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Association of D-dimer/fibrinogen ratio with pulmonary embolism in COVID-19 patients

Ahmet Can Topçu[1], Fatih Yiğit[1], Gözde Öztürk-Altunyurt[2], Ayşe Batırel[2], Murat Bülent Rabus[1]

[1]*Department of Cardiovascular Surgery, University of Health Sciences, Kartal Koşuyolu High Specialization Training and Research Hospital, Istanbul, Türkiye*
[2]*Department of Infectious Diseases and Clinical Microbiology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye*

ABSTRACT

Objectives: This study aimed to investigate whether the D-dimer/fibrinogen ratio (DDFR) measured on admission could be used as a diagnostic marker of pulmonary embolism (PE) in coronavirus disease 2019 (COVID-19) patients.

Patients and methods: This single-center, retrospective, case-control study was conducted with 204 COVID-19 patients (131 males, 73 females; mean age: 62±15.4 years; range, 28 to 97 years) between October 18, 2020, and December 18, 2020. Patients were followed during the hospital stay and for 30 days after discharge. The primary outcome was the occurrence of radiologically confirmed PE. The DDFR was calculated using the following formula: DDFR=D-dimer [ng/mL]/fibrinogen [mg/dL].

Results: Six (2.9%) patients experienced PE during the follow-up. D-dimer had 63.6% sensitivity and 76.2% specificity on admission to predict thromboembolism at a cut-off of 1,375 ng/mL (area under the curve [AUC]=0.687, 95% confidence interval [CI]: 0.530-0.845, p<0.05). The DDFR had 75% sensitivity and 90.5% specificity on admission to predict thromboembolism at a cut-off of 5.41 (AUC =0.846, 95% CI: 0.728-0.965, p<0.05).

Conclusion: A measurement of DDFR on admission does not provide incremental value over D-dimer to recognize patients who are at risk of developing PE during and early after hospitalization for COVID-19.

Keywords: COVID-19, D-dimer, fibrinogen, pulmonary embolism, venous thromboembolism.

Patients with coronavirus disease 2019 (COVID-19) have an increased risk of pulmonary embolism (PE) during hospitalization.[1] Several studies revealed that COVID-19 patients who experience PE require invasive ventilation and intensive care unit (ICU) admission at a higher rate.[2] However, a diagnosis of PE can be overlooked during COVID-19 due to an overlap of respiratory symptoms.[1] Therefore, it is essential to identify patients who face the risk of PE during COVID-19.

D-dimer, the breakdown product of cross-linked fibrin, is widely used as a screening test for venous thromboembolism (VTE) in routine clinical practice.[3] There is also previous research reporting that the D-dimer/fibrinogen ratio (DDFR) measurement provides an incremental value over D-dimer testing in the diagnosis of VTE.[4-6] The concept of the DDFR measurement in patients with VTE stems from the assumption that fibrinogen is consumed as a result of increased fibrin production, and D-dimer is produced as a result of simultaneous fibrin degradation.[6] It is expected that, in patients with a confirmed diagnosis of VTE, D-dimer levels are increased, fibrinogen levels are decreased, and DDFR is increased.

Thromboembolic processes activated during COVID-19 are slightly different from those in patients without COVID-19. A hyperinflammatory response associated with a hypercoagulable state and

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Correspondence: Ahmet Can Topçu, MD. SBÜ Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi Kalp ve Damar Cerrahisi Kliniği, 34865 Kartal, İstanbul, Türkiye.
e-mail: ahmet.topcu@icloud.com

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the direct viral infection of vascular endothelium are thought to be the main triggers.[1,7] This results in a consumption coagulopathy with a predisposition to *in situ* thrombosis.[8] However, the knowledge regarding how biochemical coagulation markers reflect COVID-19-related coagulopathy is limited.[9] Therefore, this study aimed to investigate whether a DDFR measured on admission could be used as a diagnostic marker of PE in patients with COVID-19.

PATIENTS AND METHODS

This single-center, retrospective, case-control study included 204 patients (131 males, 73 females; mean age: 62±15.4 years; range, 28 to 97 years) with COVID-19 admitted to the Department of Infectious Diseases at the Istanbul Kartal Dr. Lütfi Kirdar City Hospital between October 18, 2020, and December 18, 2020. Inclusion criteria were as follows: *(i)* a diagnosis of COVID-19 confirmed by reverse transcriptase polymerase chain reaction test and *(ii)* the existence of D-dimer and fibrinogen measurements on hospital admission and discharge. The last available measurements were used in case of mortality. Exclusion criteria were as follows: *(ii)* being younger than 18 years of age and *(ii)* pregnancy. Data concerning patient demographics, comorbidities, D-dimer and fibrinogen levels, medications, arterial and venous thromboembolic events, lengths of ICU and hospital stay, follow-up findings, and outcomes were retrospectively obtained from electronic hospital records. Patients were followed during hospital stay and for 30 days after discharge. All hospitalized COVID-19 patients underwent unenhanced chest computed tomography (CT). A CT pulmonary angiogram was ordered if unenhanced CT findings could not explain the severity of respiratory symptoms. Patients diagnosed with PE by means of CT angiogram constituted the PE group, and those without PE constituted the no-PE group. The primary outcome was the occurrence of PE confirmed by a CT pulmonary angiogram. The secondary outcome was overall mortality, defined as death due to any reason during hospitalization or within 30 days after discharge. D-dimer and fibrinogen levels were measured using commercially available automated kits (Diagnostica Stago Inc., Parsippany, NJ, USA). Results were calibrated and validated daily in accordance with institutional protocols. The DDFR was calculated using the following formula: DDFR=D-dimer [ng/mL]/fibrinogen [mg/dL].

Statistical analysis

Power analysis was performed to estimate sample size using G*Power software version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). The primary endpoint of PE was tested with a predicted incidence of 12% among COVID-19 patients, as previously reported in a meta-analysis by Porfidia et al.[1] We needed a total of 200 participants to achieve an 80% (β=0.2) power at the 5% (α=0.05) level of significance.

Data were analyzed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers (n) and percentages (%). Missing data were handled by listwise deletion. The Kolmogorov-Smirnov normality test was used to assess the distribution of numerical variables. Data with normal distribution were expressed as mean ± standard deviation (SD). Data with nonnormal distribution data were displayed as median (minimum-maximum). The chi-square test or Fisher exact test was used to assess categorical variables, and Student's t-test or the Mann-Whitney U test was utilized to assess numerical variables. Independent predictors of mortality were analyzed by logistic regression analysis. Cut-off values, sensitivity, and specificity rates of D-dimer, fibrinogen, and DDFR of patients with thromboembolic events were determined by receiver operating characteristic (ROC) curve analysis and calculation of area under the ROC curve (AUC) with 95% confidence interval (CI). Youden's index formula was used to determine optimal cut-off values on ROC curves. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

There were 100 (49%) patients with hypertension, 64 (31.4%) with diabetes, and 16 (7.8%) with active malignancy. All patients received thrombosis

Table 1. Patient demographics and comorbidities (n=204)

	n	%	Mean±SD
Age (year)			62±15.4
Sex			
Female	73	35.8	
Hypertension	100	49.0	
Diabetes	64	31.4	
Chronic kidney disease	13	6.4	
Chronic obstructive pulmonary disease	12	5.9	
Active malignancy	16	7.8	

SD: Standard deviation.

Table 2. Factors associated with PE

	PE (n=6)					No-PE (n=198)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			73.3±7.9					61.6±15.5			0.066[a]
Sex											0.424
Female	1	16.7				72	36.4				
Hypertension	4	66.7				96	48.5				0.438
Diabetes	2	33.3				62	31.3				1
Chronic kidney disease	1	16.7				12	6.1				0.33
Chronic obstructive pulmonary disease	0	0				12	6.1				1
Active malignancy	1	16.7				15	7.6				0.391
ICU LOS (days)				2.5	0-20				0	0-21	0.048*[b]
Hospital LOS (days)				13.5	3-30				8	1-34	0.414[b]
Admission D-dimer (ng/mL)				1,135	175-1,590				800	170-68,401	0.566[b]
Discharge D-dimer (ng/mL)				1,380	410-2,350				565	120-5,800	0.56[b]
Admission fibrinogen (mg/dL)			656.8±217.88					569.6±171.2			0.224[a]
Discharge fibrinogen (mg/dL)	512							447.35±143.71			0.655[a]
Admission DDFR				1.56	0.31-2.75				1.49	0.3-93.06	0.955[b]
Discharge DDFR	0.8								1.3	0.23-12.52	0.31[b]

PE: Pulmonary embolism; SD: Standard deviation; ICU: Intensive care unit; LOS: Length of stay; DDFR: D-dimer/fibrinogen ratio; a: Student's t-test; b: Mann-Whitney U-test; * p<0.05.

prophylaxis with low molecular weight heparin during hospitalization. Patient demographics and comorbidities are further detailed in Table 1.

Six (2.9%) patients experienced PE during follow-up. D-dimer, fibrinogen, and DDFR values on admission were similar between groups with and without PE (p=0.566, p=0.224, and p=0.955, respectively). D-dimer levels increased to a median of 1,380 (410-2,350) ng/mL on discharge from an admission median of 1,135 (175-1,590) ng/mL in the PE group. Conversely, an initial median D-dimer of 800 (170-68,401) ng/mL decreased to a median of 565 (120-5,800) ng/mL on discharge in the no-PE group. D-dimer, fibrinogen and DDFR

Table 3. Factors associated with mortality

	Mortality (n=40)					No mortality (n=164)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			73.5±12.71					59.19±14.78			0.000*[a]
Sex	12	30				62	37.8				0.261
Female											
Hypertension	25	62.5				76	46.3				0.088
Diabetes	13	32.5				51	31.1				0.787
Chronic kidney disease	4	10				9	5.5				0.28
Chronic obstructive pulmonary disease	5	12.5				7	4.3				0.057
Active malignancy	6	15				10	6.1				0.09
ICU LOS (days)				5	0-21				0	0-21	**0.000***[b]
Hospital LOS (days)				9	2-34				7	1-30	**0.014***[b]
Admission D-dimer (ng/mL)				1,080	170-68,401				785	180-9,720	0.073[b]
Discharge D-dimer (ng/mL)				1,660	336-4,800				550	120-5,800	**0.038***[b]
Admission fibrinogen (mg/dL)			566.49					572.6±174			0.843[a]
Discharge fibrinogen (mg/dL)			579.8					441.38±142.2			**0.034***[a]
Admission DDFR				1.79	0.31-93.03				1.42	0.3-58.82	0.089[b]
Discharge DDFR				1.36	0.64-7.05				1.29	0.23-12.52	0.643[b]
Pulmonary embolism	5	12.5				1	0.6				**0.001***
Composite thromboembolism	7	17.5				3	1.8				**0.000***

PE: Pulmonary embolism; SD: Standard deviation; ICU: Intensive care unit; LOS: Length of stay; DDFR: D-dimer/fibrinogen ratio; a: Student's t-test; b: Mann-Whitney U-test; * p<0.05.

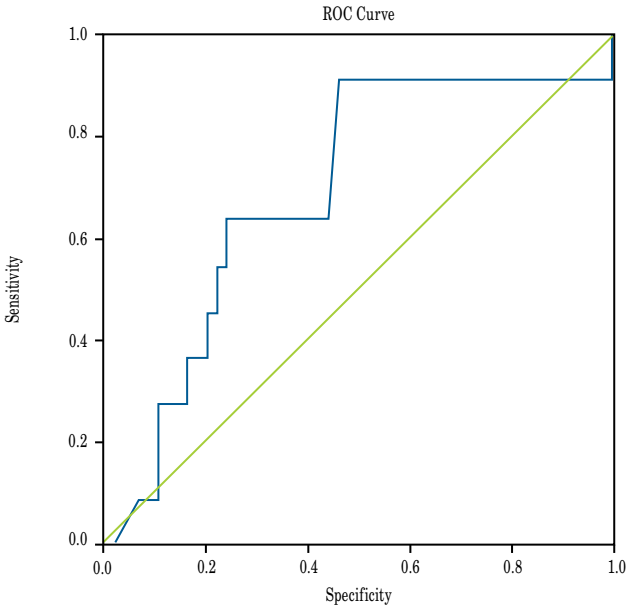

Figure 1. Receiver operating characteristic curve analysis of D-dimer on admission to predict thromboembolism.

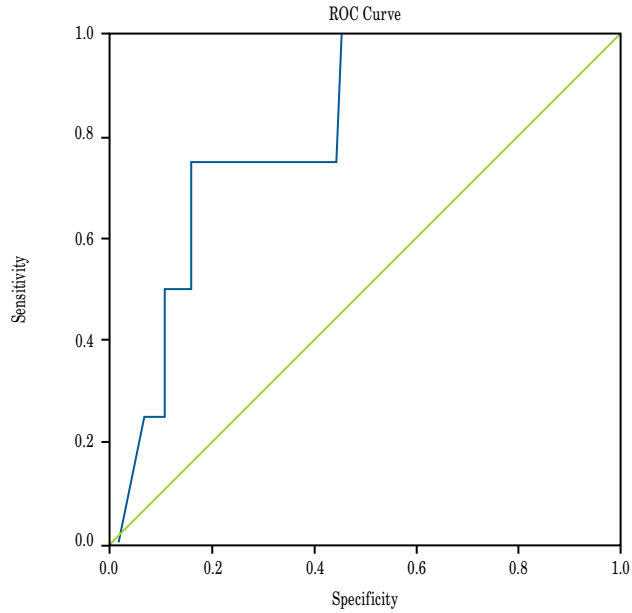

Figure 2. Receiver operating characteristic curve analysis of the DDFR on admission to predict thromboembolism.

DDFR: D-dimer/fibrinogen ratio.

values on discharge were also similar between the groups (p=0.56, p=0.655, and p=0.31, respectively). Patients with PE stayed significantly longer in the ICU (2.5 [0-20] *vs.* 0 [0-21] days, p=0.048). Length of hospital stay was statistically similar between the groups (13.5 [3-30] *vs.* 8 [1-34] days, p=0.414, Table 2).

In-hospital and overall mortality rates of the study population were 19.1% and 19.6%, respectively. Survivors had significantly lower D-dimer and fibrinogen levels at discharge compared to nonsurvivors (p=0.038 and p=0.034, respectively). The DDFR on admission and discharge did not statistically differ between survivors and nonsurvivors (p=0.089 and p=0.643, respectively). Nonsurvivors spent longer durations in the ICU and the hospital than survivors (p<0.001 and p=0.014, respectively). The occurrence of PE and a composite of all arterial and venous thromboembolic events were significantly associated with mortality (p=0.001 and p<0.001, respectively; Table 3).

D-dimer had 63.6% sensitivity and 76.2% specificity on admission to predict thromboembolism at a cut-off of 1,375 ng/mL (AUC=0.687, 95% CI: 0.530-0.845, p<0.05) (Figure 1). The DDFR had 75% sensitivity and 90.5% specificity on admission to predict thromboembolism at a cut-off of 5.41 (AUC=0.846, 95% CI: 0.728-0.965, p<0.05, Figure 2).

DISCUSSION

Results of this single-center study demonstrate that a measurement of DDFR on admission and discharge does not provide incremental value over D-dimer to recognize patients who are at risk of developing PE during and in the early period after hospitalization for COVID-19. D-dimer levels were also not predictive of PE on admission in this patient group, a finding that correlates with previous evidence gathered from non-COVID-19 and COVID-19 patients.[10-13] This is reasonable since a positive D-dimer test has low sensitivity and specificity in patients with low pretest probability according to Wells' criteria.[14] In addition, recent research performed on hospitalized COVID-19 patients reported that an uptrend of D-dimer, rather than a baseline measurement, is more valuable in predicting VTE and mortality.[11-13,15] Of note, a recent study by Özhan and Baştopçu[16] concluded that D-dimer on admission predicts the risk of VTE in hospitalized COVID-19 patients at a higher than usual cut-off value.

Patients in the PE group experienced an increase in D-dimer and a decrease in fibrinogen levels during hospitalization. This correlates with our initial hypothesis that PE would cause simultaneous formation and breakdown of fibrin with D-dimer production and fibrinogen consumption and correlates

with results from previous research.[5] In contrast, D-dimer levels of the group without PE decreased compared to baseline on discharge. Additionally, patients in this group also experienced a decrease in fibrinogen levels, which is of significance since fibrinogen is an acute-phase reactant and is expected to increase during acute illnesses.[5,6,17] A decrease in fibrinogen levels during COVID-19 infection without clinically significant thromboembolism supports the current notion that COVID-19 itself introduces a prothrombotic and hypercoagulable state.[8,18,19] It seems that, even in the absence of symptomatic thromboembolism, COVID-19 causes subclinical *in situ* activation of the coagulation system. This is in accordance with previous studies reporting elevated fibrinogen levels in the acute phase of COVID-19 infection with a subsequent decrease in the late phase.[20,21]

Although consumption coagulopathy caused by COVID-19 is associated with consumption of fibrinogen and production of D-dimer, its clinical presentation differs from that of disseminated intravascular coagulation observed in the course of severe sepsis.[8,22] While patients with disseminated intravascular coagulation often manifest hemorrhagic complications, this is not the case during severe COVID-19 infection. Patients with COVID-19 are prone to venous and arterial thromboembolic events despite thromboprophylaxis.[7] While the pathogenesis behind this phenomenon has not been clearly identified, several mechanisms have been proposed. In a postmortem analysis, Varga et al.[23] demonstrated evidence of direct viral infection in the vascular endothelium of COVID-19 patients. In addition, a hypercoagulable state is observed due to increased levels of several coagulation factors, circulating prothrombotic microparticles, and neutrophil extracellular traps.[24,25]

The DDFR measurement on admission was not predictive of the occurrence of PE in hospitalized COVID-19 patients. It was also not associated with other outcome parameters such as mortality or length of stay. Patients with PE spent significantly longer durations in the ICU than those without PE; however, this was not associated with DDFR levels on admission. Whether the DDFR measurement could be used as a prognostic marker in COVID-19 patients with a previous history of VTE remains unanswered since it was out of the scope of this study. Further research with larger sample sizes might focus on that issue.

There are several limitations to the present study. A relatively small number of patients experienced PE, and this resulted in two groups with unmatched sizes. A study with a larger population or a longer period could have enabled us to build more balanced groups. A multicenter study with a longer duration might be designed to solve this issue. Moreover, the incidence of PE was lower compared to previous studies.[1,2] This might be due to the widespread and aggressive use of parenteral anticoagulation in our patient population.

In conclusion, D-dimer, fibrinogen, and DDFR levels measured on admission do not predict patients who are at risk of developing PE during and in the early period after hospitalization for COVID-19. An increase in D-dimer and a decrease in fibrinogen observed in patients who experienced PE during COVID-19 suggest a state of consumption coagulopathy with simultaneous formation and breakdown of fibrin. Further research with a larger sample size is warranted to better understand biochemical aspects of coagulation derangements associated with COVID-19.

Ethics Committee Approval: The study protocol was approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (date/no: 2020/514/182/3). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: Individual informed consent was waived due to retrospective design.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

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