LOKMAN HEKIM HEALTH SCIENCES

DOI: 10.14744/lhhs.2022.90007
Lokman Hekim Health Sci 2023;3(1):38–44

lokmanhekimhs.com

ORIGINAL ARTICLE

Rate of Pulmonary Thromboembolism in the Ongoing Symptomatic COVID-19 Patients

Semptomları Devam Eden COVID-19 Hastalarında Pulmoner Tromboemboli Insidansı Oranı

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) pandemic, which began in December 2019, is associated with high transmission and mortality rates. It is now known that COVID-19 increases the risk of venous thromboembolism due to microvascular inflammation. We aimed to explore the rate of pulmonary thromboembolism (PTE) in ongoing symptomatic COVID-19 patients and the association between D-dimer levels and PTE.

Methods: A total of 2020 patients were retrospectively screened. Of these, 332 eligible patients over 18 years of age with a laboratory-confirmed diagnosis of COVID-19 and who underwent pulmonary computed tomography (CT) angiography due to suspected PTE 14–90 days after COVID-19 positivity were included. Over 500 µg/L was considered abnormally high for D-dimer.

Results: The mean age was 57 years, and 55.4% (n=184) were females. Of the total patients, 58 patients had PTE. Males were found to have a significantly higher risk for PTE (M/F: 33/25). A significant relationship between advanced age and PTE risk was observed as well. PTE occurred mostly in the segmental arteries in 10.8%. The use of low-molecular-weight heparin was not associated with a significant preventive effect for PTE. In a multivariate logistic regression analysis of independent variables, including age, gender, D-dimer level, and timing of pulmonary CT angiography, D-dimer level was found to have the highest predictive value for PTE. The sensitivity and negative predictive value for a cutoff of 745 µg/L were 89.7% (78.8–96.1) and 93.4% (86.7–96.9), respectively.

Discussion and Conclusion: PTE continues to pose a serious risk in these patients, and it remains unclear who was at risk for PTE.

Keywords: D-dimer; Ongoing COVID-19; Pulmonary thromboembolism

Cite this article as: *Yıldız M, Öztürk A, Öztürk Ergur F, Kavurgacı S, Uzel Şener M. Rate of Pulmonary Thromboembolism in the Ongoing Symptomatic COVID-19 Patients. Lokman Hekim Health Sci 2023;3(1):38–44.*

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E-mail: drmuratyildiz85@gmail.com **Submitted:** 26.09.2022 **Revised:** 19.10.2022 **Accepted:** 14.11.2022

As of the end of October 2020, there have been more than 36 million confirmed cases of coronavirus disease 2019 (COVID-19) and more than one million deaths globally. COVID-19, which has caused a respiratory disease pandemic that began in December 2019, is associated with high transmission and mortality rates.[1] Several reports of the cardiovascular effects of COVID-19 (e.g., myocardial injury and acute coronary syndrome) have been published. Venous thromboembolism (VTE) seems to be a common complication, particularly in patients who are hospitalized due to severe acute respiratory distress syndrome.[2] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initiates infection in cells by binding to the angiotensin-converting enzyme-2 receptor found on the surface of human cells, including endothelial cells. This leads to aberrant cytokine–paracrine signaling that involves both proinflammatory and anti-inflammatory molecules, as well as proapoptotic mediators. As previously explained by Qin et al.,[3] viral injury, abnormal cytokine release, and damage-associated molecular patterns induce localized microvascular inflammation, which in turn may trigger endothelial activation, vasodilation, and a prothrombotic predisposition. Although post-discharge bed rest is commonly recommended for patients with an acute infection, this may also lead to stasis of blood flow, potentially increasing the risk of deep venous thrombosis (DVT) and subsequent pulmonary thromboembolism (PTE).[4] In the recently published National Institute for Health and Care Excellence guideline, a period of 4–12 weeks after COVID-19 diagnosis has been defined as "ongoing symptomatic COVID-19."[5] Accordingly, dyspnea and cough are the most commonly defined pulmonary symptoms in this period.

The present study has explored the rate of PTE in the on-going symptomatic COVID-19 patients. It has also examined the association between D-dimer levels and the risk of PTE.

Materials and Methods

This study was conducted at the Health Sciences University Faculty of Medicine Atatürk Sanatoryum Training and Research Hospital between September 2020 and December 2020. The research was carried out in accordance with the conditions of the Declaration of Helsinki and approved by the local ethics committee (approval date: January 14, 2021; approval number: 709). Patients over the age of 18 years who had a laboratory-confirmed diagnosis of COVID-19 and who underwent pulmonary computed tomography (CT) angiography for suspected PTE after 14–90 days due to COVID-19 positivity were included. COVID-19 diagnoses were established via real-time reverse transcription-polymerase chain reaction (RT-PCR) tests. Exclusion criteria included age under 18 years, a previous diagnosis of PTE, a thromboembolic event within the first 14 days after a positive PCR test, and inadequate data in paper or digital patient files. A total of 2020 patients were screened retrospectively, and 332 patients who met the inclusion criteria were identified. Plasma D-dimer levels were measured quantitatively using a latex agglutination test (STA-Liatest D-dimer, DiagnosticaStago, Asnieres-sur-Seine). A D-dimer level over 500 mg/L was considered abnormally high.

Statistical Methods

All statistical analyses were performed using SPSS version 22.0 software (Chicago, IL, USA). The distribution of continuous variables was examined using a Shapiro–Wilk test, and variables with p-levels under 0.05 were considered to have an abnormal distribution. The mean values between two groups with normal distribution were compared using a Mann–Whitney U test, and these variables were expressed as means and interquartile ranges. The Chi-squared and Fisher's exact tests were used to compare categorical variables, which were expressed as sample numbers and percentages. Parameters with statistical significance in the univariate analyses were subjected to a multivariate logistic regression analysis to diagnose PTE. A receiver operating characteristic (ROC) analysis of D-dimer levels was conducted, as D-dimer level emerged as an independent predictor in this analysis. The subsequent cutoff levels were expressed using diagnostic statistics. A p-value under 0.05 was considered statistically significant.

Results

A total of 2020 patients admitted or treated on an outpatient basis due to COVID-19 between September 1 and December 31, 2020, were retrospectively screened. Of these, 1514 patients were excluded because no CT angiography was performed within 14–90 days of diagnosis, and 174 were excluded due to inadequate patient data. A total of 332 patients who underwent CT angiography with suspicion of PTE 14–90 days after a COVID-19 diagnosis were included in the study (Fig. 1). The mean age of included patients was 57 years, and 55.4% (n=184) were females. Males were found to have a significantly higher risk of developing PTE than females (p=0.038). A significant relationship between advanced age and PTE risk was observed as well (p=0.016). Of the 332 included participants, 32 were treated on an inpatient basis and 300 on an outpatient basis.

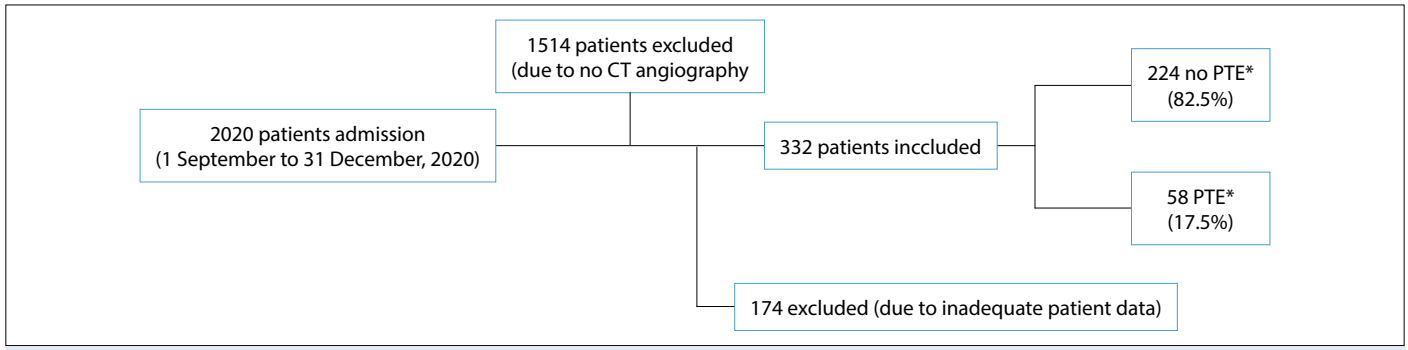

Figure 1. Flow chart of the study.

Of the patients, 58 (17.5%) had PTE. PTE occurred in the main pulmonary artery in 2.1% (n=7) of participants, in the segmental arteries in 10.8% (n=36), and in the subsegmental arteries in 1.2% (n=4). PTE was intraparenchymal in 33.3% (n=11) of participants. Slightly more than half of the participants (55.1%, n=183) had at least one comorbid condition. The most common comorbidities in the sample were chronic obstructive pulmonary disease (COPD)/asthma (25%), hypertension (HT) (22.6%), and diabetes mellitus (DM) (13.9%). However, the risk of PTE was independent of comorbid conditions. Of the 102 patients who underwent a lower-extremity venous Doppler ultrasound examination, only 6 were found to have DVT. Treatment with low-molecular-weight heparin (LMWH) was started in 67 patients at the time of the pulmonary CT angiogram (prophylactic dose in 36 patients and therapeutic dose in 31 patients). However, the use of LMWH was not associated with a significant preventive effect for PTE (p=0.235, Table 1). In the total patient group, the median D-dimer level (interquartile range [IQR]) was 1055 µg/L (710–1995); it was 1000 µg/L (660–1650) and 1750 µg/L (930–3970) in those who had or did not have PTE, respectively (p<0.001) (Table 1). In a multivariate logistic regression analysis of independent variables, including age, gender, D-dimer level, and timing of pulmonary CT angiography, D-dimer level was found to have the highest predictive value (p=0.001) for the occurrence of PTE (Table 2). A ROC analysis for D-dimer levels showed an area under curve (AUC) of 0.676, which was statistically significant (p<0.001) (Fig. 2). A statistical analysis of the diagnostic sensitivity of D-dimer cutoffs showed a sensitivity of 93.1% (83.3–98.1) and a specificity of 9.1 (6–13.2) for the upper value of the laboratory (500 µg/L), with a positive predictive value of 17.8% (16.7–19) and a negative predictive value of 86.2% (69.3–94.5) (Table 3). A cutoff of 880 µg/L was associated with a sensitivity of 81% (68.6–90.1) and a specificity of 43.1% (37.1–49.2). The Chi-squared test was then conducted again using these cutoff values. The rate of an accurate diagnosis for PTE was compared using a cutoff of 500 µg/L, 745 µg/L, and 880 µg/L. The latter two cutoff values were significantly better at accurately diagnosing PTE than a cutoff of 500 µg/L (p=0.0001 and p=0.001, respectively) (Table 4). The sensitivity and negative predictive value for a cutoff of 745 µg/L were 89.7% (78.8–96.1) and 93.4% (86.7–96.9), respectively. In PCR-positive COVID-19 subjects, the time to pulmonary CT angiogram was significantly shorter among those diagnosed with PTE (p=0.007).

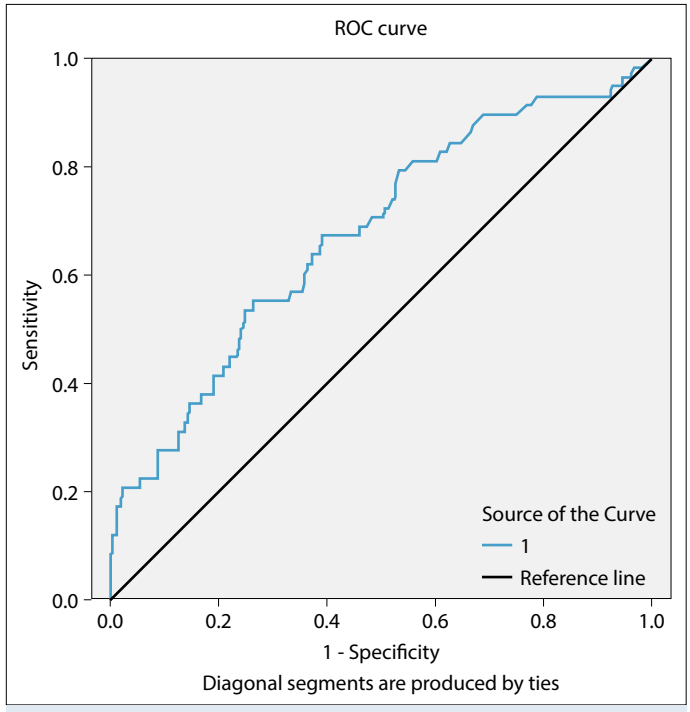

Figure 2. A ROC analysis for D-dimer levels in the diagnosis of PTE following a diagnosis of COVID-19.

Discussion

To the best of our knowledge, this is the first study to examine the incidence of PTE following the COVID-19 pneumonia period, especially the newly defined "on-

Table 1. Variables in study groups according to the presence/absence of PTE (univariate analysis)

	Total (n=332)	PTE		p
	n (%)	No n (%)	Yes n (%)	
Gender				
Male	148 (44.6)	115 (77.7)	33 (22.3)	**0.038***
Female	184 (55.4)	159 (86.4)	25 (13.6)	
Age, median (IQR)	57 (46–66)	56 (44–66)	61 (51–67)	**0.016**†
Comorbidity	183 (55.1)	146 (79.8)	37 (20.2)	0.144*
COPD/asthma	83 (25)	67 (80.7)	16 (19.3)	0.617*
CHF	7 (2.1)	6 (85.7)	1 (14.3)	1.000‡
HT 75 (22.6)	65 (86.7)	10 (13.3)	0.284*	
DM	46 (13.9)	36 (78.3)	10 (21.7)	0.411*
CAD	22 (6.6)	17 (77.3)	5 (22.7)	0.559‡
Rheumatic	13 (3.9)	10 (76.9)	3 (23.1)	0.707‡
Malignancy	18 (5.4)	12 (66.7)	6 (33.3)	0.102‡
D-dimer, median (IQR)	1055 (710–1995)	1000 (660–1650)	1750 (930–3970)	<**0.001**†
DVT				
No	96 (28.9)	76 (79.2)	20 (20.8)	0.051§
Yes	6 (1.8)	3 (50)	3 (50)	
USG not exist	230 (69.3)	195 (84.8)	35 (15.2)	
LMWH use (during CT time)				
No	265 (79.8)	222 (83.8)	43 (16.2)	0.235*
Yes	67 (20.2)	52 (77.6)	15 (22.4)	
LMWH dose				
Prophylactic	36 (53.7)	28 (77.8)	8 (22.9)	0.972*
Treatment	31 (46.3)	24 (77.4)	7 (22.6)	
LMWH use duration, median (IQR)	16 (12–30)	20 (14–40)	14 (7–30)	0.184†
CT time after PCR positivity, median (IQR)	37 (22–58)	38 (23–60)	29 (17–48)	**0.007**†

*: Pearson's Chi-squared test; †: Mann–Whitney-U test; ‡: Fisher' exact test; §: Pearson's Chi-squared test (insufficient sample counts); PTE: Pulmonary thromboembolism; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; HT: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery diseases; IQR: Interquartile range; DVT: Deep venous thrombosis; USG: Ultrasonography; LMWH: Low-molecular-weight heparin; CT: Computed tomography; PCR: Polymerase chain reaction.

Table 2. Multiple logistic regression analysis for the diagnosis of PTE

Variables	B	p	exp(B) (95% confidence interval)
Step 1a			
Gender (1)	0.158	0.620	1.172 (0.627–2.191)
Age	0.022	0.074	1.022 (0.998–1.047)
D-dimer	0.00013	0.001	1.00013 (1.00005–1.00020)
CT time after positive PCR test	-0.013	0.080	0.987 (0.973–1.002)
Constant	-2.624	0.001	0.073

a: Variable(s) entered on step 1: gender (reference: female), age, D-dimer, CT time after positive PCR test. PTE: Pulmonary thromboembolism; CT: Computed tomography; PCR: Polymerase chain reaction.

going symptomatic" period. Most existing publications examine the incidence of VTE in COVID-19 patients who are hospitalized or in intensive care units (ICUs). Our results showed significantly higher D-dimer levels in post-COVID-19 patients diagnosed with PTE than in those without PTE. However, D-dimer levels in post-COVID-19 patients without PTE were also elevated,[6] which likely reflects inflammation and microvascular endothelial injury. Although COVID-19 may increase the risk of VTE through endothelial dysfunction and inflammation-mediated ac-

Table 3. Diagnostic statistics for D-dimer cutoffs

Cutoff points	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
500	93.1 (83.3–98.1)	9.1 (6.0–13.2)	17.8 (16.7–19.0)	86.2 (69.3–94.5)
745	89.7 (78.8–96.1)	31.0 (25.6–36.9)	21.6 (19.7–23.6)	93.4 (86.7–96.9)
880	81.0 (68.6–90.1)	43.1 (37.1–49.2)	23.2 (20.4–26.2)	91.5 (86.1–94.9)
Age × 10	93.1 (83.3–98.1)	12.4 (8.8–16.9)	18.4 (17.2–19.6)	89.5 (75.8–95.8)

PPV: Positive predictive value; NPV: Negative predictive value.

Table 4. Diagnostic statistics for D-dimer cutoffs

Cut point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
500	93.1 (83.3–98.1)	9.1 (6.0–13.2)	17.8 (16.7–19.0)	86.2 (69.3–94.5)
745	89.7 (78.8–96.1)	31.0 (25.6–36.9)	21.6 (19.7–23.6)	93.4 (86.7–96.9)
880	81.0 (68.6–90.1)	43.1 (37.1–49.2)	23.2 (20.4–26.2)	91.5 (86.1–94.9)
Age × 10	93.1 (83.3–98.1)	12.4 (8.8–16.9)	18.4 (17.2–19.6)	89.5 (75.8–95.8)

AUC for D-dimer=0.676 (95% CI: 0.598–0.755); p<0.001; PPV: Positive predictive value; NPV: Negative predictive value.

tivation of the coagulation cascade, other indirect factors such as immobilization, the need for central venous catheterization, and mechanical ventilation in the ICU may also contribute to an increased risk of PTE (ICU).[7]

Previous studies have suggested that severely or critically ill COVID-19 patients who are hospitalized or admitted to the ICU have a particularly high risk of thromboembolic events.[2,8] Poissy et al.[2] conducted a study of 107 successive patients admitted to the ICU due to confirmed COVID-19 pneumonia between February 27 and March 31, 2020. PTE was observed in 22 of these patients (20.6%) after a mean duration of 6 days (range: 1–18 days). At the time of PTE diagnosis, 20 of these 22 patients were reported to be on prophylactic antithrombotic therapy (LMWH). That study also analyzed 196 patients admitted to the ICU for other reasons during the same time period in 2019; PTE occurred in COVID-19 patients more than twice as frequently as in other patients (20.6% vs 6.1%). In our study, we examined the pulmonary CT angiograms and D-dimer levels of 322 patients (including inpatients and outpatients) with a confirmed diagnosis of COVID-19 after the completion of therapy and a 14-day quarantine period.

The duration and extent of the risk of PTE in COVID-19 patients remain elusive, and most recent observational studies propose that, during hospitalization for COVID-19, PTE occurs in approximately 1%–7% of inpatients and in 7%–35% of patients admitted to the ICU. Most studies investigating the association of VTE risk with SARS-CoV-2 infection have been performed in selected patient populations with relatively small sample sizes and short follow-up periods; most are also limited to one or a few centers.[9,10] Furthermore, although approximately three-fourths of all VTE events are thought to occur outside of a hospital setting, very little is known about the risk of VTE among COVID-19 patients who are not hospitalized.[11,12] Of the 332 patients included in our study, 32 received in-hospital care, while 300 were treated on an outpatient basis. A diagnosis of PTE was established in 58 of these patients (17.5%) following a pulmonary CT angiogram. The reported incidence of PTE in the general population, irrespective of the presence of DVT, is 23/100 000. We observed a higher incidence in our patients, which might be explained by an increased predisposition to VTE even after recovery from active COVID-19.

Lodigiani et al.[13] conducted a study of 388 patients (median age 66 years, 68% males, 16% requiring ICU admission). Of these, thromboprophylaxis was administered to 100% of patients admitted to the ICU and to 75% of patients admitted to the general patient ward. Of these patients, 28 had thromboembolic events. Thirty patients (7.7% of the overall population) underwent a pulmonary CT angiography; PE was confirmed in 10 of these (33%). In our study, 67 of the 332 patients received LMWH during CT angiography, and more patients without PTE received LMWH than those with PTE, although this difference was insignificant.

A normal D-dimer level reliably rules out a diagnosis of PTE in outpatients with a low or moderate clinical suspicion of PTE, although it is not recommended as a positive marker for the presence of thrombosis due to lack of specificity. An advisory statement by the European Society of Radiology and European Society of Thoracic Imaging points

out that a contrast-enhanced CT examination should be performed to rule out PTE in COVID-19 pneumonia patients requiring additional oxygen.[14] Furthermore, the European Society of Cardiology recommends pulmonary CT angiograms when a noncontrast CT cannot explain the severity of respiratory failure.[15] In line with these recommendations, we included patients in our study for whom the diagnosis of PTE was established via pulmonary CT angiography.

In another study by Tuck et al.,[16] 15.8% of 544 patients admitted to the ICU were diagnosed with PTE; however, PTE did not correlate with mortality. Furthermore, COVID-19 severity was not associated with PTE risk, although the median D-dimer level in patients with PTE was 4664 µg/L (95% confidence interval [CI]: 2.731–11.252) vs 1101 µg/L (95% CI: 1.734–4.033) in those without PTE (p=0.008). These authors also included other factors that could explain these increased D-dimer levels, such as recent surgery or the presence of active malignancy, and they found elevated D-dimer levels (>1500 µg/L) in 109 non-COVID-19 patients, in 11 patients with active malignancy (9 solid organ and 2 hematological), and in 3 patients with a history of surgery within the previous 6 months. The median D-dimer levels in patients with active cancer were not higher than those without malignancy, and patients with cancer did not experience a significantly higher risk of PTE (p=0.297).[16] In our study, 55.1% of patients (n=183) had at least one comorbid condition; COPD/asthma (25%), HT (22.6%), and DM (13.9%) were the three most frequent conditions. However, the presence or absence of these comorbidities did not correlate with the risk of PTE.

In some previous studies, anticoagulant treatment with LMWH has been recommended for patients with severe pneumonia and excessive activation of the coagulation cascade. A cutoff of at least a fourfold increase in the normal upper limit of D-dimer levels has been suggested.[17] Tang et al.[18] observed significantly lower 28-day mortality in patients who received prophylactic heparin and whose D-dimer levels were no more than six times the normal upper limit. Of the 67 patients in our study who received LMWH, 36 received prophylactic and 31 received therapeutic doses of LMWH. The risk of PTE did not differ between these two groups.

Tuck et al.[16] reported no relationship between age-adjusted D-dimer levels and a diagnosis of PTE, with no reasonable specificity or sensitivity for a positive age-adjusted D-dimer test result (ROC AUC of 0.514). Thus, these authors used unadjusted D-dimer data to examine the specificity and sensitivity of serial D-dimer measurements. They performed subgroup analyses of patients with and without COVID-19 to determine whether different threshold values applied to these subgroups. In the overall group, a D-dimer of 500 µg/L was associated with a sensitivity of 98.5% and a specificity of 12.0%. In non-COVID-19 patients, a D-dimer threshold of 1500 µg/L had a sensitivity of 79.5% and a specificity of 68.2%, and a D-dimer threshold of 2000 µg/L had a sensitivity of 79.5% and a specificity of 75.8%. In COVID-19 patients, a D-dimer threshold of 1500 µg/L was associated with sensitivity and specificity of 81.0% and 70.0%, and a D-dimer threshold of 2000 µg/L was associated with sensitivity and specificity of 71.4% and 75.6%, respectively. In that study, for non-COVID-19 patients, a D-dimer threshold of 2000 µg/L had the same sensitivity and better specificity for PTE as a threshold of 1500 µg/L. On the other hand, compared to a D-dimer threshold of 1500 µg/L, a threshold of 2000 µg/L resulted in reduced sensitivity and increased specificity in COVID-19 cases. In the ROC analysis, the AUC for D-dimer levels for detecting PTE in COVID-19 patients was 0.676 (95% CI: 0.598–0.755), and this result was significant (p<0.001) (Fig. 2, Table 4). Thus, elevated D-dimer levels were found to be associated with PTE risk in COVID-19 patients. The sensitivity and specificity in the overall population for D-dimer thresholds of 500 µg/L, 745 µg/L, and 880 µg/L were 93.1% and 9.1%, 89.7% and 31%, and 81% and 43.1%, respectively. The sensitivity and specificity for age multiplied by 10 were 93.1% and 12.4%, respectively. These results suggest that although a D-dimer threshold of 500 µg/L is highly sensitive, its specificity is too low, while thresholds of 745 µg/L and 880 µg/L are associated with lower sensitivity and higher specificity. Again, the specificity was low for a threshold based on age multiplied by 10.

The limitations of the present study include its retrospective design and relatively small sample size. However, the lack of similar studies in the published literature may be considered a notable strength.

Conclusion

To the best of our knowledge, this is the first study investigating the incidence of PTE within the ongoing symptomatic period of COVID-19. Our results indicate an increased occurrence of PTE in these patients during the follow-up period. Also, although elevated D-dimer levels are known to occur during the course of COVID-19, the possibility of PTE increases when D-dimer levels are above 880 µg/L. However, further multicenter, prospective, larger-scale studies are warranted to corroborate these observations.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: The Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 14.01.2021, number: 709).

Authorship Contributions: Concept: SK, AÖ, MY, FÖE; Design: MUŞ, AÖ, MY; Supervision: MY, SK, FÖE, MUŞ; Fundings: MY, SK, FÖE, MUŞ; Materials: AÖ, FEÖ, MY; Data Collection or Processing: SK, MUŞ, MY; Analysis or Interpretation: MY, AÖ, SK; Literature Search: AÖ, SK, FEÖ; Writing: MY, AÖ; Critical Review: MY, AÖ, MUŞ.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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