Prevalence of thrombotic complications in ICU-treated patients with COVID-19 detected with systematic CT scanning.

Abstract:

Objective:

Severe Coronavirus disease 2019 (COVID-19) is associated with an extensive pneumonitis, and frequent coagulopathy. We sought the true incidence of thrombotic complications in critically ill patients with severe COVID-19 on the intensive care unit (ICU), with or without extracorporeal membrane oxygenation (ECMO).

Design:

We undertook a single-centre, retrospective analysis of 72 critically ill patients with COVID-19 associated acute respiratory distress syndrome admitted to ICU. CT angiography of the thorax, abdomen and pelvis were performed on admission as per routine institution protocols, with further imaging as clinically indicated. The prevalence of thrombotic complications and the relationship with coagulation parameters, other biomarkers and survival were evaluated..

Setting:

COVID-19 ICUs at a specialist cardiorespiratory centre.

Patients:

Seventy two consecutive patients with COVID-19 admitted to ICU during the study period (19/03/2020-23/06/2020).

Interventions:

None.

Measurements and Main Results:

All but one patient received thromboprophylaxis or therapeutic anticoagulation. Amongst 72 patients (M:F=74%; mean age: 52±10; 35 on ECMO), there were 54 thrombotic complications in 42 patients (58%), comprising 34 pulmonary arterial (47%), 15 peripheral venous (21%), and 5 (7%) systemic arterial thromboses / end-organ embolic complications. In those with pulmonary arterial thromboses, 93% were identified incidentally on first screening CT with only 7% suspected clinically. Biomarkers of coagulation (eg. D-dimer, Fibrinogen level, APTT) or inflammation (white cell count, CRP), did not discriminate between patients with or without thrombotic complications. Fifty-one patients (76%) survived to discharge; 17 (24%) patients died. Mortality was significantly greater in patients with detectable thrombus (33% vs. 10%, p=0.022).

Conclusions:

There is a high incidence of thrombotic complications, mainly pulmonary, amongst COVID-19 patients admitted to ICU, despite anticoagulation. Detection of thrombus was usually incidental, not predicted by coagulation or inflammatory biomarkers, and associated with increased risk of death. Systematic CT imaging at admission should be considered in all COVID-19 patients requiring ICU.

Introduction

To date, following the first report of coronavirus disease (COVID-19) in Wuhan in late December 2019, over 9 million people have acquired the disease worldwide. Just over one quarter of symptomatic patients needing hospitalization require intensive care support for ventilation and multiorgan failure, including advanced respiratory support with extra-corporeal membrane oxygenation (ECMO) ([1]).

Whilst patients with severe pulmonary infections and the acute respiratory distress syndrome (ARDS) are at risk of thrombosis due to factors such as limitation of mobility, abnormal haemodynamics and high inflammatory status ([2–6]), those with COVID-19 appear to be at particularly high risk, despite anticoagulant thromboprophylaxis or even with full dose anticoagulation ([7]). However, thrombotic complications in critically-ill patients may be clinically difficult to detect on the ICU and may go unrecognized.

Severe COVID-19 pneumonia, is characterised by fulminant cytokine release leading to the activation of a coagulation cascade ([8]). A prothrombotic state is a recognised feature of severe COVID-19 infection, manifesting as venous and systemic or pulmonary arterial thrombus; however, the true prevalence of detectable (macrovascular) thrombus and associated complications is unknown ([9]). Whilst typical pathological features of ARDS are seen in patients with COVID-19 ([1]), a recent study reported systemic thrombosis at microvascular level secondary to a systemic activation of complement pathways as an additional cause of respiratory failure in these patients ([10]).

The incidence of image-diagnosed thrombosis appears higher in COVID-19 than in comparably-ill patients with different aetiologies. In a recent study, 22% of COVID-19 ICU patients had pulmonary embolism (PE) (without systematic imaging) compared with 6.1% in

the same period the previous year and 7.5% in influenza patients admitted a month previously, despite similar severity of respiratory disease ([11]).

The aim of the present study was to evaluate the true prevalence of vascular thrombotic complications in patients with confirmed COVID-19 admitted to ICU for advanced ventilatory support, including those on ECMO, as apparent on systematic CT imaging.

Materials and Methods

We undertook a single-centre, retrospective analysis of consecutive patients admitted to our ICU for critical care support caused by COVID-19 between 19/03/2020 and 23/06/2020. Following pandemic related reconfiguration, our unit became the largest ECMO service for severe acute respiratory failure in the UK. This study was undertaken following institutional board review and the requirement for informed consent requirement was waived.

Unselected patients with COVID-19 requiring ICU, with or without ECMO, were admitted to our tertiary centre ICU via one of two possible pathways: the first group were admitted on the ECMO pathway as defined by the national ECMO guidelines, and the other patients were transferred from other hospitals due to local ICU capacity issues. Every patient was considered for ECMO if they met the national COVID-19 ECMO guidelines.

All patients had COVID-19 infection confirmed on reverse transcription-polymerase chain reaction (RT-PCR) testing prior to admission. Unless contraindicated (i.e. intracranial haemorrhage, n=1), all patients received prophylactic low molecular weight heparin (LMWH) on admission and continued or escalated to a treatment dose LMWH as indicated (D-dimer level >10 times the upper limit of normal [2600ng/mL] and a platelet count $>100x10^9$/L). Treatment was switched to unfractionated heparin (UFH) if the creatinine clearance fell below 30 ml/min, aiming for a heparin anti-Xa concentration of 0.3-0.7 IU/mL. Standard practice is to give a bolus dose of UFH at cannulation, followed by heparin infusion if there is no evidence of intracranial bleeding on the CT head within 24 hrs of ECMO ([12]). The target heparin anti-Xa concentration was 0.2–0.3 IU/mL for patients on ECMO if there was no evidence of thrombosis, or 0.3-0.5 U/mL if there was confirmed or high clinical suspicion of thrombosis. The target anti-Xa level in patients on LMWH was 05-1.0 IU/mL and

if there is evidence of thrombosis despite these levels, dose of LMWH increase by at least 20% and maintain anti-Xa levels of 1.0-1.2IU/mL.

CT Scanning

Routine practice is to perform contrast enhanced computed tomography (CECT) in all patients with COVID-19 who are admitted to ICU in our hospital. Local standard operating protocols were followed to transfer patients to and from the CT scanner that was located in close proximity to ICU. The scans were performed on the day of admission, unless clinically contraindicated. In those who did not have the scan on admission, scans were performed as soon as clinically feasible. Repeat scanning , to monitor progress and evaluate evolving clinical issues, was undertaken as clinically indicated. All CT examinations were performed on COVID-19 dedicated 128-slice, dual-source CT scanner (Definition FLASH; Siemens, Erlangen, Germany). The standard imaging protocol comprises an unenhanced CT of the head followed by CT angiogram of the thorax (following administration of 100 ml contrast agent [Visipaque 350, GE healthcare AS, Nycoveien 1-2, NO-0401, Oslo, Norway]) to achieve adequate enhancement of the pulmonary arteries and the aorta) and, finally, portal venous phase acquisition of the abdomen and pelvis to assess the abdominal / pelvic viscera and vessels. All CT examinations were independently reviewed by two consultant cardiothoracic radiologists with disagreements resolved by consensus.

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Data collection

Clinical characteristics, laboratory data and outcomes were collected using the Electronic Patient Record. Imaging data were collated from the picture archiving and communication system (IMPACS ES 5.2, Agfa HealthCare, Mortsel, Belgium). Full blood count, biochemical profile, hs-CRP and coagulation tests were performed daily, including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and D-dimer levels (with and without age-adjustment). Only the data on ICU-admission were used for analysis.

End-points assessed

The primary end-point was the detection of any venous or arterial thrombus or associated complication (deep vein thrombosis, pulmonary embolism, mesenteric ischaemia, aortic or peripheral arterial thrombosis, or cerebral ischaemic attack). We also recorded length of stay and survival to hospital discharge.

Statistical analysis

Amongst patients with COVID-19, we compared patients with, and without, thrombotic complications for the occurrence of thrombotic complications, survival and length of stay. Continuous variables are presented as mean and standard deviation (SD) and were compared using Mann–Whitney U test.

Categorical variables are presented as numbers and proportions and were compared using Pearson's $\chi 2$ tests or Fisher's exact tests. Univariate and multivariate logistic regression analysis controlling for age, gender, diabetes, BMI and ethnicity were used to compare differences between patients with and without thrombotic complications, and

survivors and non-survivors, as appropriate. A two-sided p-value of less than 0·05 was considered statistically significant. Statistical analyses were done using SPSS v.10.0 (IBM Corp., Armonk, NY, USA).

Results:

Patient cohort

Seventy-two patients with COVID-19 were admitted to our ICU for advanced respiratory support during the study period (19/03/2020-23/06/2020). The baseline clinical characteristics are shown in Table 1. Baseline biochemical and haematological data are shown in Tables 2 and 3.

Twenty-four patients (33%) had 1 CECT, 31 (43%) had 2, 12 (17%) had 3, and 5 (7%) had 4 scans. Sixty-one patients (85%) had at least one unenhanced CT of head. Systemic or pulmonary arterial thrombus or systemic venous thrombosis were diagnosed on the first CECT in 34/45 patients (76%) and on subsequent CECT in the remaining 11 patients. Thrombus was detected on CECT in 53% of patients within the first 3 days of arrival to ICU. Thrombus was detected on CECT in 38 (53%) of patients within the first 3 days of arrival to ICU. The median time from the onset of disease and hospital admission to the diagnosis of thrombosis was 15 days (3-48) and 9 days (0-36 days). The time from hospital admission to first CT scan in patients with and without thrombus was 7.8$\pm$6.8 and 7.1$\pm$5.9 days, respectively (p-value: 0.701). The time from intubation and ventilation to first CT scan in patients with and without thrombus was 6$\pm$6.3 and 6.1$\pm$5.3 days, respectively (p-value: 0.896). Ninety three percent of pulmonary thromboses (31/34) were identified on the first CECT with the remainder identified on follow up CECT, requested due to poor clinical response. The mean time interval between the onset of symptoms and from admission to our ICU and the final status (discharged alive or death) was 41 days ($\pm$20) and 32 days ($\pm$18), respectively. Fifty-five patients (76%) survived and were discharged, 17 (24%) died as at 23 June 2020 (Table 4).

The biomarkers, outcomes, and the length of stay in patients receiving ECMO support compared to those not receiving ECMO are summarised in Supplementary Tables 1 and 2. The haematological and biochemical profiles of these patients on admission to ICU were similar, with the exception of fibrinogen which was higher and CRP which was lower in patients on ECMO. The incidence of venous and arterial thrombotic complications was significantly greater among patients on ECMO compared to those patients who did not require ECMO (66% vs. ?%, p=……) driven predominantly by increased incidence of pulmonary and arterial thromboses in those on ECMO.

Thrombotic complications

Examples of thrombotic complications are shown in Figure 1. Apart from one patient with evidence of intracranial haemorrhage, all received unfractionated heparin if the patient was on ECMO. The prevalence of thrombotic complications was 54 in 42/72 patients (58%). Venous thrombosis was observed in 15 patients (21%) of whom 11 (73%) had thrombus in the iliac or femoral veins, and portal vein in one patient. There was evidence of head and neck vein thrombosis in 4 (27%) patients. Thrombus was associated with a venous catheter in 6 patients.

Pulmonary artery thromboembolism was observed in 34 patients (47%), 12 (35%) of whom had thrombi in the main pulmonary artery and/or the proximal branches, whilst in the remaining 22 (65%) patients, thrombi were only visualised in the segmental and sub-segmental pulmonary artery branches. Of the 34 patients with pulmonary artery

thrombosis, 27 (77%) did not have radiological evidence of peripheral deep venous thrombosis. Of 15 patients with deep venous thrombosis, 7 (47%) had no CT evidence of pulmonary artery thrombosis.

Arterial thrombosis and/or systemic embolism was observed in 5 patients (7%). Aortic macro-thrombosis was present in 2 patients. Embolic ischaemic changes were observed in 5 patients (splenic infarction, n=2; bowel ischaemia, n=1; ischaemic stroke, n=2; renal ischaemia, n=1). All patients with arterial thrombosis also had pulmonary thrombosis but none had peripheral venous thrombosis. Intracerebral haemorrhage was present in 2 patients. There was no difference in the mean length of ICU stay in patients with and without thrombotic complications (32 $\pm$ 18 versus 31 $\pm$ 15 days, respectively [p>0.53]; Table 4). Patients with thrombotic complications were more likely to die, and patients without thrombotic complications were more likely to be discharged alive (P=0.022; Table 4). There was no significant difference in LOS in patients with or without ECMO (p>0.74) and in those with or without thrombosis (p>0.296) (Table 4 and supplementary Table 2). There was no significant relationship between the time from intubation to ECMO initiation and the prevalence of thrombosis (p-value: 0.89).

Relation of clinical characteristics and biomarkers to thrombotic complications

Specific demographics (i.e. male gender, non-Caucasian ethnicity, history of hypertension and diabetes) were not associated with a higher risk of thrombotic complications (Table 1). The following biomarkers on ICU admission were interrogated for their relationship to subsequent thrombotic complications: D-dimer (with or without age-adjustment), APTT, INR, platelet count, white cell count, lymphocyte count, hs-CRP, and fibrinogen (Tables 2

and 3). None of these variables alone, or in univariate analysis, or in combination as part of multivariate analysis, was predictive of thrombotic complications.

Discussion

Our retrospective review of CT findings has confirmed a relatively high prevalence of thrombotic (arterial and venous) complications in patients admitted with severe COVID-19. Our study is unique for two reasons. To the best of our knowledge, this represents the first report of thrombotic complications in high-risk ICU-patients, in whom regular systematic whole body CT scanning was undertaken. Secondly, we report on the incidence of thrombotic complications in relatively large number of patients with severe COVID-19 receiving ECMO.

In our consecutive cohort of critically-ill COVID-19 patients admitted to ICU for advanced respiratory support (of whom 50% required ECMO), there is a high incidence of thrombosis, despite prophylactic or therapeutic anticoagulation. These are mainly pulmonary artery thromboses (47%). To put this into context, a review of the CT imaging data from a group of patients with infectious pneumonia-related ARDS (many due to viral pneumonitis) on routine thromboprophylaxis, admitted to our ICU for respiratory support in 2018, demonstrated an incidence of pulmonary thromboembolism that was less than half of that seen in patients with COVID-19 (14/64, 22%; M:F=34:30; mean age 47 $\pm$15 years; 75% on ECMO) (unpublished data).

Incidence of thrombosis and importance of systematic imaging

Our study reports a much higher rate of thrombotic complications than previously reported. The recent report from 3 papers on a combined total of 441 ICU-treated patients with COVID-19 receiving standard anticoagulant prophylaxis revealed a pooled 16% rate of

pulmonary thrombotic complications ([7,11,13]), and a 3.7% arterial thrombotic event rate ([7]). The main difference in these studies, compared to ours, is that their assessment with CT, or ultrasonography, was only performed for clinical indications, without routine systematic evaluation, and may therefore not have captured all thrombotic complications. There has only been one prior report of routine ultrasound imaging, in a small case series of 26 patients on admission to ICU who received anticoagulant thromboprophylaxis. The overall frequency of venous thrombotic disease was 69% in the study cohort and 100% of the patients developed thrombosis whilst on prophylactic dose anticoagulation but only in 56% of those on therapeutic anticoagulation. This study highlights the importance of systematic screening for thromboembolism in COVID-19 patients and the potential benefits of full anticoagulation [14].

A further report on 198 hospitalised patients with COVID-19 (75 of whom were treated on ICU) receiving thromboprophylaxis, showed the incidence of thrombotic complications increased over time and was linked to increased mortality ([15]). The incidence was higher in ICU patients than in those on other wards (26% at 7 days, 59% at 21 days on ICU vs. 5.8% and 9.2% respectively on the wards). Autopsy findings in 12 consecutive COVID-19 deaths revealed DVT in 7 patients in whom thromboembolism was not suspected ante-mortem; with pulmonary embolism being the direct cause of death in 4 patients ([16]) .

Clinically, pulmonary thromboembolism is difficult to recognise in intubated patients, particularly in patients with COVID-19, where deterioration in lung function may be assumed to be part of the clinical progression of the ARDS. Furthermore, imaging may be

less frequently performed due to the difficulty of moving infectious and ventilated patients to the CT scanner and the desire to limit infection risk to other staff and patients. It has been suggested that D-dimer should be used as a guide to indicate pulmonary embolism (e.g. ≥500 mg/L, or ≥1,000 mg/L when no clinical for pulmonary embolism are present ([17,18]). However, applying this criterion did not discriminate in our patient cohort as the D-dimer levels (even after age adjustment) were highly elevated in most patients. Our data does not exclude the significance of clinical and laboratory markers and the potential screening role of d-dimer in patients with less severe symptoms. In this cohort, we only present the D-dimer levels on admission to ICU. The results show that despite adjustment for age, the presenting D-dimer levels were highly abnormal in all patients (except 3 who interestingly all had evidence of vascular thrombosis). Our data do not exclude the screening role of D-dimer (with or without age-adjustment) in earlier stages of the disease and only shows that in the advanced stages of COVID-19 in these mostly middle age patients, the D-dimer levels were elevated in nearly all cases and could not differentiate patients with or without macrovascular thrombosis.

Our data highlights a number of important issues; firstly, the incidence of thrombotic complications is very high in COVID-19 patients on ICU, despite chemical thromboprophylaxis; secondly, clinicians cannot rely on clinical features to determine thromboembolic disease; and thirdly, biomarkers do not appear to be predictive of thrombotic complications in this cohort. Although ultrasound can be used on bedside to exclude peripheral venous thrombosis, it has limited application in these patients as it will not map systemic and pulmonary artery thrombosis. We would recommend that systematic imaging should be considered in all COVID-19 ICU-treated patients to adequately guide treatment decisions. We feel that the additional radiation and contrast burden is justified in

this cohort to enable diagnosis and treatment of thrombotic complications that adversely impact on outcome. This would understandably limit the use of a dedicated scanner to reduce infection risks to staff and other patients. We acknowledge that the routine imaging of these patients may not be possible in all settings due to the availability of CT scanners and safety concerns pertaining to transfer of infected patients. It may be therefore necessary to work closely with infection control teams and carefully risk assess each patient and consider institutional logistics.

Clinical relevance of identifying thrombotic complications

As with previous publications, we demonstrate that the presence of thrombotic complications in patients with COVID-19 is directly related to adverse outcome. The benefits of anticoagulant thromboprophylaxis in hospitalised COVID-19 patients are now well recognised. In late March, the International Society on Thrombosis and Haemostasis and the American Society of Haematology recommended that all hospitalized COVID-19 patients should receive prophylactic-dose LMWH unless contraindicated ([19]). More recently, a report on 3000 patients with COVID-19 in New York, reported that anticoagulation improved survival (not the thrombosis risk), particularly in patients who required mechanical ventilation, in whom in-hospital mortality fell from 62.7% to 29.1%, and in whom median survival jumped from 9 to 21 days ([20]). Bleeding complications were similar in patients treated with and without anticoagulation. Additional data to support a possible survival benefit with anticoagulation was seen in 449 patients with severe COVID-19 treated with heparin (mostly LMWH) for at least 7 days in Hunan, China ([19]). Whilst for all-comers,

mortality was similar between those receiving and not receiving heparin, those that received heparin who had a sepsis induced coagulopathy score ≥4, or a markedly elevated D-dimer, had significantly lower mortality.

Usefulness of biomarkers in predicting or diagnosing thrombotic complications on the ICU

One of the emerging hallmarks of severe COVID-19 is a coagulopathy that is detectable through markers of coagulation and inflammation in peripheral blood. In the original Wuhan cohort of 919 patients, lymphopenia, leucocytosis, and elevated ALT, lactate dehydrogenase, D-dimer and prothrombin time were reported and related to increased mortality ([1]). Since then, severe coagulation abnormalities have been reported in some 20% of COVID-19 patients and in almost all patients with very severe disease ([21,22]). A review of the recent studies of COVID-19 shows that D-dimer levels were consistently higher in patients with severe disease and linked to poorer outcome ([18]). However, estimation of D-dimer levels for predicting thrombosis risk, is generally not helpful, given the significant baseline elevations in ICU-treated COVID-19 patients ([23]). Although coagulation markers, especially significantly raised D-dimer levels, are associated with adverse outcomes in COVID-19 patients, they have not been shown to be directly predictive of thrombotic complications. Patients with infection/inflammation generally have raised D-dimer and LDH levels which are more marked when the patient reaches a more severe status requiring ICU admission. Our data support these findings.

Pathological mechanism of thrombotic complications

The cause of thrombotic complications in COVID-19 is thought to be multifactorial and includes inflammation, endothelial dysfunction, platelet activation, and disturbances in coagulation, and patient related factors such as immobility and line insertions. In severe cases, COVID-19 induces a cytokine storm, leading to activation of the coagulation cascade and impairment of fibrinolysis, which is reflected in elevated D-dimer levels ([8]). Whilst significant disturbances in coagulation markers were seen in our cohort, these did not correlate with the occurrence of thrombosis. This could suggest that the pathological mechanism in these patients may be more complex than a simple procoagulant state, with inflammation and endothelial dysfunction playing important roles, particularly in some vascular beds ([24,25]). The finding that 77% of patients in our cohort had CT evidence of pulmonary thrombosis without evidence of venous thrombosis is similar to that reported by Poissy et al ([11]) and may suggest that in some cases, the pulmonary arterial filling defect represents in situ thrombosis, rather than thrombo-embolism. Most recently, the histological pattern of the lung from patients who had died of COVID-19 were found to have a significant endotheliopathy, characterised by cell membrane disruption, intracellular viral inclusion, T cell infiltration, and pulmonary capillary microthrombotic angiopathy with intussusceptive angiogenesis. Importantly, these pulmonary microthrombi were nine times more frequently observed than in comparative lungs from those with influenza related diffuse alveolar damage ([26]). We acknowledge a limitation of this study being the lack of information regarding initial or serial d-dimer results and whether they influenced the rates and treatment of thromboses in this cohort. However, the prevailing evidence base remains uncertain as to the relationship between d dimer levels, the incidence of proven thromboses and the benefits/or not of higher versus lower anticoagulation targets [ref].

The finding that coagulation and inflammatory markers on ICU admission did not correlate with thrombotic complications should be interpreted with caution as we only analysed the admission results in a limited number of patients. The main message is that in this setting, the biomarkers did not discriminate patients with thrombosis.

Limitations

As a large observational study of COVID-19 patients, many were still intubated at the time of data collection, and although length of stay data has been collected at the latest possible point prior to publication, some patients remain in hospital so the incidence of thrombotic complications and its relationship to mortality may be under-estimated. In addition, it was difficult to assess when exactly patients developed the thrombosis and these were likely present prior to admission to ICU. This might have affected the predictive value of blood biomarkers as shown in this study.

Conclusions

Among COVID-19 patients needing ventilatory support on ICU, arterial and venous thrombosis was observed in nearly three in five patients. Thromboses were related to adverse outcome, and importantly the presence of these thromboses were not predicted based on usual biomarkers of coagulation on admission to ICU. Since many thrombotic complications are clinically silent, we propose that systematic CT imaging should be considered in all ICU-treated COVID-19 patients and may improve patient outcome if implemented early and routinely.

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Figure Legends:

Figure 1. Examples of thrombotic complications in patients with COVI-19 admitted to ICU. 1a: Large thrombus in the left lower lobe pulmonary artery (thick arrow) with wedge shape reduced lung attenuation indicating reduced perfusion (small arrows); 1b: segmental thrombus (thick arrow) in the right lower lobe with visible reduced lung perfusion (small arrows); 1c: New watershed ischemic lesions (small arrows); 1d: Multiple splenic infarctions (small arrows); 1e: Thrombus in the right iliac vein (arrow) with canula in the opposite side vein.

Clinical characteristics	All patients (n=72)	No Thromboembolic Event	Thromboembolic Event				P-val
		(n=30; 42%)	Patients with at least 1 event (n=42; 58%)	Venous (n=15; 21%)	Pulmonary (n=34; 47%)	Arterial (n=5; 7%)	
Mean Age years (SD; range)	52 (10; 29-72)	51 (11; 32-79)	52 (10; 29-72)	52 (9; 33-65)	52 (10; 29-72)	48 (6; 39-53)	0.5
Gender							
Male	53 (74%)	25 (83%)	28 (67%)	9 (60%)	22 (65%)	4 (80%)	0.0
Ethnicity							
Caucasian	33 (46%)	16 (53%)	17 (41%)	6 (40%)	12 (35%)	2(40%)	0.2
Asian	32 (44%)	10 (33%)	22 (52%)	8 (53%)	19 (56%)	2(40%)	
African or Caribbean	7 (10%)	4 (13%)	3 (7%)	1 (6%)	3 (9%)	1 (20%)	
Comorbidities							
Diabetes	19 (26%)	6 (20%)	13 (31%)	4 (27%)	12 (35%)	2 (40%)	0.2
Hypertension	26 (36%)	9 (30%)	17 (40%)	6 (35%)	13 (37%)	2 (40%)	0.4
Prior coronary or peripheral artery disease	1 (<1%)	0	0	0	1 (<1%)	0	0.5
Prior stroke	1 (<1%)	0	0	0	1 (<1%)	0	0.5
Smoking history	6 (8%)	3 (10%)	3 (7%)	1 (6%)	3 (9%)	0	0.4
Mean BMI (SD; range)	31 (7; 21-64)	32 (8; 21-64)	30 (6; 22-45)	31 (7; 23-44)	31 (6; 22-45)	30 (5; 23-38)	0.6
<30	37 (51%)	15 (50%)	22 (52%)	7 (47%)	18 (53%)	3 (60%)	
30-40	26 (36%)	10 (33%)	16 (38%);	5 (33%)	13 (38%)	2 (40%)	
>40	9 (13%)	5 (17%)	4 (10%)	3 (20%)	3 (9%)	0	
Patients receiving ECMO	35 (49%)	13 (43%)	23 (55%)	6 (40%)	19 (56%)	4 (80%)	0.4
Antiplatelet therapy	12 (17%)	6 (20%)	6 (14%)	4 (27%)	3 (9%)	0 (0%)	0.8

Table 1. Patient characteristics: demographics and medical according to the presence or absence of the primary composite end point. BMI = body mass index, ECMO = extracorporeal membrane oxygenation, SD: standard deviation. *P-value compares patients with and without thrombotic events.

	All patients (n=72)	No Thromboembolic Event	Thromboembolic Event				P-value*
Test (normal range)	Mean (SD; range)	**(n=27; 37.5%)**	**Patients with at least 1 event (n=45; 62.5%)**	**Venous (n=17; 24%)**	**Pulmonary (n=35; 49%)**	**Arterial (n=5; 7%)**	
Hb (115-151 g/L)	107 (20; 72-157)	111 (18; 85-149)	105 (21; 72-157)	106 (18; 72-128)	105 (22; 72-157)	102 (23; 74-136)	0.213
Platelet (147-397 x10^9/L)	270 (100; 69-522)	284 (108; 85-522)	261 (94; 69-473)	297 (82; 128-402)	245 (94; 69-473)	219 (57; 167-306)	0.508
White cell count (5.1-11.4 x10^9/L)	11.5 (4.9; 2.6-24)	12 (5.6; 2.6-24)	10.9 (4.2; 4.4-21)	12 (4; 6.9-21)	10.7 (4.3; 4.4-21)	7.9 (2.5; 5-11)	0.515
Lymphocyte (1.3-3.7 x10^9/L)	0.81 (0.51; 0-3.1)	0.82 (0.67; 0-3.1)	0.8 (0.4; 0.2-1.8)	0.72 (0.3; 0.2-1.3)	0.81 (0.4; 0.2-1.8)	0.74 (0.22; 0.5-1.1)	0.289
Ferritin (20-186 ug/L)	1112 (119; 103-5646)	1157 (957; 103-4044)	1102 (1204; 108-5646)	1410 (1582; 108-5646)	1070 (1245;108-5646)	671 (523; 156-1482)	0.367
CRP (0-10 mg/L)	254 (121; 18-642)	248 (112; 18-432)	259 (128; 18-642)	299 (148; 75-642)	256 (111; 26-546)	276 (54; 208-350)	0.995
Cr (60-120 umol/L)	143 (129; 29-611)	150 (139; 30-611)	132 (12; 26-642)	158 (154; 29-556)	137 (121; 30-477)	180 (176; 46-477)	0.743
Urea (2.5-7.8 mmol/L)	11 (7; 2-36)	11 (7; 4-31)	11.5 (8; 1.6-36)	13 (9; 2-36)	11 (7; 2-26)	13 (8; 6-25)	0.834
Albumin (35-50 g/L)	26 (11; 17-105)	27 (15; 18-105)	25 (5; 17-43)	24 (4; 18-32)	25 (6; 17-43)	26 (5; 17-31)	0.722
ALT (8-40 U/L)	65 (64; 8-353)	72 (81; 8-353)	59 (48; 8-294)	74 (67; 8-294)	58 (53; 8-294)	52 (30; 20-89)	0.909
ALP (30-130 U/L)	131 (125; 27-1055)	149 (178; 38-1055)	118 (63; 27-286)	147 (71; 36-283)	107 (55; 27-286)	116 (62; 57-219)	0.635
LDH (266-500 IU/L)	1053 (494; 96-3049)	1078 (468; 96-2401)	1035 (518; 333-3049)	1024 (343; 342-1545)	1048 (554; 333-3049)	968 (258; 96-3049)	0.462
D-Dimer (0-240 ng/ml)	7606 (11743; 148-56005)	5160 (6863; 511-35547)	9396 (14121; 148-56005)	12932 (17399; 451-56005)	9762 (14910; 148-56005)	6338 (5314; 727-13368)	0.744

PT sec (10.2-13.2)	14 (3; 10-33)	14 (2; 10-22)	14.5 (3.4; 11-33)	14 (1; 11-17)	14 (4; 11-33)	14 (1; 13-15)	0.265
APTT (26-36 sec)	38 (14; 16-92)	35 (9; 16-52)	41 (17; 27-92)	41 (17; 26.5-78)	40 (17; 27-92)	34 (4; 27-38)	0.367
Fibrinogen (1.5-4.5 G/l)	6.4 (1.9; 1.4-10.7)	6.5 (1.9; 1.4-10.1)	6.4 (1.9; 2.5-10.7)	6.6 (1.7; 3.8-9.4)	6.3 (1.9; 2.5-10.7)	7.9 (1.8; 6.1-10.3)	0.703
hs Troponin I (<11.6 ng/L)	528 (3420; 3-27619)	157 (333; 3-1501)	793 (4357; 3-27619)	2258 (7625; 4-27619)	77 (220; 3-1146)	13 (10; 4-24)	0.131
NT-pro BNP	197 (264; 9-1323)	234 (349; 9-1323)	162 (167; 10-673)	216 (206; 22-673)	153 (172; 10-673)	75 (115; 16-280)	0.652
CK (25-171 U/L)	973 (3211; 30-26848)	1416 (4855; 55-26848)	657 (968; 30-5538)	507 (427; 30-1393)	670 (1053; 56-5538)	1674 (2183; 257-5538)	0.728

Table 2. Laboratory results of the study cohort according to the presence or absence of the primary composite end point.

*P-value compares patients with and without thrombotic events. ALT: alanine aminotransferase, ALP: alkaline phosphatase, APTT: activated partial thromboplastin time, CK: creatine kinase, Cr: creatinine, CRP: C-reactive protein, Hb: hemoglobulin, hs Troponin I: high sensitivity troponin I, LDH: Lactate, NT-pro BNP: N-terminal pro B-type natriuretic peptide, PT: prothrombin time, Dehydrogenase, PT: partial thromboplastin time, SD: standard deviation.

	All patients (n=72)	No Thromboembolic Event (n=30; 42%)	Thromboembolic Event (n=42; 58%)	P-value*
Platelet count (10^9/L)				0.537
<147	11 (15%)	4 (13%)	7 (17%)	
147-397(N)	55 (76%)	23 (77%)	32 (76%)	
>397	6 (8%)	3 (10%)	3 (7%)	
White cell count (10^9/L)				0.448
<5.1	3 (4%)	1 (3%)	2 (5%)	
5.1-11.4 (N)	39 (54%)	17 (57%)	22 (52%)	
>11.4	30 (42%)	12 (40%)	18 (43%)	
Lymphocyte count (10^9/L)				0.275
<1.3	61 (85%)	24 (80%)	37 (88%)	
1.3-3.7 (N)	11 (15%)	6 (20%)	5 (12%)	
> 3.7	0	0	0	
Fibrinogen (G/l)				0.693
<1.5	3 (4%)	2 (7%)	1 (2%)	
1.5-4.5 (N)	8 (11%)	3 (10%)	5 (12%)	
>4.5	59 (82%)	24 (83%)	35 (83%)	
APTT (sec)				0.232
<26	2 (3%)	2 (7%)	0	
26-36 (N)	41 (57%)	16 (53%)	25 (60%)	
>36	29 (40%)	12 (40%)	17 (40%)	
D-Dimer (ng/ml)				0.427
0-240 (N)	3 (4%)	0	0	
241-2000	18 (25%)	9 (30%)	9 (23%)	
2000-10000	36 (50%)	18 (60%)	18 (46%)	
>10000	15 (21%)	3 (10%)	12 (31%)	

Table 3. Categorised biomarkers of inflammation and coagulation. ALP: alkaline phosphatase; ALT: alanine aminotransferase; APTT= activated partial thromboplastin time; CK: creatine kinase; Cr: creatinine; CRP: C-reactive protein; Hb: haemoglobin; hs Troponin I: high sensitivity troponin; LDH: Lactate dehydrogenase; N: Normal value; NT-pro BNP: N-terminal pro B-type natriuretic peptide; PT: partial thromboplastin time; SD: standard deviation. *P-value compares patients with and without thrombotic events.

	Positive thromboembolic events (n=42)	Negative thromboembolic event (n=30)	P-value *
Status			
Discharged	28 (67%)	27 (90%)	**0.022**
Died	14 (33%)	3 (10%)	
Length of hospital stay (days ± SD)	32 ± 18	31 ± 15	0.533
Presentation to final status (days ± SD)	44 ± 21	38 ± 17	0.935

Table 4. Relationship between the presence of thromboembolic events and secondary outcome (clinical recovery). *P-value compares the outcome (discharged/died) and the duration of disease in patients with and without thrombotic events.

	All patients (n=72)	Non-ECMO	ECMO	P-value*
Test (normal range)	Mean (SD; range)	Mean (SD; range)	Mean (SD; range)	
Hb (115-151 g/L)	107 (20; 72-157)	110 (17; 72-155)	105 (23; 73-155)	0.17
Platelet (147-397 x10^9/L)	270 (100; 69-522)	282 (111; 85-522)	259 (88; 69-473)	0.37
White cell count (5.1-11.4 x10^9/L)	11.5 (4.9; 2.6-24)	12 (5; 4.1-24)	11 (4.7; 42.6-22)	0.64
Lymphocyte (1.3-3.7 x10^9/L)	0.81 (0.51; 0-3.1)	0.74 (0.55; 0-3.1)	0.88 (0.5; 0.3-2.3)	0.12
Ferritin (20-186 ug/L)	1112 (119; 103-5646)	1187 (1075; 103-5646)	1060 (1046; 120-5348	0.24
CRP (0-10 mg/L)	254 (121; 18-642)	280 (110; 26-546)	228 (128; 18-642)	0.032
Cr (60-120 umol/L)	143 (129; 29-611)	117 (90; 30-431)	168 (155; 29-611)	0.26
Urea (2.5-7.8 mmol/L)	11 (7; 2-36)	10 (7; 3-36)	12 (8; 2-31)	0.25
Albumin (35-50 g/L)	26 (11; 17-105)	26 (14; 17-105)	25 (5; 17-40)	0.52
ALT (8-40 U/L)	65 (64; 8-353)	69 (71; 8-353)	60 (56; 15-294)	0.3
ALP (30-130 U/L)	131 (125; 27-1055)	142 (166; 36-1055)	121 (62; 27-286)	0.99
LDH (266-500 IU/L)	1066 (494; 96-3049)	1041 (446; 333-2401)	1035 (544; 96-3049)	0.5
D-Dimer (0-240 ng/ml)	6716 (11743; 148-56005)	8452 (11338; 183-54118)	9396 (12221; 148-56005)	0.57
PT sec (10.2-13.2)	14 (3; 10-33)	15 (2; 11-22)	14.5 (3.8; 10-33)	0.34
APTT (26-36 sec)	37 (14; 16-92)	40 (11; 25-78)	41 (17; 16-92)	0.8
Fibrinogen (1.5-4.5 G/l)	6.9 (1.9; 1.4-10.7)	6 (1.5; 3.8-11)	6.4 (2.1; 1.4-10.3)	0.026
hs Troponin I (<11.6 ng/L)	932 (3420; 3-27619)	176 (4873; 3-27619)	793 (348; 3-1501)	0.1
NT-pro BNP	157 (264; 9-1323)	225 (171; 9-673)	162 (320; 10-1323)	0.52
CK (25-171 U/L)	1200 (3211; 30-26848)	750 (4434; 37-26848)	657 (30; 30-5538)	0.39

Commented [DG3]: P values should all be to 3 decimal places.

Supplementary Table 1. Laboratory results of the study cohort according to the ECMO status. *P-value compares patients with and without thrombotic events. ALT: alanine aminotransferase, ALP: alkaline phosphatase, APTT: activated partial thromboplastin time, CK: creatine kinase, Cr: creatinine, CRP: C-reactive protein, Hb: hemoglobulin, hs Troponin I: high sensitivity troponin I, LDH: Lactate, NT-pro BNP: N-terminal pro B-type natriuretic peptide, PT: prothrombin time, Dehydrogenase, PT: partial thromboplastin time, SD: standard deviation.

	ECMO (n=36)	Non-ECMO (n=36)	P-value *
Status			
Discharged	27 (75%)	28 (78%)	0.785
Died	9 (25%)	8 (22%)	
Length of hospital stay (days ± SD)	32 ± 12	34 ± 14	0.748
Presentation to final status (days ± SD)	33 ± 12	34 ± 15	0.822

Supplementary Table 2. Relationship between the ECMO status and secondary outcome (clinical recovery). *P-value compares the outcome (discharged/died) and the duration of disease in patients with and without thrombotic events.