



Pulmonary embolism and screening for concomitant proximal deep vein thrombosis in noncritically ill hospitalized patients with coronavirus disease 2019

Álvaro Dubois-Silva^{1,2} · Cristina Barbagelata-López¹ · Álvaro Mena^{2,3} · Patricia Piñeiro-Parga¹ · Diego Llinares-García¹ · Santiago Freire-Castro¹

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Dear Editor,

Coagulation abnormalities with elevated D-dimer levels have been identified as predictors of poor prognosis in patients with coronavirus disease 2019 (COVID-19) in China [1–4]. The correlation between D-dimer levels and diagnosis and prognosis of venous thromboembolism (VTE) has been widely described [5, 6]. Thus, many questions regarding the relationship between these entities are emerging [7].

Recently, a VTE prevalence of 25% has been reported in patients with severe novel coronavirus pneumonia [8]. However, there is limited information about the clinical characteristics of noncritically ill hospitalized patients with COVID-19 who develop pulmonary embolism (PE), or their prevalence of lower limb concomitant deep-vein thrombosis (DVT). Therefore, the purpose of this study was to analyze the clinical data and assess the prevalence of concomitant proximal DVT in COVID-19 nonintensive care unit (non-ICU) patients with PE.

Methods

This cross-sectional observational study describes non-ICU patients hospitalized for COVID-19 in a single center in A Coruña (northwest Spain) during April 2020 who developed a PE. Patients met inclusion criteria if they were ≥ 18 years old, had a confirmed diagnosis of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and were diagnosed with PE. Exclusion criteria were ICU admission at enrollment (i.e., a previous ICU stay was allowed), history of VTE within the past 3 months, and presence of a venous malformation or anatomical abnormality which hindered a reliable point-of-care compression ultrasonography (CUS) of the lower limbs. All patients (or their health-care proxies) provided informed consent for their study participation. The research protocol was conducted in accordance with the 2013 Declaration of Helsinki and the local Ethics Committee requirements.

COVID-19 was diagnosed according to World Health Organization interim guidelines [9] and confirmed by RNA detection of the SARS-CoV-2 and/or serological testing. PE diagnosis was established by positive contrast-enhanced, PE-protocol, helical chest computerized tomography (CT).

Point-of-care CUS of the lower limbs was performed to assess the prevalence of concomitant proximal DVT. Prior to this, risk factors for VTE and symptoms of PE and DVT were assessed using a simple questionnaire. Trained clinicians who were caring for these COVID-19 patients conducted lower limb CUS in safe conditions (i.e., with personal protective equipment). Proximal DVT diagnosis was established if a noncompressible vein segment was detected at or above the popliteal vein on CUS. Distal DVT (i.e., below the knee) was not screened using this protocol, according to our purpose of exclude only thrombosis of the larger (i.e. proximal) veins.

✉ Álvaro Dubois-Silva
alvarodibua@gmail.com

¹ Department of Internal Medicine, Complejo Hospitalario Universitario de A Coruña (CHUAC), Servizo Galego de Saúde (SERGAS), A Coruña, Spain

² Universidade da Coruña (UDC), A Coruña, Spain

³ Infectious Diseases Unit, Department of Internal Medicine, Complejo Hospitalario Universitario de A Coruña (CHUAC), Servizo Galego de Saúde (SERGAS), A Coruña, Spain

Clinical data (demographics, comorbidities, concurrent medications, laboratory, and imaging tests) were recorded at baseline and during hospitalization until PE diagnosis. VTE was considered secondary to immobilization if it appeared within 2 months of confinement to bed with bathroom privileges for ≥ 4 days. Immobilization due to COVID-19 prior to VTE was included in this definition. D-dimer was measured by automated latex-enhanced HemosIL D-Dimer (Instrumentation Laboratory, Bedford, MA, USA) immunoassay.

Patients were managed according to the hospital's clinical practice, with no standardizations or treatment recommendations. Diagnostic tests for PE were only applied when PE was clinically suspected. Lower-limb CUS examination was performed in all patients regardless of the presence or absence of DVT symptoms. All data were recorded electronically and collected retrospectively using standardized case report forms. Continuous variables are expressed using the median and interquartile ranges (IQRs). SPSS software (v. 22.0; IBM SPSS, Armonk, NY, USA) was used for all analyses.

Results

From April 2 to April 17, 2020, a total of 171 patients remained hospitalized with confirmed COVID-19 in the Internal Medicine Department of the University Hospital of A Coruña. Among these, 8 (4.68%; 95% CI 2.39–8.96) patients diagnosed with PE participated in the study. The patient characteristics are presented in Table 1. Seven (87.5%) participants had pneumonia with bilateral pulmonary infiltration on imaging tests performed before PE diagnosis (Table 1). The remaining patient was diagnosed with bilateral pneumonia in the same chest CT scan which demonstrated the PE.

All patients were immobilized due to COVID-19 as the main risk factor for VTE. They received thromboprophylaxis with enoxaparin or biosimilar at a median daily dose of 40 mg from admission to PE diagnosis (Table 2). The prophylactic dose was increased in 3 (37.5%) patients due to rising D-dimer levels before (i.e. more than 24 h) PE diagnosis, from 40 to 60 mg/day in two patients and from 40 to 100 mg/day in one (below their respective full therapeutic dose regimen). Contrast-enhanced helical chest CT was ordered because D-dimer levels were increasing (this was the only reason for one patient), while PE symptoms and/or respiratory worsening were also considered in the decisions for the remaining patients.

Six patients (75%) had a Pulmonary Embolism Severity Index (PESI) at or above class III (Table 2). None of these patients had imaging findings suggesting right-ventricle (RV) dysfunction by CT-scan, neither by echocardiography or by laboratory findings among tested participants.

Table 1 Clinical characteristics of non-intensive care unit hospitalized patients with coronavirus disease 2019 and pulmonary embolism

	COVID-19 and PE
Patients, <i>N</i>	8
Clinical characteristics,	
Men	5 (62.5%)
Age (median years, IQR)	67 (58–74)
Body weight (median kg, IQR)	75 (67–83)
Body mass index (median kg/m ² , IQR)	24.6 (23.5–27.2)
Charlson comorbidity index ≤ 1	7 (87.5%)
Concomitant diseases,	
Hypertension	3 (37.5%)
Dyslipidemia	4 (50%)
Diabetes	1 (12.5%)
Obesity	1 (12.5%)
Current smoking	0
Chronic lung disease	0
Chronic heart failure	0
Chronic kidney disease	0
Recent major bleeding	0
Thrombophilia	0
Concomitant therapies at admission,	
Anticoagulants	0
Antiplatelets	0
Corticosteroids	0
NSAIDs	0
Immunosuppressive drugs	0
ACEI/ARB	3 (37.5%)
COVID-19 characteristics,	
Pneumonia	7 (87.5%)
Bilateral pulmonary infiltration	7 (87.5%)
Basal SpO ₂ < 93%	5 (62.5%)
ICU stay prior to PE diagnosis	2 (25%)
COVID-19-related therapies,	
Hydroxichloroquine	7 (87.5%)
Antibiotics	8 (100%)
Lopinavir/ritonavir	7 (87.5%)
Corticosteroids	7 (87.5%)
Tocilizumab	5 (62.5%)
Remdesivir	0
Interferon	2 (25%)

COVID-19 coronavirus disease 2019, PE pulmonary embolism, IQR interquartile range, NSAIDs non-steroidal anti-inflammatory drugs, ACEI angiotensin-converting enzyme inhibitors, ARB angiotensin II receptor blockers, SpO₂ oxygen saturation as measured by pulse oximetry, ICU intensive care unit

All patients received full-dose of enoxaparin or biosimilar when PE was diagnosed, and none required thrombolysis. Only one patient had ≥ 4 points in the sepsis-induced coagulopathy (SIC) score proposed by the International Society of Thrombosis and Haemostasis (ISTH).

Table 2 Venous thromboembolism-related characteristics of non-intensive care unit hospitalized patients with coronavirus disease 2019 and pulmonary embolism

	COVID-19 and PE
Patients, <i>N</i>	8
Risk factors for VTE,	
Active cancer	0
Surgery	0
Immobility for ≥ 4 days	8 (100%)
Use of estrogens	0
Pregnancy/postpartum	0
None of the above	0
Leg varicosities	3 (37.5%)
Prior VTE	0
Thromboprophylaxis,	
Enoxaparin or biosimilar	8 (100%)
Median enoxaparin or biosimilar dose (mg/day, IQR)	40 (40–60)
Dose increase during thromboprophylaxis	3 (37.5%)
Other anticoagulants	0
Clinical symptoms and signs at PE presentation,	
Chest pain	1 (12.5%)
Syncope	0
Worsening dyspnea	5 (62.5%)
Hemoptysis	1 (12.5%)
None of the above	3 (37.5%)
Heart rate > 110 /min	0
SBP < 100 mm Hg	0
PaO ₂ /FiO ₂ (median mm Hg, IQR)	233 (169–323)
RV dysfunction (by imaging and/or laboratory tests)	0
PESI \geq class III	6 (75%)
sPESI ≥ 1 point	6 (75%)
SIC score ≥ 4 points	1 (12.5%)
PE involvement,	
Subsegmental	4 (50%)
Segmental	5 (62.5%)
Lobar	1 (12.5%)
Main	0
Central	0
Time from COVID-19 to PE diagnosis, days	
Median days (IQR) from COVID-19 symptoms onset	19 (17–23)
Median days (IQR) from admission	13 (8–15)
Laboratory tests,	
Anemia	5 (62.5%)
White blood cell count $\geq 10,000/\text{mm}^3$	4 (50%)
Lymphocyte count $< 1000/\text{mm}^3$	4 (50%)
Platelet count $< 150,000/\text{mm}^3$	1 (12.5%)
INR ≥ 1.2	1 (12.5%)
CrCl < 60 mL/min	0
C-reactive protein ≥ 1 mg/dL	6 (75%)
Serum ferritin ≥ 300 mg/dL	7 (87.5%)
Lactate dehydrogenase ≥ 250 U/L	7 (87.5%)
IL-6 ≥ 5 pg/mL	8 (100%)
D-dimer levels (median ng/mL, IQR)	10,000 (5979–34,974)
D-dimer levels ≥ 2000 ng/mL	8 (100%)
D-dimer levels ≥ 5000 ng/mL	7 (87.5%)

of these indices (i.e., hypotension, pulse rate ≥ 110 beats per minute, respiratory rate ≥ 30 breaths per minute, altered mental status and SpO₂ $< 90\%$) would be present in many patients with SARS-CoV-2 pneumonia. In addition, we detected PE with low thrombotic burden, no RV dysfunction, and a poor evolution of coronavirus pneumonia in the same chest CT scan in most of our patients. Consequently, we hypothesize that many of these patients would have respiratory deterioration not explained only by the PE. PESI could be insufficiently accurate for assessing PE severity in patients with worsening pneumonia; thus, special attention to changes in their condition might be warranted when PE is suspected in COVID-19 patients.

Our study is not without limitations. First, we have described a relatively small series of patients with COVID-19 and PE at a single center in Spain. Therefore, our findings must be interpreted cautiously and require external validation in larger cohorts. Second, since this was an observational study without prospective follow-up from PE diagnosis, randomized control trials will be needed before recommendations can be made on the clinical management of these patients. Third, although no signs of RV dysfunction were detected by CT-scan, echocardiography or laboratory tests to assess RV function were not performed in all patients. Hence, data regarding RV dysfunction could be insufficiently accurate.

In summary, the study results show that a subset of non-ICU hospitalized COVID-19 patients diagnosed with PE has chiefly segmental or subsegmental events without concomitant proximal DVT of the lower limbs. Our findings suggest a predominance of small-vessel thrombosis secondary to inflammatory and immune responses in these patients.

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Author contributions AD-S contributed to the concept and design of the study, compression ultrasound examination, analysis and acquisition of data, interpretation of the results and drafting of the manuscript. CB-L contributed to the concept and design of the study, compression ultrasound examination and reviewing of the manuscript. AM contributed to the concept and design of the study, statistical analysis and drafting of the manuscript. PP-P contributed to the compression ultrasound examination, acquisition of data and reviewing of the manuscript. DL-G and SF-C contributed to the compression ultrasound examination and reviewing of the manuscript. All authors approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights and ethics approval This study was conducted in accordance with the 1964 Helsinki Declaration and its later amendments and the local Ethics Committee requirements. Ethical approval was waived in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Informed consent Informed consent was obtained from all individual participants included in the study.

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