR ratios of those with severe clinical symptoms were significantly higher ($p < 0.001$), the LCR rate was significantly lower ($p < 0.001$), and there was no significant difference in the LMR rate ($p = 0.199$). When we examined other peripheral blood parameters, we found that CRP was high, lymphocyte and monocyte were low ($p < 0.001$), but neutrophil ($p = 0.416$) and platelet ($p = 0.998$) were not statistically different between the groups. According to the results, routine blood values are abnormal in patients with COVID-19. NLR, PLR, and LCR ratios can be used as more significant biomarkers than other values in predicting the prognosis of patients.

KEYWORDS

COVID-19, LMR, NLR, PLR, LCR, SARS-CoV-2

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus.¹ COVID-19 emerged in China and soon spread to other countries and became a major public health problem. For this, it was declared as a pandemic by the World Health Organization (WHO).² Coronaviruses like SARS-CoV and Middle East respiratory syndrome coronavirus can cause severe respiratory infections in humans. COVID-19 is transmitted from person to person through direct contact or through droplets. Therefore, significant effort is required to control the epidemic.^{3,4}

General clinical signs of the disease are fever, fatigue, dry cough, sputum production, sore throat, shortness of breath, and headache.

Although most patients exhibited mild symptoms, the clinical course of some patients resulted in a poor prognosis. Patients with a poor prognosis developed severe pneumonia, pulmonary edema, acute respiratory distress syndrome, or multiple organ failure and eventually died. Especially, the elderly and those with comorbid diseases, including cardiovascular diseases, hypertension, diabetes, cancer, and chronic obstructive pulmonary disease, were among these risk groups.^{4,5}

Because COVID-19 spreads rapidly and does serious harm, it is important to continually study its clinical diagnosis and treatment. It is also important to anticipate in which patients it can be more fatal. Rapid clinical diagnosis is important both for patient isolation to prevent contamination and for the use of intensive care units by taking early precautions.⁶ Although real-time polymerase chain

reaction (PCR) is the gold standard of COVID-19 diagnosis, common routine and low-cost techniques, such as biochemical and hemogram analysis can be quick and easy tests that facilitate the diagnosis and prognosis of this disease.⁷

In inflammation seen in viral pneumonia, such as COVID-19, an imbalance of immune response is seen as a result of severe inflammatory response and poor immune response.¹ As a result, circulating biomarkers that show inflammation, as well as the immune system, can be good indicators of the prognosis of patients with COVID-19.⁸ Of these, white blood cell (WBC) count, neutrophil (NEU) to lymphocyte (LYM) ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and serum C-reactive protein (CRP) levels are beneficial for the prognosis of patients with viral pneumonia, and they were investigated as predictors.

In our study, we aimed to discover the most useful diagnostic biomarkers by investigating and comparing the prognostic effects of NLR, LMR, PLR, and lymphocyte-C reactive protein ratio (LCR) in COVID-19 cases.

2 | METHODS

We performed our research by retrospectively reviewing the archives after receiving the consent of the ethics committee. Patients who were admitted to the emergency room and pandemic outpatient clinics between April 2020 and August 2020 and were positive for the SARS-CoV-2 PCR test were included in the study. The medical records of the patients included in the study were analyzed through the hospital data processing database, and laboratory results, demographic findings, and clinical outcomes were collected from the electronic medical record network.

From the patients, those who had symptoms, such as shortness of breath, fever, cough, sore throat, diarrhea, smell, and taste disturbance were subjected to PCR amplification in case of possible infection. Combined naso-opharyngeal swabs were taken and analyzed by reverse transcription-polymerase chain reaction in the Central Laboratory of our hospital. For laboratory tests, complete

blood count, biochemistry, and CRP values were checked. Patients were divided into two groups with severe clinical and nonsevere clinical outcomes based on the provisional guidance of the WHO (2) and the national COVID-19 diagnostic and treatment guidelines. Those with nonsevere clinical outcomes were classified as Group 1, and those with severe outcomes as Group 2. Group 1: patients who are discharged or hospitalized. Group 2: patients were intubated, in need of intensive care, or died. Between groups 1 and 2; NLR, LMR, PLR, and LCR were compared.

2.1 | Statistical analysis

The data were evaluated in IBM SPSS Statistics 25.0 (IBM Corp.) statistical package program. Descriptive statistics were given as the number of units (*n*), percentage (%), median (*M*), 25th percentile (*Q1*), and 75th percentile (*Q3*). The compliance of the data of continuous variables to normal distribution was evaluated using the Shapiro-Wilk test and Q-Q graphics. NLR, LMR, PLR, and LCR values were compared using the Mann-Whitney U test between good and poor clinical outcome groups. Pearson's χ^2 test was used for other comparisons between groups. And *p* < 0.05 value was considered statistically significant.

3 | RESULTS

In this study, we examined 304 SARS-CoV-2 positive patients. We found that the median age was 45 (33;55). Three hundred and four COVID-19 positive patients were studied. Thirty-six patients had severe and 268 had nonsevere clinical outcomes. Table 1 shows the demographic characteristics of the patients. The average age of the patients with poor clinical outcomes was significantly higher than the other group and had comorbid diseases.

We compared NLR, LMR, PLR, and LCR values in severe and nonsevere patients with COVID-19. Table 2 shows these results. There was no statistically significant difference between nonsevere

	Total	Non-severe	Severe	χ^2/Z	<i>p</i>
Age (M (Q ₁ ;Q ₃))	45 (33;55)	43.5 (33;53)	69.5 (51;75)	-6.24 ^a	<0.001*
Sex (M/F)	176/128	150/118	26/10	3.43 ^b	0.064
Comorbidities (%) (P/NP)	65/221	40/212	25/9	56.707 ^b	<0.001*
Hypertension (P/NP)	45/249	27/232	18/17	39.990 ^b	<0.001*
Diabetes (P/NP)	28/266	16/243	12/23	28.271 ^b	<0.001*
Heart disease (P/NP)	16/277	10/248	6/29	10.507 ^b	0.006*
Respiratory disease (P/NP)	5/289	5/254	0/35	0.687 ^b	1.000

Abbreviations: NP, nonpresent; P, present.

**p* < 0.05 was considered statistically significant.

^aZ

^b χ^2

TABLE 1 The demographic and baseline characteristics of all the patients

TABLE 2 NLR, LMR, PLR, and LCR parameters of the non-severe group and severe group

	Nonsevere clinic			Severe clinic			Z	p
	Median	Q ₁	Q ₃	Median	Q ₁	Q ₃		
NLR	2.20	1.59	3.50	4.85	2.20	10.20	-4.190	<0.001*
LMR	3.00	2.00	4.10	2.30	1.50	4.00	-1.284	0.199
PLR	138.05	99.50	182.85	300.50	137.60	544.50	-4.757	<0.001*
LCR	0.27	0.07	1.39	0.01	0.00	0.03	-8.194	<0.001*

Abbreviations: LCR, lymphocyte-C-reactive protein ratio; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

* $p < 0.05$ was considered statistically significant.

and severe clinical outcomes in terms of the LMR variable, but there was a statistically significant difference in terms of NLR, PLR, and LCR variables. While the median value was lower in the non-severe clinical outcome group in the NLR and PLR variables, the median value in the nonsevere group in the LCR variable was higher.

In Table 3 we compared routine blood parameters and we found that there was a significant difference in many parameters between the severe group and the nonsevere group. The severe group had a higher CRP level ($p < 0.001$), but lower hemoglobin concentration ($p < 0.001$), hematocrit ratio ($p < 0.001$), lymphocyte ratio ($p < 0.001$), and monocyte count ($p < 0.001$).

4 | DISCUSSION

COVID-19 is a systemic multiorgan damage disease caused by coronavirus 2 (SARS-CoV-2) and its primary target organ is the lung, causing the severe acute respiratory syndrome. In severe cases, it can lead to death by causing acute respiratory distress syndrome.¹⁰ Recent studies have shown that the virus enters alveolar cells by binding to the receptor and activates macrophages, allowing inflammatory factors to be released.¹¹ As a result, factors and chemokines that use other mononuclear cells are released. This increases immune activation, causing inflammation storm and consequently tissue damage.³ Based on these, we investigated the

immunological properties of peripheral blood and the effect of their ratio on prognosis in patients with COVID-19.

In the study conducted by Xu et al,¹² they found that mononuclear cells, mostly lymphocytes, are dominant in the interstitial area of the lung. This explains the reason for the significant decrease in lymphocyte count. It has been found that patients with COVID-19 have defective hematopoiesis system.¹³ NEU is the primary component of the immune system that is activated and migrated. At the same time, it enables the production of a large number of cytokines and effector mediators by interacting with other cells.¹³ Supporting all of these, in our study, the lymphocyte levels of the patients with a severe clinical picture were significantly lower. However, on the contrary, there was no significant difference between neutrophil levels.

Another issue that needs to be discussed is the impaired blood coagulation functions in patients. As a result of thrombosis, thrombocyte consumption increases and the number of platelets decreases.¹⁴ Damage and inflammation in kidney tissue causes RBC destruction and anemia by reducing erythropoiesis.¹⁵ When we examined the acute phase protein, CRP, one of the new inflammatory biomarkers synthesized by hepatocytes, we found that it increased more in patients with severe clinical outcomes, similar to the studies conducted.¹⁶

What we understand from the studies conducted is that the deterioration and prognosis of the clinical symptoms in COVID-19 are directly related to the immune system and increased

TABLE 3 Laboratory results

	Nonsevere Clinic			Severe clinic			Z	p
	Median	Q ₁	Q ₃	Median	Q ₁	Q ₃		
CRP mg/dL	5.50	1.68	18.12	101	40.05	186.90	-8.085	<0.001*
Hemoglobin (g/dL)	13.90	12.90	15	11.65	10.20	13.60	-5.09	<0.001*
Hematocrit (%)	40.90	38.30	44.10	33	30	41	-4.957	<0.001*
Neutrophil	3.80	2.65	5.20	3.55	2.50	8.20	-0.814	0.416
Lymphocyte	1.60	1.10	2.20	0.85	0.50	1.20	-5.860	<0.001*
Platelet	230	186	274	217.50	151	323.50	-0.002	0.998
Monocyte	0.55	0.40	0.70	0.30	0.20	0.55	-4.192	<0.001*

Abbreviation: CRP, C-reactive protein.

* $p < 0.05$ statistically significant.

inflammatory response.¹² For this, researchers have studied some ratios, such as neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte in the diagnosis and prognosis of many inflammatory conditions.^{17,18} This study indicates the usefulness of a similar ratio in predicting the prognosis of patients with COVID-19.

Shang et al.¹⁹ showed in their retrospective analysis that NLR, CRP, and platelets are effective in determining the severity of the disease. In another study, the correlation between the hematological values of the patients and the length of stay in the hospital was examined. In severe patients, a decrease in lymphocyte count and a significant increase in NLR were detected. They also found a positive correlation with the NLR when they examined the length of stay in the hospital. As a result, they stated that they could use NLR to predict the prognosis of patients.²⁰ In our study, NLR values of patients with severe clinical manifestation were significantly higher, in support of the studies performed.

Yang et al.⁶ studied 69 nonsevere and 24 severe patients with COVID-19. They found that the ratio of NLR, LMR, PLR, and CRP was statistically significantly higher in severe patients. When we examined another study, the PLR level of 30 patients diagnosed with COVID-19 was checked and found to be high. It has been said that this height prolongs the hospitalization period of the patients and is related to the prognosis.²¹ According to the results of our study, although NLR and PLR values are higher in severe patients, LMR is lower. The LCR value we looked at, but not in other studies, was significantly lower in severe patients. Based on all these, we found in our study that NLR, PLR, and LCR values can be used to evaluate clinical severity and predict prognosis in patients with COVID-19.

As a result, COVID-19 causes changes in peripheral blood parameters. Clinical symptoms and their severity may be related to the proportion of immune cells. Therefore, these parameters should also be examined while evaluating the prognosis. According to our results, NLR, PLR, and LCR values were significantly higher in severe COVID 19 positive patients, supporting the fact that it can be a prognostic biomarker.

ACKNOWLEDGMENTS

We thank our hospital and university for providing data.

CONFLICT OF INTERESTS

The authors declare that there no conflict of interests.

AUTHOR CONTRIBUTIONS

Arife Erdogan, Fatma Ezgi Can, and Hayriye Gönüllü contributed equally to this study. All authors participated in the design, data collection and analysis, drafting of the manuscript, and approval of the final version.

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How to cite this article: Erdogan A, Can FE, Gönüllü H. Evaluation of the prognostic role of NLR, LMR, PLR and LCR ratio in COVID-19 patients. *J Med Virol*. 2021;93:5555-5559. <https://doi.org/10.1002/jmv.27097>