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CLINICAL STUDY

Lymphocyte/mean platelet volume ratio, a new marker; is it effective in predicting the prognosis of COVID-19 cases?

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ABSTRACT

OBJECTIVES: This study aims to determine the prognostic significance of the lymphocyte/mean platelet volume ratio (LMR) in terms of the clinical course of the disease in patients with COVID-19.

METHODS: Patients over 18 who were evaluated for COVID-19 during the period from April 1, to April 30, 2020 were retrospectively scanned. Patients with at least 1 positive PCR test result were as assigned to Group 1 while patients with negative test results were assigned to Group 2. The LMR ratio was calculated by dividing the lymphocyte value by that of MPV. The relationship between LMR, severity of patients' CT findings and 28-day mortality was evaluated.

RESULTS: A total of 938 patients were included in the study. It was observed that the lymphocyte and LMR levels were significantly different in those who died within 28 days ($p < 0.001$, $p \leq 0.001$). In the ROC analysis for the LMR level, the area under the curve (AUC) was found to be 0.737 (95% CI 0.639–0.834). When the cut-off value of LMR was 0.045, the sensitivity was found to be 99.0 % and specificity was 15.2 %.

CONCLUSION: LMR can be a guide in multiple cases of care provided to critical patients, as is the case in the COVID-19 pandemic and can be used in recognizing critical patients *(Tab. 5, Fig. 1, Ref. 21)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, emergency department, pneumonia, lymphopenia, mean platelet volume.

Introduction

The new coronavirus disease (COVID-19) is a systemic infection with a sub-strain of the Coronaviridae family and has a significant effect on the hematopoietic system and hemostasis. Lymphopenia can be considered as a cardinal laboratory finding, and there are different studies regarding its prognostic potential (1–4). Although the mechanism involved in the development of lymphopenia is yet to be fully clarified, it is thought that lymphocytes are degraded directly due to ACE2 receptors that they carry. At the same time, the viral load that causes a cytokine storm may trigger the apoptosis of lymphocytes through tumor necrosis factor alpha, IL6, and other proinflammatory cytokines (1, 5). Especially in severe cases requiring hospitalization, the detection of lymphopenia is an important indicator that can be used in the follow-up of the disease prognosis (6, 7).

Among the hemogram parameters, the mean platelet volume (MPV) is used especially in the follow-up of inflammation. There are many studies regarding the role of MPV in carrying important information in cardiovascular and respiratory diseases and inflammation (8, 9). MPV indicates the size of platelets and is associated with platelet function and activation. In the presence of inflammation, the release of proinflammatory cytokines such as IL6 acts directly on megakaryocytes, while affecting the cytoplasmic fluid distribution and nucleus degranulation in order to trigger thrombocyte release and accelerate migration to the inflammation area. The number of migrating platelets increases, but the ones that are smaller than normal platelets are removed from the peripheral circulation. This is significant for low MPV in cases of recurrent inflammation (10, 11).

This study aims to evaluate the relationship between the calculated lymphocyte/MPV ratio (LMR) and computed tomography (CT) findings of the patients with COVID-19, as well as to determine its prognostic significance in terms of the clinical course of the disease.

Materials and methods

Patients over 18 who were evaluated for COVID-19 in the emergency department of our hospital between April 1, and April 30, 2020 and received combined nasal and throat swab for the purpose of diagnosis with PCR (polymerase chain reaction) tests were screened retrospectively. During the planning stage, permissions were obtained from the ethics committee of our hospital

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Table 1. Demographic data

		Frequency (n)	Percent (%)
Gender	Female	498	53.1
	Male	440	46.9
PCR	Positive	473	50.4
	Negative	465	49.6
Pneumonia	Typical	97	10.3
	Intermediate	124	13.2
	Atypical	30	3.2
	Negative	687	73.2
Complaint	3 or more	642	68.4
	Cough	113	12.0
	Weakness	15	1.6
	Shortness of breath	44	4.7
	Fever	80	8.5
	Sore throat	10	1.1
	Nausea vomiting diarrhea	8	0.9
	Fever + cough	23	2.5
	Loss of taste	3	0.3
Result	Home isolation / outpatient treatment	749	79.9
	Hospital	174	18.6
	Intensive care	15	1.6
28-day mortality	Survival	905	96.5
	Mortality	33	3.5
	Total	938	100.0

PCR: polymerase chain reaction

(2011-KAEK-25 2020 / 05-12) and Ministry of Health, General Directorate of Health Services. In total, 3,006 files of patients, who were evaluated as possible COVID-19 cases and received PCR tests within a month, were retrospectively scanned. Those younger than 18 years as well as pregnant women were excluded from the study. The screening of patient files led us to exclude a significant number of files from the study namely 784 files with missing information about the presentation of symptoms and clinical states, and 839 files with incomplete laboratory data. Finally, 445 patients were excluded from the study because they could not be followed up for 28 days after clinical discharge or in form of outpatient follow-up. A total of 938 patients were included in the study. The patients were divided into two groups according to their PCR results. The patients with at least 1 positive PCR test result were assigned to Group 1, whereas the patients with negative test results were assigned to Group 2. As a result, 473 of the patients were included in Group 1 and 465 were in Group 2.

Tab. 2. Laboratory data.

	n	Mean	SD
Lymphocyte	938	2.25	2.21
Platelet	938	241.20	73.77
MPV	938	9.70	1.07
LMR	938	0.23	0.22
D-Dimer	938	0.218	1.08
CRP	938	17.18	37.18

MPV: mean platelet volume; LMR: lymphocyte/mean platelet volume ratio; CRP: C-reactive protein

The parameters of age, gender, fever, saturation values, laboratory tests and CT findings of the selected patients were recorded from the patient files and stored in the hospital automation system. CT results of the patients were evaluated according to the classification of the Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19 (12).

The lymphocyte and MPV values obtained as a result of the hemogram taken at the first admission of the patients were recorded and the LMR ratio was calculated. The relationship of LMR with the severity of patients' CT findings and 28-day mortality was evaluated.

Statistical analysis

The data of the study were analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) software. Descriptive statistics were expressed as mean ± standard deviation or median values and interquartile range (IQR) of 25–75 %, while categorical variables were expressed as numbers and percentage (%). Kolmogorov-Smirnov test was used for the normality distribution of the data. The significance of the difference between the groups in terms of continuous numerical variables where parametric test statistics assumptions were met was examined with Student's t-test, while the significance of the difference in terms of continuous numerical variables in which parametric test statistics assumptions were not met was evaluated with the Mann-Whitney U test. To analyze whether there was a relationship between categorical variables, the Chi-square and Fisher's exact tests were used. ROC curve was drawn to investigate the diagnostic value of lymphocyte/MPV ratio. The value of $p < 0.05$ was considered statistically significant. Results were presented at 95% confidence interval.

Results

A total of 938 patients were included in the study. The median age was 41 (IQR 25–75 %; 29 to 51). A proportion of 53.1 % (n=498) of the patients were male and 50.4 % (n=473) were positive for PCR.

Upon CT examination, pneumonia was not detected in 73.2 % of the patients (n=687). Of the patients, 67.7 % (n=203) had comorbidities. While three or more symptoms were detected in 68.4 % of the patients (n=642), the second most common symptom was cough with 12.0 % (n=113). Home isolation was recommended to 79.9 % of the patients (n=749), and the 28-day mortality rate was 3.5 % (Tab. 1).

The measured mean lymphocyte level of the patients was 2.25 ± 2.21x10^3/mL, mean MPV level was 9.70 ± 1.07fL, and mean LMR level was 0.24 ± 0.22 10/mL/fL (Tab. 2).

Tab. 3. Analysis of variables with chi-square test.

			28-day mortality		Total	Chi-Square analysis
			survival	mortality		
Gender	Female	n	486	12	498	χ^2=3.84 p=0.05
		%	53.7	36.4	53.1	
	Male	n	419	21	440	
		%	46.3	63.6	46.9	
PCR	Positive	n	459	14	473	χ^2=0.876. p>0.05
		%	50.7	42.4	50.4	
	Negative	n	446	19	465	
		%	49.3	57.6	49.6	
Pneumonia	Typical	n	92	5	97	χ^2=25.59 p<0.001
		%	10.2	15.2	10.3	
	Intermediate	n	115	9	124	
		%	12.7	27.3	13.2	
	Atypical	n	25	5	30	
		%	2.8	15.2	3.2	
	Negative	n	673	14	687	
		%	74.4	42.4	73.2	
Result	Home isolation/outpatient treatment	n	746	3	749	χ^2=446.16 p<0.001
		%	82.4	9.1	79.9	
	Hospital	n	159	15	174	
		%	17.6	45.5	18.6	
	Intensive care	n	0	15	15	
		%	0	45.5	1.6	
Total		n	905	33	938	
		%	100	100	100	

PCR: polymerase chain reaction

Tab. 4. Analysis of variables with the Mann-Whitney U Test.

	28–day mortality	n	Median (IQR: 25th–75th percentiles)
Lymphocyte	Survival	905	2.02 (1.44–2.75)
	Mortality	33	1.14 (0.64–2.04)
	Total	938	2.00 (1.41–2.73)
MPV	Survival	905	9.60 (9.00–10.30)
	Mortality	33	9.70 (9.20–11.10)
	Total	938	9.60 (9.00–10.30)
LMR	Survival	905	0.21 (0.15–0.29)
	Mortality	33	0.12 (0.07–0.20)
	Total	938	0.21 (0.14–0.29)

MPV: mean platelet volume; LMR: lymphocyte/mean platelet volume ratio

A statistically significant relationship was found by the Chi-square test performed to analyze the relationship between gender and 28-day mortality. The 28-day mortality was higher in males than in females (p=0.05).

No statistically significant correlation was found in the Chi-square test performed to analyze whether there was a relationship between PCR status and 28-day mortality (p > 0.05).

A statistically significant correlation was found by the Chi-square test performed to analyze whether there was a relationship between the CT findings, final status of patients and 28-day mortality (p < 0.001/p < 0.001). It was found that 42.4 % of the patients who died within 28 days had negative CT findings. It was also observed that approximately 91 % of the patients who died within 28 days were inclusive of those hospitalized and treated in the intensive care unit (Tab. 3).

The Kolmogorov–Smirnov test revealed that the data were not normally distributed. Thus, Mann-Whitney U test was performed to investigate whether there was a difference between lymphocyte, MPV and LMO levels and 28-day mortality. The results of the test showed that lymphocyte and LMO levels were significantly different in those who died within 28 days (p < 0.001, p < 0.001, respectively) (Tab. 4).

The ROC analysis conducted to investigate the LMO level revealed that the area under the curve (AUC) value was 0.737 (95% CI 0.639-0.834) (Fig. 1).

When the cut-off value of LMO was 0.045, the sensitivity was found to be 99.0 %, and specificity was 15.2 %. On the other hand, when the cut-off value for LMO was 0.075, the sensitivity was found to be 96.6 %, and specificity was 33.3 % (Tab. 5).

Discussion

Given the worldwide prevalence of COVID-19, the disease classification and prognostic indicators are of paramount importance in guiding the treatment, protecting medical resources, and saving critically ill patients (7). This

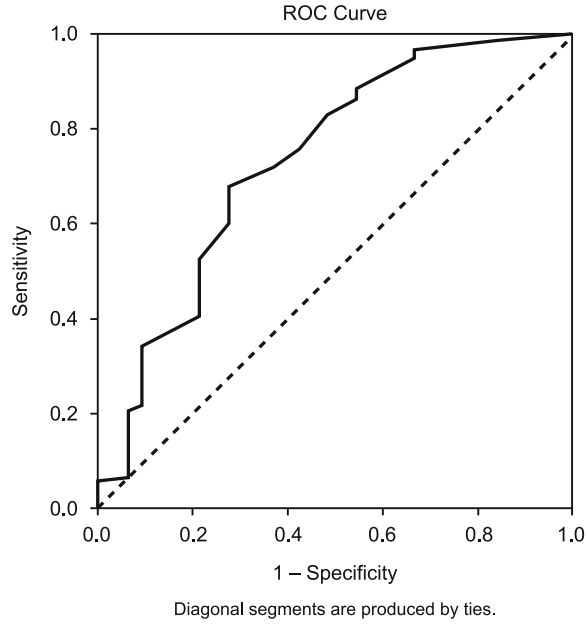

Fig. 1. Area under curve (AUC) values of lymphocyte mean platelet volume ratio to prediction mortality.

Tab. 5. ROC analysis according to LMR values at diagnosis of mortality.

AUC(95% CI)	p	Risk fact	Cutt-off value	Sensitivity %	Specificity %
			0.045	99.0	15.2
			0.075	96.6	33.3
0.737(0.639-0.834)	<0.001	LMR	0.105	88.7	45.5
			0.135	79.6	54.5
			0.165	67.8	72.7

may produce significant results in the effective evaluation of hematological parameters and monitoring the prognosis. A detailed use of inexpensive and easily accessible hemogram examination parameters in terms of providing effective and rapid treatment in COVID-19 disease may be associated with severe pneumonia requiring hospitalization, and may serve as an important prognosis indicator for the clinician. The importance of lymphopenia in the prognosis of the disease has been evaluated in literature, while some parameters such as c-reactive protein, neutrophil/lymphocyte ratio, lymphocyte percentage, lymphocyte/c-reactive protein ratio, and platelet count have been evaluated as prognostic markers (4, 6, 7, 13–15).

Studies have shown that lymphopenia is detected in the presence of severe disease in 85 % of patients followed up for COVID-19. Especially in cases with mortality, it is still valid today that there is a relationship between lymphopenia and survival and as such it is used in mortality estimation (1, 16–18). In our study, the findings demonstrating the relationship between lymphopenia with disease severity and mortality were consistent with the literature.

Decrease in MPV provides important findings in cardiovascular diseases, stroke, and respiratory diseases. Determining the cut-off value in terms of MPV is significant for the current disease development risk, development of thrombotic complications, death, and follow-up of the response to the treatment (11). Increase in MPV, which is an important marker in the presence of inflammation, was found to decrease in the presence of COVID pneumonia, which contributed to similar findings in the literature.

There are studies demonstrating the efficacy of lymphocyte/monocyte ratio, platelet/lymphocyte ratio and MPV in showing the degree of systemic inflammation in critically ill patients who are followed up in post-operative and intensive care settings (19–21). The effective use of these easily accessible parameters in predicting prognosis or determining the severity of the disease is important in providing adequate follow-up to the patient, especially in emergency departments where rapid decision-making and treatment efficiency are used simultaneously.

There are some limitations to our study. MPV measurement standardization is very difficult, measurement-related errors are common. Blood samples can be easily affected by many factors such as environment, time between blood collection and laboratory examination, test tubes, anticoagulant, and analysis and calibration of the device. The presence of fragmented platelets during the test may cause a relative decrease in MPV value. Since our study was planned retrospectively, we had some missing data during the data collection stage.

Conclusion

As identified, the lymphocyte/MPV ratio, whose prognostic significance was evaluated in this study, is the first of its kind in the literature. In our opinion, it is very important that it can be obtained from an inexpensive and easily accessible hemogram result. According to the results, it was determined that in case of LMR being 0.045, it had a very high sensitivity (99.0 %) in predicting 28-day mortality. When the LMR was 0.075, the sensitivity was 96.6 %, and specificity was 33.3 %. For this reason, LMR can be a guide in multiple cases of care provided to critical patients, as is the case in the COVID-19 pandemic, and can be used in recognizing a critical patient. We think that it can form a basis for multi-center prospective studies addressing this issue.

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