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Original Article

The use of the ferritin/procalcitonin ratio as a marker for the prognosis of disease severity in COVID-19 patients

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Abstract

Aim: COVID-19 infection caused by the SARS-CoV-2 virus emerged in Wuhan, China, in December 2019 and rapidly became a global pandemic. There is still a need for markers to predict disease severity and prognosis.
The aim of this retrospective study was to evaluate the relationship between the ferritin-procalcitonin ratio (FPR) and disease severity and prognosis in patients followed up with COVID-19 pneumonia.
Materials and methods: The study included patients with COVID-19 pneumonia confirmed by real-time polymerase chain reaction test positivity on nasal and pharyngeal smear samples.
Results: Evaluation was made of 2120 cases, comprising 1155 (54.5%) males and 965 (45.5%) females. FPR was determined to be statistically significantly lower in non-survivors, those admitted to the Intensive Care Unit, and those with diabetes, hypertension, chronic obstructive pulmonary disease, coronary artery disease, cancer, or chronic renal failure ($p<0.01$). It was found that FPR is significantly lower in critical cases compared to cases of moderate and severe disease. In this study, FPR was determined to be at a significantly lower level in cases with severe pneumonia than in cases with mild and moderate severity pneumonia.
Conclusions: FPR, which is a simple analysis, can be of use to clinicians in predicting disease severity, the course, and prognosis of COVID-19 and can be easily used in clinical practice. With this ratio's guidance, patients with a severe disease course and poor prognosis can be identified earlier. Thus healthcare resources can be assigned appropriately to suitable patients.

Keywords: COVID-19, disease severity, ferritin/procalcitonin ratio

INTRODUCTION

In December 2019, the first case of unknown viral pneumonia was reported in Wuhan, China, and in January 2020 was explained as a new coronavirus (SARS-CoV-2). This virus spread rapidly across the world, and the infection caused by this virus was named COVID-19 by the World Health Organization (WHO) (1-3).

As the infection became a pandemic affecting the whole world, there arose a need for markers to predict the severity of the disease and prognosis. In this way, taking the right approach to the right patients and using the available facilities correctly is also a determinant of health policies. Previous studies have

focussed on activation of the inflammatory cascade in severe patients and organ damage induced by complement activation and pro-inflammatory cytokines, such as interleukin-6 (IL-6) (4,5).

Despite this information and experience, the analysis of these cytokines cannot be performed routinely in most laboratories because of cost and technical facilities. Instead, infection markers correlated with IL-6 are used as they are inexpensive, easily obtained, and often in routine use. The most frequently used of these markers are ferritin and C-reactive protein (CRP) (6). In addition, some hematological parameters such as white blood cells (WBC) and lymphopenia, and some biochemical parameters such as lactate dehydrogenase, creatine kinase (CK), and troponin, have been reported to be associated with COVID-19 severity (7,8).

Procalcitonin (PCT), which is a glycoprotein, is a pro-peptide of calcitonin and has no hormonal activity. Under normal conditions, it is produced by C cells of the thyroid gland, and in healthy individuals, the level in the blood is so low as not to be determined (<0.1 ng/mL). In conditions of severe infection (bacterial, parasitic, fungal), PCT is produced by mostly non-thyroid tissues, and levels can rise to >100ng/mL (9). Although the biological effect is not fully known, PCT is thought to be an inflammation mediator (10).

The aim of this retrospective study was to evaluate the relationship between the procalcitonin-ferritin ratio and disease severity and prognosis in patients with COVID-19 pneumonia and to investigate the relationship between this ratio and comorbid diseases in the patients.

MATERIAL AND METHODS

Approval for this retrospective study was granted by the hospital Ethics Committee (approval number: 2021/34), and all procedures complied with the principles of the Helsinki Declaration. Our hospital is one of the largest COVID-19 centers in Turkey and is a reference center for most COVID-19 patients in Istanbul. The study included patients aged >18 years diagnosed with COVID-19 pneumonia and treated as in-patients between 01.05.2020 and 01.02.2021. All patients in the study provided informed consent to participate in the study.

Patients were excluded from the study if a negative result for COVID-19 was obtained in the real-time polymerase chain reaction (RT-PCR) analysis of nasal and pharyngeal smear samples, if they were aged <18 years, or were pregnant.

Information was obtained from the hospital database of the comorbid diseases of the patients, the ferritin and PCT values on admission, and the radiological images. Internal and external quality control procedures were applied to confirm the accuracy of the tests performed in the hospital's central laboratory. All the venous blood samples were collected by venipuncture, and all the blood tests were performed within 2 hours of taking the blood samples. Ferritin and PCT levels were determined using a Beckman Coulter AU5800 clinical chemistry analyzer (Beckman Coulter, Brea, CA, USA).

Thorax computed tomography (CT) images were used for the classification of pulmonary involvement of the patients. Involvement of the lungs of <25% were classified as mild, 26%-74% as moderate, and >75% as severe. Patients were also classified into four groups according to the clinical condition "mild" with mild symptoms and oxygen saturation in room air within normal limits (>98%), "moderate" with clinical signs of pneumonia (fever, cough, dyspnea, rapid breathing) but no signs of severe pneumonia including SpO2 ≥90% in room air, "severe" with additional evident tachypnea (respiratory rate >30 breaths per min) and severe respiratory difficulty or SpO2 <90% in room air, and "critical" with pulmonary leakage (>50% lung involvement), acute respiratory distress syndrome (ARDS) or a sepsis table (11).

Statistical Analysis

Data obtained in the study were analyzed statistically using NCSS software (Number Cruncher Statistical System). Descriptive statistical methods were used when evaluating the data, and results were stated as mean ± standard deviation, median, minimum, maximum values, or number (n) and percentage (%). Conformity of the data to normal distribution was assessed with the Shapiro Wilk test and graphic examinations. In the comparisons of two groups of quantitative data not showing normal distribution, the Mann-Whitney U-test was applied, and in the comparisons of more than two groups, the Kruskal-Wallis test, and the Dunn-Bonferroni test. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The evaluation was made of 2120 cases, comprising 1155 (54.5%) males and 965 (45.5%) females, with a mean age of 57 years (range, 18-102 years). Of the total patients, 1394 (65.8%) were aged <65 years, and 726 (34.2%) were aged ≥ 65 years.

The most common comorbid diseases were observed to be hypertension (HT) (23.4%) and diabetes (21.7%). COVID-19-related death was recorded in 227 (10.7%) cases (Table 1).

In the whole study population, FPR was determined to be statistically significantly lower in non-survivors, those admitted to the Intensive Care Unit (ICU), and those with diabetes mellitus (DM), hypertension (HT), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), cancer, or chronic renal failure (CRF; glomerular filtration rate <60 ml/min) ($p<0.01$).

When evaluated according to disease severity, the WHO has determined that FPR is significantly lower in critical cases compared to cases of moderate and severe disease, in this study of evaluation according to pneumonia severity, FPR was determined to be at a significantly lower level in cases with

severe pneumonia compared to cases with pneumonia of mild and moderate severity (Table 2).

When male and female patients were analyzed separately, there was determined to be no significant difference in FPR in the presence of DM and cancer in female patients, unlike in male patients. The other findings were similar to those of the general population (Table 3).

Table 1. Descriptive Characteristics of Patients

Age (years)	Min-Max (Median)	16-102 (57)
	Mean±SD	57.09±16.67
Number of patients	<65 age (%)	1394 (65.8)
	≥65 age (%)	726 (34.2)
Gender	Woman (%)	965 (45.5)
	Man (%)	1155 (54.5)
Comorbid diseases	Diabetes Mellitus (%)	461 (21.7)
	Hypertension (%)	497 (23.4)
	COPD (%)	109 (5.1)
	CAD (%)	250 (11.8)
	Cancer (%)	110 (5.2)
	CRF (%)	105 (5)
Length of stay hospital	Min-Max (Median)	1-90 (8)
	Mean±SD	10.68±8.25
Stay in ICU	Non	1856 (87.5)
	Yes	264 (12.5)
Disease severity	Mild	30 (1.4)
	Moderate	1452 (68.5)
	Severe	435 (20.5)
	Critical	203 (9.6)
Pneumonia severity	Mild	806 (38)
	Moderate	837 (39.5)
	Severe	477 (22.5)
Procalcitonin µg/L	Min-Max (Median)	0,01-100 (0.07)
	Mean±SD	1.07±6.18
Ferritin µg/L	Min-Max (Median)	2-15000 (162.3)
	Mean±SD	365.4±780.64
FPR	Min-Max (Median)	0.09-13945 (210.9)
	Mean±SD	346.49±210.9
Survival	Survivor	1893 (89.3)
	Non-survivor	227 (10.7)

Table 2. Comparisons for Ferritin to Procalcitonin Ratio (FPR) Measurement

		FPR		
		n	Median (Q1-Q3)	p
Survival	**Survivor**	1893	221.29 (95.13-442.67)	[a]**0.001****
	Non-Survivor	227	71.52 (19.33-277.37)	
Stay in ICU	**Non**	1856	220.33 (92.38-437.44)	[a]**0.001****
	Yes	264	99.3 (23.58-294.87)	
Disease severity	**Mild**	30	157.17 (56.5-346)	[b]**0.001****
	Moderate	1452	220.71 (91.51-447.58)	
	Severe	435	211.14 (72.12-377)	
	Critical	203	117.72 (25.77-346.91)	
Diabetes Mellitus	**Non**	1659	218.33 (85-428.5)	[a]**0.009****
	Yes	461	168.89 (66.67-377.64)	
Hypertension	**Non**	1623	220.75 (87.17-448.57)	[a]**0.001****
	Yes	497	168.41 (60.9-335.8)	
COPD	**Non**	2011	215 (82.48-428.5)	[a]**0.001****
	Yes	109	124.6 (40.33-276.4)	
CAD	**Non**	1867	218.33 (86.5-443.64)	[a]**0.001****
	Yes	250	133.97 (49.81-303,4)	
Cancer	**Non**	2010	213.01 (81-422.6)	[a]**0.009****
	Yes	110	133.25 (50-335)	
CRF	**Non**	2015	216.88 (86.67-432)	[a]**0.001****
	Yes	105	70.76 (38.06-211.29)	
Pneumonia severity	**Mild**	806	185 (75.41-356.6)	[b]**0.001****
	Moderate	837	262.5 (110.25-498.88)	
	Severe	477	163.34 (54.99-359.5)	

aMann-Whitney U Test [b]Kruskal-Wallis Test **p<0.01 FPR: ferritin to procalcitonin ratio, ICU: Intensive care unit, Q1-Q3: inter-quartile range, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, CRF: Chronic renal failure

Table 3. Comparisons for Measurement of Ferritin to procalcitonin Ratio in Men and Women

		FPR Woman			FPR Man		
		n	Median (Q1-Q3)	p	n	Median (Q1-Q3)	p
Survival	**Survivor**	877	182.8 (76-345)	[a]**0.001****	1016	272.7 (121.3-554.8)	[a]**0.001****
	Non-Survivor	88	60.2 (18.2-286.6)		139	75.4 (19.3-266.1)	
Stay in ICU	**Non**	858	183.3 (76-346.2)	[a]**0.001****	998	268 (118.3-553)	[a]**0.001****
	Yes	107	75.4 (16.4-265.4)		157	120.9 (26.3-319.4)	
Disease severity	**Mild**	18	93.2 (29.5-193)	[b]**0.001****	12	361.4 (129.5-562.4)	[b]**0.001****
	Moderate	699	183 (76.7-348)		753	278 (120-573.2)	
	Severe	166	156.3 (61.9-317)		269	217.8 (82.5-427.2)	
	Critical	82	88.3 (21.9-307.9)		121	143.1 (40.3-357.1)	
Diabetes Mellitus	**Non**	736	166.3 (70.1-344.5)	[a]**0.567**	923	265.7 (109.2-524.5)	[a]**0.011***
	Yes	229	169 (60.8-315.8)		232	168.5 (77,2-506,3)	
Hypertension	**Non**	685	179.2 (72.3-352.3)	[a]**0.031***	938	265.9 (109.6-548.7)	[a]**0.002****
	Yes	280	142.4 (59.2-291.3)		217	191.6 (71.4-401.3)	
COPD	**Non**	912	172 (70-346.5)	[a]**0.013***	1099	249.3 (105.7-534.8)	[a]**0.001****
	Yes	53	103.8 (42-217.3)		56	159.4 (33.9-326.9)	
CAD	**Non**	865	181.5 (72.1-347.5)	[a]**0.001****	1002	262.3 (109.6-559)	[a]**0.001****
	Yes	99	96.3 (40.2-266.3)		151	168.4 (61.8-328.4)	
Cancer	**Non**	924	166.8 (68.9-337)	[a]**0.970**	1086		[a]**0.001****
	Yes	41	172.8 (60.5-359.5)		69	123.8 (49.3-311.4)	
CRF	**Non**	914	179.8 (72.3-346.2)	[a]**0.001****	1101		[a]**0.001****
	Yes	51	63.8 (41-150.3)		54	82.7 (25.3-242)	
Pneumonia severity	**Mild**	410	142.5 (68.7-266)	[b]**0.001****	396		[b]**0.001****
	Moderate	362	230.9 (86.5-437.3)		475	298 (127.9-582)	
	Severe	193	141 (55-339.5)		284	185 (53.4-419.8)	

[a]Mann-Whitney U Test [b]Kruskal-Wallis Test **p<0.01 FPR: ferritin to procalcitonin ratio, ICU: Intensive care unit, Q1-Q3: inter-quartile range, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, CRF: Chronic renal failure

DISCUSSION

In this retrospective study with a large patient population, the FPR was evaluated as a predictor of disease severity and prognosis in COVID-19 patients, and the results showed a relationship with disease severity, mortality, and comorbidities. The global experience of COVID-19 has shown that while 80% of COVID-19 patients have a mild or moderate disease course, a severe disease requiring oxygen support develops in 15%, and 5% have a critical disease with complications such as respiratory failure, ARDS, sepsis and septic shock, and multiple organ failure (12). In such cases, it becomes more important to identify patients with a poor and severe disease course and to direct resources to the right patients. The relationship between hematological parameters and disease severity was the first to be determined as these are parameters that are readily available and often evaluated, and a relationship was found between lymphocyte count, lymphocyte- neutrophil ratio, and disease severity (13,14). In several studies, there has been shown to be a relationship between ferritin level and other inflammatory cytokine and pro-inflammatory parameters and disease severity, prognosis, and mortality.

Retrospective analyses have demonstrated that ferritin and other inflammatory markers are higher in non-survivors (15-18).

PCT synthesis can be increased through endotoxins and/or pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1b). Increasing PCT synthesis correlated with bacterial infection is suppressed in the absence of bacterial infection. An interesting aspect of this is that cytokines such as interferon-gamma (INF-γ) which are found in the environment of viral infection, lead to down-regulation of PCT (19). As a result of this characteristic, PCT is more differentiating than CRP and WBC count if there are non-bacterial inflammatory processes (20).

In the analyses of COVID-19 patients, a more significant increase in PCT has been shown in more severe patients compared to non-severe cases (21-23). In uncomplicated COVID-19 patients of mild severity, the PCT value has been observed to remain within the reference range. In contrast, a significant increase in the PCT value reflects the development of bacterial co-infection and a more severe form of the disease

with a more severe clinical table (24). Consistent with these data, with the effect of increasing PCT, the FPR in the current study was found to be low when the severity of the disease and the severity of pneumonia increased.

While ferritin and PCT values have been used separately as predictors of disease severity and prognosis in COVID-19, studies have also been conducted for FPR. In a study by Lippi et al. (24), it was determined that FPR ≥877 increased the likelihood of COVID-19 pneumonia compared to bacterial pneumonia. In the current study of more than 200 patients and real-life data, FPR was investigated as a predictor of prognosis and disease severity. As expected, FPR was found to be lower in non-survivors, those with severe disease, and those admitted to the ICU. In addition, FPR was determined to be lower in the presence of comorbidities such as DM, HT, COPD, CAD, cancer, and CRF.

Meta-analyses have shown the male gender to be one of the risk factors for COVID-19 and higher mortality in male patients (25). In the current study, the mortality of female patients treated in the hospital was found to be 9.11% (88/965), which was lower than that of male patients at 12.03% (139/1155). It was also noticeable that the presence of DM and cancer in female patients did not affect FPR.

CONCLUSION

In conclusion, FPR is a simple analysis that can be of use to clinicians in predicting disease severity, the course, and prognosis of COVID-19 and can be easily used in clinical practice. With the guidance of this ratio, patients who will have a severe disease course and poor prognosis can be identified earlier, and thus healthcare resources can be assigned appropriately to suitable patients.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Ethics committee approval was obtained from xxxx Training and Research Hospital, Education, Planning and Coordination Ethical Board (2021/34).

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