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LETTER TO THE EDITOR

Screening for venous thromboembolism in COVID-19 patients on the intensive care unit

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Abstract

Thromboembolic complications are frequently encountered in patients with severe COVID-19 disease in the intensive care unit (ICU). We assessed the prevalence of venous thromboembolism (VTE) in critically ill COVID-19 patients treated with dexamethasone and intensified thrombosis prophylaxis. To detect VTE, venous duplex ultrasonography was performed on day one and six of ICU admission, in addition to thoracic computed tomography angiography at ICU admission. Data from 57 consecutive patients were analysed and in 24 (42%) patients we detected a VTE. D-dimer levels were not useful to distinguish between patients with or without VTE; however, highly elevated D-dimer may indicate the presence of VTE. We report a high prevalence of VTE in critically ill COVID-19 patients despite intensified thrombosis prophylaxis and dexamethasone.

Dear editor,

Despite thrombosis prophylaxis, complications of venous thromboembolism (VTE) are encountered in 28% of the COVID-19 patients admitted to the intensive care unit (ICU).[1] In contrast to studies early in the COVID-19 pandemic, ICU patients are currently treated with dexamethasone and intensified thrombosis prophylaxis. However, this may result in comparable thrombosis complication rates.[2]

Recently, three randomised clinical trials on full-dose versus prophylactic anticoagulation in COVID-19 have ceased enrolment of ICU patients because potential harm of full-dose anticoagulation could not be excluded.[3] Therefore, accurate selection of patients who benefit from timely full-dose anticoagulation is warranted, such as by using biomarkers, thoracic computed tomography angiography (CTA) and/or venous duplex ultrasonography (VDUS). CTA screening for pulmonary embolism (PE) is challenging for logistical reasons during high oxygen support, but screening by VDUS is easily conducted and has the potential to timely detect VTE. While previous reports suggest the use of D-dimer levels to exclude VTE,[4,5] a retrospective study on biomarkers in Dutch COVID-19 patients reported the ability of D-dimer levels of <3.0 µg/ml to rule out VTE to be only 67%.[6]

We assessed VTE prevalence and associations with D-dimers concentrations in critically ill COVID-19 patients treated with dexamethasone and intensified thrombosis prophylaxis. We treated 73 COVID-19 patients on our ICU between 12 October 2020, and 12 January 2021. Seven patients were not eligible as their primary reason for admission was not COVID-19 pneumonia; they were admitted for a different reason and were asymptomatic COVID-19 patients. Nine patients could not be included because of transfer from another ICU after day six, or early transfer to another ICU due to lack of ICU capacity. In total, 57 patients were included for analysis. All were treated with dexamethasone 6 mg daily and six patients randomised in the REMAP-CAP trial received a single dose of tocilizumab (8 mg/kg). Patients received intensified prophylactic low-molecular-weight heparin (LMWH): nadroparin 2,850 IU twice daily for patients with a bodyweight <100 kg and 5,700 IU twice daily for those ≥100 kg. Only patients requiring full anticoagulation therapy (e.g. patients with atrial fibrillation) received LMWH at therapeutic anticoagulation dosages. Patients were screened for deep venous thrombosis (DVT) around ICU day one and six by bilateral VDUS of the femoral, popliteal, jugular and subclavian veins. Diagnosis of PE was established by CTA within 24 hours of ICU admission and repeated if respiratory deterioration occurred and patients were not on full therapeutic anticoagulation. D-dimer concentrations were measured using immunoassay (Sysmex® CS-5100, Siemens Healthcare Diagnostics) and obtained within 24 hours of VDUS

Table 1. Comparison between critically ill COVID-19 patients in the ICU with and without detected venous

	All patients *n* =57	VTE patients *n* = 24	Non-VTE patients *n* = 33	*p*-value
Patient characteristics				
Age, years, median [IQR]	71 [64-76]	71 [61-75]	71 [66-77]	0.789
BMI, kg/m^3, median [IQR]	29.5 [26.1-32.2]	29.2 [26.5-32.0]	29.7 [26.1-32.4]	0.981
Male, n (%)	38 (69)	21 (88)	17 (52)	0.005
Indication for anticoagulation prior to hospital admission, n (%)	6 (11)	2 (8)	4 (12)	0.645
SOFA, median [IQR]	5 [4-6]	5 [4-6]	5 [4-6]	0.242
APACHE IV, mean (SD)	66 (17)	65 (14)	67 (19)	0.603
Main comorbidities, n (%)				
Cardiovascular disease	11 (19)	6 (25)	5 (15)	0.352
Cerebrovascular disease	4 (7)	3 (13)	1 (3)	0.167
Diabetes mellitus type 2	16 (28)	8 (33)	8 (24)	0.451
Hypertension	22 (39)	11 (46)	11 (33)	0.339
Chronic respiratory disease	18 (32)	8 (33)	10 (30)	0.808
Active malignancy	3 (5)	1 (4)	2 (6)	0.752
ICU characteristics				
ICU admission from ED, n (%)	20 (35)	9 (38)	11 (33)	0.745
DNI order, n (%)	7 (12)	2 (8)	5 (15)	0.439
HFNC during ICU admission, n (%)	46 (87)	19 (91)	27 (84)	0.521
Invasive mechanical ventilation, n (%)	33 (58)	17 (71)	16 (49)	0.092
Treatment with tocilizumab, n (%) *	6 (11)	5 (21)	1 (3)	0.031
Length of ICU stay, days, median [IQR]	9 [6-18]	17 [7-24]	8 [6-14]	0.008
ICU mortality, n (%)	11 (22)	4 (21)	7 (22)	0.945
Laboratory characteristics at ICU admission				
CRP (mg/l), median [IQR]	138 [62-204]	138 [93-204]	137 [58-204]	0.831
Ferritin (µg/l), mean (SD)	1100 (638)	1094 (734)	1104 (574)	0.955
LDH (U/l), mean (SD)	502 (163)	518 (184)	492 (149)	0.571
Fibrinogen (g/l), mean (SD)	6.0 (1.8)	5.3 (2.1)	6.6 (1.3)	0.034
Neutrophil-to-lymphocyte ratio, median [IQR]	10.9 [6.5-16.0]	9.4 [6.7-16.3]	11.5 [5.2-16.2]	0.948
Platelets count (x10^9/l), median [IQR]	242 [193-293]	235 [171-267]	268 [195-379]	0.170
D-Dimer (µg/ml), median [IQR] thromboembolism	1.32 [0.82-3.08]	2.13 [0.87-10.11]	1.16 [0.81-2.32]	0.062

Continuous variables are presented as mean (standard deviation) and compared using a Student t-test or as median [interquartile range] and compared using a Mann Whitney U test. Categorical variables are presented as number (percentage) and compared using a χ^2 test.
IQR = interquartile range; SD = standard deviation; VTE = venous thromboembolism; ICU = intensive care unit; BMI = body mass index; SOFA = Sequential Organ Failure Assessment; APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; ED = emergency department; DNI = do-not-intubate; HFNC = high flow nasal cannula; CRP = C-reactive protein; LDH = lactate dehydrogenase.

* In three patients presence of VTE was detected previous to administration of tocilizumab of which in one patient a DVT was detected by primary VDUS in the same vein as documented in the past medical history. One patient who had received tocilizumab had a negative VDUS and CTA for VTE at ICU admission with a D-dimer concentration of 4.73 µg/ml. On day six of ICU admission, D-dimer concentration was 17.96 µg/ml and the iteration of thoracic CTA revealed the presence of PE.

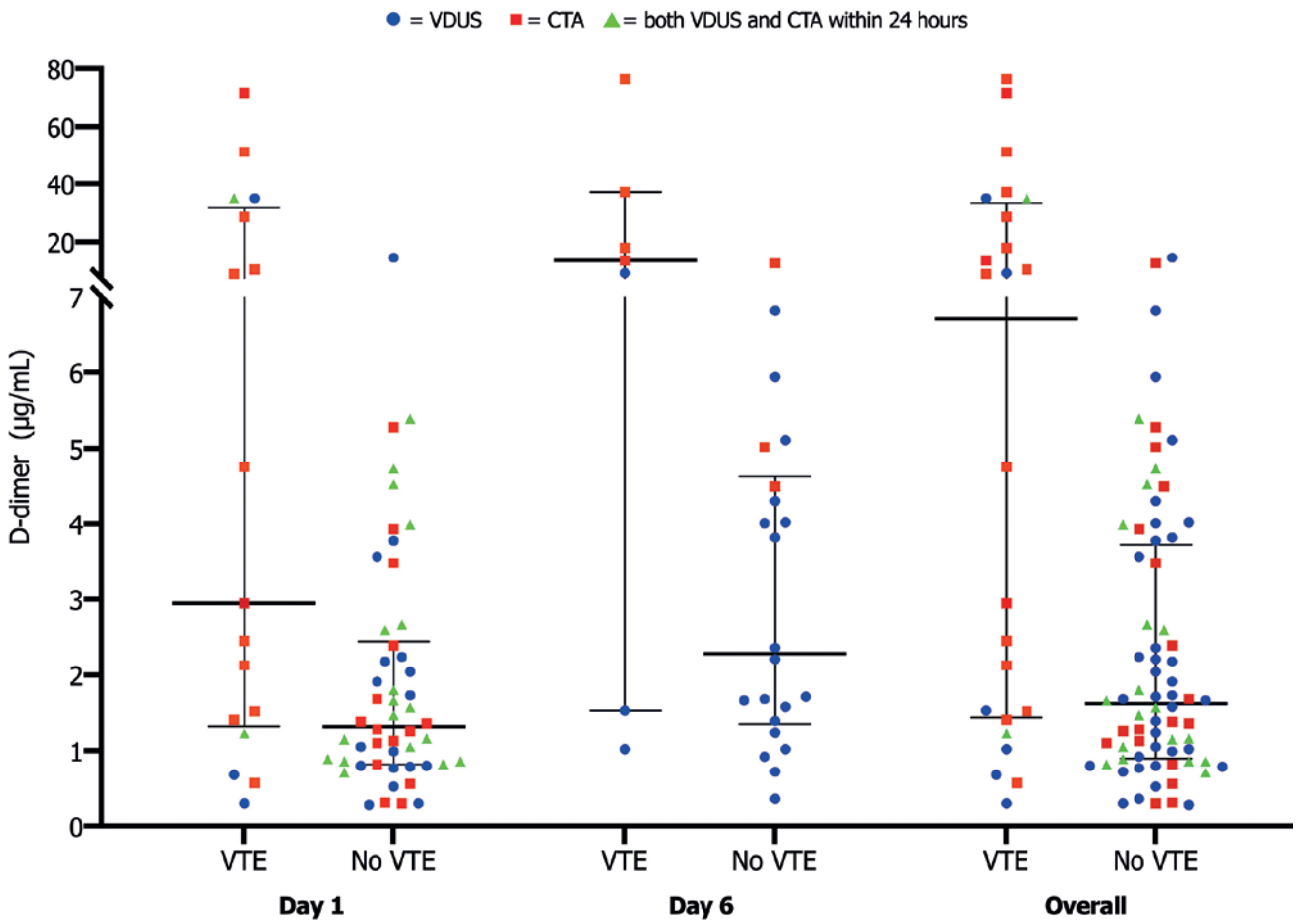

Figure 1. D-dimer concentrations in patients with and without detected venous thromboembolism
Bars and error bars present median and interquartile range. VTE = venous thromboembolism; VDUS = venous duplex ultrasonography; CTA = computed tomography angiography. CTA was not performed in three patients as these were already receiving full-dose anticoagulation, in two because of starting palliative care and one because of emergent transfer to another hospital. In total, 87 VDUS were performed. Secondary VDUS was not performed in 19 patients due to lack of ICU dependency on day 6; and in 8 patients because of a switch to full-dose coagulation during ICU admission due to positive CTA for pulmonary embolism

and CTA. Detection of DVT or PE was followed by escalating to LMWH at therapeutic anticoagulation dosages. This study was performed according to the 1975 Declaration of Helsinki (version 2008). The institutional research committee approved the study protocol and waived the need for informed consent due to anonymous data handling and the usage of observational data.

We detected a VTE in 24 (42%) patients: five with DVT, 17 with PE and two combined. VDUS around day 6 revealed two new DVTs in mechanically ventilated patients with negative CTA for PE, both related to central venous catheter positioning. Characteristics of all patients and comparison between patients with and without VTE regarding patient, ICU and laboratory characteristics are presented in *table 1*. Except for male sex, no significant differences in demographics were observed between patients with and without VTE.

Individual D-dimer concentrations in patients with and without VTE are depicted in *figure 1*. Diagnostic performance analysis of D-dimer in the diagnosis of VTE showed an area-under-the-receiver-operating-characteristic curve of 0.72 (95% CI 0.58-0.85). The optimal cut-off value of D-dimer levels to predict VTE was >7.0 µg/ml with a positive predictive value of 0.86 (95% CI 0.54-0.97), sensitivity of 0.48 (95% CI 0.27-0.69) and specificity 0.97 (95% CI 0.89-0.99).

In conclusion, in this cohort study in critically ill COVID-19 patients treated with intensified thrombosis prophylaxis and dexamethasone, we demonstrate that the prevalence of VTE, detected by both CTA and VDUS at ICU admission, remains similar to previous reports from early in the global pandemic.[1] These findings are in line with a recently published Dutch multicentre study.[2] In contrast to their report, we found a higher incidence of VTE. However, we performed a routine VTE screening strategy at ICU admission. Since isolated asymptomatic DVT occurred in our cohort, we found VDUS alongside thoracic CTA to contribute to detecting presence of VTE. Additionally, DVT in COVID-19 may present without classical clinical signs as is seen in non-COVID-19.[2] Therefore, screening by VDUS may be considered standard of care in COVID-19 patients on prophylactic LMWH with a negative CTA for PE. Also, patients on high, non-invasive oxygen support may benefit from early detection of VTE by VDUS as CTA can be unfeasible in these circumstances. D-dimer concentrations in our COVID-19 ICU patients varied markedly among VTE and non-VTE patients, which means this marker is not useful to rule out VTE. Nevertheless, highly elevated levels of D-dimer (>7.0) may indicate presence of VTE. Subsequently, CTA or VDUS should be repeated, depending on clinical signs. In case of increasing D-dimer levels together with respiratory deterioration during ICU admission we repeat CTA. If CTA is not feasible or signs of PE are absent, VDUS is performed to detect DVT. It seems reasonable to assume that this screening strategy and consecutive treatment of detected venous thrombosis improves patient outcome, but this warrants investigation in a clinical trial.

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Disclosures

This study was performed in accordance with the ethical standards of the institutional research committee.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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