ORIGINAL RESEARCH

Ferritin/lymphocyte percentage ratio to predict the severity and mortality of COVID-19

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Abstract

Objective

In this study, we aimed to investigate the relationship between ferritin/lymphocyte percentage ratio (FLPR) with clinical and radiological disease severity and mortality in COVID-19 patients.

Methods

This retrospective study was conducted with patients who had polymerase chain reaction positive results for COVID-19. We calculated FLPRs from laboratory tests taken during emergency clinic admission. The relationship between chest computed tomography (CT) scores, disease severity, and 30-day mortality with FLPR was evaluated.

Results

Our study included 309 patients. 30-day mortality occurred in 12.3% (n=38) of the patients. A statistically significant association was found between FLPR and clinical disease severity ($p < 0.001$). In the post hoc analysis, the difference was caused by the critical and severe groups and FLPR was significantly higher in these groups. A significant correlation was found between CT scores and FLPR ($r=0.496$, $p<0.001$). Logistic regression analysis revealed that hypertension, smoking, C-reactive protein (CRP), and FLPR levels were independent risk factors for mortality in COVID-19 patients. In the receiver operating characteristics curve analysis, determined the predictive value and the optimal cut-off value of FLPR. The areas under the curve of WBC, lymphocyte, neutrophil, ferritin, CRP, FLPR were found 0.707, 0.233, 0.735, 0.878, 0.831, 0.924 ($p<0.001$), respectively. This analysis showed that the FLPR can predict 30-day mortality better than the other biomarkers in the comparison. When the optimal cut-off value of FLPR is 42.4, the sensitivity is 84.2% and specificity is 86.7%.

Conclusion

FLPR can be used as an independent biomarker of disease severity and mortality in COVID-19

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Key words: COVID-19, ferritin/lymphocyte percentage ratio, inflammation, mortality, disease severity, predictive value

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory system disease caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS CoV-2). The disease was first seen in Wuhan, China, and has become a global health issue[1]. The clinical spectrum of COVID-19 covers a range from asymptomatic cases, mild and moderate respiratory infections, typically expressed similarly to the flu-like symptoms and severe cases leading to acute respiratory distress syndrome (ARDS) or multiple organ dysfunctions resulting in death[2-4]. According to the clinical data in the literature, the abnormal inflammatory response to viral infection is responsible for the multi-organ failure and mortality in most COVID-19 cases[5,6].

Biomarkers of the inflammatory response have been recurrently evaluated during the follow-up of the abnormal inflammatory response and used as a measure to predict mortality in COVID-19 cases. Studies have reported that leukopenia, lymphopenia, neutrophil/lymphocyte ratio (NLR), thrombocytopenia, and elevated levels of various other laboratory tests, including d-dimer, and C-reactive protein (CRP) have been associated with severity and mortality in COVID-19 cases[7-10]. Furthermore, higher levels of IL-2R, IL-6, IL-8, IL-10, TNF-α, ferritin, procalcitonin, and lactate dehydrogenase (LDH) were reported for critical patients compared to moderate-severe patients[11]. A high number of neutrophils are produced in COVID-19 because of the increased inflammatory response. As the cornerstone of immunity against viral infections, lymphocytes increase the release of CD8+ T-lymphocytes and decrease the release of CD4+ T-lymphocytes, resulting in lymphopenia[9]. The percentage of lymphocytes has been reported as a major indicator in predicting the risk of mortality in cases with a predominant lymphocyte response such as community-acquired pneumonia[12]. However, low lymphocyte counts have been reported in mild or overt inflammatory conditions such as liver fibrosis, cancer, diabetes, irritable bowel disease, thyroiditis, and other thyroid diseases[13-17]. In addition, researchers used various parameters such as neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratios as indicators of systemic inflammatory response[8,9,18-20]. Growing evidence indicates that such laboratory biomarker analysis, which can be easily obtained from routine tests, can be used in the diagnosis and prognosis

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of many systemic pathologies such as acute ischemic stroke, cerebral hemorrhage, major cardiac events, and cancers[21-24]. Higher values of these metrics were associated with more severe forms of the diseases with the worst prognosis[25].

Elevated ferritin level is reported in inflammatory diseases[26]. Although ferritin is considered as an indicator of total body iron stores, its prognostic value depends on acute and chronic inflammatory processes and is an acute phase reactant found in elevated levels of non-specifically in various disorders including chronic kidney disease, rheumatoid arthritis, autoimmune disorders, viral and bacterial infections[27]. The level of ferritin is prognostic predictor for COVID-19 patients[28]. Studies have shown that high serum ferritin levels are involved in the development of acute respiratory distress syndrome (ARDS) and mortality for COVID-19 patients[29,30].

The interpretation of the proportionality of ferritin and lymphocyte levels in the routine laboratory test in emergency departments where COVID-19 patients are primarily evaluated may have prognostic value at the initial evaluation stage. High ferritin/lymphocyte percentage (FLPR) may be a stronger predictor than using ferritin and lymphocyte separately in predicting increased mortality and disease severity in COVID-19. It is thought that FLPR can be used effectively as a simple parameter and a reliable measure for identifying critical cases. In-hospital mortality and misuse of limited medical resources can be effectively reduced through an early treatment plan relying on a quick, inexpensive, and repeatable test incorporated in routine examinations. This capability, especially at the initial stage of the disease, is crucial for the survival of critically ill patients, and for guiding preventive and therapeutic interventions. The aim of this article is to evaluate the relationship between ferritin/lymphocyte percentage ratio (FLPR) with clinical and radiological disease severity and 30-day mortality in COVID-19 patients. Our secondary aim is to investigate the efficacy of FLPR in predicting 30-day mortality by comparing it with other inflammatory biomarkers.

Methods

Study design and participants

Our study was conducted in the emergency clinic of Samsun Gazi State Hospital. It is a retrospective cohort study, which included patients diagnosed with COVID-19 in the emergency service isolation area from February 1st, 2021, to March 31st, 2021. Patients, who were 18 years and over, had a positive PCR, hospitalized, had complete hospital admission and follow-up data in the hospital database, and had available laboratory and imaging test results were included in the study. Patients with negative or suspected PCR test results, missing clinical data and follow-up information, and no available laboratory and imaging tests were excluded from the study. Patients' demographic data, vital signs, comorbid diseases, smoking, symptoms at admission, laboratory test results, chest computed tomography (CT) scans, hospitalization or ICU needs, and survival status (COVID-19-related 30-day mortality) were recorded and analyzed.

In all cases, a semi-quantitative CT severity scoring proposed by Pan et al. 31 was calculated per each of the 5 lobes considering the extent of anatomic involvement, as follows: 0, no involvement; 1, <5% involvement; 2, 5–25% involvement; 3, 26–50% involvement; 4, 51–75% involvement; and 5, >75% involvement. The resulting total CT score was the sum of each lobe score (0-25). CT severity scoring is not a standard protocol in the hospital the study took place. The CT scoring of the patients included in the study was performed by a radiologist working independently of the researchers.

Based on their vital signs and test results and according to the COVID-19 clinical severity classification, the patients were divided into multiple disease severity groups: mild (presence of mild symptoms and normal or non-pneumonia findings on radiological images), moderate (respiratory complaints, fever, and pneumonia in radiological images), severe (dyspnea, respiratory rate of ≥30 breaths/min, blood oxygen saturation of ≤93%, PaO2:FiO2 of less than 300 mmHg, and infiltrates in more than 50% of the lung area within 24-48 hours), and critical (respiratory failure and need for mechanical ventilation, the presence of septic shock and/or multiple organ failure, and need for intensive care)[32].

Data collection

Demographic, clinical, laboratory, and imaging data of the patients admitted to the isolation area were obtained from the electronic database of the hospital retrospectively. The complete blood count, electrolytes, glucose, urea, serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), D-dimer and ferritin levels were tested at the time of the patient's admission to the emergency clinic. Then, FLPR was calculated and the relationship of FLPR with the clinical and radiological disease severity and mortality was examined.

Data analysis

The statistical results are described by the statistical metrics such as mean and standard deviation and median (minimum-maximum) values for quantitative data. On the other hand, numerical values and percentages are used to represent the statistics for the categorical data. The compatibility of continuous data with a normal distribution was evaluated by Kolmogorov-Smirnov test. Mann–Whitney U, Kruskal–Wallis H, and Chi-square tests were used in the statistical analysis. Post-hoc analysis was conducted for the differences arising from Kruskal–Wallis H test. Bonferroni correction was made in the evaluation. Variables that may be effective for mortality were evaluated using the "enter" method in binary logistic regression analysis. The results of regression analysis were presented as odds ratio (OR) with 95% confidence interval (CI). The receiver operating characteristics (ROC) analysis was performed to investigate the diagnostic value of WBC, lymphocyte, neutrophil, ferritin, CRP, FLPR, and optimal cut-off values of FLPR to predict mortality. The correlation analysis was drawn between CT scores and FLPR. For statistical significance, p values in the confidence interval of 95% and below 0.05 were considered significant. The statistical analyses were carried out using SPSS 23.0 software.

Results

11.208 patients were admitted to the emergency department with suspected COVID-19. The data of 626 patients who were admitted to the hospital were scanned retrospectively. 309 patients with complete clinical data and a positive PCR were included in the study. Of the patients, 50.2% (n = 155) were men, the median age (interquartile range 25%-75%) was 62.0 (45-76).

Hypertension, diabetes mellitus, and cardiovascular disease was present in 33.7% (n=104), 22.0% (n=68), and 16.2%

Table 1. Demographic and clinical data of patients

Characteristics	All patients (n:309)	Non-survivor (n:38)	Survivor (n:271)	p*
Age, years (median IQR)	62.0 (45-76)	75.5 (66-83)	58.0 (44-73)	<0.001†
	n (%)	n (%)	n (%)	
Sex				
Male	155 (50.2)	17 (44.7)	138 (50.9)	0.475¶
Female	154 (49.8)	21 (55.3)	133 (49.1)	
Comorbidities				
Hypertension	104 (33.7)	26 (68.4)	78 (28.8)	<0.001¶
Diabetes mellitus	68 (22.0)	16 (42.1)	52 (19.2)	0.001¶
Cardiovascular disease	50 (16.2)	15 (39.5)	35 (12.9)	<0.001¶
Chronic obstructive lung disease	26 (8.4)	4 (10.5)	22 (8.1)	0.617¶
Cerebrovascular disease	26 (8.4)	9 (23.7)	17 (6.3)	<0.001¶
Other diseases	8 (2.6)	2 (5.3)	6 (2.2)	0.268¶
Smoking	43 (13.9)	12 (31.6)	31 (11.4)	0.001¶
Severity				
Mild	52 (16.8)	0 (0.0)	52 (19.2)	<0.001¶
Moderate	139 (45.0)	4 (10.5)	135 (49.8)	
Severe	76 (24.6)	4 (10.5)	72 (26.6)	
Critical	42 (13.6)	30 (78.9)	12 (4.4)	

† Mann Whitney U test, ¶ Chi-square test, *p <0.05 statistically significant
IQR, interquartile range.
Other diseases: Parkinson disease, malignancy, thyroid diseases, asthma, gout.

(n=50) of the patients, respectively. No comorbid diseases were present in 54% (n=167) of the patients. The most common symptoms were dyspnea (61.8%), myalgia fatigue, (47.2%), cough (38.2%), and fever (36.2%). 30-day mortality occurred in 12.3% (n=38) of the patients. In the non-survivor group, the frequencies of hypertension (p<0.001), cardiovascular disease (p<0.001), cerebrovascular disease (p<0.001), diabetes mellitus (p=0.001), and smoking (p=0.001) were significantly higher. An association was found between the clinically classified patient groups and mortality (p <0.001). Mortality was found to be higher with advanced disease severity (Table 1). WBC and neutrophil counts and the levels of creatinine, CRP, and ferritin were significantly higher (p<0.001) but lymphocyte counts (p<0.001) and hemoglobin levels (p=0.010) were lower in the non-survivors.

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Table 2. Laboratory parameters of patients

Variables	Non-survivor (n:38)		Survivor (n:271)		p*
	mean±sd	med(min-max)	mean±sd	med(min-max)	
WBC (x10^9/l, normal range 4.5-10.5)	13.62±6.32	12.75(3.3-31.1)	8.90±4.17	7.90(1.0-26.5)	<0.001
Neutrophil (x10^9/l, normal range 2–6.9)	10.19±5.66	9.23(2.0-29.2)	6.23±3.64	5.30(0.9-19.8)	<0.001
Lymphocyte (x10^9/l, normal range 0.6–3.4)	0.97±0.58	0.8(0.3-3.3)	1.65±1.00	1.5(0.1-9.9)	<0.001
Platelet (x10^9/l, normal range 142-424)	255.89±130.44	231.0(66.0-741.0)	252.99±90.72	245.0(65.0-618.0)	0.628
Hemoglobin (g/dl, normal range 12-17.4)	11.9±2.1	12.4(6.3-15.5)	13.0±2.0	12.9(5.9-17.8)	0.010
Serum creatinine (mg/dl; normal range 0.67-1.17)	1.37±0.95	1.0(0.4-4.4)	0.98±0.66	0.8(0.3-5.7)	0.002
K+ (mmol; 3.5-5.1)	4.23±0.78	4.2(2.5-6.2)	4.15±0.60	4.1(2.5-6.2)	0.434
CRP (mg/l; 0-5)	164.26±119.56	143.5(4.9-415)	42.06±51.35	19.9(0.5-301.9)	<0.001
Ferritin (ng/ml; 11-300)	1057.55±625.26	1 1 0 3 . 5 (1 0 9 . 0 - 2000.0)	271.35±300.82	156.0(11.0-2000.0)	<0.001
FLPR	175.65±205.19	130.4(13.0-1066.6)	24.21±52.59	7.7(0.3-505.6)	<0.001

† Mann Whitney U Test *p <0.05 statistically significant

WBC, White Blood Cells; K+, potassium; CRP, C-reactive protein; FLPR, Ferritin/lymphocyte percentage ratio.

Table 3. Logistic regression analysis of variables

Variables	OR	IC 95%	p
Hypertension	3.624	1.579-8.317	0.002
Diabetes mellitus	1.655	0.733-3.737	0.226
Cerebrovascular disease	2.205	0.814-5.972	0.120
Smoking	3.282	1.308-7.479	0.007
WBC	1.000	1.000-1.000	0.818
Hemoglobin	0.851	0.663-1.104	0.218
Serum creatinine	0.856	0.663-1.104	0.596
CRP	1.013	1.008-1.019	<0.001
FLPR	1.012	1.005-1.018	<0.001
OR, Odds Ratio; IC, Confidence interval; WBC, White Blood Cells; CRP, C-reactive protein; FLPR, Ferritin/ lymphocyte percentage ratio.			

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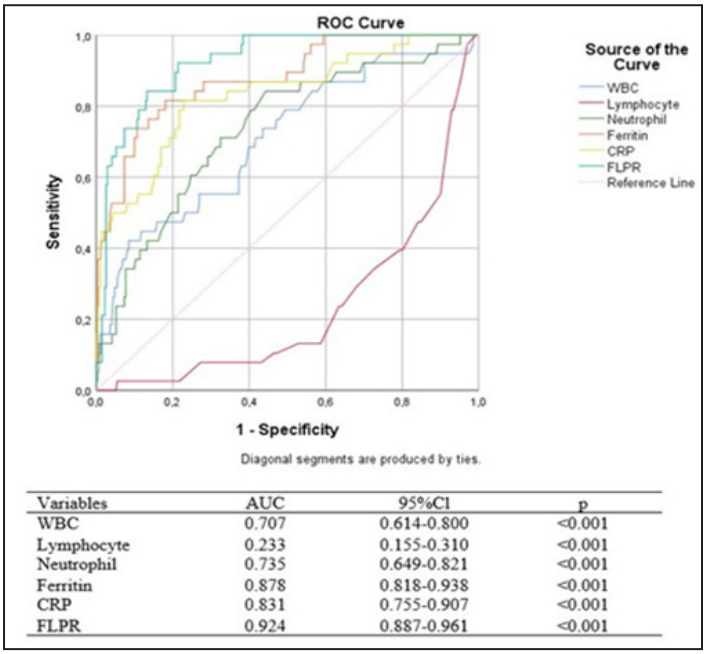
Table 4. Ferritin/lymphocyte percentage ratio to predict disease severity

Severity (n)	FLPR	p*
Mild (52)	5.10±5.24	<0.001
Moderate (139)	17.66±31.66	
Severe (76)	48.64±68.51	
Critical (42)	162.37±210.25	

FLPR, Ferritin/lymphocyte percentage ratio, mean±sd

¶ Kruskal-Wallis test, *p <0.008 statistically significant, Bonferroni correction.



Variables	AUC	95%CI	p
WBC	0.707	0.614-0.800	<0.001
Lymphocyte	0.233	0.155-0.310	<0.001
Neutrophil	0.735	0.649-0.821	<0.001
Ferritin	0.878	0.818-0.938	<0.001
CRP	0.831	0.755-0.907	<0.001
FLPR	0.924	0.887-0.961	<0.001

Fig 1. Receiver operating characteristics analysis of inflammatory parameters

The mean value of FLPR in the non-survivors was 175.65±205.19, which was significantly higher than survivors (Table 2).

Logistic regression analysis revealed that hypertension, smoking, CRP, and FLPR levels were independent risk factors for mortality in COVID-19 patients (Table 3).

We analyzed the optimal cut-off values calculated by ROC analysis, and the ROC curves are presented in Fig. 1. The areas under the curve (AUC) of WBC, lymphocyte, neutrophil, ferritin, CRP, FLPR were found 0.707, 0.233, 0.735, 0.878, 0.831, 0.924 (p<0.001), respectively. The ROC analysis indicates that the FLPR can predict 30-day mortality better than the other biomarkers in the comparison. When the optimal cut-off value of FLPR is 42.4, the sensitivity is 84.2% and specificity is 86.7%. When the cut-off value of FLPR is 35.7, the sensitivity is %84.2 and specificity is %84.1. When the cut-off value of FLPR is 13.4, the sensitivity is %97.4 and the specificity is %62.0. An association was found between FLPR and clinical severity grades (p <0.001) (Table 4). In the post hoc analysis, it was observed that the difference was caused by the critical and severe groups. The FLPR value was also significantly higher in these groups. A correlation was found between CT scores and FLPR

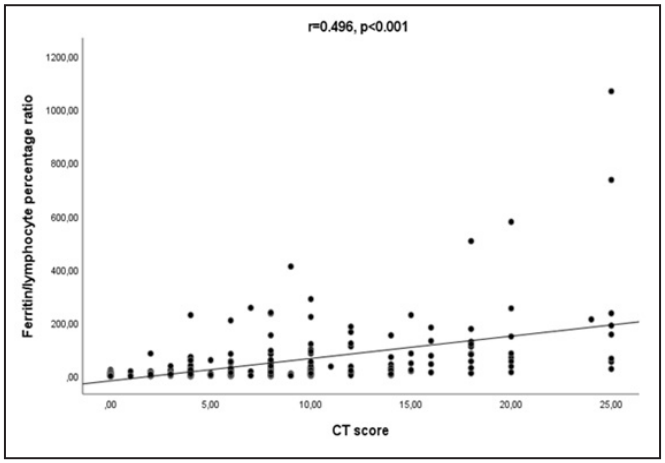


Fig 2. Correlation analysis between CT scores and Ferritin/ lymphocyte percentage ratio. CT, computed tomography

(r=0.496, p<0.001) (Fig. 2).

Discussion

COVID-19 infection has become an important problem affecting the whole world. The high mortality rates of the critically ill patients pose a major challenge for the global health system. In this study, the association of FLPR levels with early disease classification and prognosis was investigated. It has been found that FLPR is a predictor of clinical severity and mortality in COVID-19.

The mortality rate of COVID-19 was reported as 5% in previous studies[33]. It was found in a range of 10%-25% in hospitalized COVID-19 patients[34]. In our study, mortality due to COVID-19 occurred in 38 (12.3%) patients is like that found in the literature.

Although the pathophysiology of COVID-19 has not been fully elucidated, the disease is manifested by a circulating inflammatory cell response to pulmonary infection, severe lung injury, and increased levels of proinflammatory cytokines. WBC produces an immune response to viral or bacterial infections. After contacting with the virus, all respective cells become affected by secreting many cytokines, as previously demonstrated in SARS-CoV and MERS-CoV infections[35]. Based on our study results, high WBC count and lymphopenia are associated with mortality. Liu et al. reported that the novel coronavirus might be acting on lymphocytes, reducing the absolute number of lymphocytes. The result is the depletion of immune defense cells that can lead to progression to severe COVID-19[36]. Henry et

al. have suggested that lymphopenia in critically ill patients and patients with a high risk of mortality is the cause of the hindered immune response[35].

Ferritin is an intracellular iron storage protein and an essential part of innate immunity that activates macrophages. Ferritin levels are elevated in viral or bacterial infections 27. Studies in the literature have reported high ferritin levels in COVID-19 pneumonia[11,27,30]. Tang et al. reported that high ferritin levels were associated with mortality in COVID-19 patients[37]. In our study, the mean ferritin level of COVID-19 patients was 368.03±439.51 ng/ml, but the mean ferritin level in non-survivors was 1057.55±625.26 ng/ml and thus significantly higher.

In recent years, researchers have used a variety of parameters, including neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratios in the diagnosis and prognosis estimation of many inflammatory conditions[8,9,18-20]. Combined use of hematological and biochemical parameters as poor prognostic indicators, such as a decrease in the lymphocyte/CRP ratio, may provide powerful clues about prognosis[38]. Lymphopenia and ferritin are used separately as prognostic factors in COVID-19. The hematological effects, the decrease in the lymphocyte percentage as an indicator of inflammation of SARS-CoV-2 and the increase in ferritin level were related[7,18,19,28]. Considering all these findings, we think that FLPR can indicate the starting point of an aggressive immune response and can be used as a prognostic biomarker to predict disease severity and mortality. In our study, FLPR was found to be an independent risk factor for mortality. FLPR is a predictor of mortality with higher predictive power compared to WBC, neutrophil and lymphocyte counts, and ferritin and CRP levels in COVID-19. Our results have revealed that FLPR levels increase significantly as clinical disease severity advances and CT scores raise. FLPR was found to be high in severe and critical patients. It can be argued that FLPR is a biomarker related to disease severity and lung involvement. Calculation of FLPR, especially in the initial evaluation of patients in the emergency clinic, can be a guide in predicting 30-day mortality. FLPR can be effectively used as a simple parameter and a reliable measure in the determination of critical cases.

In-hospital mortality and misuse of limited medical resources can be effectively reduced with an early treatment plan using a rapid, inexpensive, and repeatable test that can be incorporated into routine examinations. Necessary treatment and interventions can be lifesaving when started early.

Conclusion

COVID-19 has become a global health problem. As COVID-19 pneumonia progresses rapidly in most cases, early diagnosis, clinical severity classification, and treatment are crucial. FLPR can be used as an independent biomarker of disease severity and mortality in COVID-19. FLPR has high predictive power in predicting 30-day mortality in COVID-19. An optimal FLPR cut-off value of 42.4 is associated with 84.2% sensitivity and 86.7% specificity.

Limitations

The limitations of the study are that it is a retrospective, single-center, 2-month design and covers the period before the omicron variant. Our study results should be supported through the conduct of large-scale, multi-center, and prospective studies.

Ethical approval

Ethical approval and the necessary permissions were obtained No. GOKA/2021/12/6 from the local ethics committee, Ministry of Health, Directorate General of Health Services, and Directorate General of Public Health of Turkey.

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