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Cutoff levels of D-dimer to predict pulmonary thromboembolism in COVID-19 at first admission: A retrospective study

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Abstract:

BACKGROUND AND AIM: In coronavirus disease 2019 (COVID-19), prothrombotic clotting abnormalities and thromboembolism are frequent complications that could be contributed to morbidity and mortality. We aimed to determine the incidence of pulmonary thromboembolism (PTE) at the time of diagnosis of COVID-19 and to evaluate the association of D-dimer levels in patients with COVID-19.

METHODS: Patients who were diagnosed with COVID-19, had elevated D-dimer levels (>500 mg/L), and underwent pulmonary CT angiography (CTA) were included. The data were reviewed retrospectively. Patients were divided into two groups based on the presence or absence of a diagnosis of PTE, and univariate and multivariate analyses were performed.

RESULTS: A total of 687 patients with COVID-19 were included. PTE was identified in 11.4% of the patients (n=78) using pulmonary CTA. There were significantly more male patients in the PTE group (60.3% vs 39.7%). PTE patients had significantly higher D-dimer levels (1535 mg/L; range: 960–3710). Age, gender, and D-dimer were found as independent predictors for a diagnosis of PTE in the multi-logistic regression analysis. Also, a receiver operating characteristic curve analysis performed to evaluate the diagnostic value of D-dimer in PTE showed an area under curve of 0.651 (0.585–0.718). A cutoff value of 1000 ng/mL provided diagnostic utility.

CONCLUSIONS: COVID-19 has constituted a predisposition to thromboembolism. Age-adjusted D-dimer levels, which have recently become prominent for suspected PTE, do not appear to be beneficial in patients with COVID-19. The results of this study suggest that a cutoff of 1000 ng/mL can be utilized in these patients.

Keywords:

COVID-19, D-dimer, pulmonary thromboembolism

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Introduction

As of September 2021, the coronavirus disease 2019 (COVID-19) has affected over 231 million people and resulted in the death of approximately 4.7 million individuals worldwide.[1] Major risk factors for morbidity and mortality in COVID-19 include advanced age and the presence of comorbidity.[2] Although causes of COVID-19-related deaths are generally multifactorial, respiratory failure due to pneumonia followed by acute respiratory distress syndrome is the major contributor.[3] In severe COVID-19, prothrombotic clotting abnormalities and thromboembolism are frequent complications that could be contributed to morbidity and mortality.[4] In these patients, elevated D-dimer levels have been reported along with high rates of pulmonary thromboembolism (PTE).[5] In particular, PTE is responsible for most thromboembolic events although the link between PTE and deep venous thrombosis (DVT) remains obscure.[6] Diagnosis of PTE in COVID-19 patients poses a significant burden in terms of contrast nephropathy, radiation exposure, and cost. For this purpose, biomarkers such as D-dimer can be useful in both cost-benefit and benefit-harm analyses. However, the use of D-dimer with standard cutoff values for this purpose causes very high false positive case rates. Despite the lack of adequate data for the diagnostic accuracy of D-dimer for PTE in COVID-19 patients, the D-dimer levels are considered to represent an independent predictor for survival[7] and thromboembolic events in COVID-19.[8]

In light of all information, we aimed to determine the incidence of PTE and DVT at the time of diagnosis of COVID-19 and to assess the relationship between D-dimer levels and PTE in this study.

Materials and Methods

Study design and settings

This retrospective case-control study was carried out at Ankara Atatürk Sanatorium Training and Research Hospital in the city center between August and December 2020. All patients included in the study were managed by the chest diseases specialists of the mentioned center.

Participants and device

Patients over 18 years of age with a confirmed diagnosis of COVID-19 based on real-time reverse transcription polymerase chain reaction test positivity or with high clinical/radiological suspicion of COVID-19 were included if they also underwent a pulmonary CT-angiography (CTA) due to suspected PTE. Patients with peripheral, bilateral (multilobar) ground glass opacities (GGOs), and multifocal round GGOs on tomography were included as typical COVID-19 pneumonia.

The exclusion criteria included age <18 years, previous diagnosis of PTE, and lack of adequate data on patient files. A total of 704 patients were retrospectively evaluated. Following the exclusion of 17 patients with no D-dimer results, 687 patients remained in the study. In our facility, plasma D-dimer levels are measured quantitatively using latex agglutination (STA-Liatest D-dimer, Diagnostica Stago, Asnieres-sur-Seine) test, which involves centrifugation of citrate plasma at 3500 rpm for 10 min.

Definition of variables, primary outcome, and data collection

Gender, age, comorbid diseases, D-dimer level, presence of PTE and DVT, and PTE localizations were recorded retrospectively from the hospital information management system and patient files. D-dimer levels were obtained by taking venous blood samples at the time of admission. The D-dimer cutoff value used for the diagnosis of PTE in our institution is >500 ng/L. PTE was differentiated using pulmonary CT angiography (CTA), and these results were analyzed with D-dimer levels to determine a new cutoff value for a diagnosis of PTE.

Ethical statements

The principles of the World Medical Association (WMA) Declaration of Helsinki were followed, and approval was obtained from the Local Ethics Committee (14.01.2021/709) for the current study. Informed consent was not obtained from the participants due to the retrospective design.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, Version 16.0, Chicago, SPSS, Inc. package program. The distribution of continuous variables was assessed using the Shapiro-Wilk test, and variables with a $p<0.05$ were considered not to have a normal distribution. The Mann–Whitney U test was used for two independent groups without normal distribution, and the variables were expressed as medians and interquartile range (IQR). The comparison of proportions in categorical variables was performed using the Chi-squared test and Fisher's exact test, and the variables were expressed with sample counts and percentages. Multiple logistic regression analysis was performed with the parameters of p<0.200 in the primary analyses between the two groups according to the PTE diagnosis. D-dimer emerged as an independent predictor, and a receiver operating characteristic curve (ROC) analysis for D-dimer was performed. Diagnostic statistics were provided for different cutoff values. Statistical significance was set at a value of p<0.05.

Results

A total of 687 patients between 19 and 94 years of age were included (median: 51.0, IQR: 40.0–63.0). Of these, 403 (58.7%) were females. The median age for male and female patients was 54 (IQR: 42–64) and 49 years (IQR: 39–61), respectively. The difference was statistically significant (p=0.005). PTE was detected in 78 patients (11.4%) by pulmonary CTA. The PTE location was the main pulmonary artery in 2 patients (2.6%), segmental artery in 47 (60.3%), subsegmental artery in 12 (15.4%), and intraparenchymal branches in 17 (21.8%). A lower extremity venous Doppler examination was performed in 32 patients (4.7%), with 12.5% (n=4) of these examinations indicating the presence of DVT, 3 among patients with PTE, and 1 among those without PTE.

Patients were divided into two groups based on the presence/absence of PTE, and primary analyses were performed. PTE patients were significantly more likely to be male (60.3% males vs 39.7% females, p<0.001). Also, PTE patients were older and significantly more likely to have comorbidities such as hypertension, COPD, and diabetes mellitus (DM) (Table 1).

While D-dimer levels did not differ significantly in women with or without PTE (p=0.087), male patients with PTE had significant elevation of D-dimer (1770, p<0.001) (Table 2). When the overall group with PTE was considered, the difference between median D-dimer levels in male and female patients was not significant (Table 2, p=0.133).

A multiple regression analysis indicated that age [exp(B): 1.031], gender [exp(B): 1.770], and D-dimer [exp(B): 1.00013] were independent predictors for the diagnosis of PTE (Table 3).

In the ROC analysis performed to determine the cutoff value for D-dimer in diagnosing PTE, the area under curve (AUC) was 0.651 (95% CI: 0.585–0.718) (Fig. 1; p<0.001).

Table 1: Demographic data and D-dimer in patient groups with or without PTE

Demographic data	PTE				p
	Without		With		
	n	%	n	%	
Gender					
Female	372	61.1	31	39.7	<0.001*
Male	237	38.9	47	60.3	
Age					
Median (IQR)	50.0 (39.0–61.0)		58.5 (50.0–69.0)		<0.001†
Mean±SD	50.4±15.0		59.0±13.5		–
Comorbidity (at least one)	128	21	30	38.5	0.001*
HT	61	10	17	21.8	0.002*
COPD	46	7.6	12	15.4	0.019*
CHF	4	0.7	2	2.6	0.141‡
DM	29	4.8	9	11.5	0.029‡
CAD	6	1	3	3.8	0.071‡
Malignancy	20	3.3	1	1.3	0.496‡
Rheumatological conditions	8	1.3	0	0	0.607‡
CKD	0	0	0	0	–
D-dimer					
Med (IQR)	1030 (700–1780)		1535 (960–3710)		<0.001†
Mean±SD	1681.3±2112.3		5700.3±12571.0		–

*: Pearson's Chi-squared test, †: Mann-Whitney U test, ‡: Fisher's exact test. PTE: Pulmonary thromboembolism, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CHF: Chronic heart failure, DM: Diabetes mellitus, CAD: Coronary artery disease, CKD: Chronic kidney disease, IQR: Interquartile range, SD: Standard deviation

Table 2: D-dimer according to PTE diagnosis

Variable	PTE		p*
	Median (IQR)		
	Present	Absent	
Gender			
Female	1270 (770–2950)	1060 (720–1720)	0.087
Male	1770 (1030–5750)	1000 (680–1920)	<0.001
p*	0.133	0.856	

*: Mann-Whitney U test

Table 4 shows the diagnostic value of different cutoff values for D-dimer levels and age-corrected D-dimer levels. As shown in Table 4, a cutoff value of 1000 ng/mL provided diagnostic utility (Youden's index=0.22).

When males were evaluated independently, the ROC analysis provided similar results in the overall group with regard to the value of D-dimer levels in diagnosing

Table 3: Multiple regression analysis for a diagnosis of pulmonary thromboembolism

	B	Sig.	exp (B)
Step 1[a]			
Age	0.030	0.002	1.031 (1.011–1.051)
Gender (1)	0.571	0.036	1.770 (1.037–3.020)
HT (1)	0.209	0.568	1.233 (0.601–2.529)
COPD (1)	0.183	0.645	1.201 (0.551–2.616)
CHF (1)	–0.227	0.824	0.797 (0.108–5.875)
DM (1)	0.371	0.435	1.450 (0.570–3.683)
CAD (1)	0.220	0.797	1.245 (0.233–6.649)
D-dimer	0.000131	<0.001	1.000131 (1.0001–1.0002)
Constant	–3.748	<0.001	0.02356

1[a]: 1. Variables entered in the 1[st] step: age and gender. HT: Hypertension D-dimer, COPD: Chronic obstructive pulmonary disease, CHF: Chronic heart failure, DM: Diabetes mellitus, CAD: Coronary artery disease

PTE [AUC: 0.685 (95% CI: 0.603–0.766); Fig. 2]. In Table 5, in which the diagnostic statistics of different cutoff values of D-dimer in PTE were shown, a cutoff value of 1000 ng/mL in males is pointed out (Youden's index=0.298).

Discussion

Although D-dimer levels could be elevated in the course of COVID-19 (worse prognostic predictor), D-dimer levels exceeding 1000 ng/mL should be researched about suspicion of PTE was underlined in this study.

COVID-19 is associated with a strong predisposition to thrombosis, and respiratory symptoms frequently prompt clinicians for a diagnostic work-up for PTE. In particular, pulmonary thromboembolism is responsible for most thromboembolic events, although the link between PTE and deep venous thrombosis (DVT) remains obscure.[9] In a study by Poissy et al.,[10] approximately 20%–30% of COVID-19 patients have been found to have PTE. The overall incidence of PTE reported by Bompard et al.[11] among patients with COVID-19 pneumonia was 24% (17%–32%), while this figure was 50% (30–70%) in those admitted in an intensive care unit, and 18% (12%–27%) in the remaining patients. In Rali et al.'s[12] study, the incidence of acute venous thromboembolism (VTE) was 17% (25 of 147 patients). Acute PTE was present in 16 of 25 patients (11 patients with PTE only and 5 patients with concomitant acute DVT). Fourteen patients were found to have acute DVT (9 with only DVT and 5 with concomitant PE). Among these 14 patients, 9 had DVT of the lower extremity, 2 had DVT of the upper extremity, and 3 had DVT in both the upper and lower extremities. In the current study, PTE was detected in 11.4% (n=78/678) of the patients using CTA as the diagnostic method. In 32 patients, a venous Doppler examination of the lower extremity was performed although only 4 patients (12.5%) had DVT, all of whom had coexistent PTE.

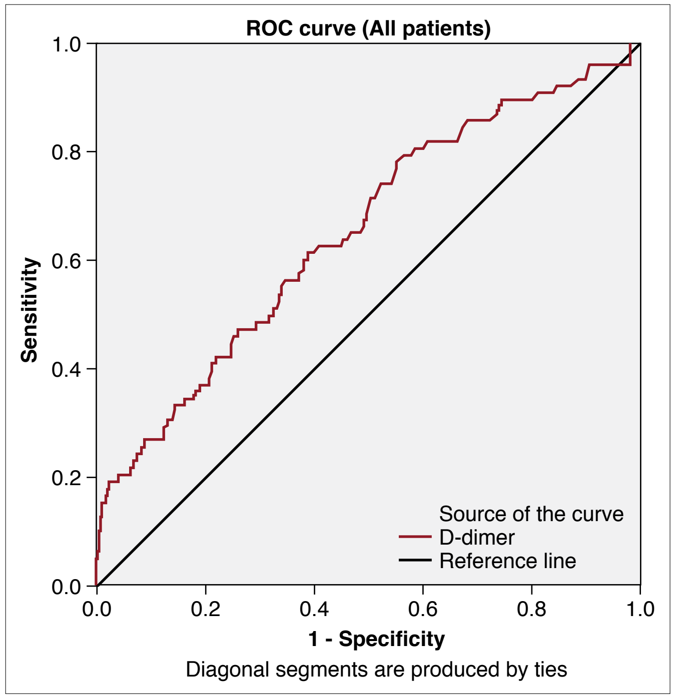

Figure 1: Receiver operating characteristic (ROC) curve analysis for the diagnostic value of D-dimer in PTE

PTE: Pulmonary thromboembolism

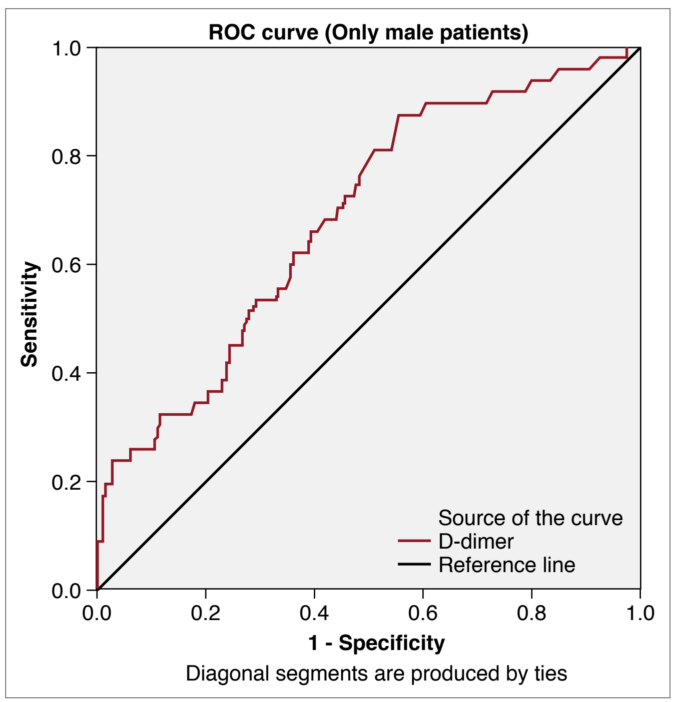

Figure 2: ROC analysis for the diagnostic value of D-dimer in male patients with PTE

Table 4: Diagnostic statistics for D-dimer cutoff levels (all patients)

Cut point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR (+)	LR (−)	Youden's index	Accuracy
Age×10	94.87	8.54	11.73	92.86	1.04	0.60	0.034	18.34
535	96.15	9.36	11.96	95.00	1.06	0.41	0.055	19.21
755	85.90	31.69	13.87	94.61	1.26	0.44	0.176	37.85
1000	74.36	47.62	15.38	93.55	1.42	0.54	0.220	50.66
1790	44.87	75.04	18.72	91.40	1.80	0.73	0.199	71.62
3690	26.92	91.13	28.00	90.69	3.03	0.80	0.181	83.84

PPV: Positive predictive value, NPV: Negative predictive value, LR: Likelihood ratio

Table 5: Diagnostic statistics for D-dimer cutoff levels (only male patients)

Cut point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR (+)	LR (−)	Youden's index	Accuracy
Age×10	95.74	9.28	17.31	91.67	1.06	0.46	0.050	23.59
500	97.87	7.59	17.36	94.74	1.06	0.28	0.055	22.54
880	89.36	39.66	22.70	94.95	1.48	0.27	0.290	47.89
1000	80.85	48.95	23.90	92.80	1.58	0.39	0.298	54.23
1765	51.06	72.15	26.67	88.14	1.83	0.68	0.232	68.66
3655	31.91	88.61	35.71	86.78	2.80	0.77	0.205	79.23

PPV: Positive predictive value, NPV: Negative predictive value, LR: Likelihood ratio

In a meta-analysis of several parameters including gender, age, body mass index (BMI), and comorbidity, a total of 1868 male and 1051 female patients were identified. There were 563 patients with PTE and 2316 patients without PTE. In general, male gender was a risk factor for PTE (OR=1.59, 95% CI=1.28–1.97, p<0.0001), and PTE patients were older (MD=2.28 years, 95% CI=0.05–4.51, p=0.04). In sensitivity analyses that excluded certain studies, the male gender remained a significant risk factor for PTE. It was interesting to note that male gender was found to be a significant risk factor for PTE among COVID-19 patients, which may be due to preexisting cardiovascular conditions in males. On the other hand, although age is a known risk factor for PTE among non-COVID-19 patients, in a sensitivity analysis, no significant associations between age and PTE in COVID-19 patients were found. Similarly, other systemic comorbidities known to be associated with PTE in non-COVID-19 patients such as pulmonary disease, obesity, heart failure, and cancer were insignificant risk factors for PTE.[13] In our study, there were a total of 687 participants between 19 and 94 years of age (median age: 51.0 years; IQR: 40.0–63.0) and 58.7% (n=403) were females. The median age of male patients was 54 years (42–64 years) and that of female patients was 49 years (39–61 years), the difference being significant. However, the incidence of PTE was significantly higher in male patients. Also, PTE patients were significantly older. Again, consistent with the literature data, comorbidities such as HT, COPD, and DM were associated with an increased risk of PTE.

Again, the diagnostic value of D-dimer for DVT in COVID-19 was explored by Cho et al.[14] in a retrospective analysis of 158 subjects, in whom a D-dimer of <6.494 ng/mL was associated with 80.8% sensitivity and 88.0% negative predictive value for ruling out. Of note, the positive predictive value (70.8%) was lower as compared with the negative predictive value (94.7%), suggesting that the diagnostic value of D-dimer may be lower as compared with patients without COVID-19. In a recent study of 1014 patients, higher threshold levels for D-dimer were explored (e.g., from 2000 ng/mL to 4000 ng/mL). However, it is unclear whether these are suitable parameters according to their sensitivity and specificity.[15] In another study, D-dimer at presentation and discharge as potential predictors of VTE was investigated. A D-dimer level of ≥1500 ng/mL at presentation was shown to predict the presence of VTE. Here, the traditional threshold of 500 ng/mL or age-corrected levels do not seem to be useful because patients had abnormal D-dimer levels at presentation. Also, significant fluctuations in D-dimer values during the course of COVID-19 make it difficult to use D-dimer levels as a predictor of VTE, so we focused on acceptable D-dimer values.[12]

In this study, PTE patients had significantly higher D-dimer levels. Although D-dimer levels in female patients with or without PTE were not significantly different (p=0.087), male patients with PTE had significantly higher D-dimer as compared with those without PTE (p<0.001). When a multiple logistic regression analysis was performed, age and D-dimer emerged as independent predictors for a diagnosis of PTE. Again, a cutoff of 1000 ng/mL was determined for a diagnosis of PTE. On the other hand, age-corrected D-dimer levels did not appear to have any superiority over the other values.

Limitations

The retrospective and single-center design are the main limitations of the study. The fact that the gender and age factors are not homogeneously distributed and that the comorbid disease burden is high in the PTE group can be considered a limitation because they may affect D-dimer levels.

Conclusion

COVID-19 has constituted a predisposition to both venous and arterial thromboembolism as a result of excessive inflammation, hypoxia, immobility, and diffuse intravascular clotting. Age-adjusted D-dimer levels, which have recently become prominent for suspected PTE, do not appear to be beneficial in patients with COVID-19. The results of this study suggest that a cutoff of 1000 ng/mL can be utilized in these patients. In addition, we believe that it would be more appropriate to evaluate D-dimer results together with age and gender parameters.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (No: 709, Date: 14/01/2021).

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Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept – A.Ö.; Design – A.Ö., F.Ö.E.; Supervision – A.Ö.; Funding – F.Ö.E.; Materials – M.U.Ş., F.Ö.E.; Data collection &/or processing – M.U.Ş., F.Ö.E.; Analysis and/or interpretation – A.Ş.; Literature search – A.Ö., F.Ö.E.; Writing – F.Ö.E.; Critical review – A.Ö.

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