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Letter to the Editors-in-Chief

Asymptomatic deep vein thrombosis in critically ill COVID-19 patients despite therapeutic levels of anti-Xa activity

To the Editors-in-Chief:

Patients with severe COVID-19 pneumonia might experience a high cumulative incidence of thrombotic complications [1], due to coagulopathy, excessive inflammation, and vascular endothelial dysfunction [2]. Data regarding the incidence of deep vein thrombosis (DVT) in this patient subset, without clinical signs of venous thromboembolism (VTE), has not been deeply analyzed even though these patients are at higher risk of death [3]. Furthermore, thrombotic complications have been found in up to 31% of patients in the intensive care unit (ICU) despite systematic thromboprophylaxis [4,5]. A recent report has also addressed the incidence of asymptomatic DVT in hospitalized patients with COVID-19 [6], where screening ultrasound examination was performed > 72 h after admission, describing a DVT prevalence as high as 46.1%. Interestingly, 37.1% of patients were only given DVT prophylaxis, and 41.3% of patients received full-dose low-molecular-weight heparin (LMWH) therapy only after DVT ultrasound findings.

Thromboprophylaxis and high prophylactic doses have been the mainstay of treatment for VTE in COVID-19 hospitalized patients. Recommendations are based on the typical non-COVID-19 high VTE risk factors, and additional hypercoagulable state in severe COVID-19 [4,7]. Those rely on clinical suspicion, abrupt laboratory, or hemodynamic changes that are usually late VTE signs or have an emergency onset, not ideal for patients' prognosis. Nevertheless, in this highly inflammatory novel viral illness, little has been explored of the role of screening ultrasound in patients admitted to the intensive care units (ICU) and the anticoagulation monitoring status by the time DVT is diagnosed.

We decided to (i) describe the clinical and ultrasonographic characteristics of patients critically ill COVID-19 who developed DVT during the stay at the ICU, and (ii) compare the characteristics of those with DVT against those who remained without DVT during the ICU stay. We performed a single-institution clinical and imaging screening to 30 critically ill COVID-19 patients admitted to the ICU, not suspected to have any VTE neither clinically nor calculated by a modified Well's scale. The Institutional Ethics Committee approved the study, and all patients had informed written consent on admission.

Calf diameter was measured 10 cm below the tibial tuberosity, and patency of the superficial and deep venous system was evaluated with bedside compression ultrasound (C-US) and high-resolution mode B imaging (Sonoscape X5 Digital Color Doppler Ultrasound System equipped with an L741 Frequency Linear probe: 4.0–16.9 MHz). More than 3 cm of difference between calf sizing was considered significant along with the presence of unilateral swelling or pitting edema. The ultrasonographic examination included saphenous veins and its junctions, calf, popliteal, femoral, and iliac veins (assessed by phasicity and augmentation responses). DVT was defined as a non-compressible venous segment with or without echogenic thrombus within the lumen, increased venous diameter, or absence of spectral color Doppler signal. The echocardiographic assessment was performed in all patients found to have DVT with the same ultrasound system but equipped with a 3P-A probe (Frequency 1.0–6.0 Sweep sector: 90°).

All patients had COVID-19 diagnosis since admission and were considered as having high thrombotic risk (Padua score > 4) and received anticoagulation since day 1. Those with lower Padua scores received high-prophylactic doses; otherwise, they received full-dose anticoagulation. The anticoagulation scheme was instaurated either with LMWH (Enoxaparin) or unfractionated heparin according to the glomerular filtration rate. A multidisciplinary consensus was created for careful decision-making in prescribing anticoagulation in high IMPROVE bleeding score patients. Anti-factor-Xa Assay (Stago®) was systematically performed for anticoagulation monitoring and adjustment in obese patients (n = 12) and those with acute renal failure (n = 20) [8]. Platelet activity was also monitored in those found to have DVT despite therapeutic anti-factor-Xa activity, with Multiplate ® due to its possible role when interacting with endothelial cells in the development of thrombosis and micro thrombosis in organs and tissues other than lungs [9].

Among the 30 evaluated patients, 30% developed asymptomatic DVT (Table 1). Patients in both groups had a high prevalence of the risk factors associated with severe SARS-Cov-2 pneumonia (age above 50 years old, male sex, hypertension, diabetes, obesity). None of them had previous chronic obstructive pulmonary disease or asthma. Few patients had previous cardiovascular disease: chronic heart failure (n = 2), acute myocardial infarction (n = 1), and cardiac surgery (n = 2). None of the patients had myocarditis, and only one had a previous VTE (non-DVT group). There were no differences in smoking between groups (33% vs. 48%, p = 0.691). All patients had mechanical ventilatory support.

Few patients in both groups had clinical signs of chronic venous

Abbreviations: VTE, Venous thromboembolism; DVT, Deep vein thrombosis; LMWH, Low molecular weight heparin; UFH, Unfractionated heparin; ICU, Intensive care unit; DD, D-Dimer; HS-CRP, High sensitivity C-Reactive protein; LDH, Lactate Dehydrogenase; PT, prothrombin time; aPTT, activated partial thromboplastin time; ASA, Acetylsalicylic acid; ADP, adenosine diphosphate

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Table 1
Comparison between patients with and without DVT. Data are shown as median (minimum-maximum) or as number of patients (percentage).

Variable	Deep vein thrombosis		p
	Yes (N = 9)	No (N = 21)	
Age (years)	64 (39–79)	61 (33–74)	0.454
Male sex	8 (89%)	15 (71%)	0.297
Diabetes mellitus	2 (22%)	11 (52%)	0.393
Hypertension	5 (56%)	6 (29%)	0.229
Body mass index (Kg/m^2)	30.0 (23.5–43.0)	27.0 (20.4–40.2)	0.141
Obesity (class I or higher)	6 (66%)	6 (29%)	0.224
Previous heart disease	1 (11%)	4 (20%)	0.634
High sensitivity CRP (mg/L)	342 (264–463)	307 (73–521)	0.428
D-Dimer on admission (μg/mL)	0.80 (0.24–15.2)	0.46 (0.17–0.96)	0.021
D-Dimer max value (μg/mL)	6.30 (1.00–15.20)	0.90 (0.25–4.68)	< 0.001
D-Dimer duplication	6 (67%)	11 (52%)	0.691
D-Dimer value > 1440 μg/mL	8 (89%)	6 (29%)	0.004
Thrombocytopenia (< 150 × 10^3/μL)	3 (14%)	1 (11%)	1.000
Lymphopenia (< 990 cel/μL)	9 (100%)	21(100%)	–
Elevated fibrinogen (> 5.13 g/L)	9 (100%)	14(66%)	0.710
PT (s)	12.0 (10.0–14.7)	12.0 (10.0–19.0)	0.818
aPTT (s)	30.7 (26.0–40.0)	33.0 (26.0–61.0)	0.174
Lactic dehydrogenase (mg/dL)	443 (269–685)	357 (251–900)	0.230
Ferritin (ng/mL)	920 (377–1481)	1172 (163–3911)	0.308
LMWH (enoxaparin)	8 (89%)	18 (86%)	1.000
Full dose anticoagulation	9 (100%)	8 (86%)	0.534
Antiviral treatment	8 (89%)	19 (91%)	1.000

CRP = C reactive protein; PT = prothrombin time; aPTT = activated partial thromboplastin time; LMWH = Low molecular weight heparin.

disease (22% vs. 5%, p = 0.207). On clinical evaluation, none of the patients had unilateral edema or a calf diameter difference > 3 cm; neither of them had thrombosis at < 1 cm of saphenofemoral junction or saphenous thrombophlebitis. DVT was predominantly distal, located in gastrocnemius or soleal veins, while only one patient had proximal DVT.

Notably, DVT was bilateral in 55% of patients (Table 2). DVT patients were treated with norepinephrine (N = 7), acetylsalicylic acid (N = 2), and lopinavir/ritonavir (N = 7). All DVT patients had a Padua score between 5 or 6, and all except 1 had IMPROVE bleeding scale between 5 and 9.5, as well as low risk modified Wells' criteria. Bilateral respiratory phasicity was preserved in every DVT patient and 86% of patients without DVT. The echocardiographic assessment was irrelevant in all DVT patients without indirect signs suggestive of pulmonary embolism.

Both groups presented with lymphopenia and a highly inflammatory, prothrombotic state without coagulopathy (Table 1). Although the D-dimer was elevated above 0.240 μg/mL in all patients with DVT and 95% of patients without DVT, the median values of D-Dimer were higher in the DVT group compared to the group without DVT (Table 1), abrupt increases in D-Dimer were no different between groups (Table 2).

Every patient in the DVT group and 86% of the non-DVT group received full-dose anticoagulation (p = 0.534). The remaining 14% received high-prophylactic doses. Most patients were treated with Enoxaparin (Table 1). Notably, DVT occurred despite therapeutic levels of anti-Xa activity in patients receiving LMWH and optimal PTT in a patient with chronic renal failure on a continuous unfractionated heparin IV infusion (Table 2). All DVT patients were tested for platelet function using a commercially available aggregometry test [10]. Two DVT patients had increased platelet function and were additionally treated with aspirin.

There were no major bleeding events and only 4 minor bleeding events (all in the non-DVT group). There was no significant difference between groups in mortality (33% vs 14%, p = 0.329), in-hospital stay: 3 (1.0–17.0) vs 8.0 (1.0–27.0) days (p = 0.104), and intensive care unit stay: 2.0 (1.0–17.0) vs 7.0 (1.0–26.0) days (p = 0.349).

Thrombotic events have outstandingly been reported in recent autopsies performed in COVID-19 patients. One-third of the patients had massive pulmonary embolism as the cause of death and associated DVT in 25% of them [11]. Contributions of pulmonary embolism, DVT, and their combination are unaddressed. C-US may decrease its sensitivity in calf veins; some additional maneuvers we described can supply supportive thrombus evidence. Nevertheless, it remains a readily available tool in severe COVID-19, where venography or other imaging studies are not feasible. Our findings must encourage early detection of these complications and possibly a paradigm change in our COVID-19 disease approach currently based on clinical, hemodynamic, and laboratory findings.

Despite the limited power of our sample size, it seems that neither clinical nor laboratory findings suggest the presence of DVT, not even the inflammatory parameters suggested to be associated with increased risk. In fact, all COVID-19 patients studied had similarly elevated inflammatory features. In highly inflammatory prothrombotic scenarios such as SARS-Cov-2, anti-Factor-Xa activity monitoring should be considered a useful tool to titrate anticoagulation in critically ill patients who are frequently obese and present with acute renal failure; and also to determine which patients may benefit from platelet activity supervision. Most advanced parameters related to platelet function and activity are still pending assessment. The later may complete the hyperactivation of coagulation and the thrombotic events in severe COVID-19 patients [9].

Unexpectedly, thrombosis was frequently found in both legs, even though VTE's classics are usually unilateral. Highly elevated D-Dimer value was the only factor associated with DVT. Moreover, abrupt changes proposed to increase VTE risk in COVID-19 patients were similar in both groups. We also observed that DVT, despite therapeutic anticoagulation, is common in critical patients with severe SARS-Cov-2 pneumonia. Resulting in substantially higher thrombotic events than other critically ill patients, that may require a more aggressive anticoagulation scheme.

The mechanisms contributing to DVT in fully anticoagulated patients and the laboratory and clinical factors associated remain unclear. Tropism of this coronavirus to endothelial tissue, secondary to high expression of angiotensin-converting enzyme 2, may play a role in the thrombosis pathogenesis of these optimally anticoagulated patients [9,12]. Thus, direct endothelial damage may intervene. As long as the thrombotic mechanism remains imprecise, in highly inflammatory prothrombotic scenarios such as SARS-Cov-2, timely immune modulation with cell-mediated and humoral strategies to avoid the COVID-19 cytokine storm syndrome and the associated complications should be considered, along with the measurement of other pro-inflammatory markers [13].

Clinical examination has low accuracy for diagnosing DVT in fully anticoagulated critically ill COVID-19 patients. Compression ultrasound is a useful screening tool in this asymptomatic group of patients to identify DVT and potentially prevent pulmonary embolism, already known to increase mortality rates. Highly elevated D-Dimer levels are associated with DVT findings. Our results show that thrombosis occurs despite therapeutic levels of anti-Factor-Xa activity. Whether these findings suggest that full-dose anticoagulation may not be enough in this subset of patients requires further investigation. Anticoagulation monitoring and aggregometry in selected cases may be beneficial in severe COVID-19. The clinical significance of asymptomatic DVT in patients with severe SARS-Cov-2 pneumonia and the mechanisms involved in these thrombotic events occurring under optimal anticoagulation warrant further study.

Table 2
Relevant findings and treatment of patients with DVT.

Patient	1	2	3	4	5	6	7	8	9
Affected limb	R	Bi	L	R	R	Bi	Bi[a]	Bi	Bi
Laboratory									
DD (0.0–0.24 μg/mL)	0.9	0.5	15.2	0.5	0.8	13.4	6.3	0.2	0.7
DD abrupt increase (μg/mL)	1.8	6.7	[b]	3.2	5.6	13.4	6.3	1.0	13.3
PT (12.8–15.4 s)	12.6	12.9	12.1	14.6	13.4	14.7	13.5	15.0	11.7
aPTT (25.8–40.4 s)	34.7	30.3	26.2	32.7	35.7	27.4	27.7	38.0	37.6
Fibrinogen (1.9–5.13 g/L)	6.5	6.5	[b]	7.8	6.3	6.1	6.6	7.3	10.4
Ferritin(ng/mL)	658	998	1125	377	1218	666	920	520	1481
Lymphocytes (cel/μL)	800	400	100	300	900	600	800	600	300
Thrombocytes (x10^3/μL)	339	382	233	211	268	112	344	274	336
Anticoagulation									
Heparin	Eno	Eno	Eno	Eno	Eno	Eno	Eno	Eno	UFH
Dose	80 mg BID	80 mg BID/100 BID[d]	80 mg BID	80 mg BID	80 mg BID	80 mg BID	60 mg BID	80 mg BID	1800 U/h/2000 U/h[d]
Anti-Xa assay[e] (UI/mL)	0.61	0.4/0.8	[b]	0.51	0.42	0.98	0.83	0.54	0.26/0.4[f]
Platelet function									
ADP test (127–224 U)	165	237	[b]	83[g]	120	107	89	196	28
ASPI test (129–224 U)	222	232	[b]	48[g]	154	64	75	171	21
Additional ASA	No	Yes	No	Yes	No	No	No	No[c]	No

R = right; L = left; Bi = bilateral; Eno = Enoxapanarin; ASA = Acetylsalicylic acid; DVT/PE = Deep-vein thrombosis/Pulmonary Embolism; RV = Right ventricle; DD = D-Dimer; HSCRP = High-sensitivity C reactive protein; LDH = Lactate dehydrogenase; PT = Prothrombin time; aPTT = activated partial thromboplastin time; UFH = Unfractionated heparin; ADP = Adenosine diphosphate.

[a] Patient also presented left proximal DVT.

[b] Measurement was not possible due to rapid patient deterioration and death.

[c] Patient already under acetylsalicylic acid.

[d] Patients 2 and 4 had initial doses of anticoagulant therapy and control after dose titration. Patient 2 was already under therapeutic levels, but dose adjustment was decided by consensus.

[e] Therapeutic levels are considered between 0.4UI/mL-1UI/mL.

[f] Patient 9 achieved therapeutic levels of anti-Xa activity 72 h after UFH infusion placement.

[g] Analysis performed after ASA was initiated according to DVT findings. The latter was maintained due to normal platelet function demonstrated with ASA therapy.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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