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Pulmonary ischaemia without pulmonary arterial thrombus in COVID-19 patients receiving extracorporeal membrane oxygenation: a cohort study

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AIM: To evaluate the incidence of pulmonary ischaemia in COVID-19 patients on extracorporeal membrane oxygenation (ECMO), and its correlation with pulmonary artery thrombosis.

MATERIALS AND METHODS: Computed tomography (CT) thorax of all patients receiving ECMO with proven COVID-19 pneumonitis between March and May 2020 were analysed for the presence and extension of pulmonary thromboembolic disease.

RESULTS: Fifty-one patients were reviewed. The mean (range) age of 45 (26–66) years; 38/51 (74.5%) were men. All patients had severe COVID-19 pneumonitis, and 18/51 (35.3%) had macroscopic thrombosis (15 with associated ischaemia); however, 13/51 (25.5%) patients had ischaemia without associated thrombus.

CONCLUSION: The majority of patients with COVID-19 who received ECMO had areas of ischaemia within consolidated lungs, almost half of these without subtending pulmonary artery thrombosis. Although the prognostic significance of these findings is unclear, they are highly suggestive of lung ischaemia due to isolated microvascular immune thrombosis.

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Introduction

Coronavirus disease 2019 (COVID-19) is a novel viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first detected in

Wuhan, China, in December 2019.^{1,2} The outbreak was declared a worldwide pandemic in March 2020.

COVID-19 patients can develop severe respiratory failure requiring invasive mechanical ventilation. Radiologically, this can present as an acute respiratory distress (ARDS)-like

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syndrome, associated with high mortality.³ However, COVID-19 patients present with characteristic features of angiogenesis and thrombotic complications due to a proinflammatory and hypercoagulable state.^{4,5} There is increasing literature documenting the prothrombotic state of COVID-19 patients, suggesting abnormally high levels of D-dimer associated with venous and pulmonary thromboembolism.^{6–8} As there may be a microangiopathic component to the disease, small vessel occlusion and ischaemia may also occur.

It was postulated that these peculiar characteristics of COVID-19 could lead to pulmonary ischaemia due to microthrombosis. This may be more prevalent in severe disease, such as in patients who require extracorporeal membrane oxygenation (ECMO) due to severe and refractory acute hypoxaemic respiratory failure (AHRF). The aim of this study was to report the prevalence and extent of pulmonary ischaemia on contrast-enhanced computed tomography (CT) of the thorax in the absence of visible pulmonary emboli (PE) in patients with COVID-19 receiving ECMO.

Materials and methods

CT thorax of all patients with confirmed COVID-19 infection placed on ECMO between March and May 2020 were reviewed retrospectively by two cardiothoracic radiologists in consensus (7 and 9 years of experience, G.B. and S.M.M.).

Local institutional ethical regulatory approval was not required for this retrospective review of anonymised clinical data. The study had waiver of individual informed consent (reference number: 10796) as it qualifies as service evaluation as defined by the UK NHS Health Research Authority (<http://www.hra.nhs.uk>) as all images were acquired as standard of care.

At our institution, ECMO retrievals and admissions undergo unenhanced CT head, CT pulmonary angiogram (CTPA), and venous-phase CT of the abdomen and pelvis on admission. CT imaging is performed with either a Somatom Force 384 (2×192) sections; Siemens Healthineer or Brilliance iCT (256 sections); Philips Healthcare. CTPA examinations are performed by bolus trigger at 110 HU.

All patients tested positive for SARS-CoV-2 by RNA polymerase chain reaction on pharyngeal swab isolates. Main laboratory parameters at admission were collected. CT images were reviewed to assess the presence and extension of pulmonary artery (PA) filling defects and geographical areas of hypodense lung parenchyma on contrast-enhanced CT thorax. Their most proximal location was assessed as central, lobar, segmental, or subsegmental. Further distal extent of thrombus was graded as “mild” when there was involvement of a single lung parenchymal segment, “moderate” when involving between two and four segments, “extensive” when involving more than five segments. The attenuation of the main PA, size of the main PA, presence of right heart dilatation, presence and extension of ground-glass

opacification (GGO) and dense consolidation (DC) were recorded. GGO and DC were graded with the same score as hypodense areas of lung parenchyma.

Results

Data were collected from the first 51 patients with COVID-19 who received ECMO for refractory AHRF. The mean (range) age was 45 (26–66) years; 38 were men (74.5%). Patients had a variable prodrome from 1–4 weeks, with fever, cough, and malaise. Upon admission to the ECMO Unit, all patients received unfractionated heparin infusion as per the local ECMO protocol unless evidence of intracranial or uncontrolled extracranial bleeding was demonstrated by CT. Admission blood parameters are shown in [Table 1](#).

On CT thorax, the average (\pm SD) density of the pulmonary arteries was 267.45 ± 88.78 HU. The high standard deviation is partly due to the variable site of venous access. Nevertheless, cases included in the final analysis were of diagnostic quality, and allowed reliable assessment of the PAs. Eighteen (35.3%) patients had filling defects within the PAs. Main PA thrombus was noted in 3/51 patients (5.9%; [Fig 1](#)); lobar PA thrombus in 3/51 (5.9%); segmental PA thrombus in 7/51 (13.7%); subsegmental PA thrombus in 5/51 (9.8%; [Fig 2](#)). Of the three patients with main PA thrombus, all had severe distal extension of disease. Of the three patients with lobar PA thrombus, all had severe distal extension. Of the seven patients with segmental PA thrombus, one had severe distal extension, three had moderate distal extension, and three had mild distal extension. Of the five patients with subsegmental PA thrombus, one had moderate distal extension, and four mild extension ([Table 2](#)).

Twenty-eight of the 51 patients had wedge-shaped low-attenuation areas within the lung parenchyma (54.9%). When assessing the most proximal lung parenchymal involvement, 2/51 had lobar distribution (3.9%), 9/51 had segmental distribution (17.6%), and 17/51 had subsegmental distribution (33.3%). Of the two with lobar distribution, one had severe extent, one had moderate extent. Of the nine with segmental distribution, five had moderate extent, and four had mild extent. Of the 17 with subsegmental distribution, four had severe extent, 10 had moderate extent, three mild extent ([Table 3](#)).

Of the above 28 patients with low-attenuation areas within the lung parenchyma, 15 had concomitant pulmonary artery thrombus (53.6%), while the other 13 did not demonstrate visible thrombus (46.4%; [Fig 3](#)). Three of the 18 patients (16.7%) with PA thrombus showed no hypodense lung parenchymal area ([Table 4](#)).

Only 12 patients had evidence of right heart dilatation (23.5%). The average (SD) diameter of the main PA was 27.37 ± 3.89 mm (range 19–37 mm), and the aorto-pulmonary ratio was altered (<1) in 17 cases (33.3%).

All patients had widespread bilateral dense consolidations (100%). Forty-nine of the 51 patients had GGO changes (96.1%): two patients had no GGO (3.9%), five patients had

Table 1

Laboratory parameters at admission of patients with severe COVID-19 pneumonitis placed on extracorporeal membrane oxygenation (ECMO).

Laboratory values (normal values)	All patients	Patients with no PA thrombus	Patients with PA thrombus	Patients without ischaemia	Patients with ischaemia	Patients with neither PA thrombus nor lung ischaemia
White cell count ($\times 10^9/L$) ($4-11 \times 10^9/L$)	11.3 (9.4–16.4)	11.2 (8.9–16.5)	12.2 (9.2–14.6)	12.2 (10–17)	11.1 (8.1–13.4)	12.1 (10.1–16.5)
Platelet ($\times 10^9/L$) ($150-400 \times 10^9/L$)	238 (169–317)	238 (205–315)	236.5 (146.5–345.5)	210 (164–290)	246 (174–348.5)	211 (173.7–289.2)
D-dimer (mg/L FEU) (0–0.55 mg/L FEU)	9.1 (5.2–35.4)	7.1 (3.4–29)	13.6 (6.9–50.4)	6.8 (3.2–21.6)	11.9 (6.5–35.5)	6.7 (3.1–23.7)
International normalised ratio (0.8–1.2)	1.10 (1–1.25)	1.1 (1–1.1)	1.1 (1–1.2)	1.1 (1–1.1)	1.1 (1–1.2)	1.1 (1–1.1)
Fibrinogen (g/L) (1.7–3.9 g/L)	7.1 (5.3–8.8)	6.7 (5.4–9)	7.2 (4.5–8.6)	6.6 (5.2–9)	7.2 (5.9–8.8)	6.4 (5.2–8.8)
Ferritin COVID-19 ($\mu g/L$) (0–150 $\mu g/L$)	1,903 (1,002–4,159)	1,907 (1,084.5–4,178)	1,644.5 (889.5–4,388.7)	1,751 (904–3,800)	1,905 (1,194.7–4,187.5)	1,680.5 (867.2–3,711.5)
C-reactive protein (mg/L) (0–4 mg/L)	315 (217–362)	320 (233–380.5)	298.5 (157–356.7)	292 (175–373)	326 (229–360.2)	299 (224.7–368.5)
Lymphocyte ($\times 10^9/L$) ($1.2-3.5 \times 10^9/L$)	0.7 (0.5–1)	0.7 (0.5–1)	0.65 (0.4–1.4)	0.6 (4–1.3)	0.7 (0.5–1)	0.6 (0.4–1.1)

Values are reported as median with interquartile ranges in brackets. Values are shown for all patients, patients without PA thrombus, with PA thrombus, patients without lung parenchymal ischaemia, patients with lung ischaemia and patients with neither PA thrombus nor lung ischaemia. PA, pulmonary artery; FEU, fibrinogen equivalent units.

an overall mild GGO involvement (9.8%), 10 patients moderate (19.6%), and 34 patients severe (66.7%).

Discussion

The current study presents the CT thorax findings of 51 patients placed on ECMO due to severe COVID-19 hypoxaemic respiratory failure refractory to mechanical ventilation. There was a high prevalence of PA thrombus and a higher prevalence of multiple peripheral wedge-shaped low-attenuation areas within the lung parenchyma, the latter suggestive of pulmonary ischaemia. Nearly half of the patients with low-attenuation areas within the lung parenchyma did not demonstrate any visible subtending PA

thrombus on CT. Although the pathological, clinical, and prognostic implications of these findings are not fully understood, it may represent microvascular thrombosis in the absence of large thrombus within the pulmonary arterial tree in the setting of COVID-19-related immune thrombosis. The prothrombotic state described in patients with COVID-19 may be due to direct effects of the coronavirus or the associated hyperinflammatory state. “Immunothrombosis” is an increasingly popular term coined to describe this phenomenon. The common phrase “pulmonary embolus” should be replaced cautiously with “pulmonary thrombus” to avoid the impression that they must be embolic.

Previous studies have reported histological findings compatible with oedema and fibrin thrombi within the

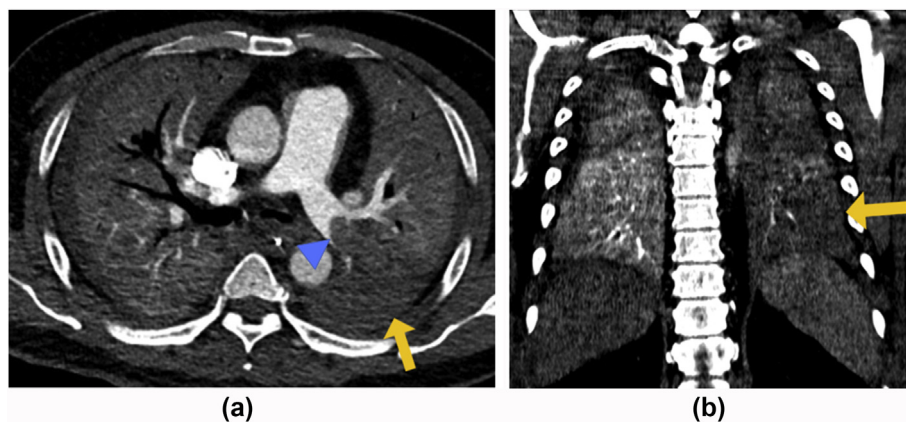


Figure 1 (a) Axial image with a large left main PA thrombus (arrowhead). There is a corresponding area of left lower lobar low attenuation (arrow). Shallow bilateral pleural effusions. (b) Coronal image showing the left lower lobar low attenuation (arrow).

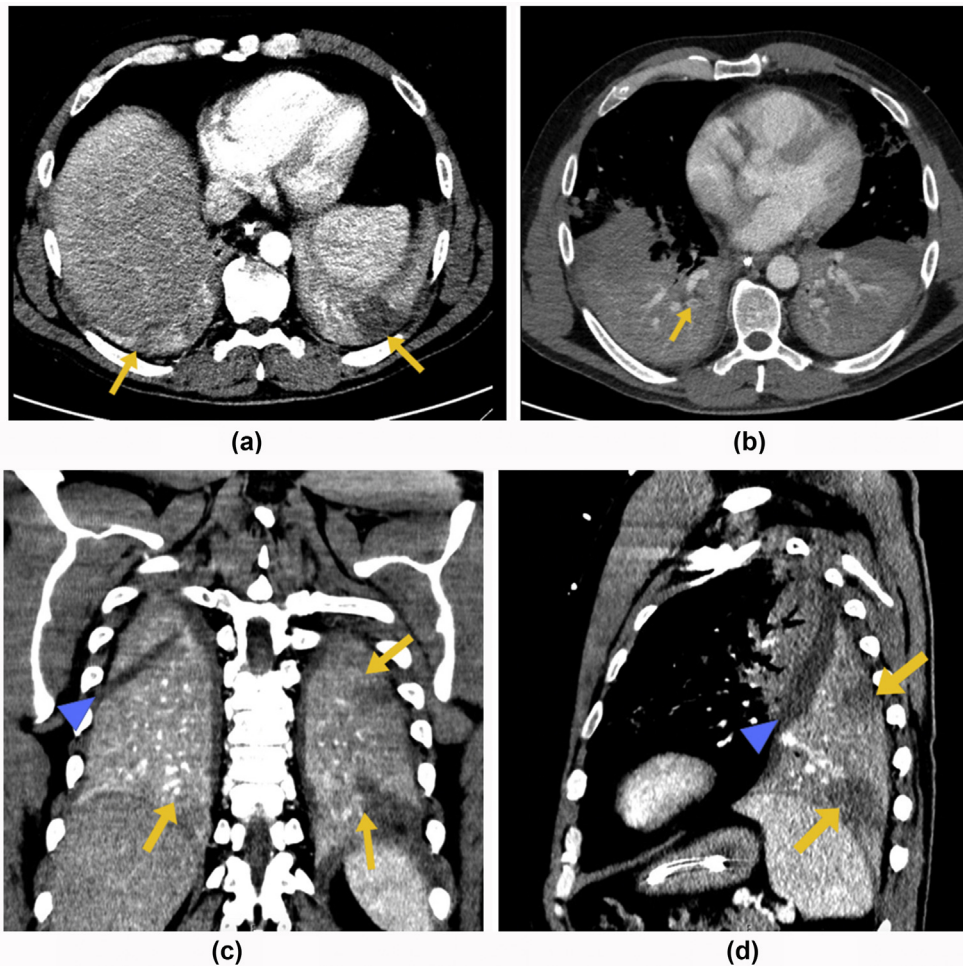


Figure 2 (a) Bilateral peripheral wedge-shaped low-attenuation areas of lung parenchyma bilaterally, subsegmental at the right base and segmental on the left (arrows). (b) This axial image shows the only PA thrombus identified on this scan: a small right subsegmental PA thrombus (arrow), which may account for the small area of low attenuation within the right lower lobe. No other PA thrombus was identified. (c) Coronal image of the admission ECMO CT demonstrating bilateral wedge-shaped low-attenuation areas of lung parenchyma (arrows), more significant on the left. There is a small right interfissural effusion (arrowhead). (d) Sagittal image of the left hemithorax demonstrating low attenuation areas (arrows) and a small interfissural effusion (arrowhead).

pulmonary microvasculature in patients infected with SARS-CoV-1, a different coronavirus responsible for an epidemic in 2003.^{9,10} Marongiu *et al.*¹¹ suggested that abnormal laboratory findings could be an expression of a local diffuse inflammatory coagulopathy (DIC) with pulmonary vascular thrombosis and subsequent activation of fibrinolysis. Whether one could translate the same underlying pathophysiological principle to COVID-19 infection and lung findings remains uncertain.

Although the optimal thromboprophylaxis in COVID-19 patients is still controversial, national societies have issued new guidance on thromboprophylaxis in COVID-19 patients, as the British Thoracic Society did for the UK.¹² These findings may have therapeutic implications in terms of short-to long-term anticoagulation.

The main limitation of this study is the absence of histological confirmation of radiological findings. In addition, all the patients presented in this paper showed

Table 2

Patients with main, lobar, segmental, or subsegmental pulmonary artery (PA) thrombus, and the extension of thrombus for each group.

	Main PA	Lobar PA	Segmental PA	Subsegmental PA
Total patients, <i>n</i> (%)	3 (5.9%)	3 (5.9%)	7 (13.7%)	5 (9.8%)
Severe extent, <i>n</i>	3	3	1	0
Moderate extent, <i>n</i>	0	0	3	1
Mild extent, <i>n</i>	0	0	3	4

Table 3

Patients with main, lobar, segmental, or subsegmental ischaemic lung, and the extension of ischaemia for each group.

	Lobar	Segmental	Subsegmental
Total patients, <i>n</i> (%)	2 (3.9%)	9 (17.6%)	17 (33.3%)
Severe extent, <i>n</i>	1	0	4
Moderate extent, <i>n</i>	1	5	10
Mild extent, <i>n</i>	0	4	3

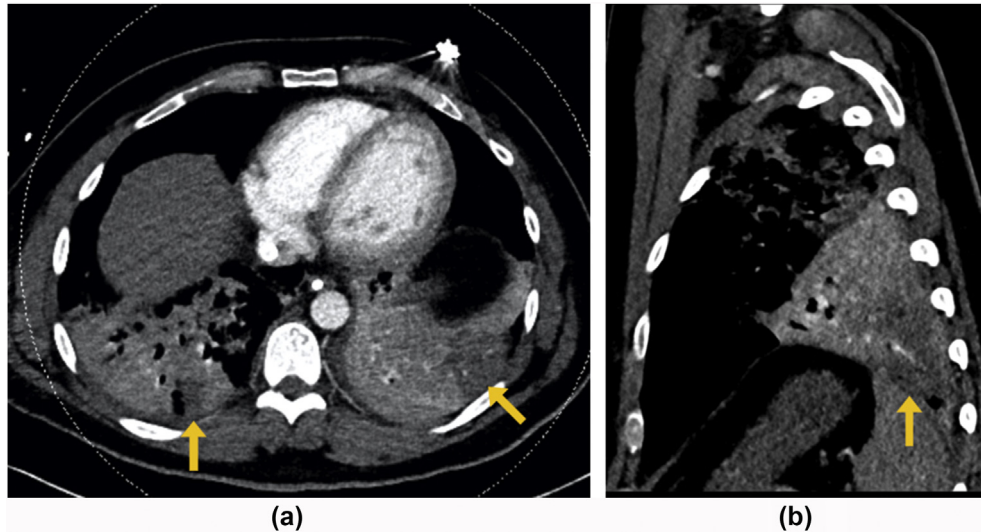


Figure 3 (a) Right subsegmental and left segmental low attenuation areas (arrows). No PA thrombus is identified on this study. (b) Sagittal image of the left lung demonstrating the low attenuation area (arrow). The subtending PAs are patent.

Table 4

Number and percentages of patients with combination of pulmonary artery (PA) thrombus and ischaemic areas within lung parenchyma.

	Presence of PA thrombus	Absence of PA thrombus	Total
Presence of ischaemic changes	15 (29.4%)	13 (25.5%)	28 (54.9%)
Absence of ischaemic changes	3 (5.9%)	20 (39.2%)	23 (45.1%)
Total	18 (35.3%)	33 (64.7%)	51 (100%)

extensive bilateral dependent dense consolidation with admixed extensive GGO on CT thorax, as expected in cases of severe COVID-19 pneumonitis. Therefore, the main findings of the paper regarding lung ischaemia cannot be generalised to all patients with COVID-19 infection, but should be limited to the group affected by severe COVID-19 pneumonitis.

Further research is needed to investigate the outcome of patients with these radiological changes.

Conflict of interest

The authors declare no conflict of interest.

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