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CASE SERIES
Other

Corona Virus Disease 2019 *in situ* arterial and venous thrombosis in critically ill patients: a case series

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Background Corona Virus Disease 2019 (COVID-19) pneumonitis associated with severe respiratory failure carries a high mortality. Coagulopathy has emerged as a significant contributor to thrombotic complications.

Case summary We describe two cases of severe COVID-19 pneumonitis refractory to conventional mechanical ventilation and proning position, transferred to our specialist centre for cardiorespiratory failure. Cross-sectional imaging demonstrated concurrent venous and aortic thrombosis with end-organ ischaemic changes. One patient received thrombolysis with a partial response. This could not be offered to the other patient due to a recent haemorrhagic event. Both patients died of multi-organ failure in the hospital.

Discussion Concurrent aortic and venous thromboses are rare. This finding in COVID-19 cases, who were both critically ill patients, likely reflects the strongly thrombogenic nature of this illness which ultimately contributed to poor outcomes. The absence of deep vein thrombosis or a potential systemic source of embolism suggests *in situ* thrombosis. Further, the management of anticoagulation and thrombolysis is challenging in patients where an attendant bleeding risk exists.

Keywords COVID-19 • Venous thrombosis • Arterial thrombosis • Thrombolysis • Case series/case reports

Learning points

- Patients admitted to the intensive care unit (ICU) for Corona Virus Disease 2019 (COVID-19) pneumonitis may have venous and arterial thromboses that require a low index of suspicion and early thorough investigations.
- Venous and arterial thromboses can coexist in COVID-19. Comprehensive imaging is required to assess this complication, among others, in critically ill patients with COVID-19.
- Thrombolysis, in addition to anticoagulation, requires consideration in COVID-19 patients with extensive thrombosis. Its timing and an assessment of bleeding risk is important.

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Introduction

Patients admitted to the intensive care unit (ICU) for severe acute respiratory syndrome coronavirus 2 (SARS-COV2) primarily present with severe acute respiratory failure (SARF) due to acute respiratory distress syndrome (ARDS). An increasingly recognized sub-phenotype of the COVID-19 lung presentation is a hyper-inflammatory and pro-thrombotic state, characterized by deep vein thrombosis (DVT), *de novo* pulmonary thrombosis [often described as pulmonary embolism (PE)] and even a micro-thrombotic angiopathy.[1,2] The result is impaired perfusion, potentially exacerbating dead-space ventilation, and refractory hypoxaemia. Whilst Virchow's triad of blood stasis, endothelial activation and hypercoagulability can effectively explain the venous thrombosis that SARS COV2 appears to generate, the presence of reported systemic arterial thrombotic events is less understood.[3] We describe two cases with severe COVID-19 pneumonitis admitted to intensive care who presented with venous and arterial thrombosis.

Timeline

Case 1	Case 2
Day 0	Day 0
Admission to local hospital with a 4-day history of dyspnoea, cough, and fever.	Admission to local hospital with 2-week history of cough and dyspnoea.
Prophylactic low molecular weight heparin (LMWH) started.	Corona Virus Disease 2019 (COVID-19) test positive.
	Prophylactic LMWH started.
Day 2	Day 11
COVID-19 test positive.	Respiratory deterioration.
Venous-venous extracorporeal membrane oxygenation (VV-ECMO) referral and transfer to our centre.	Non-invasive ventilation (NIV) commenced.
Computed tomography (CT) on admission revealed bilateral pulmonary embolisms (PEs) and aortic arch thrombus—transoesophageal echocardiogram (TOE) confirmed arterial thrombosis.	
Intravenous (IV) heparin: bolus of 3000 IU at ECMO cannulation, followed by continuous infusion targeting anti-Xa level 0.5–0.7 IU/mL.	
Day 4	Day 12
Anti Xa levels decreased to 0.2–0.35 IU/mL due to new onset melaena.	Intubation due to severe acute respiratory failure.
Day 5–Day 10	Day 13
No further melaena on Day 5.	Transfer to our centre.
Anti-Xa maintained at 0.3–0.5 IU/mL.	CT on admission revealed thrombus in pulmonary artery and abdominal aorta.
IV Sildenafil started for ongoing hypoxaemia and right ventricle (RV) dysfunction.	IV Heparin: continuous infusion started targeting anti-Xa level 0.5–0.7 IU/mL.
Escalation of antibiotics for sepsis.	Transthoracic echocardiogram (TTE) on admission showed moderately impaired RV.
	RRT commenced due to anuria and metabolic acidosis.
Day 11–Day 19	Day 14
Renal replacement therapy (RRT) commenced for ongoing renal failure.	Repeat TTE revealed severe RV dysfunction.
Ongoing sepsis, antibiotics escalated.	Milrinone infusion commenced.
Epoprostenol nebulizers commenced.	Thrombolysis performed for suspected bowel ischaemia: systemic administration of alteplase (bolus followed by infusion 1 mg/mL, 90 mg in total).
Day 20	Day 15
Corticosteroids commenced.	Some improvement in clot burden on repeat CT.
Further deterioration with brain haemorrhage.	Ongoing clinical deterioration.
Multi-organ failure.	Multi-organ failure.
Death.	Death.

Case presentation

Patient 1

A 53-year-old male without significant past medical history was admitted to his local hospital with a 4-day history of dyspnoea, cough, and pyrexia. He tested positive for COVID-19. He deteriorated on non-invasive ventilation (NIV), requiring intubation, ventilation, and prone positioning for refractory hypoxaemia. On Day 2, he was transferred to our national referral centre for SARF and need of venous–venous extracorporeal membrane oxygenation (VV-ECMO). Empirical azithromycin, hydroxychloroquine, and piperacillin/tazobactam were commenced. Computed tomography (CT) of the chest, head, abdomen, and pelvis was performed as per protocol after ECMO cannulation. The CT showed pulmonary ground-glass opacities and consolidation in all lobes. There were filling defects consistent with extensive bilateral segmental pulmonary thromboses, splenic infarcts, and eccentric thrombus in the transverse aortic arch. Multiple cerebral infarcts were also noted. A transoesophageal echocardiogram (TOE) performed to locate the position of the inserted ECMO cannulae and their relationship with the interatrial septum

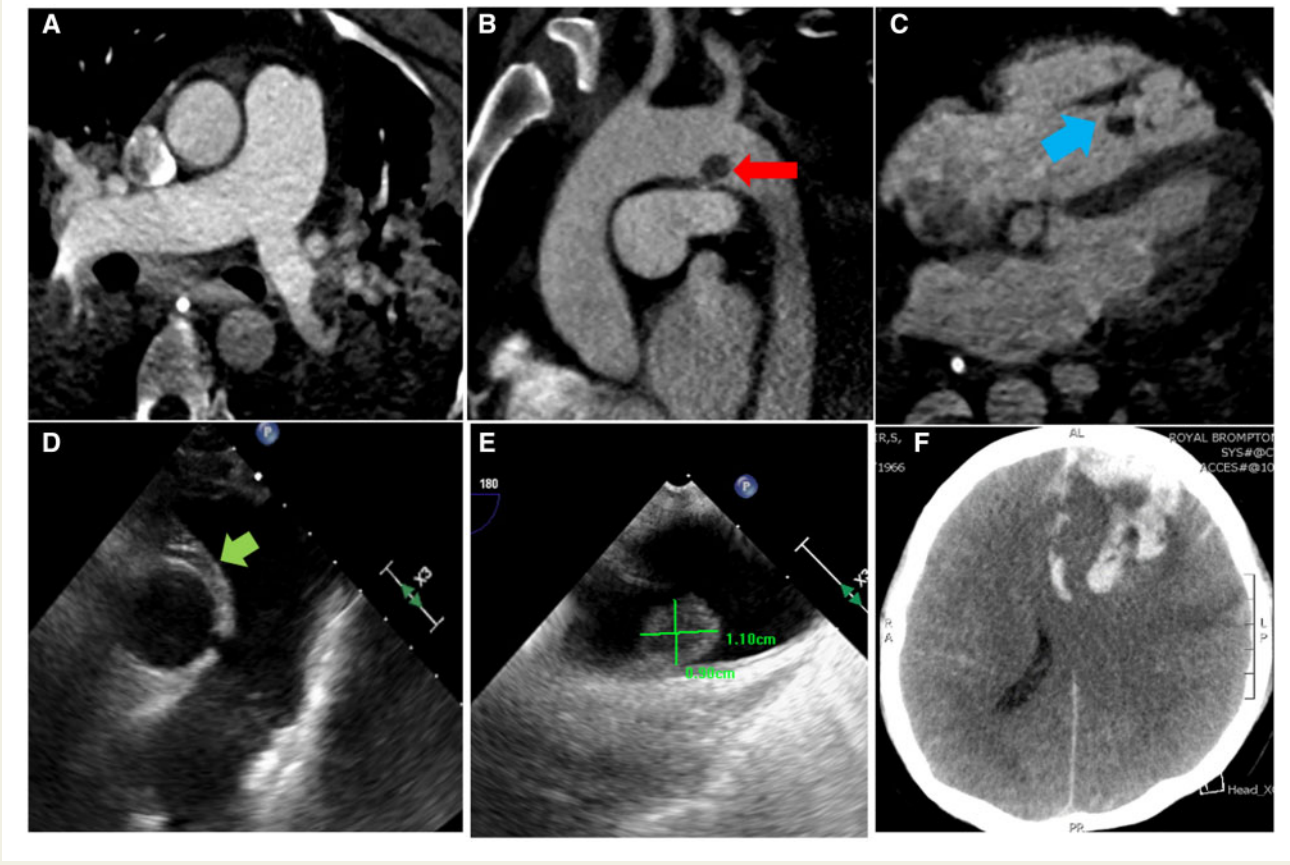

Figure 1 Case 1. Computed tomography images demonstrate pulmonary thrombosis in left main pulmonary artery (*A*), thrombus in aortic arch (red arrow) (*B*), low density structures inside right ventricle cavity suggestive of possible thrombus (blue arrow) (*C*), and massive left frontal cerebral haemorrhage (*F*). Transoesophageal echocardiogram images showing laminar thrombus adherent to wall of main pulmonary artery (green arrow) (*D*) and sessile thrombus (1.10 cm × 0.9 cm) attached to the anterior wall of aortic arch (*E*).

detected laminar thrombus and a sessile clot on the anterior wall of the aortic arch (*Figure 1* and Supplementary material online, *Video S1*). The right ventricle (RV) was severely dilated and impaired [RV fractional area change (FAC) 7%—normal value > 35%], with suspicion of a laminar thrombus in the RV outflow tract extending into the main pulmonary artery. There was also a right to the left shunt of flow across a patent foramen ovale (PFO) that resolved on repositioning the return cannula to a lower location under TOE guidance.

Regarding anticoagulation, the patient received prophylactic low molecular weight heparin (LMWH) during his stay at the local hospital and a bolus of unfractionated heparin of 3000 international units (IU) at VV ECMO cannulation, followed by continuous infusion aiming for a therapeutic anti-Xa target of 0.5–0.7 IU/mL at admission to our tertiary centre. Due to development of melaena on the following day, the anti-Xa target was reduced to 0.2–0.35 IU/mL until it resolved the next day, when it was set at 0.3–0.5 IU/mL and maintained at that range thereafter, as per discussion with haematology. Thromboelastography indicated the thrombus formation was normal in the context of heparin treatment, as was the platelet function assay, whilst there was absence of intrinsic fibrinolytic activity (0%).

Serial repeat CTs demonstrated progressive intra-cavity RV thrombosis correlating with increasing D-dimer levels (peak of 11 000 ng/mL), and worsening lung consolidation coinciding with vasopressor dependent shock. There were no carotid or cerebral artery disease detected in CT angiography. Pulmonary vasodilators were introduced (initially intravenous sildenafil followed by nebulized epoprostenol) for ongoing hypoxaemia and severe RV dysfunction. Renal replacement therapy (RRT) was started on Day 9 for worsening kidney function. Unfortunately, the patient suffered a massive intracranial haemorrhage on Day 18 and died.

Patient 2

A 53-year-old male with type II diabetes mellitus (DM) and treated hypertension, presented with a 2-week history of cough and shortness of breath to his local hospital. He tested positive for COVID-19. Despite standard treatment and prophylactic LMWH, SARF ensued on NIV, requiring intubation and mechanical ventilation at Day 10. Progressive respiratory acidosis and haemodynamic deterioration, with cold peripheries and persistent hypotension requiring high doses of vasopressors (noradrenaline 0.55 mcg/kg/min and vasopressin 0.4 U/min), initiated a transfer to our centre. Empirical

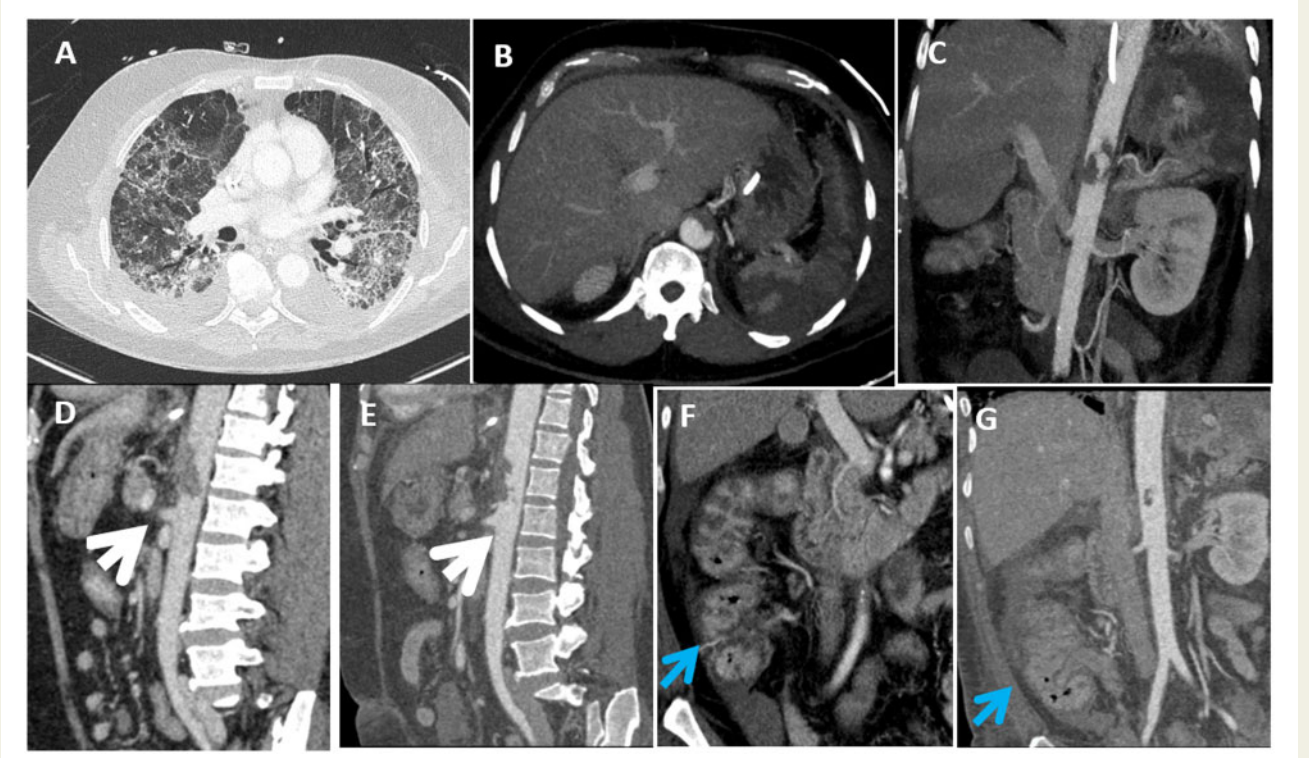

Figure 2 Case 2. Computed tomography scan showing Corona Virus Disease 2019 related changes with ground glass opacities and basal consolidation with small effusions (*A*), abdominal aorta thrombosis and splenic infarcts demonstrated on axial contrast enhanced computed tomography (*B*) and coronal reformat (*C*). Sagittal reformats demonstrate thrombus in abdominal aorta pre-thrombolysis (*D*) and post-thrombolysis (*E*). White arrow points to superior mesenteric artery (SMA) origin. Note reduction in size of thrombus post-fibrinolysis. Coeliac oedema (blue arrow) suggestive of ischaemia pre-thrombolysis (*F*), improved post-thrombolysis (*G*).

azithromycin, piperacillin/tazobactam, and hydroxychloroquine were added, and shock dose hydrocortisone. Computed tomography of the chest, abdomen, and pelvis performed as per protocol after ECMO cannulation, showed extensive bilateral ground-glass opacification, and dense dependent consolidation consisted of COVID-19 related ARDS. Additionally, there was thrombus in a small pulmonary segmental artery and a large upper abdominal aortic thrombus compromising the flow into the superior mesenteric artery (SMA) with radiological evidence of ischaemic colitis, and splenic infarcts (*Figure 2*). Unfractionated heparin infusion was commenced to achieve therapeutic anti-Xa targets (0.5–0.7 IU/mL) since admission to our tertiary centre. Despite normal imaging appearances of the kidneys, the patient became anuric and required RRT. Transthoracic echocardiogram (TTE) on admission showed a hyper-dynamic left ventricle, moderately impaired RV function (FAC 25%) with septal motion suggesting pressure overload and no significant valvular disease.

The patient's condition deteriorated with increasing vasopressor requirements and rising lactate. Further RV function deterioration (FAC 13.5%) motivated initiation of inotropic support with milrinone the following day. Following specialist multidisciplinary discussion, systemic fibrinolysis with alteplase was commenced (bolus followed by infusion at 1 mg/mL, 90 mg in total) in view of suspected hypoperfusion related progressive bowel ischaemia. A repeat CT the following day demonstrated a reduction in the size of aortic thrombus and improvement of bowel oedema, which corresponded with mild, transient clinical improvement. Unfortunately, further deterioration ensued, and the patient died on Day 3 from multi-organ failure, as renal function, respiratory failure, bowel ischaemia, and right ventricular performance continued to deteriorate.

Discussion

Several previous studies have observed high rates of thrombosis in COVID-19 patients but very few concomitant arterial and venous thrombosis.[4–6]

The range of observed thrombosis in COVID-19 patients admitted to ICU ranges from 7.7% to 31% despite prophylactic anticoagulation. Most events were PE, DVT, stroke, and acute myocardial infarction but *in situ* aortic thrombosis has not been described.[7,8] Acute thrombosis of a previously implanted aortic graft in a patient with COVID-19 related pneumonia has also been described,[9] as well as high incidence of acute leg ischaemia in patients with COVID-19.[10]

Table 1 Laboratory tests performed on admission to this centre

		Case 1	Case 2	Reference range
Haematology	Haemoglobin (g/L)	112	86	134–166
	White cell count ($\times 10^9$ L)	18.2	18.8	4.4–10.1
	Neutrophil ($\times 10^9$ L)	16.6	17.4	2.1–6.7
	Platelets ($\times 10^9$L)	69	313	136–343
Clotting profile	APTT (s)	92.3	35	60–100
	PT (s)	18.5	16.3	10.2–13.2
	Fibrinogen (g/L)	6	5.5	1.5–4.5
	Anti-thrombin (IU/dL)	89	51	70–130
	D-dimer (ng/mL)	2523	16 742	0–240
	Plasma haemoglobin (g/L)	0.5	Not measured	<0.3
Renal function	Sodium (mmol/L)	135	130	133–146
	Potassium (mmol/L)	6	6.3	3.5–5.3
	Creatinine (mmol/L)	152	203	60–120
	Urea (mmol/L)	14.5	18.1	2.5–7.8
	CK (U/L)	247	67	25–171
Liver function	ALT (IU/L)	65	201	8–40
	AST (IU/L)	140	105	16–41
	ALP (IU/L)	93	152	30–130
	Albumin (g/L)	24	22	35–50
	Total bilirubin (μmol/L)	15	35	0–20
Other	CRP (mg/L)	227	320	0–10
	Lactate	2.3	1.3	<2
	Ferritin (μg/L)	5348	4044	32–284
	LDH (IU/L)	2513	1277	266–500
	BNP (ng/L)	352	1323	0–20
	Troponin I (ng/L)	575	408	0–19.8
	Complement C4 (g/L)	<0.08	Not measured	0.16–0.38

Note the elevation of white cell count and inflammatory markers [C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin]. Clotting profile with prolonged prothrombine time (PT) and fibrinogen, and very raised D-dimer in both cases. Renal and liver function was impaired.
ALP, alkaline phosphatase; ALT, alanine aminotranferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BNP, brain natriuretic peptide.

However, these observations may have been limited by the low rates of cross-sectional imaging performed (10%) in one study.[8]

Venous thrombosis has been classically associated with the components of Virchow's triad of blood stasis, endothelial activation, and hypercoagulability, identifying predisposed subgroup of patients including those with cancer, recent surgery, and prolonged immobilization, as in ICU. Arterial thrombosis however, is more commonly related with damage to the endothelium of the vessel and increased platelet reactivity, affecting mostly patients with accepted cardiovascular risk factors for atherosclerosis such as tobacco smoking, systemic hypertension, and DM. Nevertheless, in recent years, common pathways for both venous and arterial thrombosis have been described, with inflammation and hypercoagulation being key factors in the mechanism of both types of thrombotic events.[11]

Although the mechanisms underlying vascular thrombosis in COVID-19 have not been clearly defined yet, several have been postulated. The tropism that the virus shows for the angiotensin-converting enzyme-2 receptor of the endothelial cells results in an endothelialopathy and endothelial cell apoptosis.[12] The corresponding inflammation involves cytokine release, further endothelial cell dysfunction, haemostatic activation, decreased levels of tissue factor pathway inhibitor, and increased tissue factor. In addition, liver injury can lead to impaired coagulation and anti-thrombin formation. Infection-related disseminated intravascular coagulopathy (DIC) could also generate a pro-thrombotic state that contributes to venous and arterial thrombosis, including myocardial infarction.[12,13] However, coagulopathy in COVID-19 seems to differ from classical sepsis-related DIC, associated with higher levels of D-dimer and relatively normal levels of prothrombin time (PT), fibrinogen, and platelets.[14] Additionally, the presence of antiphospholipid antibodies has been associated with micro-thrombosis in COVID-19 patients.[15] Nevertheless, these have not been tested in both cases and therefore, we are unable to suggest a correlation in this regard.

Transoesophageal echocardiogram in patient 1 demonstrated a shunt across the PFO facilitated by an advanced position of the return ECMO cannula. However, paradoxical embolism is unlikely in this case given the fact that the aortic thrombus was much larger in size

than the VV-ECMO return cannula lumen (i.e 23 Fr femoral venous cannula with an internal diameter of 0.6 mm by CT scan). In addition, intra-cannula clot and DVT were excluded by CT venography, and extensive laminar thrombus was present along the anterior wall of the ascending aorta, characteristic of an *in situ* aetiology.

Both patients had received prophylactic anticoagulation with LMWH since presentation to their local hospitals. This was not effective in preventing thrombosis, which was already present at imaging performed at admission to our centre and could likely have contributed to the clinical deterioration that motivated the transfer. Patient 1 had a short history of symptoms, whilst Patient 2 was symptomatic for 2 weeks prior to presentation to his local hospital, 13 days before transfer. Therefore, the exact timing of thrombosis in the course of the disease and optimal treatment for COVID-19 thrombosis remain unknown, but our experience suggests comprehensive imaging should be considered soon after the presentation as thrombosis may happen early and would warrant full anticoagulation. Previous studies describe thrombotic events in patients already on prophylactic anticoagulation,[7,8] and improved survival in patients with full anticoagulation has been suggested by Tang *et al.*[16] Indeed, a recent report has hypothesized that full anticoagulation is most likely needed in most COVID-19 patients and thrombolysis should be considered early in critically ill patients given the suboptimal rate of thrombus resolution on heparin alone.[17] In this regard, a case of catheter-directed thrombolysis administration for a large pulmonary embolism has been described.[18] Similarly, thrombolysis has been proposed for treating COVID-19 related ischaemic stroke.[19] In one of our patients, there was a documented improvement in the extent of aortic thrombosis and clinical status, although this did not ultimately affect the outcome. Clearly, any benefit of thrombolysis should be balanced against the risk of bleeding, which is often considerable in ICU patients and can lead to intracranial haemorrhage, particularly in patients supported by ECMO.[20]

Conclusion

Patients treated for COVID-19 pneumonitis are at high risk of thrombotic events. Our two cases suggest aortic and venous thrombosis can coexist even in the absence of significant premorbid history. Even though aortic thrombosis is not a frequent complication, it has a devastating outcome. Although the in-hospital prevalence is very low, the true incidence is an unknown and a low index of suspicion is needed in an acutely deteriorating patient. We believe that early and comprehensive imaging is needed to help detect and treat these complications.

Our case series shows that prophylactic anticoagulation was not adequate to prevent thrombotic events in critically ill COVID-19 patients and full anticoagulation or even thrombolysis should be considered early. However, this approach can be controversial in practice, as frequently a high risk of bleeding coexists in critically ill patients.

Further studies on detailed and early laboratory, clinical and imaging characterization are needed to understand better the pathophysiology of the thrombotic nature of COVID-19. The timing of its development, its trajectory and which haematological pathways can be safely manipulated remain uncertain.

Lead author biography

Dr Castro-Verdes graduated with honours from the University of Santiago de Compostela in 2010. She completed the Spanish national training in cardiology at the University Hospital of Vigo, Spain, in 2016. She is currently a fellow in paediatric cardiology at the Royal Brompton Hospital in London, where she is developing her career in imaging and congenital heart disease. She previously trained in echocardiography in critical care in the adult intensive care unit of the same hospital, where she also was a first-line doctor during the COVID-19 pandemic in 2020.

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Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case series including images and associated text has been obtained from the patients' family in line with the Committee on Publication Ethics guidance.

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