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Pulmonary thromboembolism in coronavirus disease 2019 patients undergoing thromboprophylaxis

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Abstract

We aimed to investigate the prevalence of pulmonary thromboembolism (PTE) and its association with clinical variables in a cohort of hospitalized coronavirus disease 2019 (COVID-19) patients receiving low-molecular-weight heparin (LMWH) at prophylactic dosage.

In this retrospective observational study we included COVID-19 patients receiving prophylactic LMWH from admission but still referred for lower-limbs venous Doppler ultrasound (LL-US) and computed tomography pulmonary angiography (CTPA) for clinical PTE suspicion. A dedicated radiologist reviewed CTPA images to assess PTE presence/extension.

From March 1 to April 30, 2020, 45 patients were included (34 men, median age 67 years, interquartile range [IQR] 60–76). Twenty-seven (60%) had PTE signs at CTPA, 17/27 (63%) with bilateral involvement, none with main branch PTE. In 33/45 patients (73%) patients LL-US was performed before CTPA, with 3 patients having superficial vein thrombosis (9%, none with CTPA-confirmed PTE) and 1 patient having deep vein thrombosis (3%, with CTPA-confirmed PTE). Thirty-three patients (73%) had at least one comorbidity, mainly hypertension (23/45, 51%) and cardiovascular disease (15/45, 33%). Before CTPA, 5 patients had high D-dimer (11.21 μg/mL, IQR 9.10–13.02), 19 high fibrinogen (550 mg/dL, IQR 476–590), 26 high interleukin-6 (79 pg/mL, IQR 31–282), and 11 high C-reactive protein (9.60 mg/dL, IQR 6.75–10.65), C-reactive protein being the only laboratory parameter significantly differing between patients with and without PTE ($P = .002$)

High PTE incidence (60%) in COVID-19 hospitalized patients under prophylactic LMWH could substantiate further tailoring of anticoagulation therapy.

Abbreviations: COVID-19 = coronavirus disease 2019, CTPA = computed tomography pulmonary angiography, FiO_2 = fraction of inspired oxygen, IQR = interquartile range, LMWH = low-molecular-weight heparin, PaO_2 = arterial blood oxygen tension, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: computed tomography angiography, coronavirus, coronavirus disease 2019, heparin, low-molecular-weight, pulmonary embolism

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SS and FG have contributed equally to this work and share first authorship.

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1. Introduction

Worldwide cases of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, neared 52 million on November 12, 2020, with over 1.2 million deaths.[1]

Diagnostic and therapeutic challenges are open.[2–9] Alongside various grades of lung damage and acute respiratory distress syndrome[10] with severe alterations of the ratio between arterial blood oxygen tension (PaO_2) and the fraction of inspired oxygen (FiO_2), abnormal coagulation parameters are extensively reported in COVID-19 patients,[11–16] those with poor prognosis often exhibiting a pro-thrombotic profile with increased D-dimer, prothrombin time, and fibrin degradation products.[11–13,16–19] Intravascular pulmonary thrombosis acts as a trigger to further worsening of clinical conditions,[20,21] with pulmonary thromboembolism widely reported in retrospective studies.[22–27] However, clinical contextualization of these series highlights how the overlap of pulmonary and systemic inflammation—with widespread activation of the coagulation cascade—hampers timely suspicion of pulmonary thromboembolism in COVID-19 patients.[19–21,28] The aim of this study, conducted during the first SARS-CoV-2 pandemic peak in Lombardy, Italy, was therefore to investigate the incidence of pulmonary thromboembolism in all patients from a single ward of a primarily COVID-19-dedicated hospital, all of them receiving from admission at least prophylactic dosage of low-molecular-weight heparin (LMWH).

2. Materials and methods

The Ethics Committee of IRCCS Ospedale San Raffaele approved this retrospective cross-sectional study. We analyzed 45 COVID-19 patients hospitalized from March 1 to April 30, 2020, in a single non-intensive care ward of IRCCS Policlinico San Donato (San Donato Milanese, Italy)—a primarily-dedicated COVID-19 hospital. SARS-CoV-2 infection was confirmed by reverse transcriptase–polymerase chain reaction on nasopharyngeal swabs. While coagulation parameters of 32 of these 45 patients were already analyzed in another report on the occurrence of early stage coagulopathy in COVID-19 patients,[29] we here progress further in the diagnostic pathway of these patients, focusing our attention on computed tomography pulmonary angiography (CTPA) findings. Indeed, CTPA was subsequently prompted in all these 45 patients by clinical suspicion of pulmonary thromboembolism, even though all of them had been receiving LMWH at least at prophylactic dosage from admission.

Main criteria driving the request of CTPA were the presence of lower-limbs deep vein thrombosis at ultrasound Doppler examination, onset or worsening of dyspnea, and worsening or less-than-expected improvement of the PaO_2/FiO_2 ratio. We subsequently retrieved clinical data including age, sex, weight, height, body mass index, comorbidities, pharmacological treatments during hospitalization, anticoagulant therapy at admission, PaO_2, FiO_2, and PaO_2/FiO_2 ratio. Blood tests performed at admission and before CTPA included coagulation parameters, inflammatory markers, and troponin T.

CTPA exams were performed using a 16-slice CT scanner (Somatom Emotion, Siemens Healthineers, Erlangen, Germany), including breath-hold unenhanced and contrast-enhanced scans. Patients received 1 mL/kg of contrast agent (Iopamidol 370 mg/mL, Bracco Imaging, Milan, Italy), intravenously injected at a 5 mL/s rate, plus a 35 mL saline bolus. Bolus triggering in the pulmonary artery, tube voltage 110 kVp, automatic exposure control, and cranio-caudal scanning were used.

A radiologist with 15 years of experience in body and chest CT reviewed images to assess presence and extent of thromboembolism.

Continuous variables were reported as median and interquartile range (IQR). Comparing patients with and without

Table 1

Demographic and clinical characteristics of the 45 included patients.

Group	Variable	Patients with PTE (27)	Patients without PTE (18)	*P*-value[a]
Demographics	Males/Females	20/7	14/4	.533
	Age (median)	70	62	.040
	BMI	26	28	.090
Comorbidities	Hypertension	13	10	.763
	Cardiovascular disease	10	5	.748
	Malignancy	2	2	1.000
	COPD	1	1	1.000
	Number of comorbidities (median)	1	1	.810
Laboratory and clinical variables	PaO_2/FiO_2 ratio[b]	91	102	.256
	CRP (mg/dL)[c]	4.2	0.2	.002[d]
	IL6 (pg/mL)[c]	83	17	.039
	Patients administered tocilizumab	8	8	.354
	D-Dimer (μg/mL)[c]	0.78	0.55	.026
	Fibrinogen (mg/dL)[c]	517	360	.018
	PT (%)[c]	89.5	97.0	.022
	aPTT (s)[c]	32.6	29.7	.028
	Patients with LLVT	1	3	.125
	Days of hospitalization (median)	13	21	.002[d]

aPTT = activated partial thromboplastin time; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; FiO_2 = fraction of inspired oxygen; IL6 = interleukin 6; LLVT = lower-limbs vein thrombosis; PaO_2 = arterial blood oxygen tension; PT = prothrombin time; PTE = pulmonary thromboembolism.

[a] Fisher exact test for categorical variables and Mann–Whitney *U* test for continuous ones.

[b] Median of worst values during hospitalization.

[c] Median values before computed tomography pulmonary angiography are reported.

[d] Statistically significant differences.

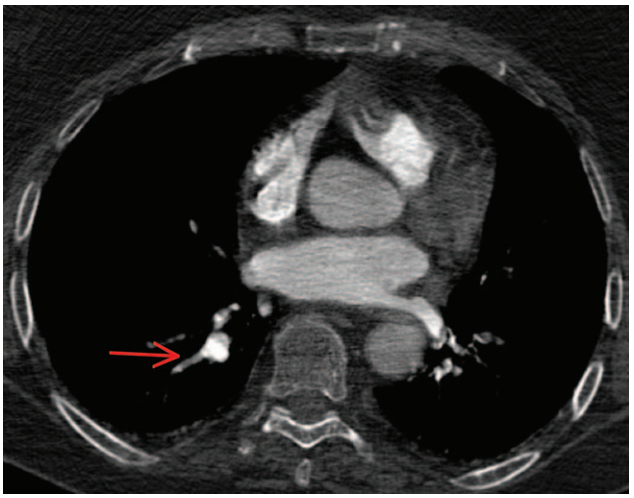

Figure 1. Axial CT pulmonary angiography showing segmental thromboembolism (red arrow) in the right lower lobe, with angiographic defect exhibiting the customary high-density appearance of thrombi in COVID-19 patients receiving low-molecular-weight heparin at prophylactic dosage. COVID-19 = coronavirus disease 2019; CT = computed tomography.

pulmonary thromboembolism, the Fisher exact test was used to assess significant differences for categorical variables, while the Mann–Whitney *U* test was used for continuous ones. Statistical analysis was performed using IBM SPSS Statistics v.26.0 (IBM SPSS Inc., Chicago, IL). As 19 comparisons were made overall, *P*-values were adjusted with the Bonferroni correction, therefore considering *P*-values <.003 as statistically significant.

3. Results

Of 45 COVID-19 patients included in this study, 34 were men (76%) and 11 women (24%), with a median age of 67 years (IQR 60–76) (Table 1). At least one comorbidity was found in 33 (73%) patients, hypertension being the most common (23 patients, 51%), followed by previous cardiovascular disease (15 patients, 33%) and diabetes mellitus type 2 (11 patients, 24%).

On admission, 16 patients had fever, cough, and dyspnea (36%), 13 fever and dyspnea (29%), 5 fever and cough (11%), 9 only fever (20%), 2 only dyspnea (4%). Median room air pulse oximetry was 89% (IQR 76%–95%).

All patients received at least prophylactic LMWH from admission (Enoxaparin 4000 UI or 6000 UI s.c. q.d.). Three patients were already taking apixaban due to permanent atrial fibrillation, while one was started on LMWH at anticoagulation dosage on admission for paroxysmal atrial fibrillation. One patient developed retroperitoneal hematoma during hospitalization, and LMWH was stopped. Tocilizumab was administered to 16 patients.

Median elapsed time from admission to CTPA was 18 days (IQR 13–21). Of 45 patients, 27 (60%, 20 men, 74%) exhibited signs of pulmonary thromboembolism at CTPA, 17 of them (63%) bilaterally. No main branch thromboembolism was found. Examples are presented in Figs. 1 and 2.

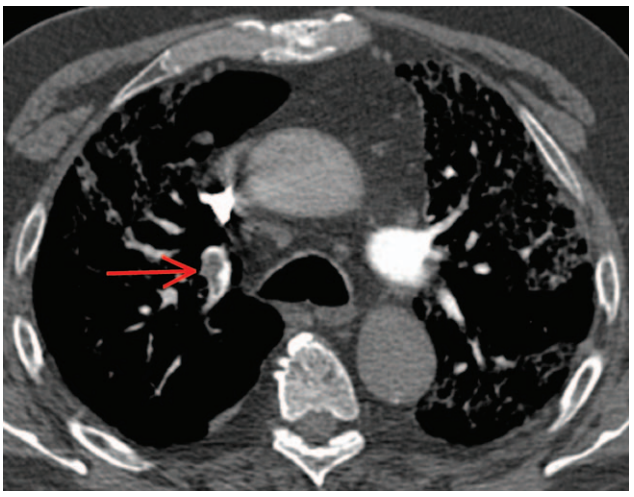

Figure 2. Axial CT pulmonary angiography showing lobar thromboembolism, with a low-density thrombus (red arrow), less frequently observed in COVID-19 patients receiving low-molecular-weight heparin at prophylactic dosage. COVID-19 = coronavirus disease 2019; CT = computed tomography.

In 12/45 patients (27%) with high clinical suspicion of pulmonary thromboembolism CTPA was directly performed without previous lower-limbs ultrasound Doppler examination, 6 of them (50%) being subsequently diagnosed with pulmonary thromboembolism. In the remaining 33/45 patients (73%) lower-limbs ultrasound Doppler examination was performed before CTPA, 3 (9%) patients having superficial vein thrombosis and only 1 patient (3%) having deep vein thrombosis. Of note, only the latter subsequently showed CTPA signs of pulmonary thromboembolism. Overall, among these 33 patients, pulmonary thromboembolism was diagnosed by CTPA in 21 patients (64%).

Before CTPA, 5 patients (11%) had high D-dimer levels (11.21 μg/mL, IQR 9.10–13.02), 19 (42%) had high fibrinogen levels (550 mg/dL, IQR 476–590), 1 (2%) had an altered prothrombin time (64%, INR 1.36), and 7 (16%) an altered partial thromboplastin time (39.6 seconds, 38.4–40.6). Eleven patients (24%) had high C-reactive protein levels (9.60 mg/dL, IQR 6.75–10.65) and 26 (58%) high interleukin-6 levels (79 pg/mL, IQR 31–282). Sixteen patients (36%) had high ferritin values (932 mU/mL, 502–1192) and 41 (91%) high lactate dehydrogenase values (458 μg/L, IQR 376–635). High troponin *T* values were found in 10 patients (22%, 26.5 ng/L, IQR 18.0–32.5).

After CTPA diagnosis of pulmonary thromboembolism, only 2 out of 45 patients (4.5%) needed intensive care, while 8 out of 16 patients (50%) which were previously administered tocilizumab were found to have pulmonary thromboembolism. One female patient with thromboembolism had autoimmune thrombocytopenia. Prevalence of pulmonary thromboembolism in subgroups of patients with altered clinical parameters was: 1 out of 4 (25%) patients with lower-limbs vein thrombosis; 5 out of 5 patients with high D-dimer levels; 14 out of 19 (74%) patients with high fibrinogen levels; 1/1 patients with altered prothrombin time; 6 out of 7 (86%) patients with altered partial thromboplastin time; 10 out of 11 (91%) patients with high C-reactive protein level; 17 out of 26 (65%) patients with high interleukin-6 levels; 10 out of 16 (63%) patients with high ferritin values; 26 out of 41 (63%) patients with high lactate dehydrogenase values; 10 out of 10 patients with high troponin values. Table 1 shows statistical comparisons between different variables in patients without and with pulmonary thromboembolism.

As of May 4, a median follow-up of 27 days (IQR 26–28) was available, with 3 patients having died during hospitalization, 2 because of complications of pulmonary thromboembolism, and 1 for retroperitoneal bleeding.

4. Discussion

SARS-CoV-2 infection—while mainly affecting the respiratory system[10]—also presents systemic inflammatory damage and activation of the coagulation cascade.[11–17] Clinical suspicion of pulmonary thromboembolism is not straightforward, hypoxia being already caused in most patients by acute pneumonia: patients are also frequently paucisymptomatic during oxygen supplementation, despite low PaO_2/FiO_2 values.

Our results show how coagulation abnormalities in COVID-19 patients represent a considerable threat, even if first-line prophylactic measures are implemented. In our cohort, we observed a 60% prevalence of CTPA-detected thromboembolism: this figure could be even higher, since all our patients were receiving at least prophylactic LMWH. Of note, among 18 compared variables between patients with and without CTPA-confirmed pulmonary thromboembolism, only C-reactive protein values and the median duration of hospitalization significantly differed between the 2 groups. Such differences could be associated with prompt anticoagulation therapy for PTE and its beneficial effect on COVID-19 patients, or with rapid worsening of patients' conditions. Of note, patients with pulmonary thromboembolism developed clinical signs suspicious for this condition and were referred for CTPA a median 8 days earlier than patients with negative CTPA findings, also having significantly higher C-reactive protein levels. Such findings are in line with the hypothesis which sees pulmonary thromboembolism in COVID-19 patients as a prevalently local byproduct of SARS-CoV-2 induced inflammation.[20,21,30–32] Lung microthrombosis triggered by autoimmune or direct viral endothelial damage is known to be associated with coronavirus infection since the SARS-CoV-1 pandemic in the early 2000s.[19,32,33] The repercussions of such pathogenetic mechanisms on diagnostic[19,21,34] and treatment[19,20,28,30,35,36] pathways of COVID-19 patients are hotly debated, with LMWH administration at prophylactic dosage increasingly deemed to be probably unable in adequately preventing severe coagulopathy.[28,29,35,36] Our study has some limitations, other than its monocentric and retrospective design with a limited sample size. First, since this study was conducted during the first pandemic peak in our area, the generalizability of our findings may be hindered by potential changes in disease spectrum and broader prophylactic measures that have since entered routine clinical use. Second, its focus on patients receiving LMWH at prophylactic dosage could have engendered a selection bias. However, our study hints that even when considering only patients under prophylactic treatment, COVID-19 is still associated with a high prevalence of pulmonary thromboembolism. This plays in favor of extending anticoagulant therapy to all hospitalized COVID-19 patients after considering their bleeding risk, even when D-dimer is not markedly elevated, sepsis-induced coagulopathy criteria are not met, or in absence of acute respiratory distress syndrome, then proceeding to rule out pulmonary thromboembolism in patients with markedly increased D-dimer or other inflammatory markers, deep vein thrombosis, or less than-expected clinical improvement despite optimal oxygen and medical therapy. Further large-scale studies are needed to precisely assess thromboembolism incidence in COVID-19 patients and its true pathophysiological nature, in order to optimize treatment and potentially lower mortality rate.

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