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CLINICAL STUDY

Can ferritin/lymphocyte percentage ratio, a new indicator, predict the clinical course of COVID-19 cases?

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ABSTRACT

OBJECTIVES: COVID-19 maintains its seriousness as a global emergency with its rapid distribution worldwide. Ferritin/lymphocyte percentage ratio (FLPR) may appear as a prognostic value at the initial evaluation stage and thus can be used as a simple, effective and reliable parameter in identification of patients critically ill with COVID-19.

METHODS: In this retrospective cohort study we evaluated patients who were hospitalized after being diagnosed with COVID-19 based on positive PCR results. We calculated FLPRs and classified disease severity due to initial emergency evaluation. The relationship between the severity of the need for hospitalization and intensive care, and 28-day mortality with FLPR were evaluated.

RESULTS: The differences between the groups as for COVID-19 severity and FLPR means were statistically significant (x2=148.284; SD=3; p=0.000). FLPR levels were found to be high in groups with critically and seriously ill patients. In the ROC analysis for the FLPR level, the area under the curve (AUC) value was found to be 0.909 (95 % CI 0.857–0.961). When the cut-off value of FLPR was 21.11, the sensitivity and specificity were 82.9 % and 82.8 %, respectively.

CONCLUSION: FLPR, a new parameter, can be used as a significant marker to predict the 28-day mortality patients *(Tab. 6, Fig. 1, Ref. 25)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, percentage of lymphocytes, ferritin, FLPR, disease severity, emergency department.

Introduction

In December 2019, an acute respiratory disease, now known to be caused by a novel coronavirus, emerged in Wuhan, Hubei district, China. The disease quickly spread around Wuhan (1, 2). On January 30, 2020, the World Health Organization recognized this rapidly spreading infectious disease as an international public health emergency, currently known as a coronavirus disease 2019 (COVID-19), and then defined it as a pandemic on March 11, 2020 (3).

COVID-19 disease is a systemic infection with a significant effect on the hematopoietic system. Its incubation period (approximately 1–14 days) is characterized by nonspecific symptoms and normal or slightly decreased peripheral leukocyte and lymphocyte levels. With the viremia developing in the following 7–14 days, SARS Cov-2 causes an increase in angiotensin-converting enzyme-2 (ACE-2) levels especially in the lungs, heart and gastrointestinal system and a systemic inflammatory response defined as a 'cytokine storm' (4). Lymphocytes having ACE receptors on their surfaces are directly lysed by this effect. Interleukins and tumor necrosis factor alpha released in cytokine storm trigger lymphocyte apoptosis and simultaneously impair lymphocyte turnover by affecting lymphoid organs (5, 6). Although its mechanism is not clearly defined, lymphopenia appears as a cardinal finding at this stage.

Biomarkers of inflammatory response have been frequently evaluated during the follow-up of this inflammatory response and used as a measure for predicting mortality. Although there is a significant correlation between the percentage of neutrophils and neutrophil count, the neutrophil count percentage (NCP) is often used in analytical control of infections. In cases such as community-acquired pneumonia where lymphocytes´ response is observed in the foreground, some studies have shown that the percentage of lymphocytes is an important marker in predicting the mortality risk (7). In the presence of high levels of white blood cells, a low lymphocyte percentage has been found to be significantly correlated in terms of hospitalization and mortality. Therefore, lymphocyte percentage is associated with poor results (8, 9).

One of the poor prognostic markers in COVID-19 patients is the ferritin level. Ferritin H-chain inactivates the secretion of inflammatory cytokines by activating macrophages. It is the pathogenesis of hyperferritinemic syndrome that can be explained in COVID-19 infection (10). Wu et al. showed the relationship between

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high serum ferritin levels and development of acute respiratory distress syndrome (ARDS). In addition, there are some studies associated with mortality rates and ferritin levels (11, 12). As a result of this significant change in lymphocyte number and percentage, and ferritin level, the use of these values together in COVID-19 cases may present an opportunity to develop a different approach.

In emergency services where COVID-19 patients are primarily evaluated, it is important to identify the critical patients, especially at the first stage, and to implement appropriate and rapid diagnosis and treatment procedures for their survival. Additionally, it is important to use first-line examinations such as hemogram and biochemistry tests and to predict the critical patients at this stage in terms of providing effective treatment. The proportional interpretation of ferritin and lymphocyte percentage values, which are included in routine examinations, appear to be of prognostic value already at the initial evaluation stage and thus can be used as a simple parameter that can be effectively used as a reliable measure for identifying critical patients.

This study aims to evaluate the relationship between ferritin/lymphocyte percentage ratio (FLPR) calculated in patients with COVID-19 disease with the severity classification of the disease and to determine its prognostic significance in terms of mortality in the course of the disease.

Tab. 1. Demographic characteristics of patients.

		Frequency	%
Gender	Female	174	52.6
	Male	157	47.4
Comorbidities	Yes	176	53.2
	No	155	46.8
Severity	Critical	42	12.7
	Serious	49	14.8
	Moderate	131	39.6
	Mild	109	32.9
Thorax CT	Typical	111	33.5
	İntermediate	120	36.3
	Atypical	43	13
	Negative	57	17.2
Symptom	None	12	3.6
	Fever	35	10.6
	Diarrhea	41	12.4
	Cough	69	20.8
	Dyspnea	48	14.5
	Weakness-myalgia	41	12.4
	Fever, cough	50	15.1
	Fever + dyspnea	13	3.9
	Fever + cough + dyspnea	19	5.7
	Loss of consciousness	3	0.9
28-day mortality	Yes	41	12.4
	No	290	87.6
Total		331	100

CT – Computed tomography

Materials and methods

All patients over the age of 18 who were hospitalized for COVID-19 during April 2020, admitted to our emergency department and whose COVID-19 polymerase chain reaction (PCR) test results were positive were retrospectively evaluated.

In addition to the demographic findings such as age and gender, vital signs at the time of admission, oxygen or advanced airway support applications in the emergency room, laboratory tests results, CT findings, and 28-day living status were recorded using patient files stored in the hospital automation system. Patients' CT results were classified as being typical, intermediate, atypical or negative according to the Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings (13). The typical results were peripheral, bilateral ground glass opacities (GGO) with or without consolidation or visible intralobular lines, multifocal GGO of rounded morphology or visible intralobular

Tab. 2. Patients´ clinical and demographic characteristics as per severity classification.

			Severity				Total	
			Critical	Severe	Moderate	Mild		
Gender	Female	Count	18	14	77	65	174	X2 = 17.11, p<0.05
		Within gender	10.3 %	8.0 %	44.3 %	37.4 %	100.0 %	
	Male	Count	24	35	54	44	157	
		Within gender	15.3 %	22.3 %	34.4 %	28.0 %	100.0 %	
Comorbidities	Yes	Count	32	34	67	43	176	X2 = 22.57, p<0.001
		Within comorbidities	18.2 %	19.3 %	38.1 %	24.4 %	100.0 %	
	No	Count	10	15	64	66	155	
		Within comorbidities	6.5 %	9.7 %	41.3 %	42.6 %	100.0 %	
Thorax CT	Typical	Count	18	31	47	15	111	X2 = 116.73, p<0.001
		On thorax CT	16.2 %	27.9 %	42.3 %	13.5 %	100.0 %	
	Intermediate	Count	19	16	63	22	120	
		On thorax CT	15.8 %	13.3 %	52.5 %	18.3 %	100.0 %	
	Atypical	Count	4	1	12	26	43	
		On thorax CT	9.3 %	2.3 %	27.9 %	60.5 %	100.0 %	
	Negative	Count	1	1	9	46	57	
		On thorax CT	1.8 %	1.8 %	15.8 %	80.7 %	100.0 %	
Total		Count	42	49	131	109	331	
		On thorax CT	12.7 %	14.8 %	39.6 %	32.9 %	100.0 %	

CT – Computed tomography

lines, reverse halo sign or other findings of an organizing pneumonia.

Based on the initial assessment of vital signs and test results, and in line with the clinical severity classification of COVID-19, the patients were separated in groups, namely mild (presence of mild symptoms and radiological findings that were normal or not suggestive of pneumonia), moderate (respiratory complaints and fever, presence of pneumonia upon radiological examination), severe (dyspnea, respiratory rate 30/min, blood oxygen saturation ≤ 93 %, paO_2/FiO_2 < 300 and/or > 50 % of lung area of infiltrates within 24–48 hours) and critical (respiratory failure and need for mechanical ventilation, septic shock and/or multiple organ failure, and need for intensive care follow-up and treatment) (14).

FLPR was calculated by recording the lymphocyte percentage values and ferritin level obtained with hemogram taken in the emergency room at the time of first admission. The relationship between FLPR, severity of patients´ clinical status, and 28-day mortality was evaluated.

Tab. 3. Presence of comorbidities and 28-day mortality.

			28-day mortality		Chi-Square Analysis
			Yes	No	
Thorax CT	Typical	n	23	88	$X^2 = 13.685$, $p<0.05$
		%	56.10 %	30.30 %	
	İntermediate	n	13	107	
		%	31.70 %	36.90 %	
	Atypical	n	4	39	
		%	9.80 %	13.40 %	
	Negative	n	1	56	
		%	2.40 %	19.30 %	
Severity	Critical	n	30	12	$X^2 = 160.49$, $p = 0.000$
		%	73.20 %	4.10 %	
	Serious	n	7	42	
		%	17.10 %	14.50 %	
	Moderate	n	2	129	
		%	4.90 %	44.50 %	
	Mild	n	2	107	
		%	4.90 %	36.90 %	
Comorbidities	Yes	n	32	144	$X^2 = 11.631$, $p<0.05$
		%	78.00 %	49.70 %	
	No	n	9	146	
		%	22.00 %	50.30 %	
Total		n	41	290	
		%	100.00 %	100.00 %	

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Statistical analysis

The data of the study were analyzed using the SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) computer program. Descriptive statistics were expressed as mean ± standard deviation or median values and an inter quartile range (IQR) of 25–75 %, while categorical variables were expressed as numbers and percentage (%). Kolmogorov–Smirnov test was used for normality distribution of the data. While the significance of the difference between the groups in terms of continuous numerical variables in which parametric test statistics assumptions were provided was examined with Student's t test, the significance of the difference in terms of continuous numerical variables where parametric test statistics assumptions were not met was evaluated with the Mann-Whitney U and Kruskal-Wallis tests. Chi-square and Fisher's exact test were used to analyze whether there was a relationship between categorical variables. The variables that may be effective for mortality were evaluated using the "enter" method in logistic regression analysis. The ROC curve was drawn to investigate the diagnostic value of the ferritin/lymphocyte percentage ratio. $p < 0.05$ was considered statistically significant. Results were given at 95 % confidence interval.

Ethics statement

Ethical approval and the necessary permissions were obtained from the ethics committee of our hospital (2011-Kaek-25 2020/05-14), Ministry of Health, Directorate General of Health Services, and Directorate General of Public Health of Turkey. PCR test results of the patients were recorded and reported as part of the data of the Republic of Turkey, Ministry of Health, Public Health Management System, and Case Tracking Module.

Results

A total of 5,530 patient files were scanned retrospectively. While 732 patients were hospitalized for probable COVID-19, PCR test results of only 357 patients were found to be positive, out of whom 26 were excluded from the study due to various reasons. A total of 331 patients were included in the study.

The median age in the study population was 56 (IQR: 25th–75th percentiles 46–66) while the median age values in critical and mild severity groups were 72.5 (IQR: 25th–75th percentiles 64, 75–79, 25) and 52 ((IQR: 25th–75th percentiles 41–62), respectively. A proportion of 52.6 % of the patients (n = 174) were female; 53.2 % (n = 176) had comorbidities, namely hypertension (20.2 %, n = 67), diabetes mellitus (5.4 %, n = 18), chronic obstructive pulmonary disease (COPD) (2.1 %, n = 7) or multiple comorbidities (19 %, n = 66). While 12.7 % (n = 42) of the patients had a clinically serious manifestation, 33.5 % (n = 111) had a typical CT finding according to the classification of the Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. The most common symptom in the patients was cough (20.8 %, n = 69). The 28-day mortality was 12.4 % (n = 41) (Tab. 1).

Demographic characteristics and clinical findings as per severity of disease category are listed in Table 2.

The median fever level of the patients was 37.0 °C (Min: 35.0, Max: 39.0), median saturation level was 97 (Min: 60, Max: 99), median pulse rate per minute was 100 (Min: 56, Max: 148),

Tab. 4. Analysis of Variables with the Mann-Whitney U test.

	Mortality in 28 days	n	Median (IQR: 25th–75th percentiles)	p
Lymphocyte	Survival	290	25.70 (18.85–34.82)	<0.001
	Mortality	41	10.10 (6.65–16.40)	
	Total	331	24.60 (14.00–33.60)	
Ferritin	Survival	290	167.15 (68.72–308.37)	<0.001
	Mortality	41	794.00 (566.80–1264.00)	
	Total	331	188.00 (79.06–416.10)	
FLPR	Survival	290	6.55 (2.47–13.07	<0.001
	Mortality	41	83.15 (31.67–184.08)	
	Total	331	7.64 (2.71–22.33)	

FLPR – Ferritin/ lymphocyte percentage ratio

Tab. 5. Kruskal Wallis-H test for FLRP and disease severity.

	Severity	n	Median (IQR: 25th–75th percentiles)	p
FLPR	Critical	42	84.62 (39.76–148.60)	<0.05
	Serious	49	27.32 (14.18–59.03)	
	Moderate	131	6.24 (2.42–10.35)	
	Mild	109	3.11 (1.91–8.08)	
	Total	331	7.64 (2.71–22.33)	

FLPR – ferritin/lymphocyte percentage ratio

Tab. 6. Investigation of the usefulness of the FLPR in the prediction of mortality.

AUC (95 % CI)	p	Risk factor	Cut-off value	Sensitivity %	Specificity %
0.909 (0.857–0.961)	0	FLPR	9.8	97.6	65.2
			12.69	95.1	74.5
			15.59	90.2	78.3
			21.11	82.9	82.8

AUC – Area Under Curve, FLPR – ferritin/lymphocyte percentage ratio

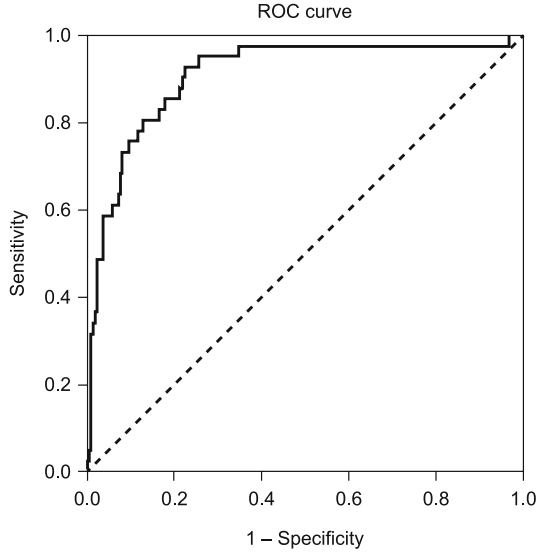

Fig. 1. ROC analysis for the ferritin/lymphocyte percentage ratio.

and median systolic blood pressure value was 110 mmHg (Min: 70, Max: 180).

The measured mean lymphocyte percentage of the patients was 24.86 ± 11.76, the mean ferritin level was 346.39 ± 443.88 ng/mL and the mean FLPR was 31.91 ± 85.10.

In the Chi-square test performed to analyze whether there was a relationship between CT findings and 28-day mortality, a statistically significant relationship was found ($p < 0.005$). Additionally, a statistically significant relationship was found between the severity of the clinical status and 28-day mortality in the Chi-square test performed to analyze whether there was a relationship between the severity of the clinical status of the patients and the 28-day mortality ($p = 0.000$). Furthermore, there was a statistically significant relationship between the presence of comorbidities and the 28-day mortality in the Chi-square test performed to analyze whether there was a relationship between the presence of comorbidities and the 28-day mortality ($p < 0.005$) (Tab. 3).

In the Kolmogorov-Smirnov test conducted to analyze the normality distribution it was observed that the data were not normally distributed. Therefore, Mann-Whitney U test was performed to investigate whether there was a difference between mean FLPR levels, ferritin levels and lymphocyte percentage alone and 28-day mortality. As a result of this test, it was seen that FLPR levels were significantly higher in those who died in 28 days ($p< 0, 01$). When evaluated alone, ferritin levels were high and lymphocyte percentages were low in the mortality group ($p < 0.001$) (Tab. 4).

In the Kruskal Wallis-H test performed to determine whether the mean FLPR levels of the patients differ significantly according to the severity classification variable, the difference between the severity groups and the mean FLPR was found to be statistically significant ($x2 = 148,284$; $SD = 3$; $p = 0.000$). It was observed that FLPR levels were high in groups with critical and serious clinical manifestations (Tab. 5).

In the logistic regression analysis performed to investigate whether the gender and comorbidities had an effect on 28-day mortality, it was seen that comorbidities were an independent risk factor.

The ROC curve presented in Figure 1 and the analyses presented in Table 6 were conducted to investigate the usefulness of FLPR in predicting mortality. In the ROC analysis for the FLPR level, the area under the curve (AUC) value was found to be 0.909 (95 % CI 0.857–0.961) (Fig. 1). When the cut-off value of FLPR was 9.80, the sensitivity was found to be 97.6 % and specificity was 65, 2 %. When the cut off value of FLPR was 21.11, the sensitivity was found to be 82.9 % and specificity was 82.8 % (Tab. 6).

Discussion

COVID-19 disease is a systemic infection commonly seen in males and individuals with comorbidities. Although its pathophysio-

logy has not been fully elucidated, it manifests with hematological findings and increased levels of proinflammatory cytokines associated with pulmonary infection and severe lung damage (3, 15, and 16). In our study, the presence of chronic disease was found to be an independent risk factor for 28-day mortality, which is consistent with the results found in literature.

The patients with critical/severe COVID-19 have a poor prognosis and high mortality rates. In studies, the rate of patients with critical/serious manifestation ranges between 18.9 % and 63.3 % (16–18). In our study, this rate was 27.5 %. The number of patients receiving intensive care and mechanical ventilation support is similar to that found in the literature.

In various studies, the mortality rate varies between 5 % and 7.2 % and this rate is correlated with age (19, 20). In our study, the patients were evaluated for 28-day mortality and the rate was found to be 12.4 %. According to the clinical classification, the mortality is relatively high in the critical and serious groups, and the coexistence of typical CT findings in these groups is remarkable.

COVID-19 is a systemic infection affecting the hematological system. Lymphopenia is used especially as a prognostic cardinal finding. In a study conducted by Guan et al. on 1,099 COVID-19 patients, the rate of lymphopenia was found to be 83.2 % and it increased to 96.1 %, especially in critically ill patients (21). In addition to the use of lymphopenia as a poor prognosis marker, there are also studies showing that low lymphocyte values are associated with the development of ARDS (12).

The neutrophil/lymphocyte ratio (NLR) and lymphocyte percentage were frequently evaluated after determining the prognostic significance of lymphopenia. As NLR increased, the percentage of lymphocytes was found to be significantly lower in COVID-19 patients as compared to healthy volunteers, and this decrease was more obvious in the severely and critically ill patients. (7, 22, 23). It is observed that the percentage of lymphocytes tends to decrease even if the lymphocyte count is within the normal range. The decrease in lymphocyte percentage is thought to be developing due to the destruction of erythrocytes infected with secondary hemophagocytic lymphohistiocytosis, and thus the ferritin level increases simultaneously after destruction (5, 18).

Lymphopenia and ferritin are used as separate prognostic markers, but the decrease in lymphocyte percentage and increase in ferritin level appear to be related to the mutual destruction of hematological cells caused by the SARS-COV2 virus. The complications that develop with the cytokine storm result in multiple organ failure and death (6). The FLPR may be the starting point of the aggressive immune response in the patient and may be prognostically significant.

The relationship of biochemical markers with the prognosis in COVID-19 was evaluated and the increase in serum ferritin level was associated with mortality and development of ARDS (12, 24). In the severely/critically ill patients, the mean ferritin level was 346.39 ± 443.88 ng/mL.

The combined use of hematological and biochemical parameters evaluated among poor prognostic markers may provide strong clues about the prognosis, as in the example of a decrease in the lymphocyte/c reactive protein ratio (22, 25). The FLPR evaluated for this purpose was found to be particularly high in the seriously and critically ill patient groups. The calculation of FLPR, especially as part of the first evaluation of patients in the emergency department, may be a guide in predicting the severity of the disease. Additionally, it can be used effectively when determining the need for clinical or intensive care hospitalization. Even if the clinical condition is good or stable, a high value of FLPR may give a clue about the prognosis of the disease and critically ill patients can be identified on time. When initiated early, the necessary treatment and interventions can be lifesaving.

Conclusion

In COVID-19 patients, it is important to use FLPR concurrently with patient clinical evaluations. When the cut-off value of FLPR is 9.80, sensitivity is 97.6 % and specificity is 65.2 %. When the cut-off value of FLPR is 21.11, sensitivity is 82.9 % and specificity is 82.8 %, which is effective in predicting mortality. Our study is the first study in the literature to use the FLPR. In this respect, it may contribute as an important mortality marker. We think that our study may form the basis for large-scale and comprehensive research.

Limitations

The most important limitation of our study is its retrospective character. Therefore, there was a loss during the collection of patient information and data.

The FLPR was calculated by recording the lymphocyte percentage values and ferritin level obtained with hemogram taken in the emergency room at the time of first admission. As we make the initial diagnosis and treatment in emergency department, we collect PCR tests and give first-line treatment, such that the admission day is the first day of diagnosis, but we do not categorize patients as to their symptomatic phase and day of symptoms.

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