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Letter to the Editors-in-Chief

Three-month follow-up of pulmonary embolism in patients with COVID-19

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Coronavirus disease 2019 (COVID-19) infection has been notable for the occurrence of pulmonary arterial thrombosis, also known as immunothrombosis, in addition to classical pulmonary embolism [1]. The pathophysiology underpinning this appears more platelet-dependent and related to viral-mediated endothelial inflammation, in addition to hypercoagulability [2]. To date, treatment of confirmed pulmonary embolism (PE) has followed established (pre-COVID) venous thromboembolism (VTE) guidelines [3] but it is not known whether the subsequent clinical behaviour of COVID-associated VTE differs from outcomes reported prior to the COVID-19 pandemic.

We have previously reported the rate, clinical characteristics and initial treatment of pulmonary embolus (PE) in a cohort of patients with clinically suspected or confirmed COVID-19 at King's College Hospital [4]. Given that the pathophysiology of immunothrombosis differs to classical pulmonary embolism, the clinical outcomes in these patients may also differ *vis a vis* risks of bleeding or recurrent thrombosis. The primary aim was to describe longer term clinical outcomes from $n = 77$ patients with confirmed COVID and with at least 90 days of follow-up, or earlier death. As patients with severe COVID-19 had further imaging as part of a structured follow up protocol [6], we also report rates of residual thrombosis in this subgroup.

Our approach to anticoagulation for VTE treatment in this cohort was to initiate anticoagulation with therapeutic enoxaparin (or an unfractionated heparin infusion for patients requiring renal replacement therapy with an APTR target of 2–2.5). Patients were then reviewed by the anticoagulation team for the longer-term plan; usually to switch to an oral anticoagulant with recovery, nearer the time of discharge. Outcome data were collected from the Electronic Patient Record (EPR; Allscripts Sunrise™, Chicago, Il) including details of bleeding, recurrent thrombotic events, further imaging performed, choice and duration of anticoagulation. Bleeding complications were defined as per the ISTH definition for major bleeding (MB) encompassing fatal bleeding, symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular bleeding with compartment syndrome) and/or bleeding causing a fall in haemoglobin level of ≥2 g/dl or leading to transfusion of ≥2 units of packed red cells or clinically relevant non-major bleeding (CRNMB; bleeding not meeting previous criteria but requiring intervention or escalation of care) [5]. This data was extracted/confirmed by two authors (RB and LR). All patients surviving to hospital discharge were discharged with a three-month supply of anticoagulants and reviewed in a dedicated Thrombosis clinic, for review of duration of anticoagulation, need for further investigations and counselling regarding future risk of VTE. Patients with severe COVID-19 (admission duration ≥48 h and oxygen requirement ≥ $Fi0_2$ 0.4 or critical care admission) were additionally seen in a specialist respiratory clinic at 4–6 weeks post discharge for comprehensive assessment as per British Thoracic Society Guidance [6]. This includes consideration of pre-contrast high resolution volumetric CT and a CT pulmonary angiogram (CTPA) in those with either persistent CXR changes and/or evidence of physiological impairment on functional assessment (desaturation of ≥4% from baseline) to assess for the presence of both interstitial lung disease and pulmonary emboli. Echocardiogram evaluation is routinely planned at three to six months post PE for patients with evidence of RV strain at PE diagnosis, central PE (without echocardiographic evaluation at diagnosis) and in those with persistent unexplained cardiorespiratory symptoms.

Seventy-seven patients had confirmed PE and COVID-19, of whom $n = 33$ received treatment on the intensive care unit (ICU). Thrombosis was limited to segmental/subsegmental vasculature in $n = 36$ cases (47%). Details of outcomes and follow up are summarised in Table 1. The 28-day survival was 79% and a further $n = 3$ patients died in hospital after 28-days, meaning $n = 58$ (75%) survived to hospital discharge. Cause of death was COVID-19 pneumonia in all cases. Median duration (IQR) of follow-up of survivors (from VTE) was 159 (129–186) days.

Major bleeds occurred seven times in $n = 6$ (7.8%) patients. These were $n = 3$ upper gastro-intestinal (GI); $n = 2$ at bronchoscopy (one fatal); $n = 1$ lower GI; and $n = 1$ chest wall. CRNMB occurred six times in $n = 6$ (7.8%) patients; a total therefore of $n = 8$ (10%) patients experiencing bleeding events. Further details are provided in Table 2. These were confined to patients requiring ICU care: all major bleeds occurred within the ICU during the index hospitalisation. All CRNM bleeds also occurred during index hospitalisation, with only one occurring after ICU discharge. Median time to first bleeding event was 31 days (range 1–62 days) from PE diagnosis.

At hospital discharge, most patients (79%) were treated with direct oral anticoagulants (DOAC) as shown in Table 1. 42 (72%) patients completed a finite course of anticoagulation (median duration 93 days, IQR 84–149). Reasons for continuing anticoagulation included coexistent atrial fibrillation/left ventricular thrombus or persistent VTE risk

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Table 1
Cohort characteristics.

		ICU $n = 33$	Ward $n = 44$	Total $n = 77$
Age (years; [mean, SD])		58.3 (12.1)	66.6 (12.9)	63.1 (13.1)
Day 28-survival, n (%)		23 (70)	38 (86)	61 (79)
Major bleed, n (%)		7 (21)	0	7 (9)
Clinically relevant non-major bleed, n (%)		6 (18)	0	6 (8)
Discharged from hospital, n (%)		20 (60)	38 (86)	58 (75)
Discharged from hospital (n = 58)				
Treatment of PE at hospital discharge	DOAC, n (%)	12 (36)	34 (77)	46 (79)
	Enoxaparin, n (%)	4 (12)	3 (7)	7 (12)
	Warfarin, n (%)	0	1 (2)	1 (1)
	Other[a], n (%)	4 (12)	0	4 (7)
Recurrent VTE, n (%)		0	1	1 (2)
Follow-up CTPA, n (%)		12 (30)	8 (18)	20 (34)
Follow-up CTPA outcome	Clot resolution	7	6	12
	Reduction in clot burden	1	1	2
	Clot persistence (unchanged)	5	1	6
Follow-up echocardiogram, n (%)		6 (18)	7 (16)	13 (22)

CTPA: Computed-tomography pulmonary angiogram, DOAC, direct oral anticoagulant, SD: standard deviation.

[a] 3 completed anticoagulation in hospital (1 enoxaparin, 2 therapeutic iv infusional unfractionated heparin; UFH), 1 transferred to local hospital on therapeutic iv infusional UFH.

factors eg active cancer. One patient (1.7%) had recurrent VTE – a deep vein thrombosis at 195 days (after completion of 3 months anticoagulation).

Follow-up imaging occurred in $n = 20$ (median 105 days [IQR 84–120]), of which $n = 6$ (30%) had residual thrombosis. Echocardiography was performed in $n = 13$, of which one showed raised pulmonary arterial pressures (PE had resolved on imaging). No patients developed evidence of chronic thromboembolic pulmonary hypertension during follow up.

We report the thrombotic and bleeding outcomes at >90-days in patients with confirmed PE and COVID-19. In our cohort, the case fatality rate (in hospital death) was 25% - significantly higher than the 9% reported in a large US series of PE just before the COVID-19 pandemic [7], but broadly comparable with UK in-hospital mortality from COVID-19 of ~30%, over a similar phase of the epidemic [8]. Furthermore, the rate of major bleeding was comparable (9%) to pooled incidence rates reported in meta-analyses of bleeding in hospitalised patients with COVID-19, and lower than that reported in those receiving intermediate/therapeutic anticoagulation (21.4%) [1]. Of note, no major bleeding events occurred after ICU or hospital discharge. Increased haemorrhage could reasonably be considered a result of endothelitis in the acute, severe manifestation of COVID-19 in the ICU.[2] Increased renal failure in ICU will also affect bleeding risk. The use of unfractionated heparin infusion with APTR monitoring may also have contributed to the bleeding rates given reports of under-estimating anticoagulant activity in those with increased fibrinogen/Factor VIII [9]. We did not routinely perform anti-Factor Xa monitoring throughout this period, although four patients with bleeding events on UFH infusions had anti-Factor Xa measured, with results within acceptable limits (data not shown). Whether LMWH would be safer in the critically ill in view of its lesser bleeding risk remains uncertain, particularly in view of potential for accumulation in those with renal impairment.

The low rate for recurrent VTE (1.7%) that we found was similar to that reported following 6 month follow-up (3.9%) of unselected PE ($n = 439$) [10] The high prevalence (30%) of residual thrombus was unexpected in those undergoing repeat imaging. Two prior studies investigated residual thrombosis in unselected PE populations; the ELOPE study reported residual thrombus in 12.2% at 12 months with no relationship to functional impairment [11]. The PROMETHEUS study reported residual thrombus in 15.9% of patients at 6 months [12]. Given the earlier timing of imaging in our study (to facilitate early detection of interstitial lung disease), it's possible residual thrombus further resolved at a later timepoint. However, as these patients did not have evidence of

Table 2
Case descriptions of patients with bleeding events.

Patient	PE extent	MB/ CRNMB	Days post PE diagnosis	Site of bleeding	Anticoagulation	Platelets ($\times 10^9$/l)	Comments
1	R subsegmental	CRNMB	1	Lower GI	UFH infusion	227	CKD, dialysis dependent pre-admission
		MB	19	Lower GI	UFH 5000 units bd	414	On CVVH at time of both events
2	Bilateral segmental and proximal DVT	MB	31	Chest wall haematoma	UFH infusion	121	On peritoneal dialysis
		CRNMB	50	Calf haematoma	UFH infusion	228	On peritoneal dialysis
		MB	99	Bronchial at bronchoscopy	UFH infusion stopped 6 h pre procedure	100	On CVVH Fatal bleed at bronchoscopy
3	R main/lobar	MB	2	Bronchial	UFH infusion	326	Required 2 unit red cell transfusion, unable to remove endobronchial clot at bronchoscopy
		CRNMB	12	Haematuria	UFH infusion	237	Bladder irrigation required
		CRNMB	14	Bronchial	UFH infusion	186	Attributed to known aspergillosis
4	L segmental & proximal DVT	MB	62	GI bleed	UFH infusion	226	Coffee grounds on NG aspirate with >20 g fall in haemoglobin. High APTR at time of bleed
5	Bilateral central	MB	40	Chest wall haematoma	UFH infusion	351	Required 4 unit red cell transfusion. CVVH transitioned to peritoneal dialysis & stopped 24 h prior to bleed Temporary pacing wire in situ
6	Bilateral lobar	MB	1	Upper GI	UFH infusion	341	Coffee grounds on NG aspirate, required 2 unit red cell transfusion
7	Bilateral lobar	CRNMB	39	Haematuria	Therapeutic enoxaparin (0.75 mg/kg bd)	358	Bladder irrigation required
8	L segmental	CRNMB	30	Bronchial	UFH infusion	431	Multiple bronchoscopy for endobronchial clot removal CKD, transitioned from CVVH to peritoneal dialysis

AKI, acute kidney injury; APTR, activated partial thromboplastin ratio; CKD, chronic kidney disease; CRNMB, clinically relevant non major bleeding; CVVH, continuous venovenous haemofiltration; GI, gastrointestinal; ICU, intensive care unit; MB, major bleeding; NG nasogastric; PE, pulmonary embolism; UFH, unfractionated heparin.

pulmonary hypertension, further serial imaging is not planned particularly as the clinical significance of residual thrombus remains uncertain. As in ELOPE, no patient developed CTEPH but this is perhaps unsurprising given the small cohort and short follow-up duration [11]. Following survival to ICU discharge, clinically important outcomes of bleeding and recurrent thrombosis are uncommon and comparable to those reported prior to COVID-19. Therefore, standard anticoagulation strategies appear appropriate.

Addendum

M.B. Whyte data acquisition, data analysis and interpretation, manuscript writing; R. Barker, E. Gonzalez data acquisition, J.R. Czuprynska, R.K. Patel, C. Rea, F. Perrin, M. Waller, C. Jolley data interpretation, P. Kelly and R. Arya study conception and data interpretation. L.N. Roberts study conception, data acquisition, analysis and interpretation. All authors were involved in manuscript revision and approved the final version.

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Declaration of competing interest

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