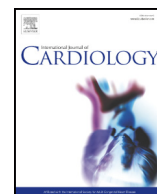




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## Short communication

## Acute pulmonary embolism in COVID-19 disease: Preliminary report on seven patients



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## ABSTRACT

There is some evidence that Covid 19 pneumonia is associated with prothrombotic status and increased risk of venous thromboembolic events (deep venous thrombosis and pulmonary embolism). Over a two-week period we admitted in our Unit 25 patients with Covid-19 pneumonia, of these pulmonary embolism was diagnosed using computed tomography angiography in 7. We report on clinical and biochemical features of these patients. They were all males, with a mean age of 70.3 years (range 58–84); traditional risk factors for venous thromboembolism were identified in the majority of patients with pulmonary embolism, however not differently from those without pulmonary embolism. Clinical presentation of pulmonary embolism patients was usually characterized by persistence or worsening of respiratory symptoms, with increasing oxygen requirement. D-dimer levels were several fold higher than the upper threshold of normal; in patients in whom PE was recognized *during* hospital stay, a rapid and relevant increase of D-dimer levels was observed. Computed tomographic findings ranged from massive acute pulmonary embolism to a segmental or sub-segmental pattern; furthermore, thrombosis of sub-segmental pulmonary arteries within lung infiltrates were occasionally seen, suggesting local mechanisms. Six out of 7 patients were treated with unfractionated or low molecular weight heparin with clinical benefit within few days; one patient needed systemic thrombolysis (death from hemorrhagic complication).

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## 1. Introduction

Infection and sepsis are traditional risk factors for deep vein thrombosis and acute pulmonary embolism (PE), as they underlie a hypercoagulable state [1]. Recent studies suggest that severe COVID-19 pneumonia may be associated with a coagulopathic state and an increased risk of venous thromboembolism [2]. Moreover, Chinese reports showed the unfavorable prognostic effect of altered coagulation parameters [3] and the favorable effects of treatment. In particular, high D-dimer levels and prolonged prothrombin time were directly related to short term mortality and patients with more severe lung abnormalities due to SARS-CoV-2 disease seemed to benefit from anti-coagulant treatment with heparin [4].

In this setting, other predisposing factors for venous thromboembolism may be long hospital stay, congestive heart failure, respiratory failure and comorbidities such as cancer, obesity, arterial disease, hypertension and diabetes [1].

One case report has recently highlighted the absence of predisposing factors other than active infection in a 75-year-old woman admitted to hospital for acute pulmonary embolism and COVID-19 pneumonia. High D-dimer levels were found while no deep venous thrombosis (DVT) was detected. The patient was treated with low-molecular-weight heparin (LMWH) [5].

## 2. Study population and results

Over the past two weeks, seven out of 25 patients (28%) hospitalized with COVID-19 pneumonia in our Unit, were diagnosed with acute pulmonary embolism, as detected by computed tomographic angiography. Three of them were admitted to the hospital

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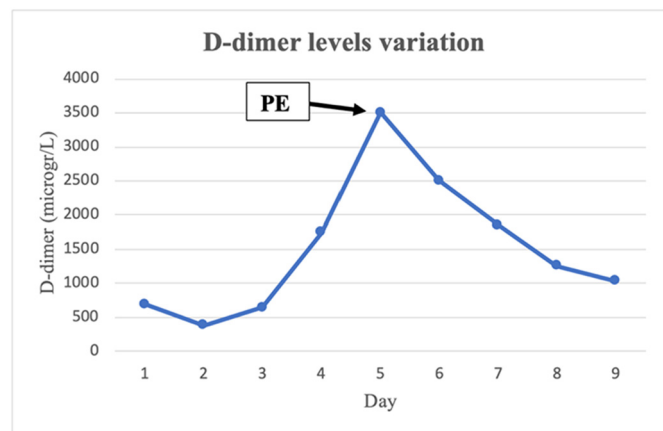
**Table 1**  
Patient characteristics.

	EP	Not-EP
Total number	7	18
Sex (male) n, %	7, 100%	14, 78%
Age mean (min-max)	70,3 (58–84)	71,5 (60–83)
Comorbidities/predisposing factors, at least 1	6, 86%	17, 94%
• Known coronary artery disease n, %	3, 43%	10, 55%
• Chronic heart failure n, %	1, 14%	3, 16%
• Cancer n, %	2, 29%	3, 16%
• Atrial fibrillation n, %	2, 29%	6, 33%
• Hypertension n, %	2, 29%	6, 33%
• Diabetes n, %	0	2, 11%
D-dimer at diagnosis, mean (µg/L)	4368	1455
DVT n, %	2, 29%	0
Previous therapy		
• Anticoagulant n, %	0	4, 22%
• Thromboprophylaxis (enoxaparine 40 mg, once daily) n, %	3, 43%	2, 11%
• No therapy n, %	4, 57%	12, 66%
PE therapy		
• UFH n, %	4, 57%	
• LMWH n, %	2, 29%	
• Oral anticoagulant n, %	0	
Death n, %	1, 14%	4, 22%

with the initial diagnosis of PE while the other four developed PE during hospital stay.

Patient characteristics are presented in the Table 1. All EP patients were males, more commonly in the seventh decade of life. Almost the totality of patients had at least one comorbidity known to predispose to venous thromboembolism with coronary artery disease being the most common [6]. Prevalence of comorbidities was similar in EP and not-EP patients.

At the time of PE diagnosis, D-dimer levels were several fold higher than the upper threshold of the laboratory test ( $\leq 288$  µg/L). Peak D-dimer value in PE patients was statistically significant higher, compared to that observed in not-PE patients ( $p < 0.05$ ). Of interest, in those patients in whom PE was recognized during hospital stay, a rapid and relevant increase of D-dimer levels was documented (Fig. 1). Only two patients had evidence of concomitant



**Fig. 1.** Male patients, 72 year old with PE. Daily changes in D-dimer values showed the relevant increase leading to PE suspicion and, then, PE confirmation by CT. Unfractionated heparin determined clinical improvement and D-dimer reduction was also documented. See text for details.

deep vein thrombosis of lower limbs, as detected by ultrasonography.

Three out of 7 patients developed PE despite being on thromboprophylaxis with LMWH, i.e. enoxaparine 40 mg once daily, according to international guidelines [7].

CT findings were variable, from massive acute pulmonary embolism in two patients to a segmental or sub-segmental pattern in the others (Fig. 2). Of interest, thrombosis of sub-segmental pulmonary arteries within lung infiltrates were occasionally seen, suggesting local mechanisms.

Six out of 7 patients were treated with unfractionated or low molecular weight heparin; one patient needed systemic thrombolysis due to a clinical presentation with shock, whose hemorrhagic complication was the cause of his death. The clinical conditions of the other patients improved within the next few days.

### 3. Discussion

The main finding of our study is a relevant incidence of PE in patients with overt heart disease or traditional cardiovascular risk factors admitted to the hospital for Covid19 pneumonia; in fact, more than one fourth (7 out of 25, 28%) of patients hospitalized over two weeks had PE. The patients in whom PE was diagnosed during hospital stay usually showed persistence or worsening of respiratory symptoms, with increasing oxygen requirement; Furthermore, their arterial blood oxygen levels declined despite radiological signs of improvement or with evolution (i.e. compactness) of parenchymal infiltrates. Again, we cannot exclude a higher incidence of PE due to silent or unrecognized cases, as often happens in patients hospitalized in medical wards.

We reported that almost all of our patients had other predisposing factors besides infection, including overt cardiovascular disease and traditional risk factors.

As a consequence of infection, in patients with COVID-19 pneumonia D-dimer levels usually rise two or three-fold. In contrast, in case of very high-level D-dimer increase during hospital stay, especially associated with clinical deterioration, PE should be considered and appropriate diagnostic process applied.

The CT finding of vascular occlusion within the alveolar infiltrates suggests a possible link between alveolar inflammation and vascular inflammation with in situ thrombosis and needs to be confirmed.

Of interest, in our case series, recommended thrombo-prophylaxis approach with low-dose enoxaparine once daily seems to lack efficacy in preventing venous thromboembolic events in Covid-19 patients with advanced lung disease.

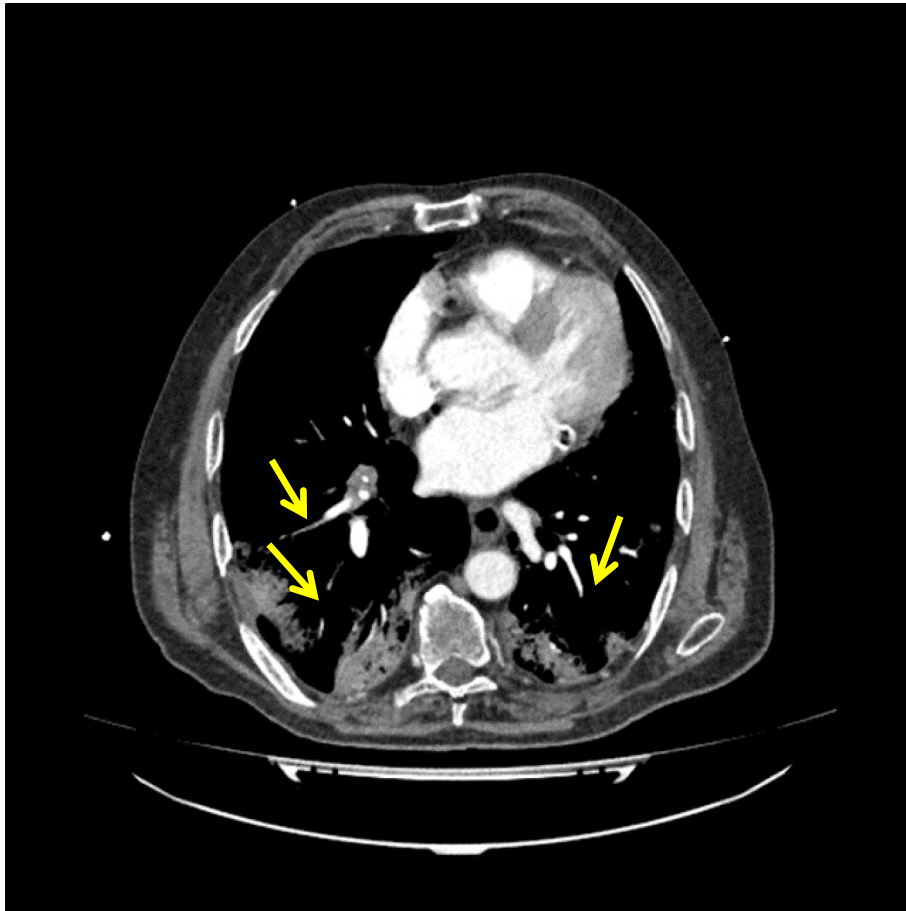
On the other hand, standard treatment of PE with unfractionated or low molecular weight heparin showed clinical benefit and was associated with a progressive decline in D-dimer levels.

In conclusion, according to this case-series of COVID-19 pneumonia, acute pulmonary embolism seems to be a non-infrequent finding. High or rapidly increasing D-dimer levels should alert the clinician, especially in case of worsening symptoms and blood gas analysis abnormalities. The real efficacy of standard prophylactic approach in these patients should be verified.

Further investigation on larger population should clarify the incidence of PE in patients with SARS-Cov-2 disease and the best strategies for its prevention and treatment.

### Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.



**Fig. 2.** Computed tomography of the chest showing pulmonary embolism in a 72 year old man, admitted to the hospital for worsening of chronic heart failure and Covid 19 pneumonia. Bilateral lung infiltrates are visible; occlusion of subsegmental arteries within lung infiltrates is indicated by arrows. See text for details.

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