Research Article

Said Incir*, Zeynep Komesli, Arzu Baygul, Zeynep Atam Tasdemir, Kerim Erhan Palaoglu, Hatice Kant, Mahir Kapmaz, Suda Tekin, Alparslan Kilic, Tuncay Dagel, Ayse Okan, Kayra Somay and Timur Selcuk Akpinar

Immature platelet fraction: is a novel early predictive marker for disease severity in patients with Covid-19 pneumonia?

[İmmatür Platelet Fraksiyonu: Covid-19 Pnömonisi Olan Hastalarda Hastalık Şiddeti İçin Yeni Bir Erken Prediktif Belirteç olabilir mi?]

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Abstract

Objectives: In many diseases, immature platelet fraction (IPF%) is related to coagulopathy and poor outcome. This study aimed to investigate the predictive value of IPF% for

the severity of pneumonia in patients with Coronavirus Disease 2019 (COVID-19).

Methods: A total of 154 patients with COVID-19 infections were included. The patients were divided into two groups according to the severity of pneumonia (severe and non-severe) regarding their oxygen demand.

Results: Given laboratory parameters, the median IPF% was significantly higher in the severe group (11.9 vs. 3.9%, $p<0.001$). Mean platelet volume ($p<0.001$), platelet-large cell ratio ($p=0.001$), platelet distribution width ($p=0.001$), D-Dimer ($p<0.001$), INR ($p=0.003$), and aPTT ($p=0.007$) were also found to be significantly higher in the severe group. Moreover, IPF ($p=0.014$, Odds ratio = 2.000, 95%CI: 1.149-3.482) was an independent predictor for the severity. The curve value from receiver operating characteristics was 0.879 ($p<0.001$, 95%CI: 0.784-0.943) for determining the severity of pneumonia. IPF% had a sensitivity and specificity value of 69.5 and 92.4% to detect the disease's severity.

Conclusions: IPF% is an independent predictor for the severity of COVID-19 pneumonia. Assessment of IPF% may both help to early determine high-risk patients with COVID-19 and to alert the physicians.

Keywords: biomarker; blood cell count; COVID-19; immature platelet fraction; SARS-CoV-2.

Öz

Amaç: Pek çok hastalıkta, immatür platelet fraksiyonu (%İPF), koagülopati ve kötü sonuçla ilişkilidir. Bu çalışma, Coronavirus Hastalığı 2019 (COVID-19) olan hastalarda

***Corresponding author: Said Incir**, MD, Clinical Biochemistry Laboratory, Koc University Hospital, Davutpasa st. No: 4 Topkapı, Istanbul 34010, Turkey, Phone: +90 850 250 8250, Fax: +90 212 311 3410, GSM: +905322183766, E-mail: sincir@kuh.ku.edu.tr. LinkedIn: <https://www.linkedin.com/in/said-incir-43084a95/> <https://orcid.org/0000-0002-7700-7388>
Zeynep Komesli and Kayra Somay, Department of Internal Medicine, Koc University Hospital, Istanbul, Turkey
Arzu Baygul, Koc University School of Medicine, Istanbul, Turkey
Zeynep Atam Tasdemir, Department of Pulmonology, Bagcilar Training and Research Hospital, Istanbul, Turkey
Kerim Erhan Palaoglu, Department of Clinical Laboratory, American Hospital, Istanbul, Turkey
Hatice Kant and Ayse Okan, Department of Clinical Laboratory, Koc University Hospital, Istanbul, Turkey
Mahir Kapmaz and Suda Tekin, Infectious Diseases and Clinical Microbiology, Koc University Hospital, Istanbul, Turkey
Alparslan Kilic, Department of Cardiology, Koc University Hospital, Istanbul, Turkey
Tuncay Dagel, Division of Nephrology, Department of Internal Medicine, Koc University Hospital, Istanbul, Turkey
Timur Selcuk Akpinar, Department of Internal Medicine, Koc University School of Medicine, Istanbul, Turkey

pnömoni şiddeti için %İPF'nin prediktif değerini araştırmayı amaçladı.

Yöntem: COVID-19 enfeksiyonu olan toplam 154 hasta dahil edildi. Hastalar, oksijen ihtiyaçları göz önüne alınarak pnömoni şiddetine göre (ağır ve ağır olmayan) iki gruba ayrıldı.

Bulgular: Laboratuvar parametrelerine bakıldığında, medyan İPF yüzdesi ağır grupta anlamlı olarak daha yüksekti (% 11.9'a karşı %3.9, $p<0.001$). Ortalama trombosit hacmi ($p<0.001$), trombosit-büyük hücre oranı ($p=0.001$), trombosit dağılım genişliği ($p=0.001$), D-Dimer ($p<0.001$), İNR ($p=0.003$) ve aPTT ($p=0.007$) ağır grupta anlamlı olarak daha yüksek bulundu. Ayrıca, İPF ($p=0.014$, Odds oranı = 2.000, %95 CI: 1.149-3.482) hastalık şiddeti için bağımsız bir öngördürücü olarak bulundu. Algılayıcı işletim eğrisinden gelen eğri değeri, pnömoni şiddetini belirlemek için 0.879 ($p<0.001$, % 95 CI: 0.784-0.943) idi. İPF, hastalığın şiddetini saptamak için %69.5'lik duyarlılık ve %92.4'lük özgüllük değerine sahipti.

Sonuç: İPF, COVID-19 pnömonisinin şiddeti için bağımsız bir öngörüdür. %İPF'nin değerlendirilmesi, hem COVID-19'lu yüksek riskli hastaları erken belirlemeye hem de hekimleri uyarmaya yardımcı olabilir.

Anahtar Kelimeler: Biyobelirteç; Tam kan sayımı; COVID-19; İmmatür platelet fraksiyonu; SARS-CoV-2.

Introduction

The novel coronavirus disease 2019 (COVID-19) is a systemic disease involving the respiratory tract that causes severe pneumonia in 10–15% of patients [1]. According to the World Health Organization, as of March 11, 2021, 117,573,007 COVID-19 cases involving 2,610,925 deaths have been confirmed [2].

Thromboembolic events incidence, such as deep-vein thrombosis, acute pulmonary embolism, myocardial infarction, ischemic stroke, is increased in patients with severe COVID-19 infection [3]. Researchers have reported an almost 30% thrombosis rate and hematologic abnormalities, including prolonged PT, thrombocytopenia, elevated D-dimer, and fibrinogen degradation products in severe COVID-19 patients admitted to the intensive care unit (ICU) [4, 5]. Recent studies have shown that thrombocytopenia is independently related to poor outcomes in cases hospitalized for COVID-19, and a decrease in platelet count during ICU stay is an indicator of increased mortality [6, 7]. Therefore, the use of biomarkers that can detect an initial decrease in platelet count may determine severe COVID-19 patients with a high risk of coagulopathy and increase the benefit of therapies.

Immature platelets, known as reticulated platelets, are released from the bone marrow into the bloodstream by megakaryocytes. Their differences from mature platelets are contained high-density granule and residual mRNA. Thus, they may be more hyper-reactive and more thrombotic than mature platelets [8]. Since IPF% reflects thrombopoietic activity in bone marrow, patients with thrombocytopenia caused by peripheral damage (e.g., coagulation disorders, infections) are expected to have increased IPF% patients with thrombocytopenia due to bone marrow deficiency have decreased IPF% [9]. The main advantage of IPF measurement, which has been recently established as a novel indicator for infection and sepsis, is that it can be analyzed with hematology analyzers and reported as a parameter of complete blood count (CBC) [10, 11].

As far as we know, no studies have determined the predictive value of IPF% to detect the severity of the disease in patients with COVID-19 pneumonia in the literature. This study aimed to determine the predictive value of IPF and its association with poor outcomes in patients with severe COVID-19 pneumonia.

Materials and methods

Study design and patient selection

We conducted this preliminary prospective cohort study at the Koc University Hospital from May to December 2020 and included 154 patients with no sepsis consecutively admitted to the COVID-19 Clinics.

The laboratory data were obtained on the first sampling after admission and before medication. Patients with a platelet count below $150 \times 10^9/L$ were not included in the study to ignore the effect of bone marrow-related infections on platelet production and the error due to physiological platelet increase after the initial decrease.

The exclusion criteria were younger than 18, lacking laboratory data, previously known hematologic and oncologic disorders, patients with chronic liver disease or rapidly deteriorating liver function (as thrombopoietin is synthesized primarily by the liver), medications that affect platelet function or number (e.g., clopidogrel, aspirin, corticosteroid) or coagulation (e.g., warfarin), a history of the other bleeding disorder (e.g., hemophilia), chemotherapy or blood transfusion and pregnancy. The study design is explained in detail in Figure 1.

All descriptive data, including demographics, diagnosis, clinical and laboratory data, and COVID-19 severity scores, were recorded from the hospital information system. The study was approved by the Institutional Review Board of Koc University (approval number: 2020.170.IRB1.038) and was conducted following Helsinki's Protocol. All patients provided written informed consent before recruitment.

COVID-19 diagnosis and severity scores

The diagnosis of COVID-19 was made according to the SARS-CoV-2 Polymerase chain reaction (PCR, RealStar®, Altona Diagnostics,

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Figure 1: Flow diagram of patient entry into the study.

Germany) test from an initial nasopharyngeal sample or significant findings on computerized thorax tomography (CT) with relevant clinical symptoms.

We categorized patients as severe and non-severe based on their clinical outcomes. Severe clinical outcomes were defined as the mechanical ventilation requirement, admission to the intensive care unit (ICU), and death. Mechanical ventilation support included both non-invasive and invasive mechanical ventilation [12].

Measurement of laboratory parameters

Blood samples were collected on EDTA (ethylenediaminetetraacetic acid) containing tubes on the first day of admission and analyzed within 4 h. CBC analysis was performed via Sysmex XN-3100 (Sysmex, Kobe, Japan) to evaluate IPF% and other platelet indices: mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR).

IPF% was determined in a separated channel via flow cytometry, utilizing a fluorescent dye. Platelets found with higher RNA content, as a result of the evaluation of cell volume and fluorescence density, are called immature platelets.

Coagulation parameters involving activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR), D-Dimer, and fibrinogen were analyzed by Sysmex-Cs

2000i (Sysmex, Kobe, Japan), CRP, ferritin, lactate dehydrogenase (LDH), lactate, interleukin-6 (IL-6) were measured by Roche Cobas 6000 (Roche, Mannheim, Germany).

Statistical analysis methods

As descriptive statistics, mean and standard deviation were used to show normally distributed continuous variables, median, minimum, maximum values were used to display non-normally distributed continuous variables.

The normality of parameters was calculated by using the Shapiro Wilks test. To compare the difference between normally and non-normally distributed groups, the Student t and Mann-Whitney U tests were used, respectively.

The χ^2 test, Fisher Exact test, or Yates Continuity Correction were used for categorical variables and expressed as observation counts (percentages). Statistical significance was accepted when a two-sided p-value was lower than 0.05.

The multivariate binary logistic regression was applied to detect the independent variables for the severity. ROC analysis was used to evaluate the diagnostic performance of IPF%.

Statistical analysis was performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2013).

Results

The demographic, clinical, and laboratory features of the total, severe, and non-severe COVID-19 patients are presented in Table 1.

Of 154 COVID-19 patients, 45 had hypertension (29%), 35 had diabetes (23%), 21 had cardiovascular disease (14%), six had chronic obstructive pulmonary

disease (4%), two had chronic kidney disease (1%), and 37 (24%) patients suffering from various chronic illnesses. The number of patients with hypertension was significantly higher in the severe group ($p=0.043$) (Table 1).

As presented in Table 1, the most frequent presenting symptoms of the COVID-19 patients were fever (93%), cough (71%), and dyspnea (51%).

Table 1: Baseline hospital admission demographic, clinical and laboratory features of all, severe and non-severe Covid-19 patients.

	All patients (n=154)	Severe (n=44)	Non-severe (n=110)	p* value
Male/Female, n	87/67	27/17	60/50	0.607 ³
Age, years	55 (18–91)	63 (20–91)	45 (18–89)	0.003 ¹
BMI	26 (19–31)	29 (20–31)	25 (19–31)	0.628 ¹
Current smoker	6 (4%)	1 (2%)	5 (5%)	0.466 ⁴
Comorbid conditions				
Hypertension (n,%)	45 (29%)	21 (48%)	24 (22%)	0.043 ³
Diabetes (n,%)	35 (23%)	8 (19%)	27 (25%)	0.781 ⁴
Cardiovascular disease (n,%)	21 (14%)	8 (19%)	13 (12%)	0.650 ⁴
Chronic obstructive pulmonary disease (n,%)	6 (4%)	4 (9%)	2 (2%)	0.424 ⁴
Chronic kidney disease (n,%)	2 (1%)	2 (5%)	0	0.522 ⁴
Other (n,%)	37 (24%)	19 (43%)	18 (16%)	0.024 ⁴
Symptoms				
Fever (n,%)	144 (93%)	42 (95%)	102 (93%)	0.859 ³
Cough (n,%)	110 (71%)	31 (71%)	79 (72%)	0.852 ³
Sputum (n,%)	30 (19%)	17 (38%)	13 (12%)	0.020 ⁴
Dyspnea (n,%)	79 (51%)	44 (100%)	35 (32%)	<0.001 ³
Fatigue or myalgia (n,%)	63 (41%)	19 (43%)	44 (40%)	0.995 ⁴
Nausea or vomiting (n,%)	15 (10%)	4 (9%)	11 (10%)	0.777 ⁴
Diarrhea (n,%)	12 (8%)	2 (4%)	10 (9%)	0.770 ⁴
Anosmia (n,%)	75 (49%)	29 (67%)	46 (42%)	0.077 ³
Laboratory findings				
Immature platelet fraction, %	4.75 (0.70–31.1)	11.9 (3.4–31.1)	3.9 (0.70–15.2)	<0.001 ¹
Platelet count ($10^9/L$)	232 (150–636)	196 (150–636)	244 (155–460)	0.065 ¹
Mean platelet volume, fL	11.2 ± 1.29	12.1 ± 1.22	10.8 ± 1.10	<0.001 ²
Platelet-large cell ratio, %	34 ± 9.87	40.5 ± 9.30	31.4 ± 8.84	0.001 ²
Platelet distribution width, fL	13.1 (7.50–24.5)	15.6 (10.3–21.9)	12.4 (7.50–24.5)	0.001 ¹
Hemoglobin, g/dL	12.1 ± 2.38	10.7 ± 2.92	12.7 ± 1.83	0.001 ²
Immature granulocyte ratio, %	0.60 (0.10–13.6)	1.20 (0.30–4.50)	0.50 (0.10–13.6)	0.001 ¹
Leukocyte count ($10^9/L$)	7.51 (3.01–28.0)	10.0 (3.23–28.0)	7.19 (3.01–19.6)	0.001 ¹
Neutrophil count ($10^9/L$)	4.77 (1.06–17.6)	7.92 (1.92–17.5)	4.36 (1.06–17.6)	<0.001 ¹
Lymphocyte count ($10^9/L$)	1.28 ± 0.59	0.97 (0.19–2.05)	1.41 (0.45–9.50)	0.002 ¹
Neutrophil-to-lymphocyte ratio	3.52 (0.26–85.2)	10.7 (1.83–85.2)	3.27 (0.26–16.7)	<0.001 ¹
Monocyte count ($10^9/L$)	0.56 (0.03–9.34)	0.54 (0.11–9.34)	0.58 (0.03–2.33)	0.768 ¹
C-reactive protein, mg/L	42.6 (0.60–308)	52.9 (0.80–308)	34.9 (0.60–192)	0.024 ¹
Ferritin, ng/mL	311 (20.0–4,427)	458 (66.0–4,427)	274 (20.0–2,306)	0.016 ¹
Lactate dehydrogenase, U/L	233 (94.0–1,015)	279 (177–1,010)	220 (94.0–1,015)	0.081 ¹
Lactate, mmol/L	2.15 (0.80–8.30)	2.85 (1.20–8.30)	2.05 (0.80–4.0)	0.090 ¹
D-dimer, ug/L	1,400 (190–8,650)	2,800 (340–8,650)	975 (190–6,600)	<0.001 ¹
Prothrombin time, %	103 (19.1–165)	103 (73.9–132)	103 (19.1–165)	0.972 ¹
International normalized ratio (INR)	1.02 (0.88–8.17)	1.07 (0.96–8.17)	1 (0.88–2.96)	0.003 ¹
Activated partial thromboplastin time (s)	29.0 (15.0–73.0)	34.0 (15.0–73.0)	27.5 (17.0–52.0)	0.007 ¹
Fibrinogen, g/L	4.47 ± 1.14	5.02 ± 1.37	4.25 ± 1.01	0.064 ²
Interleukin-6, ng/L	44.6 (1.50–2,494)	94.2 (4.70–2,494)	17.4 (1.50–216)	0.002 ¹

p* Comparison between severe and non-severe cases. ¹Mann Whitney u test, ²Student's t-test, ³Chi Square test, ⁴Fisher Exact test. Non-normally distributed data were expressed as med (min-max), normally distributed data were expressed mean ± SD.

Table 2: The multivariate logistic regression analyses to detect the independent variables for the disease severity.

Dependent variable	Predictors	OR*	95% CI (lower-upper bound)	p-Value
Severity	Age	1.039	0.947–1.141	0.419
	Gender	0.074	0.001–6.645	0.257
	IPF	2.000	1.149–3.482	0.014
	Hemoglobin	0.690	0.180–2.646	0.589
	IG	1.382	0.811–2.353	0.234
	Leukocyte count	1.497	0.835–2.684	0.176
	NLR	1.489	0.857–2.589	0.158
	CRP	0.996	0.970–1.021	0.731
	Ferritin	1.002	0.997–1.007	0.383
	D-dimer	1.001	1.000–1.003	0.061

The model was statistically significant ($p < 0.05$). The Nagelkerke R^2 was 0.888 and significance for model fit Hosmer Lemeshow was, $p = 1.00$. IPF: Immature Platelet Fraction, IG: Immature Granulocytes, NLR: Neutrophil-to-Lymphocyte Ratio, CRP: C-reactive Protein, OR* Odds ratio.

There was no significant difference in gender and body mass index (BMI) ($p = 0.607$ and $p = 0.628$, respectively). However, there was a significant age difference ($p = 0.003$) (Table 1). Given laboratory parameters, the median IPF% was significantly higher in the severe group (11.9 vs. 3.9%, $p < 0.001$). In the severe group, MPV ($p < 0.001$), P-LCR ($p = 0.001$), PDW ($p = 0.001$), immature granulocyte ratio (IG%) ($p = 0.001$), leukocyte ($p = 0.001$), and neutrophil ($p < 0.001$) counts, neutrophil-to-lymphocyte ratio (NLR) ($p < 0.001$), CRP ($p = 0.024$), ferritin ($p = 0.016$), D-Dimer ($p < 0.001$), INR ($p = 0.003$), aPTT ($p = 0.007$) and IL-6 ($p = 0.002$) were found to be significantly higher, and the levels of hemoglobin and lymphocyte count were found to be significantly lower than those in the control group ($p = 0.001$, and $p = 0.002$, respectively) (Table 1).

We performed a multivariate binary logistic regression analysis to detect the severity's independent variables (Table 2). The model was statistically significant ($p < 0.05$). The Nagelkerke R^2 was 0.888, and the significance for model fit Hosmer Lemeshow was $p = 1.000$. Moreover, IPF ($p = 0.014$, odds ratio = 2.000, 95%CI: 1.149–3.482) was an independent predictor for the severity (Table 2).

We also determined the diagnostic properties of the IPF% via the ROC curve (Figure 2). The area under the curve (AUC) value from ROC curve analysis was 0.879 ($p < 0.001$, 95%CI: 0.784–0.943) with a sensitivity and specificity value of 69.5 and 92.4%, respectively, to detect the disease's severity. We calculated a cut-off value of >9.5 for the IPF% to differentiate severe patients.

Discussion

For all we know, this is the first study investigation in the literature to determine the predicting value of IPF% to the severity of the disease in patients with COVID-19 pneumonia. The main results of the research are that (i) patients with severe COVID-19 pneumonia have higher baseline (admission) levels of IPF%, (ii) IPF% ($p = 0.014$, odds ratio = 2.000, 95%CI: 1.149–3.482) is an independent predictor for the severity of the disease in patients with COVID-19 pneumonia (iii) The AUC value from ROC curve analysis was 0.879 ($p < 0.001$, 95%CI: 0.784–0.943) for determining the severity of pneumonia. IPF% also had a sensitivity and specificity value of 69.5 and 92.4%, respectively, to detect the disease's severity.

The novel coronavirus disease continues to pose a significant strain on healthcare systems all around the World. The disease has broad manifestations ranging from asymptomatic infection to severe respiratory distress requiring mechanical ventilation support and critical care admission. As the ongoing pandemic threatens to exhaust critical healthcare resources, a significant amount of research has been dedicated to identifying possible indicators of severe disease [13, 14].

Figure 2: To detect the severity of Covid-19, the AUC value from ROC curve analysis for IPF% was, 0.879 (95% CI: 0.784–0.943) with a cut-off value of >9.5 (Sensitivity; 69.5, Specificity; 92.4). AUC, Area under the curve; ROC, Receiver operating characteristics; IPF%, Immature platelet fraction; CI, Confidence Interval.

Some of the commonly studied biomarkers and proven to indicate severe COVID-19 pneumonia include CRP, LDH, D-Dimer, IL-6, and ferritin. Hemocytometric abnormalities are also common in COVID-19 patients, and many studies aim to identify which of these abnormalities can be predictive of disease severity [15].

Previous studies have repeatedly revealed that lymphopenia is a consistent finding in COVID-19 patients and that the degree of lymphopenia correlates with disease severity [16]. Lymphocyte count appears to be more reliable at predicting worse outcomes than common inflammation biomarkers like IL-6 and CRP levels. The other most frequently reported finding is elevated NLR. Increased NLR appears to be a consistent finding in severe COVID-19 patients, and higher NLR upon admission is shown to be an independent predictor of severe COVID-19 pneumonia and mortality [17, 18]. In this study, we observed that the severe COVID-19 pneumonia group had lower lymphocyte ($p=0.020$) and hemoglobin levels ($p=0.001$) with higher leukocyte count ($p=0.001$), neutrophil count ($p<0.001$), NLR ($p<0.001$), CRP ($p=0.024$), ferritin ($p=0.016$), and IL6 ($p=0.002$) levels than non-severe COVID-19 pneumonia.

Elevation in D-dimer levels is a sign of increased thrombin formation and fibrinolysis. This finding is consistently observed in severe COVID-19 patients, suggesting that coagulation abnormalities might be associated with disease severity [16, 19]. Additional coagulation alterations that are commonly observed in COVID-19 patients include thrombocytopenia and prolonged prothrombin time. We also know from extensive clinical evidence that COVID-19 patients have an increased risk for clinical complications associated with microthrombus formation [20]. Hypercoagulation increased the risk for thrombus formation, and thrombocytopenia was also evident in both SARS and MERS, which suggests similar pathological mechanisms might be in effect in COVID-19 as well. It is important to note, though, that in SARS and MERS, the microthrombus formation was mainly limited to the pulmonary vasculature, whereas autopsy studies on COVID-19 patients have revealed the presence of thrombosis in other vascular beds as well [21, 22]. These findings have led us to believe that understanding the mechanisms of hypercoagulation and thrombocytopenia in COVID-19 patients might help us in our search for better treatment options and more effective risk stratification.

There was a significant difference between groups concerning D-Dimer ($p<0.001$), aPTT ($p=0.007$), and INR ($p=0.003$), but we did not detect a statistical significance regarding platelet count ($p=0.065$). Other coagulation parameters with a tendency to thrombosis, such as IPF% ($p<0.001$), MPV ($p<0.001$), P-LCR ($p=0.001$), and PDW

($p=0.001$), were significantly higher in the severe Covid-19 group compared in the non-severe group. This study suggests that the tendency to coagulopathy and thrombosis in patients with severe COVID-19 and coagulopathy may be closely related to the disease's severity. In multivariate analysis, we showed that IPF% is an independent predictor for the severity of disease in patients with COVID-19 pneumonia, and these data strengthen our hypothesis. Even though thrombocytopenia has been frequently reported in COVID-19 patients and has been associated with severe disease, its mechanism has not been identified yet [23]. The three possible mechanisms that have been hypothesized can be summarized as (i) inhibition of thrombopoiesis due to infection of bone marrow cells (ii) autoimmune destruction of platelets (iii) pulmonary endothelial damage, causing the microthrombi formation and accordingly, platelet consumption [24]. Several previous studies have suggested assessing parameters that reflect thrombocyte turnover, such as IPF% and MPV [21, 24]. Higher thrombocyte turnover induces younger platelets to be released into circulation, which results in increased IPF%. Younger platelets are more extensive in volume than mature ones, which can be defined as higher MPV. Previous studies have reported increased MPV in COVID-19 patients, which suggests an increased turnover, but IPF% gives us more insight into increased platelet consumption and bone marrow response [15].

IPF% has previously been studied in patients with sepsis and reported to be significant in predicting septic patients' mortality. It is also important to note that in a previous study, increased IPF% was observed before thrombocytopenia became overt, which suggests that IPF% can be used as an early predictor for severe sepsis [7]. A recent study has shown that immature platelet indices have been increased in COVID-19 patients compared to stable patients and patients with acute myocardial infarction. Increased IPF% can lead to thrombotic events in COVID-19 patients [25].

We determined the cut-off value of IPF% as >9.5 for the severity of disease in patients with COVID-19 pneumonia. Increased IPF% appears to be more significant in predicting disease severity than thrombocytopenia, increased prothrombin activity, and elevated fibrinogen levels. This result suggests that the change in IPF% precede other alterations in coagulation markers and possibly predict disease severity earlier and more reliably than them. Several studies in previous literature have evaluated the significance of IPF% in predicting disease severity and worse outcomes in patients with sepsis. At least two of these studies have reported that the increase in IPF% predicts disease severity and appears to be an early sign of

worse sepsis outcomes [7, 11]. It is important to note that thrombocytopenia was less significant in severe patients in our study than other parameters like lymphopenia or NLR. This finding can support previous literature on IPF% in septic patients, repeatedly shown to precede thrombocytopenia in disease progression. These results can have important implications for risk stratification.

In terms of the insight on the mechanism for thrombocytopenia, high IPF% suggests increased thrombocyte synthesis from the bone marrow, induced by increased platelet consumption. This result can also be supported by elevated MPV, which has been documented in COVID-19 patients [15]. These results may offer a preliminary step for further studies to improve our understanding of the definite mechanisms that cause increased thrombocyte consumption in COVID-19 patients. We believe this information will help better patient monitoring and the development of new treatment options.

There were some limitations to this study. Since it was a single-center study, the number of patients was very low. Secondly, the design of the present study was cross-sectional. Hence, we could not observe the relationship of IPF% with long-term outcomes. To evaluate IPF% in different time courses of the COVID-19 would give us a better understanding.

This study has revealed noteworthy results suggesting that IPF% can be a reliable predictive marker for disease severity in COVID-19 patients. We believe it is important to do further studies that aim to help define how clinicians can use this marker in risk stratification and patient management.

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