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.

remimazolam was infused at 12 mg kg^{-1} h^{-1} until tracheal intubation was completed because of concerns for anaesthesia awareness. Our experience indicates that when remimazolam is administered at this high infusion rate, anaesthesiologists should be aware of the possibility of anaphylaxic reactions triggered by non-IgE-mediated mechanisms.

Our case series suggests that remimazolam, which contains dextran 40, can trigger non-IgE-mediated anaphylaxic reactions. Anaesthesiologists should be aware that higher infusion rates could be associated with such reactions. Further prospective study is needed to determine the prevalence and risk factors of anaphylactic reactions to remimazolam.

Authors' contributions

Study design: JYB, BMC
Data collection: KMK, HL
Data analysis and interpretation: KMK, JYB, GJN
Contributed to the writing of the manuscript, provided critical revisions, and approved the final version: all authors.

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.07.047.

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Prevalence of pulmonary embolism and deep venous thrombosis during the COVID-19 pandemic in an intensive care unit cohort: a service evaluation

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Keywords: anticoagulation; COVID-19; deep venous thrombosis; hypercoagulability; pulmonary embolism

Editor—Both deep venous thrombosis (DVT) and pulmonary embolism (PE) are common in critically ill patients on the ICU. Nevertheless, a higher-than-expected incidence of thrombotic complications, particularly in the pulmonary circulation, has been observed in the context of COVID-19 infection,[1–3] where *in situ* thrombosis, as opposed to embolisation from peripheral vessels, is the postulated mechanism for the large thrombotic burden.[4] The high prevalence of thrombosis in COVID-19 has also contributed to a debate about the appropriate intensity of anticoagulation appropriate for this cohort: prophylactic, intermediate or therapeutic.[5,6] At the Royal Free Hospital (London, UK), all patients admitted to ICU were on standard dose thromboprophylaxis with low molecular weight heparin, although practice varied widely across London hospitals at the time.

Table 1 Comparative table showing relevant clinical and physiological details in patients with and without pulmonary embolism (PE) and with and without deep venous thrombosis (DVT). APACHE II, Acute Physiology and Chronic Health Evaluation II; CVVH, continuous veno-venous haemofiltration.

Patient characteristics	Total (n=70)	Pulmonary embolism (n=30)	No pulmonary embolism (n=40)
Male (%)	43 (61.4)	20 (66.7)	23 (57.5)
Average age (yr)	62	62.9	61.3
BMI (kg m^{-2})	28.9	27.7	29.8
Co-morbidities, *n* (%)			
Cardiovascular disease	14 (20)	5 (16.7)	9 (22.5)
Hypertension	38 (54.2)	12 (40)	26 (65)
Diabetes mellitus	31 (44.2)	16 (53.3)	15 (37.5)
Previous VTE	2 (2.8)	1 (3.3)	1 (2.5)
Current cancer	6 (8.6)	1 (3.3)	5 (12.5)
Organ support, *n* (%)			
Mechanical ventilation	66 (94.3)	29 (96.7)	37 (92.5)
Therapeutic paralysis (ever)	62 (88.6)	27 (90)	35 (87.5)
Proning (ever)	53 (75.8)	19 (63.3)	34 (85)
PO_2/Fio_2 ratio (kPa)	24.01	23.9	24.1
Current noradrenaline	42 (60)	21 (70)	21 (52.5)
Current inotrope	5 (7.1)	3 (10)	2 (5)
Current CVVH	12 (17.1)	4 (13.3)	8 (20)
Femoral line	26 (37.1)	10 (33.3)	16 (40)
APACHE II	14 (11, 17)	14 (11,17)	14 (11,18)
Admission			
Average length of hospital stay before ICU admission (days)	3.4	3.4	3.4
Average ICU length of stay before Doppler ultrasound (days)	18.8	19.4	18.4
Deep vein thrombosis, *n* (%)			
Above knee	6 (8.6)	4 (13.3)	2 (5)
Below knee	35 (50)	20 (66.7)	15 (37.5)
None	29 (41.4)	6 (20)	23 (57.5)

Another uncertainty regards the frequency and distribution of PE within the pulmonary circulation in patients with COVID-19 as well as its association with co-existing DVT.[7,8] If peripherally located clot burden within the pulmonary circulation reflects *in situ* thrombosis, it would less likely be associated with DVT. Conversely, embolisation of clot via the deep veins might be associated with a more centrally located clot burden.

To address these questions and facilitate development of local thromboprophylactic guidelines, we performed a service evaluation with the objective of comprehensively capturing the prevalence of PE and DVT in our ICU during the second wave of COVID-19 in the UK. From our experience in the first wave, all mechanically ventilated patients with COVID-19 had computed tomography pulmonary angiograms (CTPA) where clinically feasible. Complementing this, we screened 70 consecutive ICU patients over 1 week for DVT with full-length duplex ultrasonography of both legs. As a service development, the national research ethics committee does not require ethical approval. For the purposes of our evaluation, DVT was grouped into below or above knee; PE into central/lobar or segmental/sub-segmental, consonant with objective radiological and anatomical criteria.

The overall prevalence of thrombosis was 47/70 (67%): 30/70 (43%) for PE and 41/70 (59%) for DVT above or below knee (Table 1). The location of PE was evenly divided: 14/30 (49%) were located centrally in a main/lobar pulmonary artery. The remaining 16/30 (51%) were peripheral, segmental/sub-segmental. All above knee DVT associated with PE (four/six) were associated with proximal pulmonary artery thrombus (main trunk or lobar), suggesting an embolic origin. Notably, seven/35 (20%) of patients with below knee DVT also had PE located in main/lobar vessels. The remaining 13/35 (38%) of patients with below knee DVT had concomitant sub-segmental PE.

This service evaluation of DVT and PE in an ICU cohort is the first (to our knowledge) to document location of PE with location of DVT systematically in all studied patients. We showed that prevalence of both DVT and PE was more than double that previously reported in other COVID-19 patient cohorts.[9] In addition, below knee DVT was associated with peripherally located PE; 13/16 (81%) of peripheral PE had co-existing below knee DVT whereas more than one-third of below knee DVT was associated with sub-segmental PE. Thus, the presence of a below knee DVT appears to be a marker for *in situ* thrombosis/COVID-19 thrombotic phenotype. This is a significant observation because below knee DVT is traditionally regarded as of limited clinical relevance in a non-COVID-19 context.

Duplex ultrasonography is a readily available technique applicable to all levels of illness acuity, and the utility of a positive scan to inform escalation of anticoagulation to therapeutic dose until a CTPA can be performed should be explored. Those patients with DVT are more likely than not (20/35 [57%] *vs* 15/35 [43%], unadjusted relative risk [RR]= 1.32) to have PE or potentially to develop one over time. Secondly, the complete absence of DVT (29/70) would reassure the clinician that the patient is less likely to have PE (unadjusted RR ~ ×4 or 23/29 *vs* six/29 patients) at that time.

This service development study may also have implications for more resource-challenged settings where obtaining

CTPA to rule out PE is not possible. A duplex scan, which might more easily be performed, could be a useful surrogate marker of clot burden and thrombotic risk, which might trigger a life-saving decision to institute therapeutic anticoagulation.

This survey cannot infer causation. The temporal link between PE and DVT is difficult to establish as many patients had duplex scans relatively late into their ICU stay, but the length of ICU stay before duplex scan was the same in both sets of patients with and without PE (19.4 *vs* 18.4 days). In addition, a large number of patients (23%) had their CT scans >14 days after admission to ICU such that the interval between duplex scan and CT scan would have been closely related. The relative paucity of patients (<100) included precludes a more formal statistical treatment of the data; nevertheless the crude, two-way associations of below knee DVT with sub-segmental PE is a novel and striking observation. Finally, the high proportion of DVT in our survey may call into question the generalisability of our cohort. However, other studies comparing DVT and PE only screened between 10% and 30% of patients within the first 10 days of ICU stay (as opposed to an average of 18 days in our survey) leading to a much lower detected prevalence and the possibility of type II error. We believe that screening 100% of patients in our survey leads to a prevalence that is both accurate and consistent with previous data and in keeping with the biology[4] and known epidemiology of disease, with a risk of DVT present for up to 110 days after COVID-19 diagnosis.[10]

In summary, this service development study shows an association of DVT (both above and below knee) and PE (central *vs* sub-segmental) in an ICU cohort of patients with COVID-19. We report a very high prevalence of venous thrombosis. There was a notable association between presence of below knee DVT and sub-segmental PE which could have important treatment implications. Below knee DVT should not automatically be assigned as benign and could be a marker for thrombogenicity. Routine duplex ultrasonography scans warrant further exploration as a triage tool to inform intensity of anticoagulation in COVID-19 ICU patients and to expedite prompt investigation of the pulmonary vasculature.

Declarations of interest

The authors declare no conflicts of interest.

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Borderline *P*-values in critical care trials: time for a paradigm shift

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