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), platalet-lymphocyte ratio (PLR) and lymphocyte-C reactive protein ratio (LCR) in COVID-19 patients. 304 patients diagnosed with COVID-19 infection in our hospital within five months (April-August 2020) were examined. Laboratory values and demographic findings of the patients were analyzed retrospectively. 36 were diagnosed with severe cases. The ratio of NLR, LMR, PLR, and LCR of patients with severe and those non-severe clinic were statistically analyzed. The NLR and PLR ratios of those with severe clinic 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 COVID-19 patients. NLR, PLR and LCR ratios can be used as more significant biomarkers than other values in predicting prognosis of patients.

KEY WORDS: COVID-19, SARS-CoV-2, NLR, LMR, PLR and LCR

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 an pandemic by the World Health Organization (WHO).[2] Coronaviruses like SARS-CoV and MERS-CoV, 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; 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 into severe pneumonia, pulmonary edema, acute respiratory distress syndrome, or multiple organ failure and eventually died. Especially 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 which patients may 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 and the immune system can be a good indicator of the prognosis of COVID-19 patients.[8] Of these; white blood cell (WBC) count, neutrophil (NEU) to lymphocyte (LYM) ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR), serum Creactive protein (CRP) levels are beneficial for the prognosis of patients with viral pneumonia. investigated as predictors.[9]

In our study, we aimed to discover the most useful diagnostic biomarkers by investigating and comparing the prognostic effects of neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platalet-lymphocyte ratio (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 Polymerase Chain Reaction (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, 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-oropharyngeal swabs were taken and analyzed by reverse transcription polymerase chain reaction (RT-PCR) in the Central Laboratory of our hospital. For laboratory tests; complete blood count, biochemistry and C-reactive protein (CRP) values were checked. Patients were divided into 2 groups with severe clinical and non-severe clinical outcomes based on the provisional guidance of the WHO (2) and the national COVID-19

diagnostic and treatment guidelines. Those with a non-severe clinic were classified as group 1, and those with a severe clinic 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; neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), thrombocyte-lymphocyte ratio (PLR) and lymphocyte-C reactive protein ratio (LCR) were compared.

2.1.Statistical analysis

The data were evaluated in IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) 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 Shapiro Wilk test and Q-Q graphics. NLR, LMR, PLR, LCR values were compared using the Mann-Whitney U test between good and poor clinical outcome groups. Pearson's chi-square 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). 304 COVID-19 positive patients were studied. 36 patients had a severe and 268 non-severe clinic. 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, LCR values in severe and non-severe COVID-19 patients. Table 2 shows these results. There was no statistically significant difference between non-severe 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 non-severe 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 non-severe 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 multi-organ damage disease caused by coronavirus 2 (SARS-CoV-2) and its primary target organ is the lung, causing severe acute respiratory syndrome. In severe cases, it can lead to death by causing acute respiratory distress syndrome (ARDS).[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 COVID-19 patients.

In the study conducted by Xu et al, they found that mononuclear cells, mostly lymphocytes, are dominant in the interstitial area of the lung.[12] This explains the reason for the significant decrease in lymphocyte count. It has been found that COVID-19 patients have a defective hematopoiesis system.[13] Neutrophil (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 erythrogenesis.[15] When we examined the acute phase protein C-reactive protein (CRP), one of the new inflammatory biomarkers synthesized by hepatocytes, we found that it increased more in patients with severe clinical pictures, similar to the studies conducted.[16]

What we understand from the studies conducted is that the deterioration and prognosis of the clinic in COVID-19 is directly related to the immune system and increased 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 similar ratio in predicting the prognosis of COVID-19 patients.

Shang et al showed in their retrospective analysis that NLR, CRP and platelets are effective in determining the severity of the disease.[19] 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 studied 69 non-severe and 24 severe COVID-19 patients. They found that the ratio of NLR, LMR, PLR, and CRP were statistically significantly higher in severe patients.[6]

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 with 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 COVID-19 patients.

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 that it may be a prognostic biomarker.

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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 design, data collection and analysis, drafting of the manuscript, and approval of the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TABLE 1 The demographic and baseline characteristics of all the patients

	Total	Non-severe	Severe	χ^2 / Z	*P*
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
Co morbidities (%) (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

*p < 0.05 statistically significant. P/NP: Present/Nonpresent. [a]Z, [b]χ^2

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

	Non-Severe 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**

NLR: Neutrophil-to-lymphocyte ratio; LMR: lymphocyte-monocyte ratio PLR: Platelet-to-lymphocyte ratio; LCR: lymphocyte-C reactive protein ratio. $p < 0.05$ statistically significant

TABLE 3 Laboratory results.

	Non-Severe Clinic			Severe Clinic			Z	p
	Median	Q_1	Q_3	Median	Q_1	Q_3		
CRP mg/d	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**

$p < 0.05$ statistically significant