Vascular thrombosis in severe Coronavirus Disease 2019 requiring extracorporeal membrane oxygenation: A multicentre study

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ABSTRACT:

OBJECTIVES:

Coronavirus Disease 2019 has been reported to be a prothrombotic condition, however multicentre data comparing this with other viral pneumonias in those requiring extracorporeal membrane oxygenation is lacking. We conducted a multicentre study utilizing whole body CT to examine the prevalence, severity and nature of vascular complications in COVID-19 in comparison to patients with other viral pneumonias.

DESIGN:

We analysed whole-body CT scans for the presence of vascular thrombosis (defined as pulmonary artery thrombus (PAT), venous thrombus, systemic arterial thrombus, or end organ infarct) was recorded. The severity, distribution and morphology of PAT was characterised. Competing risk cumulative incidence analysis was used to compare survival to discharge.

SETTING:

Three centres of the English national ECMO service.

PATIENTS: Consecutive patients admitted with either COVID-19 or non-COVID-19 viral pneumonia admitted from January 2019.

INTERVENTIONS: None

MEASUREMENTS AND MAIN RESULTS:

136 patients (45.2±10.6 years of age, 39/146 (27%) female) requiring ECMO support underwent whole-body CT scans on admission. Of these 86 had COVID-19 pneumonia, and 50 had non-COVID-19 viral pneumonia. Vascular thrombosis was seen more often in patients with COVID-19 (OR 12.9 (95% CI 4.5;36.8)). In those with COVID-19 57 (73%) demonstrated PAT or pulmonary perfusion defects. 82% of thrombus exhibited emboli-like morphology. The location of PAT and parenchymal perfusion defects was only concordant in 30% of cases. The risk of mortality was higher in those with COVID-19 compared with non-COVID-19 pneumonia (χ^2 = 3.94, p=0.047). Mortality was no different in COVID-19 patients with or without vascular thrombosis (χ^2 = 0.44, p=0.51).

CONCLUSIONS:

In patients who received ECMO, COVID-19 is associated with a higher prevalence of vascular thrombosis compared to non-COVID viral pneumonias. The pattern of pulmonary vascular

changes suggests concurrent embolic disease and small vessel disease. Despite this, vascular thrombosis was not linked to poorer short-term prognosis in those with COVID-19.

KEYWORDS:

Embolism and Thrombosis; COVID-19; Tomography, X-Ray Computed; Extracorporeal Membrane Oxygenation

ABBREVIATIONS:

COVID-19: Coronavirus disease 2019

ECMO: extra-corporeal membrane oxygenation

CT: computed tomography

INTRODUCTION:

A high prevalence of vascular thrombosis has been reported in Coronavirus disease 2019 (COVID-19), with this associated with an elevated risk of mortality (1). The prevalence of thrombus in COVID-19 varies with disease severity, reported in 5% of non-ICU cohorts and 31% of ICU cohorts in a recent meta-analysis (1).

However other viral pneumonias have been reported to also exhibit high rates of thromboembolic events (2). Critically ill patients are generally predisposed to coagulopathy and thromboembolism due to a combination of systemic inflammation, platelet activation, endothelial dysfunction, and stasis of blood flow (3). Evidence that the prevalence or severity of vascular thrombosis is different from other viral pneumonias is limited (4). It is also not clear whether the high reported incidence of pulmonary artery thrombus (PAT) is thromboembolic, or an in situ thrombosis due to a combination of severe local inflammatory changes and microvascular angiopathy (5).

Identification of the true prevalence and risk of COVID-19 for vascular thrombosis as well as its nature is important as it may guide treatment, either in the use of current anti-thrombotic drugs, or development of new treatments targeting a virus-specific causative pathway (6).

We conducted a multicentre study utilizing whole body CT to examine the prevalence, severity and nature of vascular complications in severe COVID-19 in comparison to patients with other viral pneumonias.

METHODS:

This multicentre retrospective observational study was performed at 3 of the 5 centres providing extra-corporeal membrane oxygenation (ECMO) in England. Standard procedure in these ECMO services includes the routine acquisition of a whole-body CT at the point of admission to the ECMO centre to look for complications of ECMO insertion, intervenable complications of the condition requiring ECMO support, and any findings to suggest futility of care. The imaging assessments is done after ECMO has been initiated and the patient transferred back to the ECMO centre. The study was approved by the institutional review boards of the 3 centres (Royal Papworth Hospital Research and Development, ref: S02716) with a waiver for consent due to the observational nature of the study.

Study population:

The study included consecutive patients older than 18 years admitted for viral pneumonia between January 1st, 2019 and April 30th, 2020. Diagnoses were made based on a positive viral RT-PCR. Unless contraindicated, all patients were on prophylactic low-molecular-weight heparin prior to ECMO. Once on ECMO all patients receive heparinisation aiming APTTr 1.5-2 or anti Xa 0.3-0.7 - unless DVT/PE is demonstrated in which case full anticoagulation was initiated. None of the patients received routine anti platelets unless administered for other indications.

Data collection:

Clinical data was collected from the patients notes at the point of referral to the ECMO centre. This included past medical history, and baseline observations and biochemical markers obtained at the time of admission for ECMO.

The whole-body CT scans included a non-contrast CT head and post-intravenous contrast CT chest abdomen and pelvis to the upper thigh following the administration of intravenous contrast agent. The precise scanning protocol varied slightly between centres but ultimately provided for a minimum dataset of a systemic arterial phase chest scan and a portal venous phase abdomen and pelvis scan.

A dedicated systematic review of the CT scans was performed for the current study. Scans were reviewed for vascular thrombosis in the pulmonary and systemic circulation, and venous circulation. Pulmonary arterial thrombosis (PAT) was defined as a filling defect within the pulmonary vasculature including within the central, branch, segmental or subsegmental vessels. PAT were further characterised according to their morphology and severity. The morphology was considered consistent with embolus if it exhibited features of central filling defect within the vessel with peripheral contrast opacification; straddling bifurcations with clot extending into both branches; visualisation of contrast distal to the location of the clot (presence of this was considered strongly suggestive of embolus, but its absence was not considered exclusive of embolus). Morphology suggestive of an in-situ thrombus (IST) was considered if there was complete pulmonary occlusion with a proximal concave morphology, with the clot occurring in regions of diseased lung (see Figure 1 for examples of the two morphology types). Where neither of these patterns were met or there was overlap, the morphology was considered indeterminate. To assist in inter-centre homogeneity of classification, slides with the above criteria were circulated to each centre with several exemplar images of each classification contained within this. For this classification a single reader at each centre re-read all the studies with PAT. Any initially scored as indeterminate were re-read with the lead centre before final classification was assigned. For severity, the PAT was characterised as unilateral versus bilateral, extent of distribution (central, branch, segmental, subsegmental) with this recorded based on the most proximal clot, with the number of segments involved recorded on an ordinal scale (single segment, 2-4 segments, ≥5 segments). The presence, location and segmental involvement of pulmonary parenchymal hypoperfusion was also recorded (Figure 1).

The presence of end organ infarcts and evidence of hemorrhage were also collected. End organ infarcts were considered present in the presence of a perfusion defect in a vascular territory, or whole organ hypoperfusion with a visible arterial or venous occlusion. Central nervous system watershed infarcts or global hypoxic ischemic injury were not classed as ischemic events as these are typically due to global hypoperfusion rather than focal vascular thrombosis. Ischemic colitis was similarly not classed as an ischemic event if it occurred in a watershed territory. Hematomas at the sites of ECMO cannulation were not classed as hemorrhagic events.

Patient status at the time of data collection was recorded using the World Health Organisation COVID-19 Therapeutic Trial Synopsis 7-point ordinal scale (where 1=deceased, 2=ECMO, 3=invasive ventilation, 4=non-invasive ventilation, 5=hospital on oxygen, 6=hospital not requiring oxygen, 7=discharged). In patients transferred back to their base hospital for longer term care following discharge from the Intensive Care Unit (ICU), their status at the time of transfer was used, and the date of discharge was used in the analysis. In patients still in ICU, their data was censored at the point of data collection.

Outcomes

The primary outcome was the relative frequency of vascular thrombosis in COVID-19 compared with non-COVID-19 viral pneumonia. Vascular thrombosis was defined as imaging evidence of: PAT, venous thrombus, systemic arterial thrombosis or end organ infarct. Secondary outcomes included the relative frequency of hemorrhage; and association of the presence of vascular thrombosis with clinical outcomes.

Due to a combination of patient factors and resource limitation, 22 patients with COVID-19 and 1 patient with non-COVID-19 pneumonia had a delay of more than 24 hours between their initiation of ECMO and their CT. The use of continuous heparin infusion while on ECMO is likely to have impacted the prevalence of both thrombosis and hemorrhage. As a result, only those patients with a CT acquired within 24 hours of ECMO initiation were included for analyses.

Statistical analysis:

Continuous variables are reported as mean±SD while categorical variables are reported as n/N (%). For continuous variables, independent t-tests were used to compare the baseline variables and prevalence of vascular outcomes between those with and without COVID-19, as well as to compare characteristics between those with and without vascular thrombosis. Chi-square or Fisher exact tests were used for categorical and ordinal variables as appropriate. Logistic regression was used to compare rates of vascular thrombosis between those with and without COVID-19, and factors associated with thrombus. A competing risk analysis was performed using the *cmprsk* package within R. Cumulative incidence plots were

constructed for death and survival until discharge with censoring for those still in ICU at the time of data collection. For modelling of factors associated with mortality in COVID-19, a competing risk regression was performed using a proportional hazards model as per Fine and Gray (7). Multivariable analysis was not performed due to the limited number of endpoints. Statistical significance was defined as $P<0.05$. All analysis was performed using SPSS v25 (IBM, US) and R (RStudio Version 1.1.463, RStudio, Inc.).

Results:

A total of 149 patients supported with veno-venous ECMO were admitted. We excluded 12 who did not have a CT, 3 who died after ECMO initiation and before CT, and 23 who had a CT >24 hours after admission (Figure 2). The remaining 113 patients (44.7±10.5 years of age, 35/113 (31%) female) included 64 with COVID-19 pneumonia, and 49 with non COVID-19 viral pneumonia.

No difference in age was present between those with and without COVID-19. Those with COVID-19 were more likely to be male (COVID: 49/64 (77%), non-COVID: 30/49 (59%), p=0.048), and had a higher prevalence of background hypertension (COVID: 14/64 (23%), non-COVID: 0/50 (0%), p<0.001), and diabetes (COVID: 16/64 (25%), non-COVID: 3/49 (6%), p=0.01) (Table 1).

The prevalence of vascular thrombosis was 38/64 (59%) for patients with COVID-19 and 5/49 (10%) for patients with non-COVID-19 pneumonia (Table 2). PAT made up the majority of these, with 33/64 (52%) COVID-19 patients having PAT, 5/64 (8%) having venous thrombosis, and 4/64 (6%) demonstrating end organ ischemia. Of those with end-organ ischemia, 3 patients had strokes, 2 had splenic infarcts, and 1 had ischemic colitis secondary to portal vein thrombosis. No systemic arterial thrombosis was evident.

There was no difference in the location, or extent of PAT between COVID-19 and non-COVID pneumonia (Supplemental Table S1). Pulmonary parenchymal perfusion defects were significantly more common in COVID (42/64, 66%) than non-COVID pneumonia (7/49 (14%) - Supplemental Table S1. In those with COVID-19 the majority of thrombi exhibited embolus like features (82%), with only 12% exhibiting IST-like features and 6% being indeterminate. 57 (73%) demonstrated evidence of PAT or parenchymal perfusion defects. Of these PAT occurred in isolation in 5 (8%) of patients with no perfusion defect, 14 (22%) patients had perfusion defects with no pulmonary emboli, and 28 (44%) had both PAT and perfusion defect. 36% of PAT were in regions of the lung most severely affected by consolidation and ground glass changes, and the location of PAT and perfusion defects were only concordant in 30% of cases.

On binary logistic regression, the diagnoses of COVID-19 was associated with an odds ratio of 12.9 (95% CI 4.5;36.8, p<0.001) for vascular thrombosis. On multiple variable regression in a model including age, sex, hypertension and diabetes the risk remained elevated with an odds-ratio for vascular thrombosis of 7.4 (95%CI 2.4;22.5, p<0.001). COVID-19 was associated with an odds ratio of 11.5 (95%CI 4.4;29.7, p<0.001) for pulmonary parenchymal perfusion defect. If these were considered evidence of thrombotic event then 51/64 (79.7%) of patients with COVID had evidence of thrombosis of their admission study, with an odd ratio of 20.1 (95% CI 7.6;53.1, p<0.001) for thrombosis.

The prevalence of hemorrhage was 10/64 (16%) in the COVID-19 patients, and 4/49 (8%) in non-COVID-19 patients (OR 2.1 (95%CI 0.6;7.1)) – Table 2. Intracranial hemorrhage accounted for the majority of these events, with 9/64 (14%) patients with COVID-19 having evidence of an intracranial bleed, and 1/64 (2%) having an intramuscular rectus sheath hematoma.

There was no difference in baseline clinical variables, observations nor biochemical markers in COVID-19 patients, with and without vascular thrombosis (Supplemental Table S2).

Outcomes:

At the time of data collection, follow-up of a median of 13 days (range 0-36) was available for the COVID-19 patients and 15 days (range 1-67) for the non COVID-19 patients.

On May 30th, 2020, of the 64 COVID patients: 18/64 (28 %) had died; 13/64 (20%) remained on ECMO; 9/64 (14 %) were off ECMO support but remained on ventilatory support; 8/64 (13 %) remained in ICU on non-invasive ventilation; 7/64 (11 %) remained in hospital on oxygen therapy; 3/64 (5 %) were in hospital without supplemental oxygen therapy; and 6/64 (9 %) had been discharged. In those with non-COVID 19 viral pneumonia 15/50 (30%) had died, and 35/50 (70%) survived to discharge.

In those patients with COVID-19, there was no difference in the cumulative incidence of death (χ^2=0.43, p=0.51) or discharge (χ^2=0.57, p=0.45) between those with or without vascular thrombosis on CT – Figure S1. Nor was there any difference in the cumulative

incidence of death (χ^2=3.62, p=0.057) or discharge (χ^2=0.53, p=0.47) between those with or without hemorrhage. In univariate competing risk regression age, history of CVD, CKD, D-Dimer levels, Fibrinogen and Troponin were positively associated with mortality in those with COVID-19 (Supplemental Table S3).

Discussion:

In this multicenter study of patients with severe viral pneumonia requiring ECMO support we found that those with COVID-19 had a twelve-fold greater risk of vascular thrombosis compared with other viral pneumonias. Despite this, there was no difference in outcomes between COVID-19 patients with and without vascular thrombosis.

Vascular thrombosis rates in COVID-19 range from 3-23% of patients admitted to hospital requiring ward level care (8, 9), through to 10-69% in patients admitted to ICU (10–12). Concerns have been raised that this is an overestimate as most studies report the cumulative incidence, with a further risk of confirmation bias (11). In one study comparing COVID-19 patients with a historical control, 66% of COVID-19 patients compared to only 28% of the historic cohort received CT pulmonary angiogram due to a hyperawareness of a potential COVID-19 thrombosis interaction leading to greater efforts to investigate for it (12). Our findings of a 59% vascular thrombosis rate confirm a high prevalence of vascular thrombosis when a systematic approach free from referral bias is undertaken. This is similar to the 51% prevalence reported in a smaller single centre study of COVID-19 patients requiring ECMO (13).

Post-mortem examinations show increased thrombosis, microangiopathy and endothelialitis in COVID-19 compared to other viral pneumonias (14). Consistent with these autopsy findings we observed both a high prevalence of PAT and peripheral wedge perfusion defects. The predominate morphological appearances of the PAT was that of thromboembolism, further supported by its distribution in regions of lung which were least affected by consolidation. As consolidation induces regional hypoxia which in turn induces vasoconstriction, higher blood flow in the regions of normal lung aeration is relatively increased, increasing the likelihood of emboli ending up in the segments. While we only observed peripheral venous thrombus in 8% of our cohort, which might suggest that the

PAT was not embolic, this may be due to the CT scan not covering the whole length of the legs and could only assess for proximal venous thrombosis. Previous studies using ultrasound to scan the whole leg report rates of 15-46% of screened hospital-patients with COVID-19 with 58% reported in post-mortem studies (15–18). That 37% of wedge parenchymal perfusion defects occurred without visible PAT, and even when the two were present in the same patient their distribution was only concordant in 30% of cases supports the notion of separate parallel pathophysiological process driving micro and macrovascular disease. A recent study has shown that the spike protein of the COVID virus directly damages vascular mitochondria (19). Thus, the perfusion defects may represent microangiopathy secondary to this, while the macrovascular thrombosis are secondary to a severe inflammatory and hypercoaguable state, although further work is necessary to better explore these hypotheses.

The need for an understanding of the processes that lead to thrombosis is heightened by the finding of a twelve-fold higher rate of vascular thrombosis in COVID-19 compared with other viral pneumonias. A 26% PAT incidence was reported in 107 ICU patients at a single center with COVID-19 compared with a 7% prevalence admitted with influenza in 2019 (20). Helms et al. reported a 3-fold higher rate of PAT in 150 COVID-19 patients, although the study compared this to a historical cohort of ARDS patients admitted to ICU rather than a viral pneumonia cohort (12). Our multicentre study in consecutive patients confirms these findings of an elevated thrombotic risk particular to COVID-19. The collective trial group (ACTIV-4, REMAP-CAP, and ATTACC) found no benefit of routine therapeutic dose anticoagulation in intensive care patients, while the INSPIRATION trial found no benefit of intermediate dose anticoagulation (21, 22). Thus, despite our findings of a high prevalence of vascular thrombosis, current evidence does not support more aggressive pre-emptive treatment. It does however highlight the high incidence of such findings, which if identified in a routine and systematic manner as performed in the current study may identify those with most to gain from more aggressive therapy. The ongoing anti-platelet arms of the REMAP-CAP and RECOVERY trial will provide further evidence on alternate approaches to tackling the thrombotic complications of COVID-19.

There are several limitations to the current study. Included patients were all suffering from a severe form of pulmonary disease justifying the use of ECMO. Due to the wide geographical catchment areas of the ECMO centres, data availability on treatment prior to transfer is incomplete limiting comment on, or comparison of differences between, pre-transfer treatment approaches between the two groups. The first wave of the COVID-19 pandemic was a national emergency and resulted in an acute increase in intensive care workload. As a result, differences in care may have resulted between the groups as highlighted by the delay in acquisition of the CT in 27% of COVID patients, but only 2% of non-COVID pneumonias. We have attempted to address this issue comparing those with immediate CT scans between the groups but cannot exclude further downstream differences in care which could influence results. Our assessment of perfusion defects was limited to visual assessment of contrast enhanced CT, rather than dedicated dual energy CT which could more directly quantify perfusion. Thus, subtle hypoperfusion will have been overlooked. Indeed a dual energy study in COVID-19 patients on ECMO showed hypoperfusion in all patients despite PAT only being evident in 39%, further supporting a parallel microvascular and macrovascular process (23).

In conclusion, in patients who received ECMO, COVID-19 is associated with a significantly higher prevalence of vascular thrombosis compared to non-COVID viral pneumonias of similar severity. The pattern of pulmonary vascular changes suggests concurrent embolic disease and local small vessel disease with further work required to explore this issue. Despite this, vascular thrombosis was not linked to poorer short-term prognosis in those with COVID-19.

Author contributions:

Jonathan R Weir-McCall, Gabriel Galea, Nicholas Screaton, and Alain Vuylsteke were involved in the design of the study, delivery of the study, interpretation of the results and writing of the report. Sze Mun Mak, Kushal Joshi, Bobby Agrawal, Mark Toshner, Giulia Benedetti, Jan Brozik, Ruth Machin, Indrajeet Das, Marusa Kotnik, Julia Sun, and Luigi Camporota were involved in the delivery of the study and writing of the report. Joseph Jacob, Jonathan CL Rodrigues, were involved in the design of the study and writing of the report. All authors have reviewed the final version of the manuscript.

Declaration of interests:

The authors have no conflict of interest to declare

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Figure 1: Morphological features of pulmonary artery thrombus (PAT), and parenchymal perfusion defects.

In the top two images the PAT exhibits typical characteristic of multiple emboli with central filling defects with peripheral contrast opacification, extending into both branches at a bifurcation points with some of these exhibiting opacification of the pulmonary arteries distally (black arrowheads). In the middle two images there is complete occlusion of the right lower lobe pulmonary artery with a large wedge perfusion defect in an area of severely disease lung. Rather than the classical crescent of a PE, the clot is creeping along the outer edge of the vessel towards a more proximal branch (white arrow). The bottom images demonstrate two examples of parenchymal perfusion defects.

Figure 2: Study flow chart of participants included in the study.