


Incidence of Deep Venous Thrombosis in Patients With COVID-19 and Pulmonary Embolism

Compression Ultrasound COVID Study

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Abbreviations

COVID-19, coronavirus disease 2019; CUS, compression ultrasound; DVT, deep venous thrombosis; PE, pulmonary embolism; SARS-CoV, severe acute respiratory syndrome coronavirus

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Objectives—Several reports had observed a high risk of pulmonary embolism (PE) in patients with coronavirus disease 2019 (COVID-19), most of them in the intensive care unit. Reported findings indicate that a direct viral-mediated hyperinflammatory response leads to local thromboinflammation. According to those findings, the incidence of deep venous thrombosis (DVT) in patients with COVID-19 and PE should be low. The objective of this study was to evaluate the incidence of DVT in patients with COVID-19 who developed PE.

Methods—In this prospective observational study, consecutive patients hospitalized in the internal medicine ward with a diagnosis of COVID-19 who developed PE were screened for DVT in the lower extremities with complete compression ultrasound.

Results—The study comprised 26 patients. Fifteen patients (57.7%) were male. The median age was 60 years (interquartile range, 54–73 years). Compression ultrasound findings were positive for DVT in 2 patients (7.7%; 95% confidence interval, 3.6%–11.7%). Patients with DVT had central and bilateral PE. In both, venous thromboembolism was diagnosed in the emergency department, so they did not receive previous prophylactic therapy with low-molecular-weight heparin. Patients without DVT had higher median D-dimer levels: 25,688 µg/dL (interquartile range, 80,000–1210 µg/dL) versus 5310 µg/dL ($P < .05$).

Conclusions—Our study showed a low incidence of DVT in a cohort of patients with COVID-19 and PE. This observation suggests that PE in these patients could be produced mainly by a local thromboinflammatory syndrome induced by severe acute respiratory syndrome coronavirus 2 infection and not by a thromboembolic event.

Key Words—compression ultrasound; coronavirus disease 2019; COVID-19; deep venous thrombosis; pulmonary embolism; thromboinflammatory syndrome

Arterial and venous thrombotic events seem to emerge as important issues in patients with coronavirus disease 2019 (COVID-19).^{1,2} Increased levels of D-dimer, fibrin degradation products, and prothrombin time prolongation are associated with a poor prognosis in several studies of patients with COVID-19.^{3–5} Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

infects the epithelial cells by using the angiotensin-converting enzyme 2 receptor.⁶ Consequently, a hyperinflammatory response is initiated, which sets the stage for thrombosis through several mechanisms.

Pulmonary embolism (PE) is the most common thrombotic manifestation of COVID-19. An increase of PE has been reported in intensive care unit patients with COVID-19.^{7–13} Previous outbreaks of SARS-CoV-1 and Middle Eastern respiratory syndrome have been associated with an increased risk of thrombosis.^{14,15} Despite previous experience with these coronaviruses, the pathophysiologic characteristics of PE in SARS-CoV-2 infection are not well documented. In patients with COVID-19, it has been hypothesized that the pathophysiologic characteristics of PE are different than in patients without COVID-19. Proposed hypotheses include a severe inflammatory response that leads to local thromboinflammation through mechanisms such as complement activation, a cytokine storm, endotheliitis, and activation of the coagulation cascade.^{6,16} In fact, in several autopsies from patients who died of COVID-19, the lung histologic analysis showed widespread thrombosis with microangiopathy in pulmonary vessels.^{17–19} These mechanisms of thromboinflammation triggered by SARS-CoV-2 infection could explain the microvascular pulmonary thrombosis. A recent study suggested that microvascular COVID-19 lung vessel obstructive thromboinflammatory syndrome determines this pulmonary thromboinflammatory mechanism.²⁰ This local hypercoagulable state in the pulmonary tissue seems to be the pathophysiologic characteristic of PE in patients with COVID-19 rather than the classic emboli coming from the lower extremities. According to that idea, the incidence of deep venous thrombosis (DVT) in patients with COVID-19 and PE should be low. The aim of this study was to investigate the incidence of concomitant lower limb DVT using compression ultrasound (CUS) in patients with COVID-19 and PE admitted to the general ward of an internal medicine department.

Materials and Methods

Study Design and Setting

We conducted a prospective observational study in patients older than 18 years admitted to the internal

medicine ward for COVID-19 and PE at Infanta Leonor University Hospital, a second-level hospital in Madrid. The COVID-19 diagnosis was defined by RNA detection of SARS-CoV-2 from a nasopharyngeal swab or by the presence of clinical, radiologic, and analytical findings highly suggestive of the disease in patients with reverse transcription polymerase chain reaction–negative results and absence of an alternative diagnosis, according to the World Health Organization guideline.²¹ The diagnosis of PE was achieved by pulmonary computed tomographic angiography.

Study Protocol

Patients with COVID-19 and PE underwent complete CUS examinations of both legs, which included the proximal territory (common femoral vein, saphenofemoral junction, and popliteal vein). As described in previous reports,^{22,23} 3-point compression means doing CUS scans in 3 regions with higher turbulence and at the greatest risk of developing thrombosis. Ultrasound examinations were performed with a MyLab 2 system (Esaote SpA, Genoa, Italy) using a high-frequency linear transducer (6–15 MHz). Compression ultrasound examinations were performed by 2 clinically accredited, trained operators. Patients were excluded if they were receiving therapeutic doses of anticoagulation for a previous PE diagnosis. Demographic and clinical data were obtained from the clinical charts. This study was conducted according to the international ethical principles to guide physicians in medical research involving humans in the latest revision of the Declaration of Helsinki. Considering the isolation of patients, written informed consent was obtained by an impartial witness, who was present during the entire consent process. The witness attested to the voluntariness of the patient's consent and the adequacy of the consent process by ensuring that the information was accurately conveyed and that the patient's questions were answered. The study was approved by the Institutional Ethics Committee.

Statistical Analysis

Quantitative variables are presented as the median and interquartile range when they had a non-normal distribution. Qualitative variables are presented as percentages.

Results

From March 30, 2020, to May 6, 2020, a total of 412 patients were admitted to the internal medicine ward with COVID-19. Thirty-nine patients (9.46%) had a diagnosis of acute PE. Among of them, CUS examinations were performed in 26 patients. Three patients were excluded because they were receiving therapeutic doses of anticoagulation (2 for atrial fibrillation and 1 for prior unprovoked venous thromboembolism); 2 patients died before CUS examinations were performed; 1 patient was transferred to another geographic location; in 7 patients, CUS examinations were not performed.

Compression ultrasound findings were positive for DVT in 2 patients (7.7%; 95% confidence interval, 3.6–11.7) with left popliteal vein thrombosis (Figure 1A) and left femoral vein thrombosis (Figure 2A). Basal characteristics, laboratory test results, and CUS findings are summarized in Table 1. Seventeen patients (65.4%) had a diagnosis of COVID-19 with reverse transcription polymerase chain reaction–positive results, and 9 patients had clinical, laboratory, and radiologic findings suggestive of SARS-CoV-2 infection with reverse transcription polymerase chain reaction–negative results. Fifteen patients (57.7%) were male, and the median age of the sample was 60 years (interquartile range, 54–73 years). Median time from

Figure 1. A, Thrombosed popliteal vein. Transverse ultrasound scan shows an echogenic clot in the left popliteal vein (arrowhead). **B**, Bilateral PE. Computed tomographic pulmonary angiography shows bilateral filling defects in the right pulmonary artery and the left lower lobar artery (arrows).

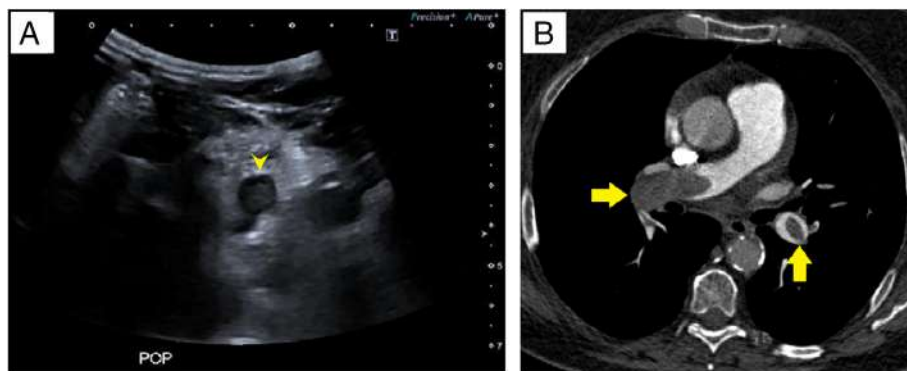


Figure 2. A, Thrombus in the common femoral vein (CFV). Transverse ultrasound scan shows a partial filling defect in the saphenous vein (arrowhead) and the common femoral vein (asterisk) just above the saphenous junction. **B**, Bilateral pulmonary embolism. Coronal maximum-intensity projection CT pulmonary angiography shows bilateral filling defects in the two main pulmonary arteries and their lobar branches (arrows).

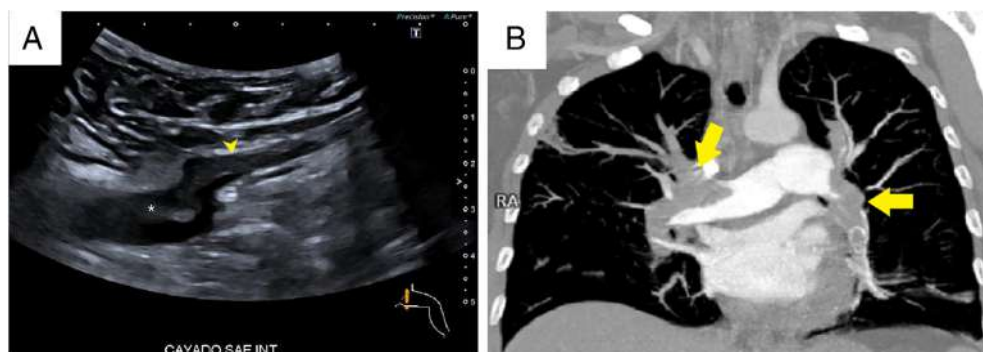


Table 1. Basal Characteristics, Laboratory Test Results, and CUS Findings of Hospitalized Patients With COVID-19 and PE

Patient	DVT	Sex	Age, y	Obesity, BMI >30 kg/m ²	History of VTE	Known Thrombophilia	Active Cancer	Days*	PE Location	Thromboprophylaxis on Admission	Oxygen Therapy	Lymphocytes, ×10 ³ /μL	Platelets, ×10 ³ /μL	D-Dimer, μg/dL	Peak LDH, U/L	IL-6, U/L	Ferritin, ng/dL	CRP, mg/dL
1	No	Male	65	35.3	No	No	No	28	Unilateral peripheral	Enoxaparin, 60 mg OD	Nasal cannula	2,500	286	24,880	277	123	538	0.4
2	No	Male	73	30.1	No	No	No	21	Bilateral peripheral	Enoxaparin, 40 mg OD	NIV	1,300	186	80,000	727	NA	NA	1
3	No	Male	75	NA	No	No	No	15	Bilateral peripheral	Enoxaparin, 40 mg OD	NIV	1,000	482	63,590	946	476	1,698	2.5
4	No	Male	73	27.3	No	No	No	1	Bilateral central	No prophylaxis	Nasal cannula	2,800	162	8,980	266	NA	420	0.9
5	No	Male	49	26.7	No	No	No	9	Bilateral central	Enoxaparin, 40 mg OD	NIV	1,300	349	35,200	950	NA	801	NA
6	No	Male	68	27.3	No	No	No	15	Unilateral peripheral	Enoxaparin, 60 mg OD	Nasal cannula	600	322	19,510	256	19.4	1,122	1.2
7	No	Male	56	24.6	No	No	No	9	Bilateral peripheral	Enoxaparin, 40 mg OD	High flow	500	540	45,350	480	NA	810	106
8	No	Female	58	26.9	No	No	No	8	Unilateral peripheral	Enoxaparin, 40 mg OD	High flow	1,000	370	14,940	408	486.0	461	NA
9	No	Female	37	27.3	No	No	No	12	Unilateral peripheral	No prophylaxis	No oxygen	1,800	240	1,400	151	NA	200	1
10	No	Male	58	32.4	No	No	No	20	Bilateral peripheral	Enoxaparin, 40 mg OD	Nasal cannula	1,300	455	26,160	245	NA	NA	30.6
11	No	Male	60	32.9	No	No	No	7	Unilateral peripheral	Enoxaparin, 40 mg OD	High flow	1,000	288	7,470	172	6.8	406	3.5
12	No	Female	78	26.2	No	No	No	9	Unilateral peripheral	No prophylaxis	High flow	700	548	5,530	319	6.1	3,565	267
13	No	Male	80	30.5	No	No	No	5	Unilateral central	Enoxaparin, 60 mg OD	High flow	4,500	234	28,740	253	5.8	1,373	53
14	No	Male	70	31.8	No	No	No	2	Bilateral central	Enoxaparin, 60 mg OD	NIV	1,000	207	80,000	619	93	1,389	470.7
15	No	Male	43	22.9	No	No	No	2	Bilateral peripheral	Enoxaparin, 80 mg OD	No oxygen	300	566	10,630	228	2.8	990	3.6
16	No	Female	67	32.3	No	No	No	0	Bilateral central	No prophylaxis	Nasal cannula	1,800	149	21,380	306	NA	NA	32.5
17	No	Female	75	19.7	No	No	No	12	Bilateral peripheral	Enoxaparin, 80 mg OD	Nasal cannula	600	149	47,970	283	NA	566	238.9
18	No	Female	81	33.3	No	No	No	3	Unilateral peripheral	No prophylaxis	Nasal cannula	1,000	230	5,540	248	NA	NA	5.3
19	No	Female	58	31.5	No	No	No	7	Bilateral peripheral	Enoxaparin, 60 mg OD	Nasal cannula	2,200	429	11,520	231	5.3	419	16.9
20	No	Male	54	24.9	No	No	No	0	Bilateral central	No prophylaxis	Nasal cannula	2,200	333	36,170	164	73.8	677	71
21	No	Male	60	25.3	No	No	No	0	Unilateral peripheral	No prophylaxis	Nasal cannula	1,500	302	1,210	139	66.4	754	157
22	No	Male	54	27.0	No	No	No	1	Bilateral peripheral	Enoxaparin, 60 mg OD	Nasal cannula	1,000	256	18,680	224	40.0	387	90.9
23	No	Female	54	NA	No	No	No	15	Unilateral peripheral	Enoxaparin, 80 mg OD	NIV	1,000	164	22,460	621	1001	1,807	273
24	No	Female	53	27.1	No	No	Yes	11	Unilateral peripheral	No prophylaxis	Nasal cannula	1,900	182	4,210	136	211	202	12.1
25	Yes	Female	53	33.5	No	No	No	0	Bilateral peripheral	No prophylaxis	Nasal cannula	2,500	287	3,430	163	10	115	11.3

26	Yes	Female	21.8	No	No	No	No oxygen	1,700	240	7,190	NA	NA	NA	126
68				central	Bilateral	central								
56				0										

BMI indicates body mass index; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; NA, not available; NIV, noninvasive ventilation; OD, once daily; and VTE, venous thromboembolism.

^aDays from admission to hospital to PE diagnosis.

PE diagnosis until CUS was 6 days. Five hospitalized patients did not receive thromboprophylaxis with low-molecular-weight heparin for a previous PE diagnosis, and in 5 patients, including the 2 patients with DVT, venous thromboembolism was diagnosed in the emergency department. The 2 patients with DVT had central and bilateral PE (Figures 1B and 2B). Patients without DVT had higher median D-dimer levels: 25,688 µg/dL (interquartile range, 80,000–1210 µg/dL) versus 5310 µg/dL ($P < .05$). None of the included patients died.

Discussion

Severe acute respiratory syndrome caused by SARS-CoV-2 may predispose patients to thrombotic complications in the arterial and venous circulations because of excessive inflammation, platelet activation, endothelial dysfunction, and stasis.^{1,2} Several recent studies reported a high incidence of PE in patients with COVID-19 admitted to the intensive care unit.^{7–13} However, scarce data have been published about the incidence of DVT in patients with SARS-CoV-2 infection and PE. In a meta-analysis, the prevalence of DVT in the general population with PE was estimated as 35% to 45%.²⁴ Our investigation showed that the incidence of DVT was remarkably lower. Only 2 previous studies investigated the incidence of DVT in patients with COVID-19 and PE. Although in both the sample sizes were smaller, similar observations were reported. In a study conducted by Poissy et al,⁹ the incidence of PE was 20.6% (22 of 107) in patients with severe COVID-19 admitted to the intensive care unit. It is interesting to note that 3 of these patients (13.6%) had DVT. In a series of 362 patients with COVID-19 admitted to the intensive care unit and general wards, PE occurred in 10 patients (2.8%). Among of them, DVT was confirmed in 1 patient.¹⁰ Although our study was limited by a small sample size, to our knowledge, this is the largest study reported to date of a cohort of non-critically ill patients with COVID-19 and a diagnosis of acute PE in whom concomitant DVT was investigated.

Our findings suggest a local hypercoagulable state rather than emboli from lower extremity veins. In close connection with our hypothesis, the studies that have investigated the incidence of asymptomatic DVT in patients with COVID-19 have shown controversial

results. A single-center study from Wuhan including 48 critically ill patients with COVID-19 reported an 85.4% rate of asymptomatic DVT.²⁵ Surprisingly, the incidence of DVT was extremely high. This finding could have been limited by the small sample size. Furthermore, the incidence of venous thromboembolism is higher in patients with severe COVID-19. Demelo et al²⁶ observed an incidence rate of 14.7% for asymptomatic DVT in a cohort of patients admitted to medical wards with COVID-19 pneumonia. However, in an Italian study, none of the 64 tested patients with COVID-19 admitted to the medical ward developed asymptomatic DVT.²⁷ A study in Germany that included 12 autopsies of patients who died of COVID-19 revealed PE as the cause of death in 4 patients, with the thrombi derived from the deep veins of the lower extremities. In another 3 patients, DVT was present in the absence of PE. In all cases with DVT, both legs were involved.¹⁸

Few studies have investigated the location of PE in patients with concomitant DVT. In a retrospective study, Lee et al²⁸ reported an association between concomitant DVT and a proximal location of PE. According with this data, in our study, in 2 patients with DVT, the lung thrombus was located in the main bilateral pulmonary arteries. In our cohort of patients, there was no relationship between the presence of concomitant DVT and a PE-related unfavorable outcome or all-cause mortality.

This study had several limitations: First, the main limitation was the small sample size, which could have limited the significance of our findings. Second, the 3-point CUS protocol does not evaluate distal DVT; nevertheless, distal DVT is associated with a low rate of embolization.

In conclusion, our observations suggest that PE in SARS-CoV-2 infection could be due to pulmonary thromboinflammation syndrome rather than a thromboembolic event.

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