Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

High rate of pulmonary thromboembolism in patients with SARS-CoV-2 pneumonia

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To the Editor,

Recently, thromboembolic events have been reported in 20 of 81 individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) severe pneumonia admitted to intensive care units. About 90% of patients showed an increased coagulation activity, including high D-dimer concentrations, which demonstrated 85% sensitivity and 89% specificity for identifying groups at high risk for thromboembolic events [1]. Moreover, cytokine storm syndrome has been proposed to cause a hypercoagulable state in individuals with coronavirus disease 2019 (COVID-19) [2,3].

During 1 week, between 30 March and 6 April 2020, all the individuals admitted to the 60-bed COVID-19 unit of our hospital and at high risk for pulmonary thromboembolism (PTE) underwent a computerized tomography pulmonary angiography (CTPA) scan. Patients were considered at high risk if presenting with pneumonia caused by laboratory-confirmed SARS-CoV-2, persistent respiratory impairment and a D-dimer value at least five times the upper reference limit. CTPA scan was performed on a 64-row multiple detector CT scanner (Brilliance 64, Philips, Amsterdam, the Netherlands) after administration of a weight-based amount of contrast material—350 mg/mL Omnipaque (GE Healthcare, Chalfont St Giles, UK) or 370 mg/mL Ultravist (Bayer Schering Pharma, Berlin, Germany)—followed by a 50-mL saline bolus administered through a dual-head injector (Medrad Stellant, Indianola, IA, USA). Scan timing was determined using a bolus-tracking technique, focusing on the pulmonary trunk. Patients' demographic characteristics, underlying conditions, clinical features, and laboratory and radiological findings were collected. The institutional ethics committee approved the study and informed consent from patients was obtained.

During the study period, ten individuals underwent a CTPA scan. PTE was detected in six of them, all displaying D-dimer values > 10 000 μg/L, and a persistent Pao_2/Fio_2 ratio <150. Consistent with the diagnosis of viral pneumonia, in all of these six individuals, the CTPA scan showed peripherally distributed bilateral ground-glass opacities, reticular opacities and areas of consolidation in the posterior basal segments. Multiple filling defects involving lobar or segmental and subsegmental branches of the pulmonary arteries with subsegmental vessels enlargement were also detected in all patients. These features were bilateral in four patients. One of them showed involvement of both principal and segmental pulmonary arteries, with filling defects affecting the corresponding pulmonary vein branches.

Four out of six of the patients were male and the median age was 75 (range 55–86 years). None of the patients had a previous history of thromboembolic events, four had a history of arterial hypertension, and only one had a relevant risk factor for thromboembolic diseases (cancer). The mean time between COVID-19 symptom onset and hospital admission was 12 days (range 9–16 days) whereas the mean time between hospital admission and the diagnosis of PTE was 9.3 days (range 5–17 days). On the day that PTE was diagnosed, the Pao_2/Fio_2 ratio was <150 in all patients; the leucocyte count ranged between 5970 and 31 480/μL. Five patients showed reduced C-reactive protein values compared with the assessment at the hospital admission. Interleukin-6 levels were increased in three patients (Table 1).

The prevalence of PTE was substantially higher than those recorded in the previous 3 years in the same 60-bed unit, admitting

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Table 1
Demographic characteristics, clinical features and laboratory findings of six patients with coronavirus disease 2019 and pulmonary thromboembolism

Patient	1	2	3	4	5	6
Age (years)	59	71	78	86	86	55
Sex	Female	Male	Male	Male	Female	Male
Co-morbidities	Type 2 diabetes COPD Obesity	Arterial hypertension Post-traumatic epilepsy	Arterial hypertension CKD	Arterial hypertension CHD	Breast cancer (stage 4)	Arterial hypertension Liver steatosis
Symptoms onset to HA (days)	9	10	15	10	16	Not known
Days from hospital admission to PTE	11	11	7	5	5	17
Chest X-ray on HA	Bilateral lung opacities	Bilateral lung opacities	Bilateral lung opacities	Bilateral thickening of parenchymal interstitium	Bilateral lung opacities	Bilateral lung consolidations
Pa_{O_2}/Fi_{O_2} ratio*	76	110	125	50	86	130
D-dimer* (μg/L)	>10 000	>10 000	>10 000	>10 000	>10 000	>10 000
CRP on HA (mg/L)	49	138	208	180	104	26
CRP* (mg/L)	43	<1	17	36	104	5
WBC* (no./μL)	31 480	5970	16 420	11 120	7230	14 720
Platelets* (no./μL)	244 000	114 000	245 000	188 000	274 000	209 000
IL-6 (pg/mL)	68.2	137	<7.8	65.51	NA	NA

Abbreviations:CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HA, hospital admission; IL-6, interleukin-6; PTE, pulmonary thromboembolism; WBC, whole blood count.
* On the day of PTE diagnosis.

mainly individuals with infectious diseases: 1.6% (13/801) in 2019, 1.4% (11/799) in 2018, and 1.8% (16/869) in 2017. Although the prevalence in our small cohort of non-intensive care unit patients is less than the one recently reported in intensive care unit patients [1], it seems to confirm the increased risk of PTE in individuals with COVID-19.

In our case series, the involvement of segmental and subsegmental branches of the pulmonary arteries, along with the peculiar distribution of multiple and bilateral filling defects, suggest a non-embolic origin of the pulmonary artery thrombosis [4]. Furthermore, the contiguity of most filling defects to the parenchymal opacities suggests a link between the SARS-CoV-2-induced lung inflammation and vascular occlusion, possibly explaining the severe respiratory impairment detected in patients.

Compared with the rates previously reported in individuals with pneumonia or other severe infections, a higher prevalence of PTE in individuals with SARS-CoV-2 pneumonia might be inferred from this small series. The absence of major risk factors for thromboembolic events in five of the six patients seems to further confirm the role of bilateral SARS-CoV-2 pneumonia as a risk factor for PTE.

Considering that an undiagnosed thromboembolic process might worsen patient outcome, we would suggest including a CTPA scan in the diagnostic assessment of individuals with SARS-CoV-2 pneumonia, high D-dimer, and refractory or rapidly deteriorating hypoxaemic respiratory failure. Nevertheless, the role of prophylactic heparin remains controversial [2,5] as the incidence of PTE needs to be further explored and the risk factors of major haemorrhagic adverse events partially overlap with those of severe SARS-CoV-2 pneumonia. Moreover, there are some ongoing studies on possible preventive and therapeutic effects of other agents (i.e. anticoagulants other than heparin, antiplatelet agents) on hypercoagulability observed in association with COVID-19 infection. A prospective cohort study with an appropriate sample size is required to confirm the association between diffuse bilateral SARS-CoV-2 pneumonia and PTE, to support therapeutic indications, and to better define the target population.

Transparency declarations

All authors have stated that they have nothing to disclose.

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Authors' contributions

PM and GM conceived the study and wrote the first draft. All authors collected data and improved the manuscript, which was finalized by FM, MS and ET.

PM and GM contributed equally to this work.

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