Radiology

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Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels

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Summary statement

Thirty-two of 106 (30%, [95%CI 22-40%]) patients with COVID-19 infection were positive for acute pulmonary embolus on pulmonary CT angiograms.

INTRODUCTION

Reports of acute pulmonary embolism associated with COVID-19 have emerged in the literature. For example, Chen et al. described 25 pulmonary CT angiograms examinations from 1008 COVID-19 patients; 10 were positive for pulmonary embolism mostly as segmental or sub-segmental APE [1]. In addition, D-dimer levels have been reported as elevated in patients with COVID-19 [2; 3] with the suggestion of an independent association between the severity of the disease and the level of D-dimer [4]. The purpose of this report is to describe the rate of pulmonary embolus in patients classified as COVID-19 infection and who underwent chest CT at a tertiary referral centre.

Materials and Methods

Patient Population

The local ethics committee of Strasbourg University Hospital approved this retrospective study and waived the need of informed consent. Full methods are provided in Appendix E1 (online). From March 1st to March 31st, medical records of all consecutive patients who underwent a CT examination 1) including the chest and 2) performed for either suspicion or follow-up of SARS-CoV-2 infection at one of our 2 hospital sites (Nouvel Hôpital Civil and Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg, France) were evaluated. CT examinations that included pulmonary CT angiographic images were evaluated for further study. Clinical and demographic parameters for patients with and without pulmonary embolus in CT pulmonary angiogram were evaluated.

CT Pulmonary Angiography

CT angiograms were acquired on 64 row or greater scanners after injection of 50 to 75 mL of high concentration iodine contrast media, with the use of a bolus-tracking technique and a threshold of 160 HU to 250 HU in the main pulmonary artery. Images were reconstructed with a slice-thickness of 1 mm

in mediastinal and parenchymal windows. A single reader (ILL) classified pulmonary embolism location as main pulmonary arteries, lobar, segmental or subsegmental based on the location of the most proximal luminal defect.

Laboratory Analysis

Fibrinogen and D-dimer levels were recorded for all patients who had pulmonary CT angiography. All patients with pulmonary CT angiography were evaluated for reverse transcriptase polymerase chain reaction (RT-PCR) results for SARS-CoV-2. All initial samples were obtained by nasopharyngeal swab; some patients had second or third sampling using sputum or bronchoalveolar lavage. Any positive result was classified as confirmed COVID-19 infection. When RT-PCR was negative, chest CT was reviewed by a senior chest radiologist (MO, with 14 years of experience) to look for characteristic COVID-19 lung parenchyma lesions. When CT images were considered typical (*i.e.* extensive bilateral and peripheral ground glass opacities and/or alveolar consolidation) and clinical data were compatible, the patient was also adjudicated as having COVID-19 [4; 5].

RESULTS

A flowchart of all patients with CT scans performed from March 1st to March 31st, 2020 is shown in Figure 1. During this period, 1696 patients had CT for suspicion or follow-up of COVID-19 infection. Dedicated pulmonary CT angiograms were performed in 135/1696 (8%) patients, 25 additional patients had pulmonary arterial phase images included in the chest/ abdomen/ pelvic CT scan (total, 160 patients). Of these 160 patients, 106 patients were classified as COVID-19 infection (97 patients by RT-PCR and 9 patients with positive CT and negative RT-PCR test). The reason for CT angiography in these patients was suspicion of pulmonary embolus in 67/106 (63%) patients and other CT indication in 39/106 (37%) patients.

Thirty-two of 106 (30%, [95%CI 22-40%]) patients with COVID-19 and with pulmonary CT angiogram were positive for acute pulmonary embolus; 74 were negative on CT. Relevant clinical and biological data are summarized in the Table.

Patients with COVID-19 infection and pulmonary embolus had higher D-dimer levels than those without pulmonary embolus (median, IQR 6110±4905 versus 1920±3674 µg/L, respectively, p<.001), were more likely to be in the intensive care unit (24/32 (75%) versus 24/74 (32%), p<.001) and were treated more often with low weight molecular heparin before CT angiography (25/32 (78%) versus 17/74 (23%), p<.001) (Table). In these patients with COVID-19 infection, D-dimer greater than 2660 µg/L had a sensitivity of 32/32 (100%, 95%CI 88-100) and a specificity of 49/74 (67%, 95% CI 52-79) for pulmonary embolism on CT angiography. See Figure 2 for an example patient.

DISCUSSION

Our study demonstrated that of 106 pulmonary CT angiograms performed for COVID-19 patients over a one-month period in a tertiary care centre; 32/106 (30%) of patients had acute pulmonary embolus. This rate of pulmonary embolus is higher than usually encountered in critically ill patients without COVID-19 infection (1.3%, [6]) or in emergency department patients (3 to 10% [7]). In our patient population, a D-dimer threshold of 2660 µg/L detected all patients with pulmonary embolus on chest CT. This threshold of 2660 µg/L is higher than previously reported median level of 2400 [8] and 900 [2] and is higher than cut-off values used to exclude pulmonary embolus in non-ICU patients [9]. High values of d-dimer could be related to a higher activation of blood coagulation in COVID-19 patients secondary to a systemic inflammatory response syndrome – or as a direct consequence of the SARS-CoV-2 itself. Although a single center retrospective report, our results of the potential for pulmonary embolism associated with COVID-19 infection may serve to alert the medical community to heighted vigilance of this complication.

Acknowledgement

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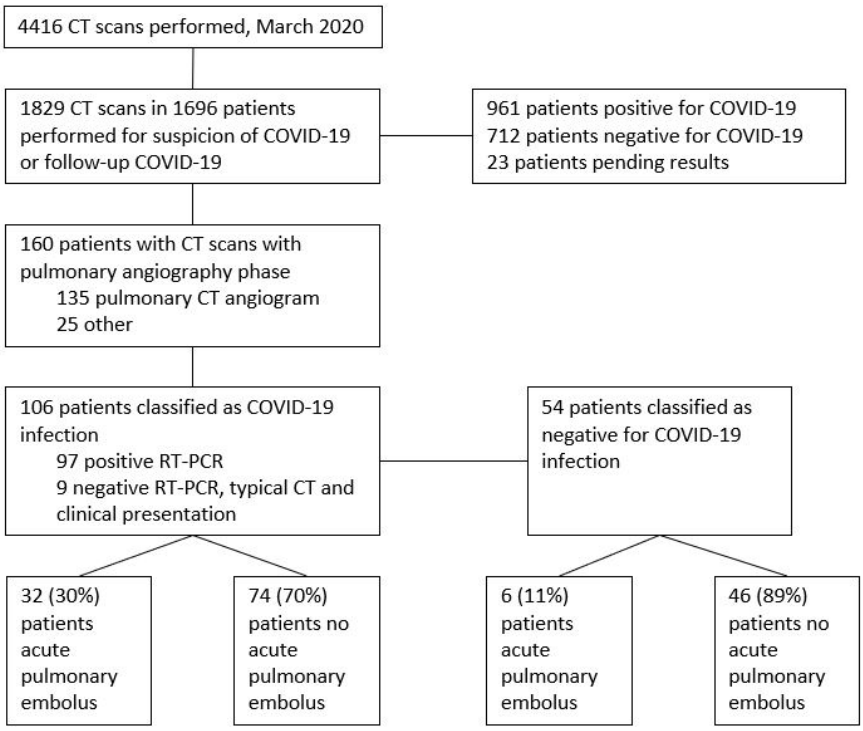

Figure 1. Flowchart of the study.

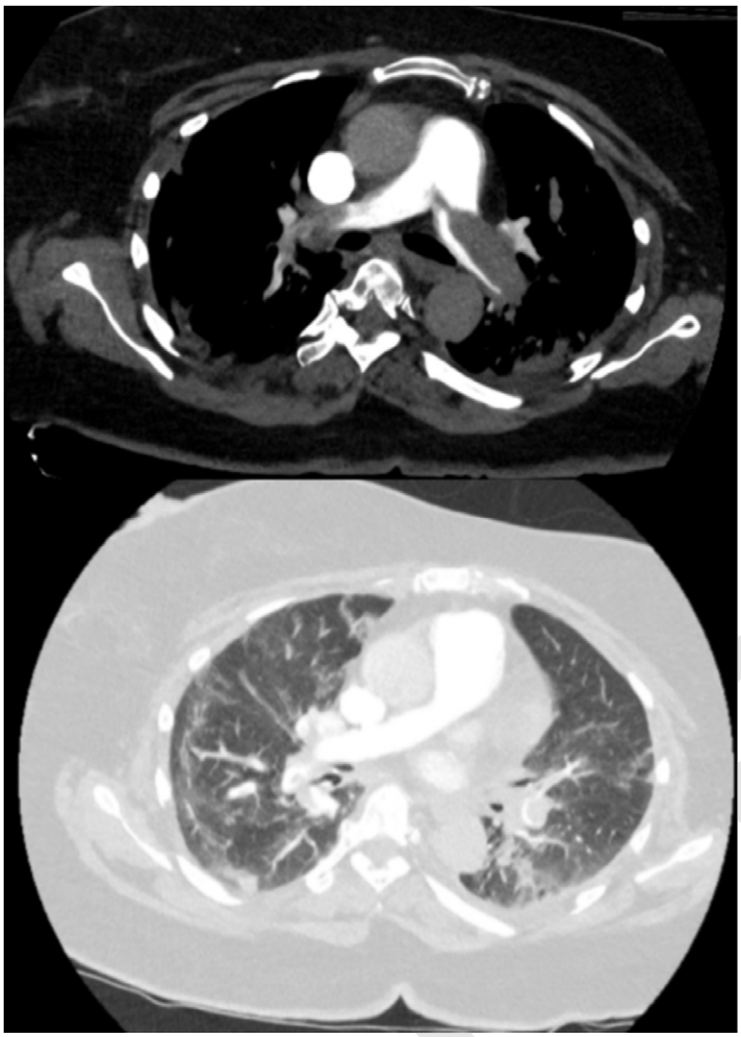

Figure 2. 71-year-old woman at day 3 of ICU stay for ARDS secondary to COVID-19. Pulmonary CT angiography was performed to investigate elevated of D-dimer value above 20 000 µg/L. The CT angiogram demonstrates bilateral filling defects in the main pulmonary arteries. Bilateral peripheral ground glass opacities and small areas of consolidation are present.

References

1 Chen JaW, Xiang and Zhang, Shutong and Liu, Bin and Wu, Xiaoqing and Wang, Yanfang and Wang, Xiaoqi and Yang, Ming and Sun, Jianqing and Xie, Yuanliang (2020) Findings of Acute Pulmonary Embolism in COVID-19 Patients. Available at SSRN: https://ssrncom/abstract=3548771 or http://dxdoiorg/102139/ssrn3548771

2 Huang C, Wang Y, Li X et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395:497-506

3 Chen N, Zhou M, Dong X et al (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395:507-513

4 Gao Y, Li T, Han M et al (2020) Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 10.1002/jmv.25770

5 Shi H, Han X, Jiang N et al (2020) Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 20:425-434

6 Lim W, Meade M, Lauzier F et al (2015) Failure of anticoagulant thromboprophylaxis: risk factors in medical-surgical critically ill patients*. Crit Care Med 43:401-410

7 Corrigan D, Prucnal C, Kabrhel C (2016) Pulmonary embolism: the diagnosis, risk-stratification, treatment and disposition of emergency department patients. Clin Exp Emerg Med 3:117-125

8 Cui S, Chen S, Li X, Liu S, Wang F (2020) Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 10.1111/jth.14830

9 Douma RA, Tan M, Schutgens RE et al (2012) Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded. Haematologica 97:1507-1513

Table. Clinical and biological data for patients undergoing pulmonary CT angiogram and classified as COVID-19 infection.

Clinical and CT features	**Pulmonary embolism present (n=32) (% or SD)**	**Pulmonary embolism absent (n=74)**	***p***
RT-PCR positive for COVID-19	30 (94%)	67 (91%)	0.59
Male	25 (78%)	45 (57%)	0.04
Age - median IQR (y-o)	64±22	63±15	0.60
BMI - median IQR (kg/m²)	27±8	29±10	0.10
ICU Hospitalization	24 (75%)	24 (32%)	0.001
SPAS II - median IQR (points, if ICU)	46±16	42±13	0.37
Worst PaO_2/FiO_2 ratio - median IQR (if ICU)	116±50	168±74	0.06
Clinical suspicion for pulmonary embolus	17 (53%)	50 (68%)	
Thromboembolic prophylaxis before CTPA	25 (78%)	17 (23%)	0.001
Anticoagulation before CTPA	2 (6%)	5 (7%)	1
Interval between initial symptom and CTPA: median and IQR (d)	14 [11;18]*	10 [7;13]*	0.001
Higher D-dimer (µg/L) : normal range < 500 µg/L	28 (88%)	50 (68%)	
Median and IQR	15385 ± 14410	1940 ± 3060	0.001
< 5000	5 (18%)	39 (78%)	
5000 to 20000	12 (43%)	9 (18%)	
> 20 000	11 (39%)	2 (4%)	
Higher Fibrinogen – median and IQR (g/L): normal range 2-4 g/L	7.89 ± 3.12	7.03 ± 3.29	0.19
Location of embolus on chest CT			
Main pulmonary artery	7 (22%)		
Lobar artery	11 (34%)		
Segmental artery	9 (28%)		
Subsegmental artery	5 (16%)		

SD standard deviation *Interquartile range

PaO2/FiO2 ratio is the ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2 expressed as a fraction)