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Research

Diagnostic Approach to Pulmonary Embolism in Patients with COVID-19 Pneumonia: A Single-center Study

COVİD-19 Pnömonili Hastalarda Pulmoner Emboliye Tanısal Yaklaşım: Tek Merkezli Bir Çalışma

Işıl Kibar Akıllı[1], Müge Bilge[2]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pulmonary Disease, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye

ABSTRACT

Objective: During coronavirus disease-2019 (COVID-19), numerous studies have delineated an increased risk of developing pulmonary embolism (PE). The aim of this study was to determine the prevalence of PE diagnosed on computed tomography (CT) pulmonary angiography (CTPA) in patients with COVID-19 pneumonia. To evaluate the clinical features and outcomes of PE in these individuals. In addition, the use of D-dimer and predictive scores for the diagnosis of PE in COVID-19 were assessed.

Methods: All patients with COVID-19 pneumonia who underwent CTPA for suspected PE were retrospectively reviewed. Data of all clinical, laboratory, and CTPA images were obtained from electronic medical records. CTPA images were assessed for PE presence, PE distribution, and extent of lung involvement. The severity of lung involvement was graded by chest CT. D-dimer levels within 24 hours from CTPA were obtained. Clinical characteristics and laboratory data were analyzed and compared between patients with and without PE.

Results: PE was detected in 96 of 220 (43.63%) patients who underwent CTPA for suspected PE. Women had a higher rate of PE ($p<0.05$). D-dimer values were significantly higher ($p=0.001$) in PE patients, and the median value in the PE group was 5.6 µg FEU/mL (range 2-5.9). A D-dimer cut-off value of 3.95 µg FEU/mL provides a sensitivity of 0.64 and specificity of 0.69. Area under the curve of the receiver operating characteristic curve is 0.626 [95% confidence interval (CI) = 0.550-0.703. $p=0.001$]. PE cases had significantly higher severe CT lung parenchymal involvement compared with non-PE ($p<0.05$). PE was seen in major vessels in 31.25% (30 cases) and in minor vessels 34.37% (33 cases). Backward logistic regression analysis revealed that female sex and hemoptysis increased the risk of PE by 2.643 and 10.6, respectively ($p<0.05$ for both). The Wells score three-level model was similar in the PE and non-PE group ($p>0.05$). However, only 16.7% of patients with PE had a Wells score more than 4 points ($p<0.05$).

Conclusion: We observed that almost half of the COVID-19 pneumonia patients assessed following contrast media administration had PE on CT. The Wells score used in the general population was not helpful in the diagnosis of PE, and the pulmonary embolism severity index score was unreliable in predicting the mortality risk of PE in these patients. Higher D-dimer values may detect COVID-19-related PE. These findings indicate that CTPA could be more widely used when assessing individuals with COVID-19 pneumonia, particularly in those with elevation of D-dimer and presence of hemoptysis.

Keywords: Pulmonary embolism, COVID-19 pneumonia, D-dimer, computed tomography pulmonary angiography

ÖZ

Amaç: Çok sayıda çalışma koronavirüs hastalığı-2019 (COVİD-19) pandemisi sırasında pulmoner emboli (PE) gelişme riskinin arttığını bildirmiştir. Bu çalışmanın amacı, COVİD-19 pnömonisi olan olgularda bilgisayarlı tomografi pulmoner anjiyografi (BTPA) ile PE prevalansını belirlemek, bu olgularda PE'nin klinik özelliklerini ve sonuçlarını değerlendirmektir. Bununla birlikte COVİD-19 ile ilişkili PE tanısında D-dimer ve prediktif skorların kullanımı değerlendirilmiştir.

Gereç ve Yöntem: PE şüphesi ile BTPA yapılmış tüm COVİD-19 pnömonisi olguları retrospektif olarak incelendi. Tüm klinik, laboratuvar ve BTPA görüntülerinin verileri elektronik tıbbi kayıtlardan elde edildi. BTPA görüntüleri PE varlığı, PE dağılımı ve akciğer parankim tutulumu açısından değerlendirildi. BTPA'nın 24 saati içindeki D-dimer düzeyleri elde edildi. PE saptanan ve saptanmayan olguların klinik özellikleri ve laboratuvar verileri analiz edildi ve karşılaştırıldı.

Address for Correspondence: Işıl Kibar Akıllı, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pulmonary Disease, İstanbul, Türkiye
Phone: +90 0212 414 71 71 E-mail: isilkibar@yahoo.com ORCID ID: orcid.org/0000-0002-4969-4512

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Bulgular: BTPA yapılan 220 olgunun 96'sında (%43,63) PE saptandı. Kadın cinsiyette PE oranı yüksek bulundu (p<0,05). PE olgularında D-dimer değerleri daha yüksekti (p=0,001); bu olgularda D-dimer medyan değeri 5,6 µg FEU/mL (2-5,9) bulundu. 3,95 µg FEU/mL D-dimer cut-off değeri ile 0,64 sensitivite ve 0,69 spesifite saptandı. PE olgularında BTPA'da akciğer parankim tutulumunun daha ağır olduğu görüldü (p<0,05). PE olgularında majör damar tutulumu %31,25 (30 olgu) ve minör damar tutulumu %34,37 (33 olgu) olarak saptandı. Regresyon analizi ile hemoptizi varlığının 10,6 kat ve kadın cinsiyetin 2,64 kat artmış PE riski ile birlikte olduğu bulundu. Wells skoru üçlü sınıflama modeli açısından iki grup arasında farklılık saptanmadı (p>0,05). PE olgularının sadece %16,7'sinde Wells skoru 4 puanın üzerinde bulundu (p<0,05).

Sonuç: BTPA ile değerlendirilen COVİD-19 pnömoni olgularının yaklaşık yarısında PE geliştiğini gözlemledik. COVİD-19 ilişkili PE olgularında, genel popülasyonda PE tanısını öngermede kullanılan Wells skoru ve PE mortalite riskini öngörmede kullanılan pulmoner emboli şiddet indeksi skorun güvenilir olmadığı, yüksek D-dimer değerlerinin bu olgularda tanıya yardımcı olabileceği saptandı. Bu bulgular COVİD-19 pnömonisi olgularını değerlendirirken, özellikle belirgin D-dimer yüksekliği ve hemoptizi varlığında BTPA'nın daha yaygın olarak kullanılması gerektiğini düşündürmektedir.

Anahtar Kelimeler: Pulmoner emboli, COVİD-19 pnömonisi, D-dimer, bilgisayarlı tomografi pulmoner anjiyografi

INTRODUCTION

Coronavirus disease-2019 (COVID-19) has been identified as a thrombogenic virus with an increased incidence of pulmonary embolism (PE) and other venous thromboembolic events, resulting in an increase in mortality (1). It has been reported that the incidence of PE in COVID-19 cases is higher than that in influenza and community-acquired pneumonia cases (2). Studies on this subject have reported that the incidence of PE in COVID-19 cases is 10-25% in patients hospitalized in the general ward and 23.4-50% in patients treated in the intensive care unit (ICU) (1-3). As a contradictory finding; the incidence of deep vein thrombosis (DVT) was 14.8% in hospitalized patients with COVID-19, and surprisingly, more than half of COVID-19 patients with PE had no DVT (1). Virchow's triad consists of three components which are reduced blood flow, endothelial damage, and hypercoagulability that leads to increased thromboembolism. Hypercoagulability in COVID-19 emerges due to endothelial injury in all organs, which is accompanied by increases in ferritin, C-reactive protein, D-dimer, fibrinogen, and proinflammatory cytokines, including interleukin-6 (4).

In the setting of COVID-19-related venous thromboembolism (VTE); activation of macrophages, endothelial dysfunction, hyperinflammation, disseminated intravascular coagulation, platelet dysfunction, and *in situ* thrombosis are thought to be involved in the pathogenesis. This condition is called microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (5,6). D-dimer elevation, thrombocytopenia, and prolonged prothrombin time have been reported as coagulation disorders accompanying worse prognosis in COVID-19 cases. D-dimer measurements may contribute to the diagnosis of PE in patients with COVID-19, but an absolute diagnostic threshold value has not yet been determined (7). Clinical pre-test probability criteria such as the Wells score recommended by clinical practice guidelines to predict the diagnosis of PE and the pulmonary embolism severity index (PESI) used to predict PE mortality are unreliable in COVID-19 patients (8-11). Definitions of Wells and PESI scores are given in tables Supplementary Table S1 and S2.

In our study, PE clinical, imaging [computed tomography pulmonary angiogram (CTPA)], laboratory features, and pulmonary distribution were examined in COVID-19 pneumonia cases who underwent CTPA. The aim of this retrospective study was to determine the prevalence of PE diagnosed on CTPA, the distribution of PE, and the severity of chest CT involvement in patients with COVID-19 pneumonia. The usefulness of the D-dimer levels, Wells' criteria, and PESI scale in the diagnosis and prognosis of PE in these individuals was another goal of our study.

METHODS

This retrospective, cross-sectional, single-center study was conducted at the Department of COVID-19 Clinic, Prof. Dr. Murat Dilmener Emergency Hospital, İstanbul, Türkiye, a tertiary pandemic hospital, from June 1, 2021 to 31 December 2021. All consecutive adult (>18 years) hospitalized patients who were diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia by real-time polymerase chain reaction testing and also underwent CTPA imaging for PE within the given time period were searched in the hospital electronic registry system. Patients with no radiological involvement, incomplete clinical and laboratory data were excluded from the study. Another criterion for exclusion was pregnancy. After exclusion, 220 patients (older than 18 years) were included in the study.

The following data were retrospectively extracted from the database of the patient management system of the Department of COVID-19 Clinic, Prof. Dr. Murat Dilmener Emergency Hospital, İstanbul, Türkiye: demographic (age, sex), clinical (comorbidities, pharmacological treatment before and during hospitalization, time between symptoms

onset and hospitalization, time between symptoms onset to CTPA, time between admission and CTPA, the length of hospitalization days), laboratory (D-dimer, PRO-BNP, and high-sensitivity troponin T/hs-TnT), CTPA data, clinical outcomes (death, discharge or ICU admission), and treatment. The reasons patients had been sent for CTPA were obtained from the electronic medical records as an elevated D-dimer level or accompanying symptoms, including chest pain, hemoptysis, dyspnea, or sudden unexplained clinical deterioration. D-dimer levels within 24 hours (h) from CTPA were obtained. In addition, all the components relevant for Wells score and PESI scale systems were noted (8-10). All patients enrolled in the study were over the age of 18. They were managed in accordance with the COVID-19 treatment protocol of the Turkish Health Ministry, and weight-based thromboprophylaxis was started with low-molecular-weight heparin (LMWH), enoxaparin sodium once daily for all inpatients with COVID-19 pneumonia if no contraindication (12). Nonetheless, it was observed that the course of treatment was continued for patients who were already on non-vitamin K antagonist oral anticoagulant (NOAC) or vitamin K antagonist (VKA).

The clinical findings of the hospitalized patients were classified as moderate or severe according to the NIH criteria (13). CT graded the severity of COVID-19 pneumonia lung paraenchymal changes into three categories; low, moderate, and severe involvement (14). CTPA images were evaluated for the presence of PE, anatomic distribution of PE such as major vessel or minor vessel involvement. Cases were categorized as patients with PE and patients with non-PE on the basis of CTPA imaging. PE related to major vessel was defined as main pulmonary artery and/or lobar artery involvement, while minor vessel was defined as segmental artery and/or subsegmental involvement. Early PE diagnosis was discretionary when diagnosis was confirmed within 24 h of admission. The Wells score and PESI scale systems were calculated by the authors. The primary outcome was PE confirmed by CTPA. It was also assessed the death, admission to the ICU, hospital length of stay, D-dimer value, Wells score, and PESI scale in COVID-19 pneumonia with PE.

The research protocol was approved by the Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2022-02-11, date: 17.01.2022) and was conducted following the principles of the Declaration of Helsinki. The requirement for informed consent from individual patients was waived because of the observational retrospective design of this study.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) v. 26. Continuous data were reported as the mean ± standard deviation for normally distributed data or the median and interquartile range (IQR) for non-normally distributed data. Categorical data are reported as counts and percentages. Numerical variables are given as frequencies (percentages). Student's t-test was used for two-group comparisons of quantitative data with normal distribution, and the Mann-Whitney U test was used for two-group comparisons of data that did not show normal distribution. For comparison of qualitative data, Pearson's chi-square test, Fisher's Exact test were used. Diagnostic screening tests [sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)] and receiver operating characteristic (ROC) curve analysis were performed and area under the curve (AUC) calculated to identify the cutoff value for the D-dimer level. Multivariate logistic regression analysis was performed to identify risk factors for developing PE. Significance was assessed at least at $p<0.05$ level.

RESULTS

All consecutive patients who underwent CTPA scanning for PE were excluded. Ultimately, 220 patients met all the inclusion criteria. Of these, 96 (43.63) patients had PE. Flow chart of the study population in Figure 1. The mean age was 65.7±16.28 (range 24-94 years), and the male to female ratio was 51.4:48.6. Dyspnea (184-83.6%), cough (48-21.8%), and

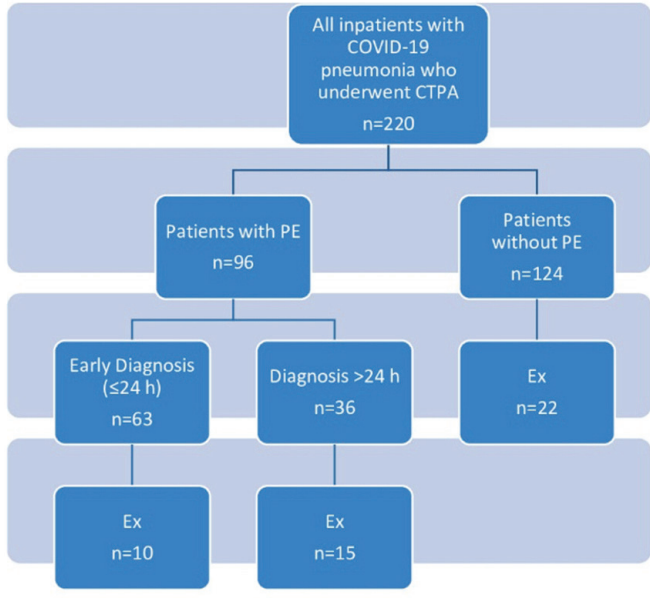

Figure 1. Flow chart of the study population
CTPA: Computed tomography pulmonary angiography, PE: Pulmonary embolism, COVID-19: Coronavirus disease-2019

Table 1. Demographic and baseline clinical characteristics of study participants with and without pulmonary embolism

		All patients (n=220)	Pulmonary embolism		
			Absent (n=124)	Present (n=96)	p-value
Age, years mean ± SD		65.70±16.28	66.94±15.17	64.10±17.56	[a]0.210
Sex, n (%)	Male	113 (51.4)	71 (57.3)	42 (43.8)	[b]0.047*
	Female	107 (48.6)	53 (42.7)	54 (56.3)	
Symptoms, n (%)	Dyspnea	184 (83.6)	106 (85.5)	78 (81.3)	[b]0.400
	Cough	48 (21.8)	30 (24.2)	18 (18.8)	[b]0.332
	Chest pain	32 (14.5)	11 (8.9)	21 (21.9)	[b]0.007**
	Haemoptysis	11 (5.0)	3 (2.4)	8 (8.3)	[c]0.062
	Nausea	3 (1.4)	1 (0.8)	2 (2.1)	[c]0.582
	Fever	17 (7.7)	9 (7.3)	8 (8.3)	[b]0.767
	Weakness	29 (13.2)	12 (9.7)	17 (17.7)	[b]0.081
	Back pain	3 (1.4)	1 (0.8)	2 (2.1)	[c]0.582
	Abdominal pain	10 (4.5)	5 (4.0)	5 (5.2)	[c]0.751
	Leg swelling or pain	4 (1.8)	0 (0.0)	4 (4.2)	[c]0.035*
	Dizziness	8 (3.6)	5 (4.0)	3 (3.1)	[c]1.000
	Syncope	4 (1.8)	3 (2.4)	1 (1.0)	[c]0.634
Time between symptom onset and hospitalization, days mean ± SD		7.25±5.03	6.77±5.43	7.86±4.41	[d]0.006**
Time between symptom onset to CTPA, days mean ± SD		9.45±6.72	8.74±7.13	10.36±6.06	[d]0.005**
Time between admission and CTPA, days mean ± SD		3.13±4.52	2.74±4.13	3.64±4.96	[d]0.057
Early PE diagnosis (≤24 h from admission), n (%)				63 (65.62)	
Physical findings, mean ± SD					
Body temperature, °C		36.76±0.5	36.74±0.52	36.79±0.48	[d]0.134
Systolic blood pressure, mmHg		125.79±15.73	124.27±14.67	127.75±16.87	[d]0.073
Diastolic blood pressure, mmHg		68.2±8.96	67.93±8.53	68.55±9.53	[d]0.149
Heart rate per minute		89.29±13.12	87.72±13.83	91.32±11.92	[a]0.043*
Respiratory rate, breaths per minute		25.32±5.26	23.16±4.11	28.11±5.29	[d]0.001**
SpO_2 under oxygen support		93.72±6.29	94.32±2.01	92.94±9.22	[d]0.043*
Oxygen support, L/per min		8.07±7.37	7.48±6.85	8.82±7.97	[d]0.262
Comorbidities, n (%)		183 (83.2)	109 (87.9)	74 (77.1)	[b]0.033*
Hypertension		122 (55.5)	74 (59.7)	48 (50.0)	[b]0.152
Diabetes mellitus		81 (36.8)	51 (41.1)	30 (31.3)	[b]0.132
Coronary artery disease		53 (24.1)	32 (25.8)	21 (21.9)	[b]0.499
Atrial fibrillation		16 (7.3)	11 (8.9)	5 (5.2)	[b]0.300
Congestive heart failure		39 (17.7)	23 (18.5)	16 (16.7)	[b]0.717
Dyslipidemia		21 (9.5)	14 (11.3)	7 (7.3)	[b]0.317

Table 1. Continued

Cerebrovascular disease		16 (7.3)	10 (8.1)	6 (6.3)	[b]0.607
Chronic kidney disease		26 (11.8)	16 (12.9)	10 (10.4)	[b]0.571
Rheumatic disease		7 (3.2)	4 (3.2)	3 (3.1)	[c]1.000
Malignancy		30 (13.6)	21 (16.9)	9 (9.4)	[b]0.105
Valvular heart disease		8 (3.6)	5 (4.0)	3 (3.1)	[c]1.000
Peripheral artery disease		7 (3.2)	6 (4.8)	1 (1.0)	[c]0.140
COPD		22 (10.0)	13 (10.5)	9 (9.4)	[b]0.786
Asthma		18 (8.2)	10 (8.1)	8 (8.3)	[b]0.942
Disease severity status, n (%)	Severe	182 (82.7)	103 (83.1)	79 (82.3)	[b]0.880
	Moderate	38 (17.3)	21 (16.9)	17 (17.7)	
Hospital length of stay, days mean ± SD		18.50±14.58	18.81±16.88	18.09±10.99	[d]0.350
ICU length of stay, days mean ± SD		3.77±7.76	3.38±7.47	4.28±8.14	[d]0.377
Outcomes, n (%)					
Admission to ICU, n (%)		71 (32.3)	38 (30.6)	33 (34.4)	[b]0.557
Death in the ICU, n (%)		43 (19.5)	20 (16.1)	23 (24.0)	[b]0.146
Death, n (%)		47 (21.4)	22 (17.7)	25 (26.0)	[b]0.136

COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, PE: Pulmonary embolism, CTPA: Computed tomography pulmonary angiography, ICU: Intensive care unit
[a]Student's t-test; [b]Pearson chi-square test; [c]Fisher's Exact test; [d]Mann-Whitney U test *p<0.05; **p<0.01. Bold indicates statistical significance. Categorical data are presented as n (%). Continuous data are presented as mean ± SD

chest pain (32-14.5%) were the most common symptoms. Time between symptom onset and hospitalization was 7.25±5.03 days (IQR 6 range 4-10) was. The mean length of hospital stay was calculated as 18.50±14.58 days. Seventy-one (32.3%) cases were referred to the ICU. Forty-seven cases (21.4%) died, 43 (19.5%) of whom were in the ICU. The incidence of PE diagnosis was 43.63% (96/220) in patients who underwent CTPA with suspicion of PE. In addition, 65.62% (63/96) of all PE cases were diagnosed with PE within the first 24 h after admission. Table 1 summarizes the baseline characteristics of the study population.

The incidence of PE was statistically significantly higher in women than in men (p<0.05). The mean age of women in the PE group was higher than men (p=0.008; p<0.01) (Summary statistics by age and gender in Supplementary Table S3). The incidence of chest pain and lower leg pain in patients with PE was found to be statistically significantly higher than that in patients without PE (respectively, p<0.01 vs. p<0.05). Time between symptom onset and hospitalization in patients with PE was found to be significantly higher than that in patients without PE (7.86±4.41 vs. 6.77±5.43 days; p<0.01). Time between symptom onset to CTPA in cases with PE was significantly higher than that in cases without PE (10.36±6.06 vs. 8.74±7.13 days; p<0.01).

The D-dimer value of the cases with PE was found to be significantly higher than that of the cases without embolism (4.5±2.68 vs. 3.71±3.6; p<0.01) (Table 2). The D-dimer/hs-TnT ratio was significantly higher in the PE group (153.91±323.51 vs. 55.40±156.75; p<0.01). Figure 2 evaluates the performance of the D-dimer assay in determining PE as a ROC curve. AUC of the ROC curve is 0.626 (95% CI = 0.550-0.703; p=0.001). A D-dimer with a best cut-off value of 3.95 µg FEU/mL provided a sensitivity of 64.21%, specificity of 69.11%, PPV of 61.6%, NPV of 71.4%, and odds ratio (OR) of 4.013 (95% CI: 2.275-7.080).

PE anatomic localization distribution was as follows: 56.25% (54 cases) unilateral, 62.5% (60 cases) multiple, 40.6% (39 cases) multilobar/bilateral, 86.5% (83) right-sided, and 66.6% (64 cases) lower lobe artery. 31.25% (30 cases) major vessels (main pulmonary artery and lobar pulmonary artery) and 34.37% (33 cases) minor vessels (segmental and subsegmental artery) localized PEs were detected. Severe CT lung paraenchymal involvement was significantly higher in PE cases (p<0.05) (Table 3).

Classifying all cases according to the Wells three-level score, 215 (97.7%) cases had intermediate clinical risk and 5 (2.3%) cases had high clinical risk (Table 4). The Wells

Table 2. Laboratory data of the study population COVID-19 patients at the time of CTPA

Laboratory findings Mean ± SD	Pulmonary embolism			
	All patients (n=220)	Absent (n=124)	Present (n=96)	p-values
Neutrophil count, cells/mL	8.87±4.78	8.63±4.37	9.19±5.26	[d]0.748
Lymphocytes count, cells/mL	1.32±1.2	1.41±1.43	1.2±0.82	[d]0.392
Neutrophil/lymphocyte ratio	11.81±14.79	11.46±16.27	12.27±12.73	[d]0.306
Platelet count, $10^3/mm^3$	241.73±121.15	232.09±120.77	254.07±121.15	[a]0.183
Hematocrit, %	35.18±6.65	35.24±7.07	35.1±6.1	[a]0.878
Glucose, mg/dL	163.52±70.48	164.12±74.61	162.76±65.18	[d]0.746
Urea, mg/dL	54.19±43.76	57.14±44.93	50.4±42.15	[d]0.109
Creatinine, mg/dL	1.3±2.08	1.32±1.82	1.29±2.4	[d]0.103
ALT, U/L	38.54±66.25	36.38±70.78	41.33±60.16	[d]0.101
AST, U/L	45.63±70.50	47.30±86.39	43.47±42.26	[d]0.099
Albumin, g/dL	33±6.13	32.81±6.36	33.26±5.86	[a]0.599
LDH, U/L	449.42±498.49	438.73±484.11	463.23±518.71	[d]0.127
C-reactive protein, mg/L	124.82±89.74	125.26±95.88	124.24±81.6	[d]0.733
Procalcitonin, ng/mL	1.22±4.11	1.16±3.45	1.3±4.85	[d]0.125
Ferritin, µg/L	964.59±1457.21	967.11±1487.59	961.33±1424.76	[d]0.390
D-dimer, µg FEU/mL	4.06±3.25	3.71±3.6	4.5±2.68	**[d]0.001****
D-dimer >1 µg FEU/mL n, (%)				
No	26 (11.8)	15 (12)	11 (11.4)	b0.841
Yes	194 (88.2)	109 (88)	85 (88.6)	
Troponin T is highly sensitive, ng/mL	26.16±51.53	27.87±46.56	23.89±57.64	**[d]0.002****
D-dimer/troponin T high sensitive	97.75±247.11	55.40±156.75	153.91±323.51	**[d]0.001****
Fibrinogen, mg/dL	618.68±203.47	622.87±220.64	613.23±179.76	[a]0.724
International normalized ratio	1.24±0.48	1.20±0.44	1.28±0.53	[d]0.183
ProBNP, ng/L	4614.91±6291.9	3442.77±3507.28	5179.27±7258.57	[d]0.851

SD: Standard deviation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CTPA: Computed tomography pulmonary angiography, COVID-19: Coronavirus disease-2019
[a]Student's t-test, [b]Pearson chi-square test, [c]Fisher's exact test, [d]Mann-Whitney U test, *p<0.05, **p<0.01. Categorical data are presented as n (%). Continuous data are presented as mean ± SD. Bold indicates statistical significance

three-level score was similar in the groups with and without PE groups (p>0.05). If the study population was classified according to the Wells two-level score, the Wells score of >4 (PE likely) was 9/124 (7.3%) without PE vs. 16/96 (16.7%) with PE (p<0.05). When the Wells score and D-dimer values were evaluated together, D-dimer value of the cases with PE in the PE unlikely probability group was found to be statistically significantly higher than the cases without PE (p<0.01) (Figure 3) (Likely considered as Wells score of >4). Considering the Wells score components in patients with PE, signs or symptoms of DVT (4-4.2%; p<0.05), previous DVT or PE (6-6.3%; p<0.01), and immobilization/surgery in the past 4 weeks (14-14.6%; p<0.05) were found to be significantly higher compared with patients without PE. The mean PESI scale was 120.35±49.36 (median 32-223) (Table 4). It was observed that 39.6% (n=38) of the cases were PESI Class V (PESI scale distribution and mortality rates in Supplementary Table S4).

Female sex, leg swelling or pain, heart rate, respiratory rate, lower SpO_2 levels, late hospitalization after symptom onset, time between symptom onset to CTPA, D-dimer, D-dimer/hs-TnT, higher chest CT involvement score, signs or symptoms of DVT, previous thromboembolic disease, and immobilization/surgery in the past 4 weeks were all significantly associated with PE by univariate analysis. When the variables found to be effective on PE (p<0.200) were put on backward stepwise multivariate logistic regression

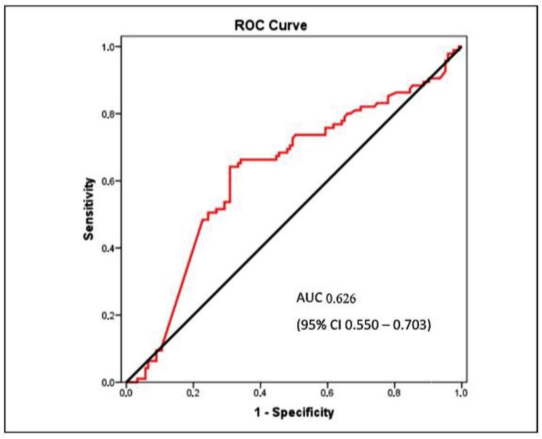

Figure 2. Receiver operating characteristic curve for D-dimer for the diagnosis of pulmonary embolism
AUC: Area under the curve, ROC: Receiver operating characteristic, CI: Confidence interval

Table 3. Findings on CTPA in the study population

	All patients (n=220)	Non-PE (n=124)	PE (n=96)	p-values
CT involvement, n (%)				[b]0.040*
Low	47 (21.4)	25 (20.2)	22 (22.9)	
Moderate	96 (43.6)	63 (50.8)	33 (34.4)	
Severe	77 (35.0)	36 (29.0)	41 (42.7)	
Major vessel			30 (31.2)	
Only the main pulmonary artery			13 (13.5)	
Only the lobar pulmonary artery			17 (18.8)	
Minor vessel			33 (34.3)	
Only segmental artery			23 (23.9)	
Only the subsegmental artery			10 (10.4)	
Both (major + minor)			33 (34.3)	
Lower lobe artery			64 (66.6)	
Bilaterally			42 (43.75)	
Unilaterally			54 (56.25)	
Right sided			83 (86.45)	
Multiple			54 (56.3)	
Multilobar/ bilaterally			39 (40.6)	

Values are n (%). [b]Pearson chi-square test
PE: Pulmonary embolism, CT: Computed tomography, CTPA: Computed tomography pulmonary angiography

analysis, the model was found to be significant and had a coefficient of determination 76.8%. Because of the logistic regression analysis, female gender, hemoptysis, time between symptom onset and hospitalization, time between symptom onset and CTPA, time between admission and CTPA, systolic blood pressure, and respiratory rate were independent risk factors for PE (Table 5). The presence of female sex and haemoptysis both showed a higher risk of acquiring PE by 2.643 (OR 2.643, 95% CI: 1.291-5.414, $p<0.05$), and 10.6 (OR 10.698, 95% CI: 1.886-60.68, $p<0.05$), respectively, by backward logistic regression analysis (Table 5).

Patients were also evaluated about drugs that were regularly taken before hospitalization and continued during hospitalization. Only VKA use in the PE group was found to be statistically significantly higher ($p<0.05$). Three of seven patients were using VKA for AF diagnosis before hospital admission and PE had developed despite anticoagulant therapy. However, the remaining 4 patients began VKA treatment after the diagnosis of PE. The LMWH title covered both prophylaxis and PE treatment (Table 6).

Although not statistically significant, the mortality was higher in individuals with PE than in those with both deaths in the ICU (24% vs. 16.1%) and overall mortality (26% vs. 17.7%) ($p>0.05$).

DISCUSSION

This research provides information about the incidence of PE in patients hospitalized for COVID-19 pneumonia at the COVID-19 departments of our hospital. We found 96 (43.63%) patients with verified PE and COVID-19 pneumonia out of 220 CTPAs performed. These data strengthen the hypothesis that COVID-19 patients have an increased thromboembolic risk. Females with hemoptysis

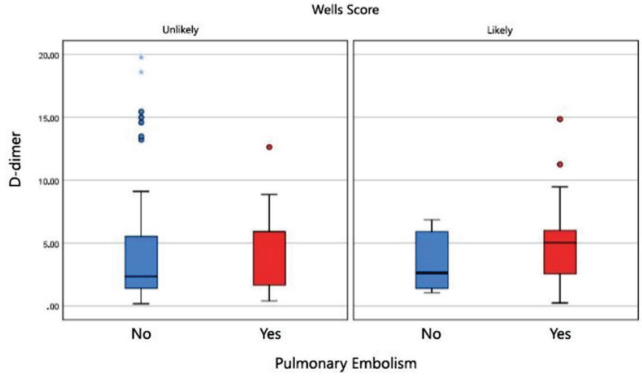

Figure 3. Distribution of D-dimer values in patients at likely and unlikely probability for pulmonary embolism (Wells score of >4, PE likely)

have a higher risk of PE occurrence. Patients with PE who have severe lung paraenchymal involvement are more common on CT. D-dimer levels are higher among COVID-19 hospitalized patients with PE, but its use to exclude PE in this population may have limited clinical utility. Although a Wells score of 4 or more points helps to predict PE in our cohort, the outcome can be present even with lower scores. The PESI scale in patients with PE secondary to COVID-19 underrates the risk of in-hospital mortality.

Our cohort showed a diagnostic performance of 43.63% in hospitalized patients with SARS-CoV-2 who underwent CTPA because of a clinical suspicion for PE. In previous

Table 4. Predictive scores of study participants

	All patients (n=220)	Pulmonary embolism		p-value
		Absent (n=124)	Present (n=96)	
Components of Wells score, n (%)				
Signs or symptoms of DVT	4 (1.8)	0 (0.0)	4 (4.2)	[c]**0.035***
Heart rate >100/min	38 (17.3)	18 (14.5)	20 (20.8)	[b]0.219
Previous thromboembolic disease	6 (2.7)	0 (0.0)	6 (6.3)	[c]**0.006****
Immobilisation/surgery in the past 4 weeks	22 (10.0)	8 (6.5)	14 (14.6)	[b]**0.048***
Haemoptysis	11 (5.0)	3 (2.4)	8 (8.3)	[c]0.062
Malignancy	30 (13.6)	21 (16.9)	9 (9.4)	[b]0.105
Wells score				[c]0.655
Low risk (0-1 points)	0	0	0	
Intermediate risk (2-6 points)	215 (97.7)	122 (98.4)	93 (96.9)	
High risk (>6 points)	5 (2.3)	2 (1.6)	3 (3.1)	
Likely >4	25 (11.4)	9 (7.3)	16 (16.7)	[b]**0.029**
Unlikely ≤4	195 (88.6)	115 (92.7)	80 (83.3)	
PESI score			120.35±49.36	
Class I			10 (10.4)	
Class II			15 (15.6)	
Class III			23 (24.0)	
Class IV			10 (10.4)	
Class V			38 (39.6)	

[b]Pearson chi-square test, [c]Fisher's Exact test, *p<0.05, **p<0.01. Categorical data are presented as n (%). Continuous data are presented as mean ± standard deviation.
Bold indicates statistical significance
DVT: Deep vein thrombosis, PESI: Pulmonary embolism severity index

Table 5. Multivariate logistic regression analysis of risk factors for PE

	OR	p-value	95% CI	
			Lower	Upper
Female sex	2.643	**0.008****	1.291	5.414
Haemoptysis	10.698	**0.007****	1.886	60.681
Time between symptom onset and hospitalization, days	2.407	**0.029***	1.094	5.297
Time between symptom onset to CTPA, days	0.431	**0.036***	0.196	0.945
Time between hospitalization and CTPA, days	2.432	**0.038***	1.049	5.639
Systolic blood pressure, mmHg	1.037	**0.002****	1.013	1.062
Respiratory rate, breaths per minute	1.357	**0.001****	1.231	1.495

OR: Odds ratio, CI: Confidence interval, CTPA: Computed tomography pulmonary angiography, PE: Pulmonary embolism

Table 6. Medication during hospitalization before and after PE diagnosis

		All patients (n=220)	Pulmonary embolism		
			Absent (n=124)	Present (n=96)	
		n (%)	n (%)	n (%)	p-value
Drugs used during hospitalization	ASA	39 (17.7)	24 (19.4)	15 (15.6)	[b]0.473
	Clopidogrel	20 (9.1)	13 (10.5)	7 (7.3)	[b]0.414
	DAPT	13 (5.9)	9 (7.3)	4 (4.2)	[b]0.335
	VKA	8 (3.6)	1 (0.8)	7 (7.3)	[c]**0.023***
	NOAC	7 (3.2)	5 (4.0)	2 (2.1)	[c]0.473
	β-Blocker	51 (23.2)	31 (25.0)	20 (20.8)	[b]0.468
	Ca++ channel blocker	25 (20.2)	25 (26.0)	50 (22.7)	[b]0.302
	ACE-I	20 (9.1)	11 (8.9)	9 (9.4)	[b]0.897
	ARB	21 (9.5)	14 (11.3)	7 (7.3)	[b]0.317
	Statin	21 (9.5)	14 (11.3)	7 (7.3)	[b]0.317
	LMWH	201 (91.4)	114 (91.9)	87 (90.6)	[b]0.731
Trombolytic therapy	Alteplase	7 (3.2)		7 (7.3)	-

PE: Pulmonary embolism, ASA: Acetylsalicylic acid, DAPT: Dual antiplatelet therapy, VKA: Vitamin K antagonist, NOAC: Non-vitamin K antagonist oral anticoagulant drugs, ACE-I: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, LMWH: Low molecular weight heparin
Alteplase, recombinant human tissue-type plasminogen activator (t-PA). Categorical data are presented as n (%). [b]Pearson chi-square test. [c]Fisher's Exact test. *p<0.05. Bold indicates statistical significance.

studies, the incidence of PE in COVID-19 cases was reported to be 14-38% (3,15-18). In the studies conducted with patients who were hospitalized for any reason in the pre-COVID-19 period, the diagnosis of PE with CTPA was found to be 12-17% (19). Various studies have reported different values for PE incidence because of diverse protocols or the availability of CTPA (3,15,17,18). The incidence of PE was higher in prospective studies, in studies that did not include anticoagulation therapy, in ICU admission or critical cases, and in studies in which CTPA was applied to all cases according to a meta-analysis (1).

Unlike previous studies, the female gender had a 2.6 times higher risk of developing PE in our study. PE cases were elderly female cases consistent with the general population (20). Although many studies on COVID-19 announced that the frequency of PE, severe disease, and mortality were higher in males, some studies reported that there was no difference in terms of gender (5,21).

The incidence of hemoptysis was calculated as 8.3% (8 cases) in the PE group in our study. The incidence of hemoptysis was 2.2% in a study of PE developing in cases with COVID-19; PE in non-COVID cases in the general population has been reported as 13% (Table 5) (22,23).

The D-dimer level was significantly higher in COVID-19 pneumonia patients with PE than in those without PE, consistent with previous data (5,7). Meanwhile, high D-dimer levels were common in COVID-19 patients even in the absence of PE in our study, in concordance with previous studies (7,24). Ultimately, higher D-dimer levels are not only a marker of pneumonia severity but also linked with a higher risk of PE (21,25,26). A higher cut-off value specifically as 3.95 µg FEU/mL for D-dimer, could predict the risk of PE in COVID-19 patients with a sensitivity of 64.21% and specificity 69.11%. AUROC was 0.626 in our calculations, which demonstrates the lower discriminative power of D-dimer levels used to detect PE in previous research (1,24,25,27). There are many studies reporting different sensitivity and specificity with different threshold values (15,17,18,24,28,29). Indeed, higher cut-off values than those conventionally used (1000 mg/L) reduced the sensitivity of D-dimer levels as a scanning examination to rule out PE (1). Therefore, some studies recommend D-dimer thresholds used in outpatients who have no COVID-19 to safely exclude PE (27,29). Elevation of D-dimer levels in the COVID-19 population may originate in the presence of various conditions such as prothrombotic coagulopathy or pulmonary microvascular thrombosis, and systemic inflammation (6,7).

There was a significant association between the D-dimer/hs-TnT ratio in PE. Cardiac troponins may be elevated in patients with right ventricular dysfunction or severe PE, and high troponin levels are associated with poor prognosis (27,30). One study reported that the D-dimer/troponin I

ratio is a simple and useful test to distinguish between PE and acute non-ST-segment elevation myocardial infarction (31). Studies on COVID-19 have reported that high troponin and ProBNP levels are associated with poor prognosis and mortality (32). Ultimately, natriuretic peptides and troponins can increase in various pathological situations and are not specific to VTE. Simultaneously, both BNP and troponin levels can be used to assess the risk of intermediate short-term adverse events in patients with PE (27). In patients with acute dyspnea and high PE clinical suspicion, high troponin values are also expected. While higher troponin levels in the non-PE group indicate cardiac dysfunction, its lower rate in the PE group can be interpreted as an appropriate cohort of the studied patient group, since this finding indicates that acute dyspnea is non-cardiac in the PE clinic. The fact that ProBNP levels are not different in the presence of PE or cardiac dyspnea in patients presenting with acute dyspnea may support this hypothesis.

Only 16.7% of patients with PE had a Wells score of 4 points or higher, and 3.1% of patients with PE had a high risk probability (>6 points). In the Wells score high-risk probability group, only 3 out of 5 cases were PE; however, PE was detected in 215 cases in the intermediate-probability risk group, and these results showed that the incidence of PE was higher than expected in the intermediate group.

These findings indicate that the Wells score may be insufficient or unreliable in predicting PE. Although some studies have previously shown that a Wells score of 4 or more points can predict PE in patients with COVID-19, there are also contradicting studies reporting that the Wells score is a weak indicator for predicting PE in patients with COVID-19 (5,15,17,29,33,34). Nonetheless, there are also studies reporting that combining Wells score and D-dimer levels is a more logical approach in predicting PE in COVID-19 cases (25,34,35).

If Wells score components were evaluated separately, the presence of symptoms or signs of DVT, history of thromboembolic disease, and immobilization/surgery (in the past 4 weeks) were significantly higher in patients with PE, although in small numbers. At the same time, it was reported that regarding traditional risk factors (advanced age, history of venous thromboembolic disease, thrombophilia, cancer, smoking, diabetes, hypertension, chronic heart failure, or coronary artery disease) for VTE, there were no differences between patients with and without PE (5,21). However, one study reported that DVT signs and symptoms were associated with PE (15). In our study, lower extremity Doppler ultrasonography (USG) was performed in only 4 patients. Higher rates of DVT have been reported in studies that screened all patients with Doppler USG, regardless of symptoms (36). The Wells score is based on the assumption that PE is a consequence of DVT or immobilization; however, it has been reported that 55-85% of COVID-19-related PE cases do not have DVT (1,33). PE may arise from direct endothelial cell damage caused by the virus or from an inflammatory process related to alveolar damage in COVID-19 patients (4-6). This may be the reason why the Wells score performs weakly in predicting COVID-19-related PE. Although the pathophysiology of PE development in COVID-19 has aspects that can be explained by the Virchow triad; COVID19-associated hypercoagulability is still special and distinctive with involvement of the immune system (4).

Our results showed that the PESI scale underestimates the risk of inhospital mortality, similar to other studies; however, it maintains its acceptable ability to discriminate patients with Class I and Class V (11,27). Ultimately, according to our findings, the Wells score was found insufficient to predict the diagnosis of PE, and the PESI scale was again inadequate to determine the prognosis of PE.

The same as earlier research, although there was no significant difference in mortality between the PE group and the non-PE group, the mortality was non-significantly higher in the PE group (26%, 25 cases) (5,22). Contradicting with this fact, there are studies reporting that mortality is high in cases of PE with COVID-19, as well as studies mentioning increased mortality compared to non-COVID cases (22,28).

Consistent with published studies, in our cohort, there was a significant association between PE and severity of COVID-19 disease paraenchymal involvement on CTPA imaging (17,37). In our study, major vessel and minor vessel involvement rates were found to be very close to each other (30 cases, 31.25% vs. 33 cases, 34.37%). There are also contradicting studies in which peripheral and lower lobe artery involvement are reported to be higher (15,17,22) and studies reporting that 44-56% central/lobar pulmonary artery involvement is more frequent (38).

In our cohort, the presence of clinical signs of DVT in COVID-19 patients with PE was very small in number; also, similar rates of major and minor vessel involvement of PE suggest that both conventional thromboembolic origin and *in situ* immunothrombosis may be involved in the pathophysiology of COVID-19-associated PE (5,6).

The duration between the onset of symptoms and admission to the hospital and time to CTPA were longer in the PE group. The reasons for these findings may be longer bed rest and/or immobilization; late initiation of prophylactic anticoagulants, or an unknown immune system-related pathophysiological mechanism (28). Haemoptysis, chest pain, lower leg pain,

and dyspnea symptoms should be noted.

This study showed that 65.62% of all PE cases were diagnosed with CTPA within the first 24 h of admission. In various studies, early diagnosis rates ranged from 14.2% to 68.8% (11,16). Studies have shown that the diagnosis of PE is made earlier with increased CTPA requests in the pre-ICU stage after the first wave in cases with COVID-19, and as a result, the risk of PE in the ICU is reduced (37). The diagnosis of most cases with PE within the first 24 h in the early stage of this process suggests that hypercoagulation may have started before hospitalization (15,28).

The presence of MicroCLOTS and macrovascular disease findings in PE developing in COVID-19 cases indicates that there are still many things unknown; it also highlights the difficulty of distinguishing between clinical and/or CTPA findings and separating conventional thromboembolism and *in situ* immunothrombosis (5,6).

The limitations of this study include its retrospective nature and small sample size. There is a potential selection bias because only cases with clinical and laboratory findings and suspected PE are evaluated with CTPA. Doppler ultrasound imaging of the lower extremity for deep venous thrombosis and transthoracic echocardiography could not be performed.

CONCLUSION

Our research showed that PE appears to be a common complication of SARS-CoV-2 infection, the Wells score used in the general population was not helpful in the diagnosis of PE, and the PESI score was unreliable in predicting the mortality risk of PE in these patients. Higher D-dimer values may detect COVID-19-related PE. These findings indicate that CT with contrast could be more widely used when assessing individuals with COVID-19 pneumonia, particularly in those with elevation of D-dimer and presence of hemoptysis.

ETHICS

Ethics Committee Approval: The research protocol was approved by the Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2022-02-11, date: 17.01.2022) and was conducted following the principles of the Declaration of Helsinki.

Informed Consent: The requirement for informed consent from individual patients was waived because of the observational retrospective design of this study.

Authorship Contributions

Surgical and Medical Practices: I.K.A., M.B., Concept: I.K.A., M.B., Design: I.K.A., M.B., Data Collection or Processing: I.K.A., M.B., Analysis or Interpretation: I.K.A., M.B., Literature Search: I.K.A., M.B., Writing: I.K.A., M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Table S1. Wells clinical prediction rule for pulmonary embolism

Items	Clinical desicion rule points
Previous PE or DVT	1.5
Heart rate ≥100 bpm,	1.5
Immobilisation or surgery in the past 4 weeks	1.5
Haemoptysis	1
Active cancer	1
Clinical signs of DVT	3
Alterative diagnosis less likely than PE	3
Clinical probability	
Three-level score	
Low risk	0-1
Intermediate risk	2-6
High risk	≥7
Two-level score	
PE unlikely	0-4
PE likely	≥5

PE: Pulmonary embolism, bpm: Beats per minutes, DVT: Deep vein thrombosis

Table S2. Pulmonary embolism severity index in risk stratification

Parameter	Score
Age	Age in years
Male sex	+10 points
Cancer	+30 points
Chronic heart failure	+10 point
Chronic pulmonary disease	+10 point
Pulse rate ≥110 bpm,	+20 points
Systolic blood pressure <100 mmHg	+30 points
Respiratory rate >30 breaths per min	+20 points
Temperature <36 °C	+20 points
Altered mental status	+60 points
Arterial oxygen saturation <90%	+20 points
Risk strata	**Class I:** ≤65 points very low 30 day mortality risk (0-1.6%) **Class II:** 66-85 points low mortality risk (1.7-3.5%)
	Class III: 86-105 points moderate mortality risk (3.2-7.1%) **Class IV:** 106-125 points high mortality risk (4.0-11.4%) **Class V:** >125 points very high mortality risk (10.0-24.5%)

bpm: Beats per minutes

Table S3. Summary statistics by age and gender in study population

		Gender		
		Male	**Female**	**p-value**
Age mean ± SD	Non-PE	66.59±13.61	67.40±17.17	[a]0.771
	PE	58.81±18.09	68.22±16.13	[a]**0.008****

PE: Pulmonary embolism, SD: Standard deviation
[a]Student's t-test, **p<0.01

Table S4. PESI score distribution and mortality rates

PESI score	n (%)	Death	Predicting inpatient mortality	Predicting 30 day mortality
Class 1	10 (10.4)	0	0.8	0-1.6
Class 2	15 (15.6)	2 (2.8)	1.8	1.7-3.5
Class 3	23 (24.0)	5 (5.2)	4.2	3.2-7.1
Class 4	10 (10.4)	2 (2.8)	5.9	4.0-11.4
Class 5	38 (39.6)	16 (16.6)	15.8	10.0-24.5

PESI: Pulmonary embolism severity index