Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

Image-proven thromboembolism in patients with severe COVID-19 in a tertiary critical care unit in the United Kingdom

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The novel coronavirus 2 (SARS-CoV-2) was first described in Wuhan, China, in December 2019, and causes the infectious disease; COVID-19, which has been declared a pandemic by the World Health Organization. COVID-19 pneumonia may lead to acute respiratory distress syndrome and severe respiratory failure [1]. Other complications include myocarditis, renal failure and neurological involvement [2].

All studies of haemostasis in COVID-19 have identified a prothrombotic state [3–7]. What is apparent from the current literature is that many of the "PE" described on CT pulmonary angiograms (CTPA) are segmental or subsegmental, indeed all the "PE" cases described by Middeldorp [7] fulfilled these criteria. We and others have been concerned that these lesions are not pulmonary emboli but are *in situ* microvascular thromboses (immunothromboses) secondary to the severe inflammation seen within the pneumonic areas of COVID-19 infections [8].

We aimed to assess the prevalence and risk factors for image proven changes of immunothrombosis and venous thromboembolism (VTE) for patients admitted to critical care with COVID-19.

This was a service evaluation approved by the Guy's and St Thomas' NHS Foundation Trust audit department (reference number 10802). We retrospectively identified all patients with COVID-19 admitted to critical care at Guy's and St Thomas' NHS Foundation Trust, London, UK, between 1st March 2020 and 31st March 2020.

All patients were treated with thromboprophylaxis using dalteparin once a day with dose adjustment for patients with renal failure, or who weighed less than 50 kg or more than 100 kg. Patients with VTE had their dose escalated to treatment doses of dalteparin, and those on ECMO received UFH with a target anti-Xa level of 0.3 to 0.7 units/mL for VV ECMO, and 0.6 to 1.0 units/mL for VA ECMO or for those who developed VTE on ECMO. Patients were only investigated for VTE if they were symptomatic.

The primary outcome was the proportion of patients with image–proven thromboembolism. Secondary outcomes were the proportion of patients with: image proven pulmonary embolism (PE); image-proven deep vein thrombosis (DVT); PEs that were central or lobar; DVTs that were line-related; and major bleeding. We also assessed whether there were differences in coagulation parameters (PT, aPTT, Clauss fibrinogen and d-dimer) and inflammatory markers (ferritin, CRP, procalcitonin) between patients with and without VTE; and between those alive at 28 days and those who died.

Follow-up was for 28 days after admission to critical care or until death or when last seen alive. Radiological findings of subsegmental or segmental thrombi in the absence of a DVT were considered to be probable immunothromboses. Clinically relevant major bleeding was defined using modified International Society of Thrombosis and Haemostasis (ISTH) criteria [9].

Data are presented as median; interquartile range (IQR); range for continuous variables and N (%) for dichotomous variables. Where appropriate groups were compared using a 2-tailed Mann-Whitney test for continuous variables or a 2-tailed Fisher's exact test for dichotomous variables. A p-value of less than 0.05 was considered to be statistically significant.

79 patients were admitted to critical care between 1st March 2020 and 31st March 2020 and also had a positive antigen test for COVID-19 (AusDiagnostics Coronaviruses panel). 13 patients were excluded because they had been discharged from critical care before developing symptoms of COVID-19 leaving 66 patients for analysis. Eleven patients were treated with treatment dose anticoagulation (17%) because of ECMO or atrial fibrillation; the other patients were treated with prophylactic renal and/or weight-adjusted dalteparin. Eight patients were treated with ECMO (12%).

Overall, 10 (15%) patients had at least one episode of image-proven thromboembolism (11 in total); there were six (9%) DVT and five (8%) patients with changes on CTPA. Admission characteristics of patients with VTE were compared to those without VTE (Table 1).

10/66 (15%) patients had Doppler ultrasound to assess for DVT, of which six were positive (9% of all patients, 60% of those who had an ultrasound). 19/66 (29%) patients had a CTPA of whom five had a CTPA changes (8% of patients, 26% of those checked). One patient had both a DVT and lobar PE. All six of the DVT were associated with indwelling lines. Four were upper limb DVTs, one lower limb and one both upper and lower limb.

In the five image-proven pulmonary thromboses found, the most proximal veins with thrombosis were: lobar (3), segmental (1) and subsegmental (1). Overall 3/66 (5%) patients had a VTE that was not

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Table 1
Clinical characteristics of all included patients. VTE: venous thromboembolism. Results given are "median; IQR; range" for numeric variables and "N (% of total, excluding missing data)" for binary categorical variables. There were missing values for body mass index (8 patients), time from symptoms to admission (3), duration of hospital admission (4) and duration of critical care admission (4). For diabetes mellitus, two had type I and 25 had type II. Comparisons calculated with Mann-Whitney test for continuous variables and Fisher's exact test for dichotomous variables.

Characteristic		All (N = 66)	No VTE (N = 56)	VTE (N = 10)		Alive (N = 46)	Dead (N = 20)	
Age (years)		59; 49–66; 22–83	59; 52–67; 22–83	54; 45–63; 26–73	p = 0.34	55; 45–64; 22–82	64; 57–72; 22–83	p = 0.01
Gender	Male	48 (73%)	40 (71%)	8 (80%)	p = 0.72	36 (78%)	12 (60%)	p = 0.14
	Female	18 (27%)	16 (29%)	2 (20%)		10 (22%)	8 (40%)	
Body mass index (kg/m^2)		28; 24–34; 19–47	27; 23–34; 19–47	31; 26–33; 21–40	p = 0.46	28; 24–34; 19–47	26; 23–35; 19–46	p = 0.62
Co-morbidities	Hypertension	30 (45%)	25 (45%)	5 (50%)	p = 1.00	21 (46%)	9 (45%)	p = 1.00
	Cardiac disease	7 (11%)	6 (11%)	1 (10%)	p = 1.00	1 (2%)	6 (30%)	p = 0.002
	Diabetes mellitus	27 (41%)	25 (45%)	2 (20%)	p = 0.18	15 (33%)	12 (60%)	p = 0.06
	Chronic kidney disease	9 (14%)	9 (16%)	0 (0%)	p = 0.33	6 (13%)	3 (15%)	p = 1.00
	Chronic lung disease	6 (9%)	5 (9%)	1 (10%)	p = 1.00	4 (9%)	2 (10%)	p = 1.00
	Cancer	5 (8%)	3 (5%)	2 (20%)	p = 0.29	3 (7%)	2 (10%)	p = 0.63
	Previous venous thromboembolism	5 (8%)	4 (7%)	1 (10%)	p = 0.57	3 (7%)	2 (10%)	p = 0.63
Medications	ACE inhibitor	16 (24%)	14 (25%)	2 (20%)	p = 1.00	10 (22%)	6 (30%)	p = 0.54
	Angiotensin II inhibitor	4 (6%)	4 (7%)	0 (0%)	p = 1.00	2 (4%)	2 (10%)	p = 0.58
Covid-19 findings	Pulmonary	60 (91%)	51 (91%)	9 (90%)	p = 1.00	43 (93%)	17 (85%)	p = 0.36
	Myocarditis	24 (36%)	19 (34%)	5 (50%)	p = 0.48	12 (26%)	12 (60%)	p = 0.01
	Acute kidney injury	32 (48%)	26 (46%)	6 (60%)	p = 0.51	18 (39%)	14 (70%)	p = 0.03
Organ support	Non-invasive ventilation	13 (20%)	12 (21%)	1 (10%)	p = 0.67	8 (17%)	5 (25%)	p = 0.51
	Intubation and mechanical ventilation	52 (79%)	43 (77%)	9 (90%)	p = 0.68	38 (83%)	14 (70%)	p = 0.33
	Extracorporeal membrane oxygenation	8 (12%)	5 (9%)	3 (30%)	p = 0.09	5 (11%)	3 (15%)	p = 0.69
	Inotropes	31 (47%)	27 (48%)	4 (40%)	p = 0.74	19 (41%)	12 (60%)	p = 0.19
	Renal replacement therapy	18 (27%)	13 (23%)	5 (50%)	p = 0.12	11 (24%)	7 (35%)	p = 0.38
Time from first symptoms to hospital admission (days)		7; 4–8; 0–20	6; 3–7; 0–20	7; 5–11; 2–14	p = 0.20	6; 4–10; 0–20	7; 4–7; 0–14	p = 0.60
Duration of hospital admission (days)		15; 9–24; 1–56	12; 9–23; 1–45	23; 21–33; 17–56	p = 0.008	21; 11–31; 5–56	10; 5–15; 1–23	p = 0.0003
Duration of critical care admission (days)		9; 3–15; 1–40	8; 3–14; 1–40	17; 11–25; 3–27	p = 0.02	9; 4–17; 1–40	6; 2–11; 1–17	p = 0.07

associated with a line and not thought to be due to immunothrombosis.

Major bleeding occurred in seven cases; of which there were four intracranial bleeds, two pulmonary haemorrhages and one retroperitoneal haemorrhage. 5/7 (71%) of patients with major bleeding were being treated with extracorporeal membrane oxygenation (ECMO). Two patients had both major bleeding and VTE. Two patients not on ECMO had major bleeding: one presented with an acute spontaneous intracerebral haemorrhage and was not on thromboprophylaxis or anticoagulation; the second patient was on enoxaparin 20 mg once a day (low dose thromboprophylaxis due to dialysis-dependent renal-failure) and had a traumatic intracranial bleed after a fall.

There was a significant difference between plasma D-dimer levels on admission to critical care between those who went on to have a VTE (median 69.1 mg/L FEU; IQR 22.0 to 803.5 mg/L FEU) and those that did not (median 2.1 mg/L FEU; IQR 1.1 to 6.7 mg/L FEU; p = 0.005). There were no significant differences in the other laboratory parameters (Table 2).

Overall this cohort of critically ill patients with severe COVID-19 infection had image-proven thrombosis rate of 15% in their first month; although only 5% had a VTE not thought to be line-related or immunothrombosis. Notably 11% patients also had major bleeding. Patients were given thromboprophylaxis with dalteparin with the dose adjusted according to weight and renal function or treatment dose LMWH or UFH because of ECMO or atrial fibrillation.

Other recent cohort studies of VTE risk in severe COVID-19 pneumonia found similar or higher rates of symptomatic thrombosis ranging between 16.7 and 27% [3,4,6]. In each of these cohorts, patients were only investigated if they became symptomatic and all patients were treated with at least standard dose thromboprophylaxis. By contrast, a French study imaged all patients on admission to intensive care with whole leg ultrasound and reported DVT rates of 69% (23%PE). 22% of the DVTs were however superficial thromboses and it was not reported how many were line-related [5]. We are aware of one study that investigated the risk of major bleeding and reported no cases [5].

The patients in our cohort with VTE had a similar mortality rate to those who did not. By contrast, Middeldorp [7] found that VTE was associated with an increased risk of death. 26% patients who underwent a CTPA were found to have a segmental or subsegmental occlusions which they described as PE but probably represent immunothrombosis. These rates are similar to those published in other case series of 22 to 45% [4,6].

D-dimer levels were significantly higher among patients who went on to have a PE than those who did not, although disappointingly the D-dimer levels did not discriminate between those with and without VTE.

A strength of this study is the completeness of the data and the granularity that this has allowed. This is a consecutive cohort and is

Table 2
Laboratory data, on day of critical care admission. Results given are "median; IQR; range" for all variables. Some laboratory results were missing for INR time (2 patients), APTT (2), Clauss fibrinogen (9), D-dimer (30), ferritin (21), CRP (5) and procalcitonin (29). APTT: activated partial thromboplastin time; CRP: C-reactive protein; INR: international normalised ratio; VTE: venous thromboembolism. Comparisons calculated with Mann-Whitney test.

Laboratory parameter	All (N = 66)	No VTE (N = 56)	VTE (N = 10)		Alive (N = 46)	Dead (N = 20)	
Haemoglobin (g/L)	116; 97–136; 7–175	121; 97–137; 8–161	100; 91–112; 7–175	p = 0.12	126; 99–141; 7–175	111; 94–121; 84–153	p = 0.07
White cell count ($\times 10^9$/L)	9.5; 6.9–13.7; 2.8–247.0	9.5; 6.9–13.8; 2.8–247.0	9.6; 7.1–11.0; 6.0–105.0	p = 0.99	9.5; 6.9–13.3; 2.8–247.0	8.8; 6.7–14.7; 3.4–22.1	p = 0.89
Platelet count ($\times 10^9$/L)	207; 154–272; 1–666	200; 152–269; 1–666	239; 180–287; 1–360	p = 0.41	209; 162–287; 1–666	187; 132–263; 78–532	p = 0.60
INR	1.0; 1.0–1.1; 0.9–1.2	1.0; 1.0–1.1; 0.9–1.2	1.0; 1.0–1.1; 1.0–1.2	p = 0.71	1.0; 1.0–1.1; 0.9–1.2	1.0; 1.0–1.1; 0.9–1.2	p = 0.62
APTT ratio	1.2; 1.0–1.4; 0.8–7.7	1.2; 1.0–1.4; 0.8–7.7	1.3; 1.0–1.4; 1.0–7.7	p = 0.43	1.2; 1.0–1.3; 0.8–7.7	1.2; 1.0–1.4; 0.8–2.1	p = 0.53
Clauss fibrinogen (g/L)	6.5; 4.6–7.5; 1.8–10.8	6.5; 4.6–7.2; 1.8–10.8	7.9; 6.3–9.6; 3.0–10.8	p = 0.23	6.7; 4.6–7.6; 2.0–10.8	6.4; 4.6–7.2; 1.8–9.7	p = 0.79
D-dimer (mg/L FEU)	2.4; 1.1–26.2; 0.3–6161.0	2.1; 1.1–6.7; 0.3–2966.0	69.1; 22.0–803.5; 1.2–6161.0	p = 0.005	2.1; 1.0–22.0; 0.3–6161.0	7.8; 1.6–43.7; 1.1–73.4	p = 0.28
Ferritin (mcg/L)	1023; 592–2293; 0–10,111	879; 602–2130; 4–10,111	2101; 711–4667; 0–5968	p = 0.47	885; 592–1992; 0–5968	1889; 744–3850; 273–10,111	p = 0.23
CRP (g/L)	169; 93–330; 1–665	164; 92–285; 1–655	375; 135–441; 1–498	p = 0.09	158; 93–292; 1–557	250; 110–332; 6–665	p = 0.33
Procalcitonin (mcg/L)	1.0; 0.3–3.9; 0.1–68.0	0.8; 0.3–3.1; 0.1–55.7	2.9; 1.0–6.3; 0.1–68.0	p = 0.41	1.0; 0.3–3.3; 0.1–68.0	1.1; 0.7–8.2; 0.2–55.7	p = 0.34

representative of patients who have been admitted to this tertiary care centre. These patients were treated with a thromboprophylactic dose of LMWH once a day with weight adjustment, which appears to be relatively effective at reducing the risk of hospital –associated VTE. Unlike previous studies, the majority of these patients (88%) had been discharged from hospital or died and all had been followed up for 4 weeks or until death.

A shortcoming of this study like all the other early studies on hospital-associated VTE rates in patients with severe COVID-19 infection is that we have not followed them for 90 days post discharge because the risk of VTE persists for at least this long.

What is apparent from this study is that all of the DVT were line related and if we consider that segmental and subsegmental changes on CTPA represent immunothromboses rather than pulmonary emboli, then the rate of hospital-associated VTE seen in our severely ill COVID-19 patients was only 5% using our thromboprophylaxis regime. This is the lowest rate of VTE reported so far in the literature. We think it is important to consider that other papers looking at VTE in COVID-19 may have overestimated rates of VTE including immunothrombosis as PE. Furthermore, there is no evidence that anticoagulation is effective in the prevention of immunothromboses associated with COVID-19, and upstream treatment in the pathogenesis such as treatment to reduce the extent of local inflammation would be more logical.

The ongoing REMAP-CAP trial will investigate outcomes for critically ill patients with COVID-19 pneumonia randomised to treatment dose low molecular weight heparin or unfractionated heparin; or to thromboprophylaxis with low molecular weight heparin and standard or intermediate doses (NCT02735707). Future strategies concentrating on thromboprophylaxis regimens to reduce rates of hospital-associated VTE are recommended but we advise caution with use of treatment dose anticoagulation for patients without VTE outside clinical trials due to a significant bleeding risk.

Contributions

MJRD wrote the manuscript. MJRD, AJD, AR, BJH & KAB jointly devised the project and extracted data for analysis. AG & MD did the statistical analysis. All authors critically revised the final manuscript.

Declaration of competing interest

MJRD has received fees for consultancy from Takeda and Portola. None of the other authors have any competing interests to declare.

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