Journal of The Cardiovascular Thoracic Anaesthesia and Intensive Care Society

GKDA Derg 2022;28(1):56-63
DOI: 10.14744/GKDAD.2022.32848

Research Article / Araştırma

Comparison of High-Risk Pulmonary Embolism Patients with and without COVID-19

COVID-19 sonrası olan ve COVID-19 dan bağımsız oluşmuş Yüksek Riskli Pulmoner Emboli Hastalarının Karşılaştırılması

Bengü Şaylan,[1] İsmail Selçuk,[2] Bülent Barış Güven,[3] Tayfun Çalışkan,[2] Nehir Selçuk,[4] İnşa Gül Ekiz İşcanlı[5]

[1]**Department of Pulmonology, University of Health Science, Sultan 2. Abdulhamid Han Training and Research Hospital, Istanbul, Turkey**
Sağlık Bilimleri Üniversitesi, 2. Sultan Abdülhamid Han Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Anabilim Dalı, İstanbul, Türkiye
[2]**Department of Cardiovascular Surgery, University of Health Science, Sultan 2. Abdulhamid Han Training and Research Hospital, Istanbul, Turkey**
Sağlık Bilimleri Üniversitesi, 2. Sultan Abdülhamid Han Eğitim ve Araştırma Hastanesi, Kalp ve Damar Cerrahisi Anabilim Dalı, İstanbul, Türkiye
[3]**Department of Anesthesiology, University of Health Science, Sultan 2. Abdulhamid Han Training and Research Hospital, Istanbul, Turkey**
Sağlık Bilimleri Üniversitesi, 2. Sultan Abdülhamid Han Eğitim ve Araştırma Hastanesi, Anestezi ve Reanimasyon Anabilim Dalı, İstanbul, Türkiye
[4]**Department of Cardiovascular Surgery, University of Health Science, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey**
Sağlık Bilimleri Üniversitesi, Dr. Siyami Ersek Göğüs Kalp ve Damar Cerrahisi Eğitim ve Araştırma Hastanesi, Kalp ve Damar Cerrahisi Anabilim Dalı, İstanbul, Türkiye
[5]**Department of Intensive Care, University of Health Science, Sultan 2. Abdulhamid Han Training and Research Hospital, Istanbul, Turkey**
Sağlık Bilimleri Üniversitesi, 2. Sultan Abdülhamid Han Eğitim ve Araştırma Hastanesi, Yoğun Bakım Bölümü, İstanbul, Türkiye

ABSTRACT

Objectives: There has been a significant increase in pulmonary embolism (PE) cases during the coronavirus disease of 2019 (COVID-19) pandemic. In this study, we aimed to compare the effects of COVID-19 positivity on morbidity and mortality in patients treated with a diagnosis of high-risk PE.

Methods: In this single-center and observational study, patients who were referred to our center with the diagnosis of PE between January 1, 2019 and 2021 were retrospectively evaluated. Patients with moderate- and low-risk PE according to the European Society of Cardiology PE guidelines, those who did not undergo computed tomography pulmonary angiography (CTPA) or the ones who did not accept treatment were excluded from the study. The patients included in the study were divided into two groups, as those with and without COVID-19, and compared in terms of demographic data, comorbidities, symptoms, thromboembolism in vessels other than the pulmonary artery, laboratory parameters, treatments, and prognosis.

ÖZ

Amaç: "Coronavirus Disease-2019 (COVID-19)" pandemisi sırasında pulmoner emboli olgularında önemli bir artış oldu. Bu çalışmada, yüksek riskli pulmoner emboli tanısıyla tedavi edilen hastalarda COVID-19 pozitifliğinin morbidite ve mortalite üzerine etkilerinin karşılaştırılması amaçlandı.

Yöntem: Bu tek merkezli gözlemsel çalışmada, 1 Ocak 2019-1 Ocak 2021 tarihleri arasında merkezimize pulmoner emboli tanısıyla sevk edilen hastalar geriye dönük olarak değerlendirildi. Avrupa Kardiyoloji Derneği pulmoner emboli kılavuzlarına göre orta ve düşük riskli pulmoner emboli hastaları, bilgisayarlı tomografi pulmoner anjiyografi yapılmayan veya tedaviyi kabul etmeyen hastalar çalışma dışı bırakıldı. Çalışmaya alınan hastalar COVID-19 olan ve olmayan olarak iki gruba ayrılarak demografik veriler, komorbiditeler, semptomlar, pulmoner arter dışındaki damarlarda tromboembolizm, laboratuvar parametreleri, tedaviler ve prognoz karşılaştırıldı.

Please cite this article as: "Şaylan B, Selçuk İ, Güven BB, Çalışkan T, Selçuk N, Ekiz İşcanlı İG. Comparison of High-Risk Pulmonary Embolism Patients with and without COVID-19. GKDA Derg. 2022;28(1):56-63".

Address for correspondence: İsmail Selçuk, MD. Sağlık Bilimleri Üniversitesi, 2. Sultan Abdülhamid Han Eğitim ve Araştırma Hastanesi, Kalp ve Damar Cerrahisi Anabilim Dalı, İstanbul, Türkiye

Phone: +90 552 237 37 26 **E-mail:** ismailselcuk35@gmail.com

Submitted Date: December 10, 2021 **Accepted Date:** January 31, 2022 **Available Online Date:** February 25, 2022

ABSTRACT

Results: A total of 384 PE cases were identified during the study period. Among them, 322 cases that were in the intermediate or low-risk category, 21 cases who did not undergo CTPA, and one case who did not accept thrombolytic therapy were excluded from the study. A total of 40 cases were included in the study. The groups with and without COVID-19 consisted of 23 and 17 patients, respectively. In the group of patients with COVID-19, inflammatory markers were higher, Wells score was lower, and thromboembolism was seen in vessels other than the pulmonary artery. The two groups were similar in terms of other laboratory parameters, demographic data, comorbidities, symptoms, treatment, and prognosis.

Conclusion: While the involvement of COVID-19 in PE etiology does not change mortality, it may cause more thrombosis development in both venous and arterial systems outside the pulmonary area by significantly increasing inflammation. However, the lower Wells scores in COVID-19 PE cases in our study indicate that new clinical assessment tools are needed to detect PE risk in COVID-19 patients.

Keywords: Acute pulmonary embolism, COVID-19, SARS-CoV 2, thrombolysis, venous thromboembolism, Wells score

ÖZ

Bulgular: Çalışma süresi boyunca toplam 384 pulmoner emboli olgusu tespit edildi. Bunlardan orta veya düşük risk kategorisindeki 322 olgu, bilgisayarlı tomografi pulmoner anjiyografi yapılmayan 21 olgu ve trombolitik tedaviyi kabul etmeyen bir olgu çalışma dışı bırakıldı. Toplam 40 olgu dahil edildi. COVID-19 olan ve olmayan gruplar sırasıyla 23 ve 17 hastadan oluşuyordu. COVID-19 olan hastalar grubunda inflamatuvar belirteçler daha yüksek, Wells skoru daha düşük ve pulmoner arter dışındaki damarlarda daha fazla tromboembolizm görüldü. Diğer laboratuvar parametreleri, demografik veriler, komorbiditeler, semptomlar, tedavi ve prognoz açısından iki grup benzerdi.

Sonuç: COVID-19'un pulmoner emboli etiyolojisinde yer alması mortaliteyi değiştirmezken, inflamasyonu önemli ölçüde artırarak pulmoner alan dışında hem venöz hem de arteriyel sistemlerde daha fazla tromboz gelişimine neden olabilir. Ancak çalışmamızda COVID-19 pulmoner emboli olgularında Wells skorlarının düşük olması, COVID-19 hastalarında pulmoner emboli riskini tespit etmek için yeni klinik değerlendirme araçlarına ihtiyaç olduğunu göstermektedir.

Anahtar sözcükler: Akut pulmoner emboli, COVID-19, SARS-CoV-2, venöz tromboembolizm, Wells skoru, tromboliz

Introduction

Pulmonary embolism (PE) is an acute cardiovascular syndrome with high mortality and increasing frequency. It ranks 3rd among the most common causes of death in society after myocardial infarction and stroke.[1,2] In epidemiological studies, its annual incidence varies between 85 and 109/100,000.[2]

The SARS-CoV-2 epidemic continues to affect the world. The negative effects of this disease on the respiratory and circulatory systems have caused mortality and morbidity in millions of people in the past year. Recent articles have reported that thrombotic complications, which can cause high rates of Venous Thromboembolism (VTE) and PE, have been observed in coronavirus disease of 2019 (COVID-19) disease.[3,4] Studies are reporting a high rate (6.4%) of PE developing in COVID-19 patients receiving thromboprophylaxis.[5] The mechanism by which the SARS-CoV-2 virus activates the coagulation system is still a mystery. Hyperinflammatory response, endothelial dysfunction, and platelet-activating effects of the disease are the most emphasized pathophysiological factors of VTE.[6] Recent reviews suggested that inflammatory processes during viral infections may cause endothelial cell damage. The entry of SARS-CoV-2 into the cell through Angiotensin Converting Enzyme 2 (ACE2) causes downregulation of membrane-bound ACE2 and simultaneous loss of activity of ACE2 in the Renin Angiotensin System (RAS). Therefore, SARS-CoV-2 infection may damage cardiovascular homeostasis by changing the subtle balance between two competing arms of the RAS in favor of the pressor arm.[7] In addition, desquamation of endothelial cells in the systemic venules together with pulmonary Type 2 alveolar epithelial cells and an inflammatory reaction in blood vessel walls (vasculitis) in the lung autopsies of patients who died from SARS suggested intense vascular reactions.[8] Cardiopulmonary findings in the first series of autopsies in the United States also showed intense neutrophil infiltration and acute pulmonary capillaritis.[9] All these pathologies may trigger PE by disrupting endothelial system.

Our clinical observations and our laboratory findings about acute and discharged COVID-19 patients have brought to mind that accompanying PE diagnosis may contribute to the mortality of those patients.

In this observational retrospective study, which we designed based on this hypothesis; we aimed to compare the effects of COVID-19 positivity on morbidity and mortality in patients treated with a diagnosis of high-risk PE.

Methods

Study Design and Participants

This retrospective study was approved by the Istanbul Health Sciences University Umraniye Research and Training Hospital's Local Ethics Committee. All patients provided a general signed informed consent for all study purposes; however, the informed consent for this study was waived by the Ethics Committee due to the retrospective nature of the study design.

This study was conducted between January 1, 2019 and 2021 in a tertiary referral hospital for PE patients. The hospi-

tal also works as a COVID-19 pandemic hospital. All patients treated with a diagnosis of high-risk PE according to the European Society of Cardiology PE guidelines were included in the study.[10] The data of the patients were analyzed retrospectively from the hospital records and the registry. Medium- and low-risk PE patients, those who did not undergo computed tomography pulmonary angiography (CTPA) or the ones who did not accept treatment were excluded from the study. Alteplase, which is a recombinant tissue plasminogen activator (rTPA) in thrombolytic therapy, was administered to the patients in the intensive care unit in full and half doses. The full dose of rTPA was administered at a rate of 50 mg/h for 2 h. This dose is known to cause major hemorrhagic complications, especially cerebral hemorrhage. Taking into account, the patients' present comorbidities, age, and laboratory parameters, patients with a high risk of bleeding, especially elderly patients (>80-years-old), were given half a dose of the thrombolytic, while other patients were given a full dose. Half-dose thrombolytics were administered to the patients at 0.6 mg/kg (maximum 50 mg) rTPA within 2 h. Thrombolytic therapy is contraindicated in patients with recent surgery or an intracranial aneurysm. Angiojet or EKOS (Corp., Bothell, WA, USA) treatments were administered in these cases. For Angiojet or EKOS treatment, patients were taken to the cardiovascular surgery hybrid operation room and the femoral vein was used for vascular access. In Angiojet therapy, a catheter was placed in the unilateral or bilateral pulmonary arteries and thrombus aspiration was performed for at least five, at most 10 min (8 min on average). For the EKOS procedure, catheters were placed in unilateral or bilateral pulmonary arteries and 1 mg bolus alteplase was administered on each side, and the patients were transferred to the intensive care unit to continue the treatment. In the intensive care unit, ultrasound waves of 2 and 1 mg/h alteplase infusion were administered into the thrombus through the catheter placed in the pulmonary arteries for 24 h, and then the catheters were removed. Patients who did not consent to thrombolytic therapy and treatments through the catheter(s) were excluded from the study. Treatment results, symptoms at admission, comorbidities, troponin, D-dimer, international normalized ratio (INR), activated partial thromboplastin time (aPTT), lactate dehydrogenase (LDH), ferritin, C-reactive Protein (CRP) levels, platelet count, right ventricular dysfunction, thrombus location, lymphocyte count, and Wells scores were recorded. Mortality during treatment in the hospital was recorded as a short-term prognosis. The long-term prognosis included 6 months after discharge. Patients in the high-risk PE category were divided into two groups as those with and without COVID-19 disease. Both groups were compared statistically in terms of demographic data, comorbidities, symptoms, laboratory parameters, treatments, and prognosis.

Statistical Analysis

Patients meeting the inclusion criteria were divided into two subgroups depending on the positive or negative diagnosis of COVID-19. The data of the patients were analyzed using the IBM Statistical Package for the Social Sciences for Windows 23.0 program. The descriptive values of categorical and continuous data were presented in frequency and percentage, and median (range), respectively. The Mann–Whitney U test was used for the comparison of two groups and the Chi-square test was used for the comparison of categorical variables. Results were considered significant in cases where $p<0.05$. The risk factors affecting PE in COVID-19 patients were analyzed by logistic regression analysis. Variables with $p\leq0.1$ in Mann-Whitney U and Chi-square analyzes were included in the logistic regression test. Parameters that were found significant in the univariate model were included in the multivariate model.

Results

During the study period, a total of 384 PE cases were admitted to our hospital, 322 of which were excluded from the study because they were in the intermediate- or low-risk category according to the European Society of Cardiology (ESC) guidelines. Twenty-one patients were excluded because CTPA could not be obtained, and one patient did not accept thrombolytic therapy (Fig. 1). A total of 40 patients in the high-risk category were included in the study. There were 23 patients in the COVID-19 group and 17 patients in the non-COVID-19 group. The mean age of the patients was 59 (32-87) years. The two groups were similar in terms of age, gender, smoking, body mass index, and comorbidities such as atrial fibrillation, ischemic heart disease, malignan-

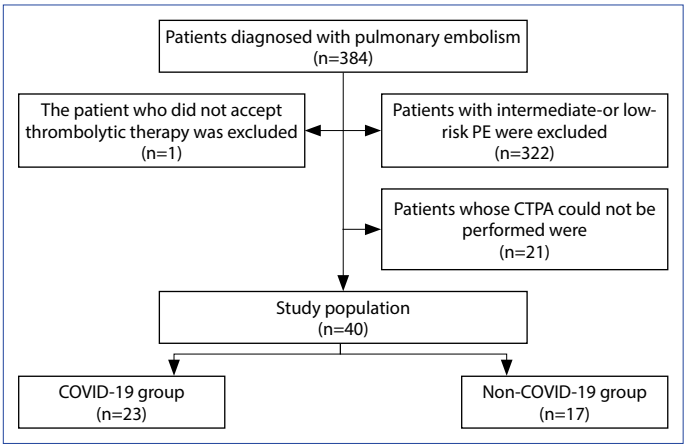

Figure 1. Flowchart of patient selection.

CTPA: Computed tomography pulmonary angiograph; PE: Pulmonary embolism.

Table 1. Demographic characteristics of the study population

Demographic data	Total (n=40)	COVID-19 (n=23)	Non-COVID-19 (n*=17)	p
Age	59 (32-87)	56 (32-87)	60 (42-87)	0.80
Gender				
Male	24 (60.0)	17 (73.9)	7 (41.2)	0.07
Female	16 (40.0)	6 (26.1)	10 (58.8)	
Body Mass Index (kg/m^2)	29 (21-38)	27 (21-34)	28 (23-38)	0.72
Smoking	12 (30)	7 (30.4)	5(29.4)	0.89
Never Smoked	21 (52.5)	10 (43.5)	11 (64.7)	0.40
Current Smoker	7 (17.5)	5 (21.7)	2 (11.8)	
Former Smoker	12 (30.0)	8 (34.8)	4 (23.5)	
Comorbidities				
Atrial fibrillation	10 (25)	5 (21.7)	5 (29.4)	0.71
Ischemic heart disease	3 (7.5)	3 (13.0)	-	NA
Malignancy	4 (10.0)	3 (13.0)	1 (5.9)	0.62
Diabetes mellitus	18 (45.0)	12 (52.2)	6 (35.3)	0.46
DVT history	9 (22.5)	4 (17.4)	5 (29.4)	0.14

*n (%) or median (minimum-maximum); DVT: Deep venous thrombosis; NA: Not applicable.

Table 2. Some laboratory parameters and clinical characteristics of the study patients and comparison between groups

Clinical and laboratory parameters	Total (n*=40)	COVID-19 (n*=23)	Non-COVID-19 (n*=17)	p
Symptoms				
Dyspnea	40 (100.0)	23 (100.0)	17 (100.0)	NA
Chest pain	34 (85.0)	19 (82.6)	15 (88.2)	1.00
Hemoptysis	4 (10.0)	1 (4.3)	3 (17.6)	0.29
Syncope	22 (55.0)	13 (56.5)	9 (52.9)	1.00
Troponin (ng/L)	163.5 (1.6-2840)	157 (5-973)	170 (1.6-2840)	0.96
D-dimer (µg/mL)	5070 (1300-32100)	4780 (1300-26000)	7120 (2351-32100)	0.20
Lactate dehydrogenase(U/L)	937(142-2462)	1174 (216-2462)	615 (142- 1544)	0.04**
Ferritin (ng/mL)	1362 (178-3873)	2005 (251-3873)	1078 (178-2145)	0.01**
C-reactive protein (mg/L)	129 (12-318)	139 (31-318)	104 (12-203)	0.031**
Wells score	5 (3-9)	4.5 (3-7)	7.5 (6-9)	<0.001**
Right ventricular dysfunction	40 (100.0)	23 (100.0)	17 (100.0)	NA
Thrombus localization				
Unilateral	1 (2.5)	-	1 (5.9)	0.23
Bilateral	39 (97.5)	23 (100.0)	16 (94.1)	
INR	1.15 (1.05-1.99)	1.13 (1.05-1.99)	1.16 (1.07-1.59)	0.11**
aPTT (s)	25 (15-55)	26 (15-44)	28 (17-55)	0.34
Thrombosis in vessels other than the pulmonary artery	12 (30)	10 (43.5)	2 (11.8)	0.04**
Platelet (10^3/mm^3)	255.5 (118-500)	261 (118-500)	250 (158-428)	0.48
Lymphocyte (10^3/mm^3)	1320 (245-7170)	1100 (400-7170)	1870 (245-3110)	0.07

*n (%) or median (minimum-maximum); **Statistically significant. (p< 0.05). INR: International normalized ratio; aPTT: Activated partial thromboplastin time.

cy, diabetes mellitus, and previous DVT (Table 1). Thrombotic complications in vessels other than pulmonary artery were higher in the COVID-19 group compared to the non-COVID-19 group (p=0.04). All patients complained of shortness of breath and symptoms of chest pain, syncope, and hemoptysis were similar between the two groups (Table 2). There was no significant difference in terms of troponin, D-dimer, INR, aPTT, platelet count, and lymphocyte count results between the two groups (Table 2). The Wells score was significantly lower in the COVID-19 group compared to the non-COVID-19 group (4.5 [3-9] vs. 7.5 [6-9], p<0.001). Ferritin, CRP, and LDH values were significantly higher in

Table 3. The comparison of patients in terms of treatment and prognosis

	Total (n*=40)	COVID-19 (n*=23)	Non-COVID-19 (n*=17)	p
Treatment				
EKOS	15 (37.5)	8 (34.8)	7 (41.2)	0.796
Full dose thrombolytic therapy	3 (7.5)	1 (4.3)	2 (11.8)	0.564
Half dose thrombolytic therapy	18 (45.0)	12 (52.2)	6 (35.3)	0.157
AngioJet aspiration thrombectomy	3 (7.5)	1 (4.3)	2 (11.8)	0.564
Hospital stays (days)	8 (1-25)	8 (1-20)	8 (5-25)	0.829
Short term prognosis				
Died	6 (15.0)	3 (13.0)	3 (17.6)	1.000
Recovered	34 (85.0)	20 (87.0)	14 (82.4)	
Long term prognosis				
Died	1 (2.9)	1 (5.0)	-	1.000
Recovered	33 (97.1)	19 (95)	14 (100)	

*n (%) or median (minimum-maximum). EKOS: EkoSonic Endovascular System.

the COVID-19 group (Table 2). Thrombus localization and right ventricular dysfunction were similar between the two groups (p=0.23 and N/A). There was no difference between the two groups in terms of the treatments including EKOS, Angiojet, full-dose thrombolytic, and half-dose thrombolytic agents (Table 3), length of hospitalization (p=0.82), and short- and long-term prognosis (p=1.00). The short- and long-term mortality rates in the COVID-19 groups were 13% and 5%, respectively (Table 3). Male gender (OR:4.00 [% 95 CI:1.10-15.5], p=0.041) and Wells score (OR:0.07 [% 95 CI:0.01-0.42], p=0.004) were found significant in univariate analysis. The multivariate analysis showed that the Wells score is inversely correlated with PE in COVID-19 patients (OR:0.06 [% 95 CI:0.01-0.45], p=0.005).

Discussion

In this study, we observed that COVID-19 positivity did not change mortality in patients treated with the diagnosis of high-risk PE. However, we detected a significant increase in infection-related inflammation and a high rate of thrombosis in the venous and arterial systems, except for the pulmonary area. We also observed that Wells clinical scores were lower in the coexistence of PE and COVID-19.

Acute PE is a life-threatening condition caused by the sudden occlusion of the pulmonary arteries, usually due to embolism of thrombi in the deep veins of the lower extremities or pelvis. It is associated with high mortality and morbidity and the 30-day mortality rate in hemodynamically affected patients varies between 16% and 25%.[11] In this single-center and retrospective observational study, we identified 384 PE patients during the study period and the mortality rate in our study population (n=40) with acute high-risk PE was 17.5%. There was no statistically significant difference in the short- and long-term mortality rates between the two groups. In their study on COVID-19 patients, Gomez et al.[5] reported that mortality did not change with PE. In our COVID-19 group, mortality was observed in only one patient due to his present malignancy, after his treatment in the hospital ended (long-term prognosis). No long-term mortality was observed in our non-COVID-19 group.

It is not always easy to diagnose PE. CTPA, which is considered the gold standard in diagnosis, is not a practical diagnostic method for every patient. It is risky, especially in pregnant women, patients with iodine allergy, hemodynamically unstable patients in the intensive care unit, and those with kidney function disorders. Diagnostic difficulties also affect the treatment decision. The European Heart Journal (ESC) 2019 guidelines emphasize that in case of clinical compliance, reperfusion therapy can be administered in a hemodynamically unstable PE patient based on echocardiographic findings.[10] We excluded 21 patients whose CTPA imaging could not be performed.

Demographic data of the patients in our study were similar in both groups. The number of male patients was relatively higher in the COVID-19 group, which is in line with the reports that COVID-19 disease more frequently affects male patients.[12] In both groups, the rates of patients receiving anticoagulant medication for reasons such as atrial fibrillation and ischemic heart disease, and INR and aPTT values were similar. Dyspnea was a common symptom in all patients. There was no difference between the groups in terms of clinical symptoms. It is highly challenging to distinguish low- and intermediate-risk PE cases from COVID-19 disease, but the differential diagnosis can be made with CTPA when in doubt. Existing publications support the under-reported incidence of acute PE in COVID-19 disease.[6]

Many recent studies report that both arterial and venous thrombotic events are triggered by the pathogenesis of COVID-19.[6] According to the results of our study, more patients in the COVID-19 group had thromboembolism in arteries and veins other than pulmonary arteries. Thrombosis was observed in vena cava superior, femoral artery, brachial artery, carotid artery, brachiocephalic artery, and bilateral iliofemoral veins in the COVID-19 group, whereas in the non-COVID-19 group, apart from the PA, thrombosis was observed in vena cava superior only. This difference between the two groups was statistically significant and it was remarkable that more arterial thromboembolism was seen in the COVID-19 group. In our study, CRP, LDH, and ferritin levels were significantly higher in COVID-19 patients compared to patients without COVID-19, which supports that inflammation is more prominent in the COVID-19 group. Lymphocyte values were similar in both groups. Since lymphocyte count, which is low in the acute stages of COVID-19 disease, normalizes within a shorter time with the treatment compared to other inflammatory markers, the lymphocyte counts of the patients were close to the normal range when thromboembolism was observed. Therefore, the lymphocyte counts were similar in both groups. D-Dimer levels, signs of the right ventricular dysfunction, and localization of the thrombus did not differ between the two groups. According to these results, it is not possible to say that inflammation alone triggers thrombosis in COVID-19 patients, as multiple factors are combined. Similarly, in their study conducted on COVID-19 patients admitted to the emergency room, Pizzi et al.[13] reported that other conditions that trigger coagulation (arrhythmias, hereditary hematological disorders, drugs, trauma, atherosclerotic plaque, etc.) must also be present.

In addition to the initial symptoms and signs, a patient with suspected PE should be evaluated in terms of risk factors. The non-specificity of clinical findings, elevated risk of bleeding with anticoagulant treatment, and high mortality rates in PE requires confirmation or exclusion of the diagnosis as soon as possible. For this purpose, Wells clinical risk scoring system was developed to further strengthen the probability of clinical diagnosis.[14] Accordingly, a score of 2 or less indicates low clinical probability, while a score of 6 and above indicates high clinical probability. In our study, Wells scores were evaluated on the day when CTPA images were obtained in all patients and found to be higher in the group without COVID-19. We can easily say that PE seen in COVID-19 patients is not only due to traditional thromboembolic risk factors, and COVID-19 patients who use low-molecular-weight heparin (LMWH) and still develop PE are the best examples. In their study conducted on COVID-19 patients, Zotzmann et al.[15] reported that Wells scores being above 2.5 highly supported PE in the absence of CTPA and anticoagulant therapy should be initiated. Supporting this statement, the lowest Wells score of the patients in both groups was three in our study.

Since hypotension and shock may develop within seconds in acute high-risk PE, reperfusion therapy with thrombolytic agents should be initiated as soon as possible. All patients in our study group had signs of right heart failure on echocardiography, and all but three patients received thrombolytic therapy with alteplase, an rTPA. Thrombolytic therapy carries a significant risk of bleeding. The most feared bleeding complication is intracranial hemorrhage.[11] Most bleeding occurs along with the vascular access site, and gastrointestinal or retroperitoneal bleeding is rare. Intracranial bleeding was not observed in any of our cases. Bleeding was observed at the femoral venous access site in only two cases and hemoptysis was observed in one case. Both complications were controlled with simple interventions. Transfusion due to bleeding was not required in any of our patients. Only the AngioJet aspiration, thrombectomy procedure was performed in three patients with a high risk of bleeding. Pharmaco-mechanical thrombolysis was performed in eight patients from the COVID group and seven patients from the non-COVID group with the EkoSonic ultrasound-enhanced infusion system (EKOS™ by Boston Scientific). There were no significant differences between the two groups in terms of the treatment modality and mortality.

Our study had some limitations. The major ones include its retrospective, non-randomized, single-center design, and the small number of patients. The use of LMWH in prophylactic doses during the treatment in some patients with COVID-19 constitutes another limitation. The COVID-19 guide published in our country recommends the prophylactic use of LMWH (enoxaparin) during in-hospital treatment in all COVID-19 patients if there is no evidence of active bleeding or thrombocytopenia.[16] However, we noticed that no COVID-19 patients were recently prescribed LMWH after discharge from our hospital. With the update of our National COVID-19 guideline in November 2020, LMWH prophylaxis was extended to 45 days only in patients with D-dimer levels twice the upper limit. Interestingly, some studies have also reported the development of PE ranging from 6.4% to 60% in patient groups receiving prophylactic doses of LMHW.[5,17] Study includes only severely ill patients who were recruited from a tertiary hospital setting, which is also a referral center of PE. Selection bias cannot be totally excluded in this observational study. In addition, small number of patients makes subgroup analysis impossible for rarely observed risk factors. However, Wells scores helped to identify overall embolism risks and to make additional analysis accordingly. Hypothesis generated from this

study should be tested in a multicentered, prospective, and randomized controlled study for conclusive results.

Symptoms, comorbidities, laboratory parameters, treatments, length of stay, and short and long-term prognoses were similar in high-risk PE patients with and without COVID-19. While the involvement of COVID-19 in PE etiology does not change mortality, it may cause more thrombosis development in both venous and arterial systems outside the pulmonary area due to the significant increase in inflammation. However, in our study, the higher Wells scores in non-COVID-19 PE cases indicate that new clinical risk assessment tools are needed to detect PE in COVID-19 patients. The clinically meaningless but statistically significant relationship between low Wells score and high PE also supports our opinion that revision of the Wells score is necessary in COVID-19 patient group.

Disclosures

Ethics Committee Approval: The study was approved by The Istanbul Health Sciences University Umraniye Research and Training Hospital Clinical Research Ethics Committee (Date: 14/01/2021, No: B.10.1.TKH.4.34.H.GP.0.01/3).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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

Authorship Contributions: Concept – B.Ş., İ.S.; Design – B.Ş., İ.S.; Supervision – İ.S., B.B.G.; Fundings – T.Ç.; Materials – B.Ş., İ.S.; Data collection &/or processing – İ.S.; Analysis and/or interpretation – İ.S., B.B.G.; Literature search – İ.G.E.İ.; Writing – B.S., N.S.; Critical review – N.S., İ.S.

Etik Kurul Onayı: Çalışma İstanbul Sağlık Bilimleri Üniversitesi Ümraniye Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu tarafından onaylandı (Tarih: 14/01/2021, Numara: B.10.1.TKH.4.34.H.GP.0.01/3).

Hasta Onamı: Hastalardan yazılı onam alınmıştır.

Hakem değerlendirmesi: Dışarıdan hakemli.

Çıkar Çatışması: Çıkar çatışması bulunmamaktadır.

Finansal Destek: Yazarlar bu çalışmanın herhangi bir finansal destek almadığını beyan etmişlerdir.

Yazarlık Katkıları: Fikir – B.Ş., İ.S.; Tasarım – B.Ş., İ.S.; Denetmeler – İ.S., B.B.G.; Kaynaklar – T.Ç.; Malzemeler – B.Ş., İ.S.; Veri Toplanması ve/veya İşlemesi – İ.S.; Analiz ve/veya Yorum – İ.S., B.B.G.; Literatür Taraması – İ.G.E.İ.; Yazıyı Yazan – B.S., N.S.; Eleştirel İnceleme – N.S., İ.S.

References

1. Jiménez D, de Miguel-Díez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, et al. Trends in the management and outcomes of acute pulmonary embolism: Analysis from the RIETE registry. J Am Coll Cardiol 2016;67:162–70.
2. Keller K, Hobohm L, Ebner M, Kresoja KP, Münzel T, Konstantinides SV, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J 2020;41:522–9.
3. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol 2020;75:2352–71.
4. Fried JA, Ramasubbu K, Bhatt R, Topkara VK, Clerkin KJ, Horn E, et al. The variety of cardiovascular presentations of COVID-19. Circulation 2020;141:1930–6.
5. Mestre-Gómez B, Lorente-Ramos RM, Rogado J, Franco-Moreno A, Obispo B, Salazar-Chiriboga D, et al. Incidence of pulmonary embolism in non-critically ill COVID-19 patients. Predicting factors for a challenging diagnosis. J Thromb Thrombolysis 2021;51:40–6.
6. Roncon L, Zuin M, Barco S, Valerio L, Zuliani G, Zonzin P, et al. Incidence of acute pulmonary embolism in COVID-19 patients: Systematic review and meta-analysis. Eur J Intern Med 2020;82:29–37.
7. Amraei R, Rahimi N. COVID-19, renin-angiotensin system and endothelial dysfunction. Cells 2020;9:1652.
8. Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): A report from China. J Pathol 2003;200:282–9.
9. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: An autopsy series from New Orleans. Lancet Respir Med 2020;8:681–6.
10. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543–603.
11. Yamamoto T. Management of patients with high-risk pulmonary embolism: A narrative review. J Intensive Care 2018;6:16.
12. Cai H. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med 2020;8:e20.
13. Pizzi R, Gini G, Caiano L, Castelli B, Dotan N, Magni F, Virano A, Roveda A, et al. Coagulation parameters and venous thromboembolism in patients with and without COVID-19 admitted to the Emergency Department for acute respiratory insufficiency. Thromb Res 2020;196:209–12.
14. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: Management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 2001;135:98–107.

15. Zotzmann V, Lang CN, Wengenmayer T, Bemtgen X, Schmid B, Mueller-Peltzer K, et al. Combining lung ultrasound and Wells score for diagnosing pulmonary embolism in critically ill COVID-19 patients. J Thromb Thrombolysis 2021;52:76–84.
16. Republic of Turkey Ministry COVID-19 Information Page. COVID-19 (SARS-CoV-2 infection) Antitoxin-Anti-inflammatory treatments, management of coagulopathy [Article in Turkish]. Available at: https://covid19.saglik.gov.tr/Eklenti/39296/0/covid-19rehberiantisitokin-antiinflamatuartedavilerkoagulopatiyonetimipdf.pdf. Accessed Mar 29, 2021.
17. Schiaffino S, Giacomazzi F, Esseridou A, Cozzi A, Carriero S, Mazzaccaro DP, et al. Pulmonary thromboembolism in coronavirus disease 2019 patients undergoing thromboprophylaxis. Medicine (Baltimore) 2021;100:e24002.