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Early View

Research letter

Pulmonary embolism in patients with Covid-19 pneumonia

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TITLE: **PULMONARY EMBOLISM IN PATIENTS WITH COVID-19 PNEUMONIA**

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TEXT

To the editor:

Acute respiratory distress syndrome developing in patients with COVID-19 pneumonia is associated with a high mortality rate and is the main cause of death in patients with SRAS-Cov-2 infection [1]. Myocardial injury has also been reported to be significantly associated with fatal outcome, with 37% mortality rate for patients without prior cardiovascular disease but elevated troponin levels [2]. Regarding other biomarkers of severity, a D-dimer level greater than 1 µg/mL has been clearly identified as a risk factor for poor outcome in SARS-Cov-2 infection [3], with recent reports highlighting a high incidence of thrombotic events in intensive care unit (ICU) patients [4]. A normal D-dimer level allows excluding safely pulmonary embolism in outpatients with low or intermediate clinical probability of pulmonary embolism (PE) but there is no recommendation to use D-dimer as a positive marker of thrombosis because of lack of specificity. An advice paper from the European Society of Radiology and the European Society of Thoracic imaging suggested that contrast-enhanced CT should be performed to rule out PE if supplementary oxygen is needed in COVID-19 pneumonia patients with limited disease extension [5]. The European Society of Cardiology also recommends CTPA before leaving the radiology department when unenhanced CT findings cannot explain the severity of respiratory failure [6]. Indeed, it is not recommended to base PE diagnosis on pulmonary ventilation-perfusion imaging [7]. The cumulative incidence of VTE on the wards is reported to be lower than in the ICU (10% versus 48% at 14 days, respectively) [8] where investigation for PE is not always feasible due to critical illness and prone position [9].

We conducted a retrospective study evaluating all CT pulmonary angiographies (CTPA) performed between March 1^{rst} and April 16th, 2020 in patients with COVID-19 pneumonia at

in two hospitals of Université de Paris (Cochin and Pompidou hospitals). The study was approved by the ethics committee of Cochin Hospital (CLEP Decision N°: AAA-2020-08009). The reason why patients had been referred for CTPA was obtained from the electronic medical records, as well as the number of days of hospitalization at time of CT examination, the categorization as ICU or ward patient and need for mechanical ventilation. Information regarding D-dimer level within 24 hours of the CT examination was also obtained, together the modalities of prophylactic anticoagulation in hospitalized patients. CT acquisitions had been performed on multidetector CT units (SOMATOM Definition Edge or SOMATOM Definition AS, both Siemens Healthineers, Erlangen, Germany) using standard CTPA protocols. Images were analyzed by 2 experienced radiologists who evaluated COVID-19 disease extent, presence or absence of intraluminal filling defects in the proximal or distal (segmental or subsegmental) pulmonary arteries and signs of acute right ventricular dysfunction.

During the study period, a total of 137 patients with confirmed SARS-Cov-2 infection and COVID-19 pneumonia underwent contrast-enhanced CT examination. All but two CT examination with major respiratory motion artifacts were of diagnostic quality, as assessed by the two expert readers. Thus, 135 patients (94 men, 70%) with a median age of 64 years [interquartile range (IQR) : 54-76 years] were included. Sixty-three of them (47%) were outpatients seen at the emergency department. They were referred for CTPA at initial presentation, because of hesitation between COVID-19 pneumonia and pulmonary embolism, after clinical probability assessment and D-dimer dosage, applying the same cutoff as for non-COVID patients. The remaining 72 patients (53%) were already hospitalized for a median of 5 days [IQR : 4-8 days] and had presented clinical respiratory deterioration, with an increase of oxygen needs. Twenty-four patients were in ICU under mechanical ventilation.

There was no disagreement between the two expert readers as well as between initial and expert reading regarding the presence of PE. A total of 32 PE were identified resulting in a 24% (95% CI; 17-32%) overall cumulative incidence, 50% (30-70%) in ICU and 18% (12-27%) in other patients. Fifteen PE were diagnosed in outpatients at initial presentation whereas the remaining 17 were diagnosed in patients who had presented clinical deterioration during hospitalization. All inpatients received prophylactic anticoagulation (enoxaparin 40 mg once daily in ward patients, or twice daily in obese and ICU patients according to local practice). There were ten proximal PE whereas eighteen involved segmental pulmonary arteries and the remaining four PE multiple sub segmental pulmonary arteries. On CTPA there were signs of acute right ventricular dysfunction (right-to-left ventricular diameter ratio >1) in six patients, four with proximal PE including one saddle PE, and two others with segmental PE, one patient having moderate and the other severe disease extent on CT. Comparison between the PE positive and PE negative groups of patients is summarized in the Table. No statistical difference between groups was noted regarding age or gender. Interestingly, disease extent on CT pulmonary angiography was not significantly different between patients with or without PE. Conversely, among the 53 patients referred for clinical respiratory deterioration who had a previous CT, increase of disease extent was more frequently observed in the PE negative group. Patients with PE were more frequently hospitalized in ICU and more frequently under mechanical ventilation, with longer median hospitalization duration (15 [9 - 17] versus 8 [4 - 12] days, P=0.04). Regarding the outcome, there were 4 deaths in the PE positive group (4/32, 13%) and twelve in the PE negative group (12/135, 12%) within a median follow-up of 26 [22 - 29] and 27 [20 - 32] days, respectively. D-dimer level was significantly higher in the PE group; meaning that D-dimer increase is not only a marker of pneumonia severity but is associated with a higher risk of PE. Our data do not allow defining an accurate threshold for PE risk in this specific population. However the

high cumulative incidence of PE we observed suggests to more frequently use contrast medium for the evaluation of COVID-19 patients on CT.

Some authors suggested using low molecular weight heparin anticoagulant therapy in patients with severe pneumonia who have excessive activation of coagulation, defined as D-Dimer values 4-times higher than the normal upper limit [10]. Tang et al reported lower 28-day mortality in patients with D-dimer > 6 fold of upper limit of normal who received heparin at a prophylactic dose, as compared with those who did not [11].

In our study, prophylactic anticoagulation did not avoid the occurrence of PE in hospitalized patients, highlighting the need to adapt thrombosis prophylaxis in patients with SARS-Cov-2 infection.

Pulmonary embolism and deep venous thrombosis (DVT) have been reported to occur in other viral pneumonias, but not as frequently as in COVID-19 patients. Of 119 individuals admitted to the hospital with H1N1 Influenza A virus infection, seven (5.9%) experienced thrombotic vascular events, including 1 PE and three DVT [12].

Our study presents several limitations. Since contrast administration was not systematically used, our study does not allow assessing the incidence of PE for all COVID-19 patients. Whereas all patients referred because of clinical deterioration had contrast-enhanced CT, the reason why PE was suspected as concurrent diagnosis of COVID-19 pneumonia at initial presentation cannot be precisely assessed, in view of the retrospective design of our study. For the same reason, an in-depth analysis of comorbidities and especially history of venous thromboembolism was not possible. We were not able to evaluate the presence of deep venous thrombosis in our study population since none of the patients underwent compression ultrasound. . Lastly, our study does not allow defining which cutoff value of D-dimer should trigger contrast administration, when evaluating COVID-19 patients on CT. This remains an open question to be solved by a prospective evaluation.

In conclusion, we observed that almost a quarter of the COVID-19 pneumonia patients evaluated after contrast administration had acute pulmonary embolism on CT. This suggests more largely using contrast when performing thoracic CT examination in patients with COVID-19 pneumonia, especially for those with marked elevation of D-dimer.

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Table

	All (n=135)	With PE (n=32)	Without PE (n=103)	p value
Male	94 (70)	26 (81)	68 (66)	0.103
Age (years)	64 [54 - 76]	70 [59 - 77]	63 [52 - 75]	0.207
D-dimer (μ/L)	1600 [1010 - 3644]	9841 [2921 - 10000]	1285 [891 - 2742]	**<0.001**
Days since symptoms onset	8 [5 - 12]	7 [5 - 14]	8 [5 - 11]	0.597
Days of hospitalization	5 [4 - 8]	7 [3 - 11]	5 [4 - 8]	0.239
CTPA for clinical deterioration	72 (53)	17 (53)	55 (53)	0.979
Increase of disease extent as compared to previous CT°	43 (81)	5 (50)	38 (88)	**0.009**
Disease extent Low (<25%) Moderate (25-50%) Severe (>50%)	 19 (14) 47 (35) 69 (51)	 3 (9) 9 (28) 20 (63)	 16 (16) 38 (37) 49 (47)	0.146*
ICU	24 (18)	12 (38)	12 (12)	**0.001**
Mechanical ventilation	18 (13)	10 (31)	8 (8)	**0.001**

* Cochran-Armitage trend test
°: Only 53 of the 72 inpatients had a previous CT

Continuous variables are presented as median and interquartile range in brackets and were compared between with PE and without PE groups using Mann Whitney U test.
Categorical variables are presented as numbers and percentages and were compared between the two groups using chi-squared test.

PE: Pulmonary Embolism
CTPA: Computed Tomography Pulmonary Angiography
ICU: Intensive Care Unit