



# Pulmonary thrombosis in Covid-19: before, during and after hospital admission

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Accepted: 7 December 2020 / Published online: 1 January 2021

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## Abstract

Disordered coagulation, endothelial dysfunction, dehydration and immobility contribute to a substantially elevated risk of deep venous thrombosis, pulmonary embolism (PE) and systemic thrombosis in coronavirus disease 2019 (Covid-19). We evaluated the prevalence of pulmonary thrombosis and reported RV (right ventricular) dilatation/dysfunction associated with Covid-19 in a tertiary referral Covid-19 centre. Of 370 patients, positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), 39 patients (mean age  $62.3 \pm 15$  years, 56% male) underwent computed tomography pulmonary angiography (CTPA), due to increasing oxygen requirements or refractory hypoxia, not improving on oxygen, very elevated D-dimer or tachycardia disproportionate to clinical condition. Thrombosis in the pulmonary vasculature was found in 18 (46.2%) patients. However, pulmonary thrombosis did not predict survival (46.2% survivors vs 41.7% non-survivors,  $p = 0.796$ ), but RV dilatation was less frequent among survivors (11.5% survivors vs 58.3% non-survivors,  $p = 0.002$ ). Over the following month, we observed four Covid-19 patients, who were admitted with high and intermediate-high risk PE, and we treated them with UACTD (ultrasound-assisted catheter-directed thrombolysis), and four further patients, who were admitted with PE up to 4 weeks after recovery from Covid-19. Finally, we observed a case of RV dysfunction and pre-capillary pulmonary hypertension, associated with Covid-19 extensive lung disease. We demonstrated that pulmonary thrombosis is common in association with Covid-19. Also, the thrombotic risk in the pulmonary vasculature is present before and during hospital admission, and continues at least up to four weeks after discharge, and we present UACTD for high and intermediate-high risk PE management in Covid-19 patients.

**Keywords** Covid-19 · SARS-CoV-2 · Pulmonary embolism · Pulmonary thrombosis · UACDT · Thrombolysis · Pulmonary hypertension

## Abbreviations

Covid-19      Coronavirus disease 2019  
CT              Computed tomography  
CTPA          Computed tomography pulmonary angiography

LV              Left ventricle  
PE              Pulmonary embolism  
RV              Right ventricle  
SARS-CoV-2      Severe acute respiratory syndrome coronavirus 2  
tPA              Tissue plasminogen activator  
UACDT          Ultrasound-assisted catheter-directed thrombolysis

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## Highlights

1. Pulmonary thrombosis may be present on admission to hospital and is probably underdiagnosed due to an observed tendency to limit investigations in this popu-

lation or to the fact that PE and Covid-19 overlap and share features.

2. High and intermediate-high risk PE disproportionate to associated lung disease may occur both during and after recovery from acute SARS-CoV-2 infection due to systemic prothrombotic processes associated with inflammation other than in the lungs.
3. UACTD may prove a useful method to manage high and intermediate-high risk PE in Covid-19 patients.
4. We demonstrated one case of pre-capillary pulmonary hypertension with RV dysfunction in a Covid-19 patient, likely associated with extensive lung disease.

## Introduction

The current coronavirus disease 2019 (Covid-19) pandemic has been associated with a substantial increase in thrombotic events; deep venous thrombosis, pulmonary embolism (PE) and systemic thrombosis have all been reported [1–5].

Thrombosis of the microvasculature and endothelial dysfunction secondary to dysregulated complement activation may contribute to both lung damage and pulmonary vascular remodelling [6–8]. Pulmonary microthrombi have been proposed as an explanation for the unusual level of gas exchange abnormalities [6, 9]. Extensive pulmonary thrombosis with microangiopathy and microthrombi in alveolar capillaries have been reported after an autopsy examination of lungs from 7 patients, who died from Covid-19 [10].

Tissue plasminogen activator (tPA) has been suggested as a possible treatment that may address the thrombotic component of this condition and improve outcomes [11].

The importance of dysregulated coagulation and immobility leading to embolism versus local factors leading to in-situ thrombosis may be of relevance in the precise treatment strategy.

The current study evaluated the prevalence of pulmonary thrombosis and reported RV (right ventricular) dilatation/dysfunction associated with Covid-19 patients in a tertiary referral Covid-19 centre. We also demonstrated that the thrombotic risk in the pulmonary vasculature is present before and during hospital admission, and continues at least up to four weeks after discharge, and we present 5 cases of Covid-19 patients who were managed with ultrasound-assisted catheter-directed thrombolysis (UACTD) for high and intermediate-high risk PE.

## Methods and results

### Prevalence of PE and RV dilation during the Covid-19 pandemic

From March 23rd to April 5th 2020, 370 patients that tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were admitted to the Royal Free Hospital. Of these, 39 patients (mean age  $62.3 \pm 15$  years, 56% male) underwent computed tomography pulmonary angiography (CTPA), because of increasing oxygen requirements or refractory hypoxia, not improving on oxygen, very elevated D-dimer ( $> 5000$  ng/ml, upper limits of normal 500 ng/ml) or tachycardia disproportionate to clinical condition.

Study was approved by Royal Free Hospital Institutional Review Board, as an audit of current practice.

Among those undergoing CTPA, thrombosis in the pulmonary vasculature was found in 18 (46.2%) patients. CTPA was performed in 15 of the 39 cases within 24 h of admission, six of whom had pulmonary thrombosis. Pulmonary thrombosis was located in main/lobar pulmonary artery in 6 patients (33.3%), in segmental artery in 9 patients (50%), and in subsegmental artery only in 3 patients (16.7%). All patients with pulmonary thrombosis had significant lung parenchymal changes associated with SARS-CoV-2.

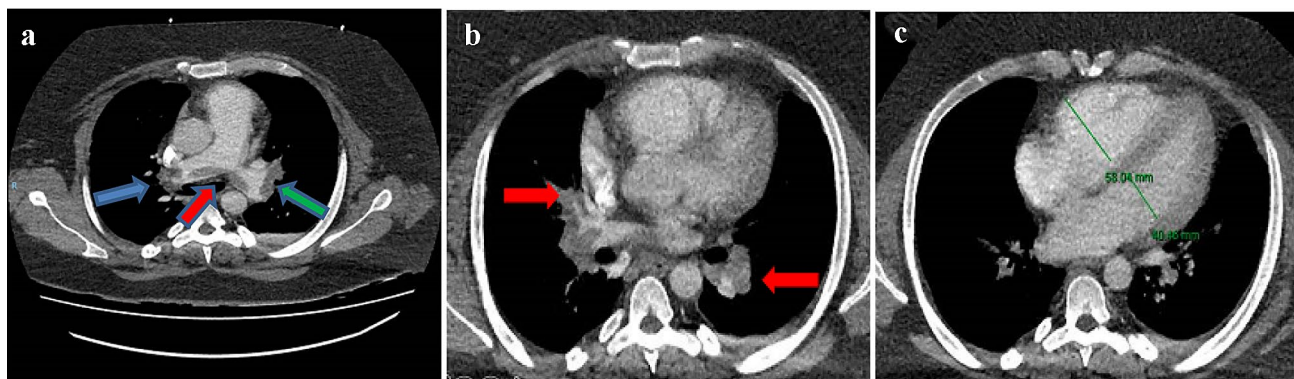
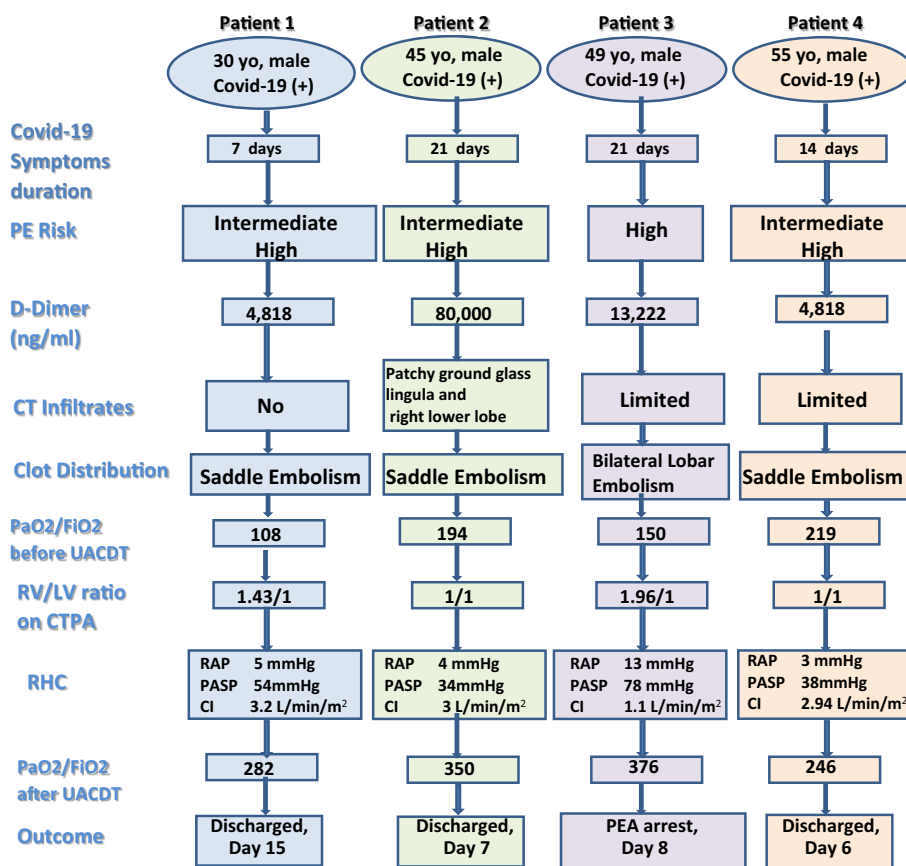
Pulmonary thrombosis did not predict survival (46.2% survivors vs 41.7% non-survivors,  $p = 0.796$ ). However, RV dilatation, defined as RV/LV (left ventricular) ratio  $\geq 1$  at CTPA, was less frequent among survivors (11.5% survivors vs 58.3% non-survivors,  $p = 0.002$ ), and not always clearly proportionate to thrombus load. Though the mechanism remains unclear, RV dilation may reflect thromboembolism, microvascular thrombosis or endothelial dysfunction leading to increased afterload.

### Massive and submassive PE in patients with active Covid-19

As shown in Fig. 1, saddle PE (Fig. 2) occurred in four Covid-19 patients, even without substantial lung parenchymal involvement. Characteristics of these patients are described in Fig. 1. Regarding right heart catheterisation, normal ranges for right atrial pressure are 1–6 mmHg, for pulmonary arterial systolic pressure 15–29 mmHg and for cardiac index 2.4–4 L/min/m<sup>2</sup> [12].

Three of these patients were admitted directly from home (Fig. 1, patient 1, 3 & 4) while patient 2 developed PE after three days of hospitalization for Covid-19 pneumonia despite thromboprophylaxis (Figure 1, patient 2).

**Fig. 1** Characteristics of active Covid-19 patients with saddle/bilateral pulmonary embolism. *CI* cardiac index, *CT* computed tomography, *CTPA* computed tomography pulmonary angiography, *Covid-19* Coronavirus disease 2019, *F<sub>IO2</sub>* fractional inspired oxygen, *PaO<sub>2</sub>* arterial oxygen partial pressure, *PE* pulmonary embolism, *PEA* pulseless electrical activity, *RAP* right atrial pressure, *PASP* pulmonary arterial systolic pressure, *RHC* right heart catheterisation RV/LV ratio – diameter of right ventricle divided by diameter of left ventricle measured at their widest midventricular point on axial images; yo-years old



**Fig. 2** Computed Tomography Pulmonary Angiography in a Covid-19 patient (patient 1), presented with saddle pulmonary embolism. **a** Saddle pulmonary embolism (red arrow) with emboli within the right (blue arrow) and left pulmonary artery (green arrow). **b** Large volume emboli extending into the more peripheral pulmonary arterial branches (red arrows). **c** Computed tomography features of right heart strain with flattening of the interventricular septum. Right Ventricular/Left Ventricular ratio is 1.43

ume emboli extending into the more peripheral pulmonary arterial branches (red arrows). **c** Computed tomography features of right heart strain with flattening of the interventricular septum. Right Ventricular/Left Ventricular ratio is 1.43

PE early mortality risk was classified as intermediate-high in patients 1, 2 and 4, while PE early mortality risk was high in patient 3.

As per standard practice in our institution, all these patients underwent UACTD which minimizes tPA dosage

(12 mg over 6 h, 6 mg each lung), potentially reducing the risk of haemorrhage into inflamed lungs [13, 14].

UACDT in this subpopulation was associated with a very rapid improvement in oxygenation. Three patients recovered from PE and were discharged, while one patient suffered from a pulseless electrical activity cardiac arrest during the eighth day of his hospitalization and died.

**Table 1** Characteristics of Covid-19 patients who were admitted with pulmonary embolism, post recovery from Covid-19

Parameter	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	49	92	82	61
Sex	Male	Female	Female	Female
Covid-19 History	48 h admission with Covid+ve pneumonia 1 week prior to PE admission	48 h admission with Covid+ve associated hypoxaemia 30 days prior to PE admission	Seen in ED 32 days prior to PE admission, Covid+ve, considered safe for discharge	22 day admission with Covid+ve pneumonia, discharged 3 weeks prior to PE admission
Risk factors for VTE	Confined to bed since discharge	Newly dependent on carers	Confined to bed at home	Slow recovery, mobilising x 1 week; Hodgkins lymphoma
Presentation	3 days left pleuritic chest pain	3 days worsening breathlessness, haemoptysis, hypoxaemic	Syncope with extensive bruising to left knee. Haemodynamically stable, preserved oxygen saturation	Collapse with severe hypoxia, intubated on admission
Covid-19 status	Negative	Negative	Negative	Negative
CTPA pulmonary vessels	Segmental and subsegmental emboli	Embolism right main left lower and mid zone pulmonary arteries	Bilateral main pulmonary artery embolism	Segmental and subsegmental emboli, largely right sided
CTPA lung parenchyma	Minimal patchy peripheral infiltrates	Normal	Normal	Extensive ground-glass infiltration, new traction bronchiectasis
CTPA RV/LV ratio	1.1/1	1.3/1	3/1	1.4/1
Pulmonary Embolism Severity Treatment	Intermediate-Low LMWH	Intermediate-High UACTD	Intermediate-Low LMWH	High Inotropes, systemic thrombolysis & intubation
Outcome	D/C D 5	D/C D 15	D/C D 10	Remains ventilated

CTPA computed tomography pulmonary angiogram; D-day, D/C discharged, ED emergency department, RV/LV ratio diameter of right ventricle divided by diameter of left ventricle measured at their widest midventricular point on axial images, LMWH low molecular weight heparin, PE pulmonary embolism, UACTD ultrasound assisted catheter directed thrombolysis, VTE venous thromboembolism

## PE after recovery from acute Covid-19

PE was observed even after recovery from acute Covid-19. Four patients were admitted after discharge, having recovered from Covid-19 pneumonia, all were SARS-CoV-2 positive at first review and negative at the time of PE diagnosis on their second admission (Table 1). Their characteristics are described in Table 1.

PE was of intermediate-low early mortality risk in patient 1 and patient 3. Patient 2, with an intermediate-high early mortality risk PE, was treated with UACTD and was discharged 15 days after her admission. Patient 4, with a high early mortality risk PE, was treated with systemic thrombolysis and required intubation and inotropic support.

Failure to mobilize post discharge was the most likely explanation for PE, after acute Covid-19 recovery. However, this may be in fact no different to other medical patients who have recently been in hospital.

## Incidental RV dysfunction and pulmonary hypertension in a patient with Covid-19

Of note, RV dysfunction and pre-capillary pulmonary hypertension was also observed as incidental finding in a Covid-19 patient. A 53-year-old woman, SARS-CoV-2 positive, was admitted and treated with high flow oxygen and oxygen requirements improved the following week. On day seven, she complained of non-pleuritic chest pain and increased breathlessness. Electrocardiogram showed new widespread T wave inversion and Troponin-T rose from 16 to 38 ng/l. CTPA was performed and showed no evidence of PE, but widespread consolidation in all lobes, and RV dilatation (RV/LV ratio 1.2/1). A diagnosis of non-ST segment elevation myocardial infarction was made. Coronary angiogram demonstrated a 70% proximal left anterior descending artery stenosis, treated with a percutaneous coronary intervention.

In view of her RV dilation, right heart catheterisation was performed. Pulmonary artery systolic/diastolic pulmonary pressures were 55/25 mmHg respectively, mean pulmonary arterial pressure was 36 mmHg, with a pulmonary capillary wedge pressure of 11 mmHg, a cardiac index of 1.6 L/min/m<sup>2</sup>, and a pulmonary vascular resistance of 10 Wood Units.

In this case, extensive lung disease, causing microvascular thrombosis or hypoxaemia, leading to pulmonary hypertension and secondary right heart strain, is the most likely explanation for the observed RV dilatation.

## Discussion

Though this is a highly selected subpopulation, our article illustrates several points:

1. Pulmonary thrombosis may be present on admission to hospital and is probably underdiagnosed due to an observed tendency to limit investigations in this population.

Many of the clinical clues to the presence of pulmonary thromboembolism are also present in patients presenting with Covid-19, so lowering the index of suspicion.

2. High and intermediate-high risk PE may occur both during and after recovery from acute SARS-CoV-2 infection, and it can be disproportionate to associated lung disease. We believe this may be the case due to other systemic prothrombotic processes associated with inflammation other than in the lungs.

3. UACTD may prove a useful method to manage high and intermediate-high risk PE in Covid-19 patients. However, the number of patients we studied is too small to reach anything other than the most guarded conclusions.

4. We demonstrated one case of pre-capillary pulmonary hypertension with RV dysfunction in a Covid-19 patient, likely associated with extensive lung disease; pulmonary thrombosis was not evident in this case.

Several reports suggest that PE prevalence in Covid-19 patients is high [4, 15–18]. The European Society of Radiology and the European Society of Thoracic Imaging recommended contrast-enhanced CT (computed tomography) to exclude PE in Covid-19 patients who present with limited lung disease, but have supplementary oxygen requirements [19]. The European Society of Cardiology suggested CTPA before leaving the radiology department in Covid-19 patients, when respiratory failure cannot be explained by the findings of the unenhanced CT chest [20]. PE is also frequent in Covid-19 patients with lung involvement [8, 17]. In our study, we demonstrated a high prevalence of pulmonary thrombosis in Covid-19 patients that undergo CTPA (46.2%). Furthermore, as van Dam et al., we found that thrombotic lesions in Covid-19 were distributed mostly in segmental and subsegmental arteries and less commonly in main/lobar arteries (66.7% vs 33.3%, respectively), likely in the context of extensive inflammation, alveolar injury and profound prothrombotic state in Covid-19 [10, 21–24].

Furthermore, we observed PE up to four weeks after Covid-19 recovery, likely associated with failure for mobilization after discharge, as it has been observed to other medical patients who have recently been discharged from the hospital. Of note, in our patients, PE was not always associated with significant lung involvement. It is unclear why this is the case, but other systemic prothrombotic processes associated with inflammation other than in the lungs may be the cause.

European Society of Cardiology suggests that “percutaneous catheter-directed thrombolysis should be considered for patients with high risk PE, in whom thrombolysis is contraindicated or has failed, if appropriate expertise and resources are available on site (Class II, Level of evidence C)” [13]. UACTD is associated with more rapid reduction of RV dilatation, improvement of RV function, and decrease in thrombus burden in patients with acute massive and submassive PE [14, 25]. As this technique uses lower dose of tPA compared to the standard thrombolysis (we used one eighth of the standard dose of tPA that is used for the standard thrombolysis)—it has been associated with low major or non-access related bleeding rates, while intracerebral bleeding is very rare [14, 25]. No bleeding event occurred in our patients treated with UACTD. Possibly, UACTD decreases the risk of haemorrhage into inflamed lungs of Covid-19 patients. Also, local administration of tPA may also be more effective in addressing microvascular thrombosis.

In our study, four out of five patients treated with UACTD for PE were discharged home. Though our high risk PE patient did not have an absolute or relative contraindication for systemic thrombolysis, we treated him with UACTD, as knowledge regarding systemic thrombolysis effect on Covid-19-related PE remains restricted [13]. Also, we treated our four intermediate-high risk PE patients with UACTD, though haemodynamically stable, as significant clot burden and impaired oxygenation in the context of SARS-CoV-2 infection, raised concerns for deterioration of respiratory function [14, 25]. Of note, Qanadli et al. performed catheter-directed thrombolysis in an intermediate-low PE patient with Covid-19 pneumonia, with subsequent improvement of respiratory function [26].

Finally, we identified a patient with pre-capillary pulmonary hypertension as an incidental finding in a Covid-19 patient, not associated with pulmonary thrombosis. This raises the possibility that RV dilatation which appears to be a stronger predictor of outcome than thrombosis, in some cases, is due to microvascular injury and likely undiagnosed thrombosis. If so, this may help identify the sub-population most likely to respond to fibrinolytic therapy in the forthcoming and ongoing ARDS trials, registered on Clinicaltrials.gov (NCT04357730, NCT04453371, NCT04356833).

We postulate that both pulmonary microvascular thrombosis and PE contribute to the spectrum of pulmonary thrombotic presentations associated with Covid-19.

Further understanding of the incidence, evolution and pathobiology of pulmonary vascular involvement will inform our understanding of Covid-19. It is unclear whether thrombolytic, immunomodulatory or antiviral therapy or a combination of all three is optimal for microvascular dysfunction associated thrombosis. Thus, when appropriate personal protection equipment and access to investigations

are not limited, Covid-19 patients should be evaluated thoroughly for pulmonary thrombosis and RV dysfunction.

## Conclusions

In conclusion, optimal anticoagulant or thrombolytic approach should be considered for the management of a patient with PE and current or recent SARS-CoV-2 infection. Our experience suggests that targeted use of tPA may hold particular promise in the above patients, who present with high and intermediate-high risk PE. Also, assessment of RV performance in Covid-19 patients may help identify patients at particular risk, who may require optimal management and specific follow up by the pulmonary hypertension services, in those with evidence of acute pulmonary hypertension.

## Compliance with ethical standards

**Conflict of interest** All the authors declared that they have no conflict of interest.

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