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Imbalance between procoagulant factors and natural coagulation inhibitors contributes to hypercoagulability in the critically ill COVID-19 patient: clinical implications

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Abstract. – OBJECTIVE: Coronavirus Disease-2019 (COVID-19) predisposes patients to thrombosis which underlying mechanisms are still incompletely understood. We sought to investigate the balance between procoagulant factors and natural coagulation inhibitors in the critically ill COVID-19 patient and to evaluate the usefulness of hemostasis parameters to identify patients at risk of venous thromboembolic event (VTE).

PATIENTS AND METHODS: We conducted an observational study recording VTEs defined as deep vein thrombosis or pulmonary embolism using lower limb ultrasound (92% of the patients), computed tomography pulmonary angiography (6%) and both tests (2%). We developed a comprehensive analysis of hemostasis.

RESULTS: Ninety-two consecutive mechanically ventilated COVID-19 patients (age, 62 years [53-69] (median [25th-75th percentiles]); M/F sex ratio, 2.5; body-mass index, 28 kg/m² [25-32]; past hypertension (52%) and diabetes mellitus (30%)) admitted to the Intensive Care Unit (ICU) from 03/11/2020 to 5/05/2020, were included. When tested, patients were receiving prophylactic (74%) or therapeutic (26%) anticoagulation. Forty patients (43%) were diagnosed with VTE. Patients displayed inflammatory and prothrombotic profile including markedly elevated plasma fibrinogen (7.7 g/L [6.1-8.6]), D-dimer (3,360 ng/mL [1668-7575]), factor V (166 IU/dL [136-195]) and factor VIII activities (294 IU/dL [223-362]). We evidenced significant discrepant protein C anticoagulant and chromogenic activities, combined with slightly decreased protein S activity. Plasma D-dimer >3,300 ng/mL predicted VTE presence with 78% (95%-confidence interval (95% CI), 62-89) sensitivity, 69% (95% CI, 55-81) specificity, 66% (95% CI, 51-79) positive predictive value and 80% (95% CI, 65-90) negative predictive value [area under the ROC curve, 0.779 (95%CI, 0.681-0.859), *p*=0.0001].

CONCLUSIONS: Mechanically ventilated COVID-19 patients present with an imbalance between markedly increased factor V/VIII activity and overwhelmed protein C/S pathway. Plasma D-dimer may be a useful biomarker at the bedside for suspicion of VTE.

Key Words:
COVID-19, D-dimer, Deep vein thrombosis, Hemostasis disorder, Lower limb ultrasound, Protein C.

Abbreviations

95% CI: 95%-confidence interval; COVID-19: coronavirus disease-2019; CTPA: computed tomography pulmonary angiography; DUE: duplex ultrasound examination; DVT: deep vein thrombosis; F: factor; ICU: intensive care unit; PE: pulmonary embolism; ROC curve: receiver operating characteristic curve; RT-PCR: reverse

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transcriptase-polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; VTE: venous thromboembolic event; VWF: Von Willebrand Factor.

Introduction

Critically ill coronavirus disease-2019 (COVID-19) patients present with marked predisposition to thrombosis[1-4]. Previous studies performing prospective systematic screening using lower limb ultrasound and/or computed tomography pulmonary angiography (CTPA) established a strikingly high deep vein thrombosis (DVT) and pulmonary embolism (PE) prevalence, up to ~85% in patients treated with standard prophylactic anticoagulation[5-9].

The underlying mechanisms of COVID-19-related coagulation disorders are complex, including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-induced endothelialitis, marked inflammation and hypercoagulability[4]. Among natural coagulation inhibitors, the activated protein C pathway exerts negative feedback downregulation of excessive inflammation and thrombin generation, which involves proteolytic inactivation of activated procoagulant factors V and VIII. Interestingly, to date, the protein C pathway has been poorly investigated in COVID-19 patients[10-12].

Therefore, in mechanically ventilated COVID-19 patients, we searched for venous thromboembolic events (VTE) using duplex ultrasound examination (DUE) of the lower limb veins and/or CTPA to diagnose and appropriately manage DVT/PE patients. Aiming to understand the reasons for such an elevated DVT/PE prevalence, we performed hemostasis tests, including thrombophilia screening and sought to investigate their possible association with the presence of VTE in our patients. Since during epidemic circumstances, the ability to perform screening tests like lower limb ultrasound and CTPA may be limited, we additionally attempted to determine whether hemostasis parameters are useful in diagnosing VTE in the mechanically ventilated COVID-19 patients.

Patients and Methods

Study Design

We conducted a prospective observational study in the medical and surgical intensive care units (ICU) of our university hospital. Consecutive mechanically ventilated COVID-19 adults admitted from 03/11/2020 to 05/05/2020 were included. The study was performed in agreement with the 2013 Declaration of Helsinki of the World Medical Association and was part of the French COVID-19 and ICU-COVID cohort registries. Our Institutional Ethics Committee approved the study (No. IDRCB, 2020-A00256-33; CPP, 11-20-20.02.04.68737). Signed informed consent was not required, but when possible, it was obtained from the patients or the next of kin.

Parameters, Patient Management and Data Collection

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was diagnosed using standard RT-PCR technique in upper airway swabs (Cobas SARS-CoV-2 kits®, Roche, France). Diagnosis and severity of acute respiratory distress syndrome (ARDS) were based on the Berlin definition[13]. Supportive care included optimized mechanical ventilation, sedation, muscular paralysis and vasopressors for mean arterial pressure $\geq$ 65 mmHg. Prophylactic anticoagulation was administered as subcutaneous enoxaparin and if glomerular filtration rate < 15 mL/min, as 15,000 IU unfractionated heparin. Therapeutic anticoagulation was administered if indicated including after DVT/PE diagnosis.

Two certified ultrasound operators (S.V. and P.B.) systematically performed DUE during the first week of ICU admission. The presence of a thrombus was evaluated by vein compression, color Doppler imaging and spectral Doppler waveforms, determined in the common femoral artery, allowing for the assessment of circulatory flow at this level, as recommended[14]. Compression was performed every 2 cm from the inguinal ligament to the ankle, visualizing the common femoral veins, the deep and superficial femoral veins, the popliteal veins, the posterior tibial and fibular veins and the gastrocnemius and soleus veins of the calf. When possible, a second DUE was performed in DVT-free patients, approximately seven days later. CTPA was performed as part of the systematic screening process in patients in whom lung CT was ordered by the physicians in charge if no DUE was already available if the patient was safely transportable and in the absence of contraindication to contrast injection.

Hemostasis tests were obtained within 72 hours of VTE screening tests. Venous blood was collected in 105 mmol/L trisodium citrate. Platelet-poor plasma was obtained after double-cen-

trifugation at 2,300 g for 10 min at 20°C and stored at −80°C until assays. All hemostasis tests were performed on STA-R-MAX coagulation analyzer® (Diagnostica Stago, France) according to the manufacturer's recommendations. They included prothrombin time ratio, activated partial thromboplastin time (aPTT), fibrinogen, D-dimer (Liatest-DDI Plus®), factor (F) II, FV, FVII+X and FVIII coagulant activities, Von Willebrand Factor (VWF) antigen, antithrombin, protein C (both clotting-based and chromogenic) and protein S (clotting-based) activities, and free protein S antigen. Of note, protein C results obtained with the chromogenic method (Biophen® Protein C (Hyphen, Neuville/Oise, France) are known to be not influenced by procoagulant FV and FVIII levels, nor the presence of lupus anticoagulant and heparin or the presence of FV Leiden mutation, in contrast to those obtained with the aPTT clotting-based method (Protein C COAG® Siemens, Marburg, Germany)[15]. Anti-Xa activity level was systematically measured in all samples and found < 0.9 IU/mL, thus excluding heparin interference with protein C aPTT clotting-based activity (due to the presence of a heparin quenching agent in the reagent). Genetic testing for *F5G1691A* and *F2G20210A* was performed using allele-specific-PCR-discrimination. Blood counts were analyzed using Sysmex-XN-3000 Hematology Analyzer® (Sysmex, Kobe, Japan).

Statistical Analysis

Quantitative variables are expressed as medians [25th-75th percentiles] and categorical variables as percentages. Parameters were compared using Mann-Whitney and Fisher's exact tests as required. For D-dimer, the receiver operating characteristics (ROC) curve was built and the area under the receiver operating characteristic (ROC) curve was calculated to determine the cutoffs of maximum accuracy for TE diagnosis. We reported the corresponding diagnostic characteristics with the 95%-confidence intervals (95% CI). *p*-values < 0.05 were considered significant. Statistical analysis was performed using MedCalc® version11.0.1.0 (MedCalc Software, Ostend, Belgium).

Results

Ninety-two mechanically ventilated COVID-19 patients (age, 62 years [53-69]; M/F sex ratio, 2.5; body-mass index, 28 kg/m^2 [25-32]; past hypertension (52%), diabetes (33%) and ischemic heart disease (15%)) were included. DUE was performed in 85 patients (92%), CTPA in five patients (6%) and both tests in two patients (2%). Baseline characteristics of the patients are presented in Table I. At the time of the screening test, patients presented with severe (17%), moderate (37%), mild (27%) and no ARDS (19%); 42% required vasopressors. They received prophylactic (74%) or therapeutic anticoagulation (5% in relation to extracorporeal membrane oxygenation and 21% to supraventricular arrhythmia or renal replacement therapy). None of the patients had active cancer or osteoarticular conditions requiring immobilization.

Forty patients (43%) exhibited VTE including DVT (35 patients, 37%), PE (four patients, 4%) and both (one patient, 1%). VTE was diagnosed five days [2-8] after mechanical ventilation, corresponding to 12 days [9-16] from the first COVID-19 symptoms. Thirty-four patients had a second DUE of which eight (24%) showed DVT. Of the 40 DVT, 15 (38%) were femoral or popliteal. Three patients were diagnosed with VTE before intubation. The SOFA score on admission was seven [4-10]. Baseline characteristics did not significantly differ between VTE and non-VTE patients except for lactate concentrations which remained within the normal range in most patients (Table I).

All patients presented a marked increase in the plasma concentrations of acute phase reactant proteins, including fibrinogen, FVIII and VWF (Table II). Remarkably, in contrast to normal vitamin K-dependent procoagulant factor levels, FV levels were extremely high; only two patients including one with DVT presented with a moderate deficiency in FV (~50 IU/dL) associated with disseminated intravascular coagulation.

Regarding the natural coagulation inhibitors, we observed no significant differences between patients with and without VTE. Median antithrombin activity was normal, slightly decreased in only 33% of the patients, partly explained by heparin treatment. Protein S activity was < 50 IU/dL in 53% of the patients, subsequent to the acute inflammatory response. Median protein C chromogenic activity was normal; however, we evidenced an unusual and significant discrepancy between protein C chromogenic *vs.* clotting-based activities in both patients without (107 IU/dL [77-140] *vs.* 85 IU/dL [59-114], $p = 0.02$) and with VTE (105 IU/dL [74-129] *vs.* 75 IU/dL [57-95], $p = 0.002$) (Figure 1A). Unusually high levels of FV

Table I. Characteristics of 92 consecutive mechanically ventilated patients with SARS-CoV-2-related pneumonia at baseline according to the presence of a venous thromboembolic event (VTE).

	All patients (N = 92)	Absence of VTE (N = 52)	Presence of VTE (N=40)	*p*-value
Male gender, N (%)	66 [72]	36 [69]	30 [75]	0.64
Age (years)	62 [53-69]	60 [54-69]	63 [56-69]	0.41
Body mass index (kg/m^2)	28 [25-32]	29 [25-33]	28 [25-30]	0.21
Obesity N (%)	29 [32]	20 [38]	9 [23]	0.16
Hypertension, N (%)	48 [52]	27 [52]	21 [53]	1.0
Diabetes mellitus, N (%)	33 [36]	18 [35]	15 [38]	0.83
Ischemic heart disease, N (%)	14 [15]	9 [17]	5 [13]	0.57
Previous heart failure, N (%)	9 [10]	5 [10]	4 [10]	1.0
ACE inhibitors, N (%)	20 [22]	12 [23]	8 [20]	0.80
ARBs, N (%)	16 [17]	8 [15]	8 [20]	0.59
Long-term anticoagulation before admission, N (%)	6 [7]	3 [6]	3 [8]	1.0
Aspirin treatment, N (%)	21 [27]	14 [27]	7 [18]	0.32
Blood lactate (mmol/L)*	1.2 [1.0-1.7]	1.5 [1.0-1.8]	0.9 [1.1-1.3]	0.01
Plasma proteins (g/L)*	63 [58-67]	62 [59-66]	64 [57-68]	0.84
Serum creatinine (µmol/L)*	99 [69-170]	99 [68-171]	102 [69-159]	0.84
Serum ALT (IU/L)*	37 [23-52]	37 [23-52]	35 [22-51]	0.44
Serum bilirubin (µmol/L)*	10 [6-20]	10 [6-16]	12 [7-20]	0.30
Popliteal or femoral DVT, N (%)	15 (16)	15 [29]	0 [0]	< 0.0001
Survival to ICU discharge, N (%)	38 [41]	24 [46]	14 [35]	0.30

DVT, deep vein thrombosis; ACE; angiotensin-conversion enzyme; ARB, angiotensin II receptor blocker; ALT, alanine transferase; ICU, intensive care unit; *parameters assessed within 24h of the screening test. Data are expressed as median [25th-75th percentiles] or absolute value (%) as appropriate. Comparisons were performed using Mann-Whitney and Fisher's exact tests as required.

and FVIII contributed to lower anticoagulant protein C activity levels when measured using aPTT-clotting-based assay, in contrast to chromogenic assay based on the ability of activated protein C to cleave a synthetic chromogenic substrate.

D-dimer ranged from 590 to > 20,000 ng/mL (median value, 3,500 ng/mL [2060-8610]), reflecting a wide inter-individual variability, with only 7.1% of the patients displaying levels ranging between 590 and 1,000 ng/mL, and 56% of them presenting levels > 3,000 ng/mL. Of all hemostasis parameters measured, only D-dimer concentration was significantly different between the two groups. VTE patients had significantly higher D-dimer in comparison to non-VTE patients ($p < 0.0001$). Based on the ROC curve analysis, using a cutoff of 3,300 ng/mL for VTE diagnosis, D-dimer had 78% (95% CI, 62-89) sensitivity, 69% (95% CI, 55-81) specificity, 66% (95% CI, 51-79) positive predictive value and 80% (95% CI, 65-90) negative predictive value, with an area under the curve of the model of 0.779 (95% CI, 0.681-0.859, $p = 0.0001$; Figure 1B). For a cutoff of 1730 ng/mL, D-dimer had 100% (91-100) sensitivity, 45% (31-60) specificity, 58% (45-70) positive predictive value, and 100% (85-100) negative predictive value.

Discussion

In the critically ill COVID-19 patient, we showed a disequilibrium between marked elevated procoagulant factors and normal or slightly decreased natural coagulation inhibitor levels. Marked elevated C-reactive protein, fibrinogen, VWF and FVIII values are consistent with those of previous reports[4,11,12,16-18]. Several mechanisms are involved in elevated FVIII and VWF levels, such as endothelial activation and/or damage and inflammation, promoting VWF release from endothelial cell Weibel-Palade bodies[19]. Elevated FV activity may also result from endothelial activation, since FV is stored in endothelial cell Weibel-Palade bodies in addition to the platelet alpha-granules. Noteworthy, the combination of elevations in FV and VIII is not commonly observed in critically ill patients with sepsis.

While several studies reported data on inflammation parameters and procoagulant factors[9,16-18], only few studies focused on protein C pathway[11,12,18]. Using two functional protein C assays, namely aPTT-clotting-based protein C assay (sensitive to high FV/FVIII levels) and chromogenic protein C assay (not influenced by procoagulant factor levels), we were able to

Table II. Inflammation and coagulation parameters in 92 consecutive mechanically ventilated patients with SARS-CoV-2-related pneumonia according to the presence of a venous thromboembolic event (VTE).

	Normal range	All patients (N = 92)	Absence of VTE (N = 52)	Presence of VTE (N = 40)	*p*-value
C-reactive protein (mg/L), N=63*	≤ 5	217 [112-254]	192 [115-285]	218 [129-258]	0.8
Procalcitonin (µg/L), N=89	< 0.05	0.71 [0.27-2.27]	0.66 [0.28-2.07]	0.71 [0.26-2.62]	0.8
D-dimers (ng/mL)	< 500	3,360 [1,668-7,575]	2,120 [1,150-3,590]	6,560 [3,458-13,343]	< 0.0001
Prothrombin time (ratio)	1.18-1.20	1.19 [1.09-1.26]	1.18 [1.11-1.28]	1.18 [1.09–1.21]	0.2
APTT (ratio)	< 1.20	1.34 [1.12-1.60]	1.41 [1.13-1.63]	1.29 [1.11-1.53]	0.2
Fibrinogen (g/L)	2.0-4.0	7.7 [6.1-8.6]	7.7 [5.7-8.5]	7.7 [6.2-8.8]	0.3
Factor II (IU/dL), N=86	70-130	97 [84-107]	98 [83-107]	96 [87-106]	0.2
Factor V (IU/dL), N=86	70-130	166 [136-195]	170 [145-197]	160 [126-184]	0.2
Factor VII +X (IU/dL), N=86	70-130	93 [76-110]	91 [72-111]	96 [81-104]	0.6
Factor VIII (IU/dL), N=69	50-150	294 [223-362]	274 [213 -370]	312 [237-351]	0.09
Von Willebrand factor antigen (IU/dL), N=58	50-150	514 [418-662]	522 [407-653]	503 [426-686]	0.9
Antithrombin activity1 (IU/dL), N=68	80-120	92 [77-109]	98 [78-117]	82 [75-98]	0.08
PC activity (IU/dL), N=70					
- clotting-based assay[2]	70-130	80 [58-102]	85 [66-103]	71 [57-93]	0.6
- amidolytic assay[3]	70-130	102 [73-124]	107 [79-140]	105 [74-127]	0.2
PS (IU/dL), N=68					
- activity assay[4]	50-130	58 [35-57]	49 [34-57]	44 [35-60]	0.2
- free PS antigen[5]	50-130	79 [65-100]	78 [67-96]	84 [64-105]	0.9
F5 G1691A , N=60 heterozygotes, N (%)	-	3 (5.0%)	2 (3.3%)	1 (1.7%)	-
F2 G20210A, N=60 heterozygotes, N	-	0	0	0	-
Platelets (G/L)	150-450	285 [185-368]	262 [183-360]	298 [203-380]	0.4
White blood cells (G/L)	4.0-10.0	10.6 [8.4-16.0]	11.4 [8.7-16.3]	9.7 [8.4-14.5]	0.2
Lymphocytes (G/L)	1.50-4.00	0.88 [0.51-1.20]	1.00 [0.66-1.26]	0.66 [0.48-1.10]	0.04
Hemoglobin (g/dL)	13.0-17.0 (12.0-16.0 in females)	10.3 [9.1-11.9]	10.7 [9.9-11.9]	9.4 [8.7-11.6]	0.04

TE, thromboembolic event; APTT, activated partial thromboplastin time; PC, protein C; PS, protein S; *data were available in all patients unless otherwise specified; [1]AT III (Stago), [2]Protein C COAG® (Siemens, Marburg, Germany), [3]Biophen® Protein C (Hyphen, Neuville /Oise, France); [4]Staclot® PS (Stago), [5]Liatest free PS (Stago), Stachrom®. Data are expressed as median [25th-75th percentiles] or absolute value (%) as appropriate. Comparisons were performed using Mann-Whitney and Fisher's exact tests as required.

evidence a significant unusual discrepancy in median protein C activities, thus indicating an *ex vivo* alteration of protein C pathway. Moreover, given the high prevalence of lupus anticoagulant in these patients[16,19], this discrepancy might have been more pronounced than without lupus anticoagulant. This coagulation pattern mimicking an acquired resistance to activated protein C is partly related to inflammation. I*n vivo*, protein C/S pathway is likely overwhelmed due to the extremely high FVIII and FV levels, reducing the coagulation control. Moreover, this phenomenon could have been emphasized by SARS-CoV-2-induced endothelialitis, and the subsequent alteration of protein C activation by the thrombin/thrombomodulin complex. Overall, high procoagulant factor levels combined with normal or slightly decreased natural coagulation inhibitor levels resulted in a coagulation imbalance with increased thrombin generation and thus, a prothrombotic profile in agreement with previous findings[10,16,17].

We showed that patients with and without VTE cannot be differentiated based on the procoagulant factor and coagulation inhibitor levels, suggesting additional mechanisms such as endothelial damage[20] that may play a role in COVID-19-attibuted thrombotic process. Altogether, prothrombotic state, mechanical ventilation-induced associated immobility and SARS-CoV-2-induced endothe-

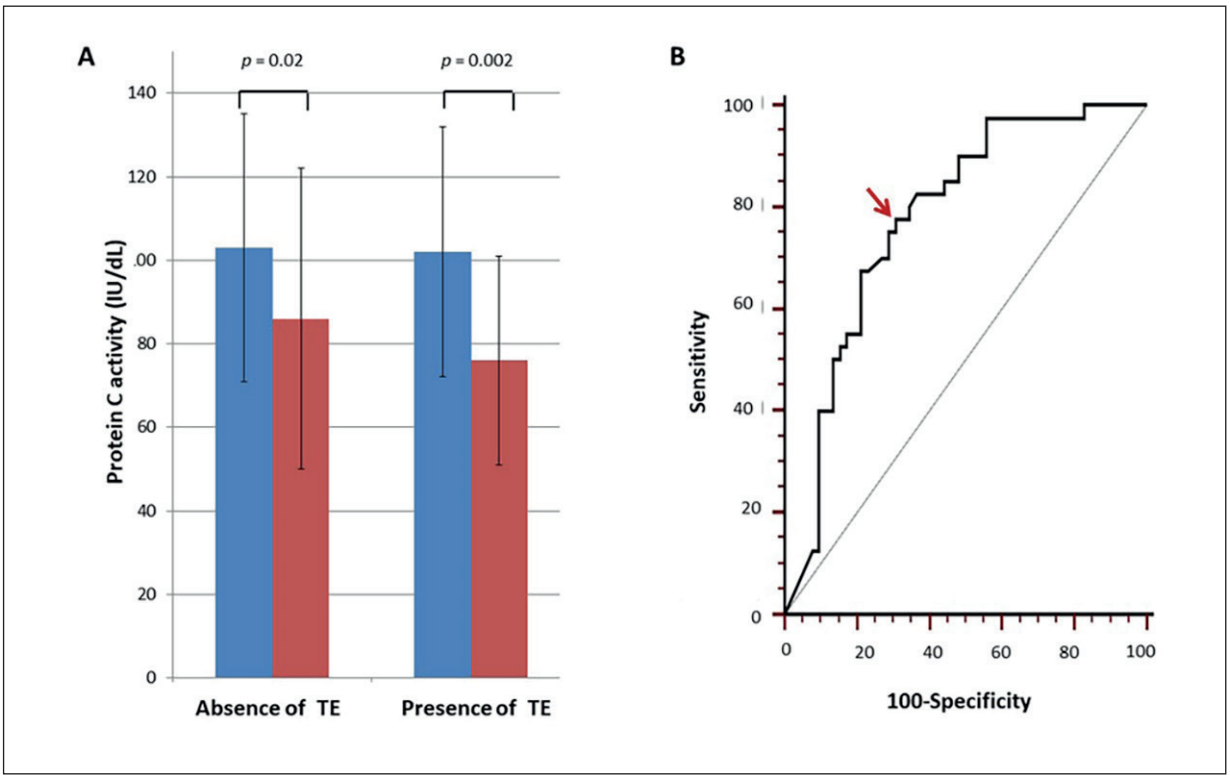

Figure 1. Protein C activity and plasma D-dimer receiver operator characteristic curve for thromboembolic event diagnosis. **A,** Protein C activity in 92 mechanically ventilated COVID-19 patients with (right set) and without thromboembolic event (TE; left set). Blue bars represent the chromogenic protein C activity and red bars indicate the clotting-based protein C activity (normal range, 70-130 IU/dL for both); bars indicate standard deviation. **B,** Diagnostic characteristics of plasma D-dimer for TE diagnosis thromboembolic event (TE) at the initial ultrasound examination in the 92 patients. The receiver operator characteristic curve shows the point of maximum accuracy (*arrowhead*) corresponding to a cutoff of 3,300 ng/mL with a 78% (95%-confidence interval, 62-89) sensitivity, a 69% (55-81) specificity and an area under the curve of the model of 0.779 (0.681-0.859; $p = 0.0001$).

lial cell injury, i.e., the well-known Virchow's triad, may explain the high VTE prevalence in the critically ill COVID-19 patient.

Another important finding in our study is that plasma D-dimer was the only parameter that significantly differed between VTE and non-VTE patients. We showed that D-dimer is helpful in diagnosing VTE in COVID-19 patients and based on a specific cutoff in this COVID-19 population, we additionally established that it could be used to rule out the presence of DVT/PE. Interestingly, several studies have found that D-dimer is higher in patients with DVT/PE[6,7,21,22] including two studies suggesting that D-dimer may contribute to VTE diagnosis[7,22]. However, both studies were retrospective and criteria used to screen DVT/PE were either non-specified[8] or based on clinical suspicion[22], therefore raising the question of selection biases. Our D-dimer cutoff for VTE diagnosis (3,300 ng/mL) was derived from a prospective systematic screening in mechanically ventilated COVID-19 patients, thus avoiding such biases. Interestingly, it was consistent with the previous cutoff values (i.e., 3000 ng/mL[7] and 2660 ng/mL[22]), probably because the increasing awareness of thrombotic complications in COVID-19 patients encouraged relatively wide screening in clinical practice and led to cutoff values similar with those derived after systematic screening.

Studies documenting high VTE prevalence suggested the usefulness of systematic VTE screening, especially using DUE[5,6,9,23], which may not be readily available in the epidemic circumstances. Therefore, our findings appear useful to elaborate therapeutic strategies based on D-dimer while awaiting DVT screening tests, especially since anticoagulation might be associated with survival, especially if prescribed to patients with D-dimer above 3,000 ng/mL, as suggested[1,24] and bleeding complications being a concern, as showed in a recent study[25].

Our investigation has several limitations. It is a single-hospital study although it included a homogeneous ICU population, systematically screened for TE. Our screening process relied on two different tests, mainly DUE and in 6% of the cases, on CTPA. This was due to the logistical difficulties encountered during the epidemic crisis, when DUE by certified ultrasound operators was not always available and CTPA had limited availability and much higher risk related to contrast injection and patient transport. This resulted in most patients undergoing DUE not having CTPA, therefore PE may have been missed, and most patients with CTPA not having DUE, therefore DVT may have been missed. However, a study performing both tests in all patients would be very difficult to perform and the risk/benefit ratio potentially questionable. Here, some limited missing data were also due to logistical difficulties encountered during the COVID-19 crisis. Another limitation is the absence of global hemostasis test assessment able to evidence the patient prothrombotic phenotype, such as thrombin generation tests or viscoelastic assays[10,17]. Finally, the D-dimer cutoffs suggested as a possible diagnostic tool of DVT/PE and for ruling out the diagnosis should require further validation in an external patient cohort before being used in clinical practice.

Conclusions

We demonstrated that critically ill COVID-19 patients present with marked thrombo-inflammation and hypercoagulability, with an imbalance between markedly increased factor V/VIII activity and protein C/S pathway. Plasma D-dimer may be a useful biomarker at the bedside for diagnosing and/or ruling out DVT/PE if future studies validate the suggested cutoffs.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval and Consent to Participate

The study was part of the French COVID-19 and ICU-COVID cohort registries. Our Institutional Ethics Committee approved the study (N°, IDRCB, 2020-A00256-33; CPP, 11-20 20.02.04.68737).

Availability of Data and Materials

The datasets generated analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

SV, VS and BM contributed to study concept and design. SV and PB performed the duplex ultrasound examinations. SV, BGC, IM, ND, CK, AM and BM managed the patients and extracted the clinical data. MD, AS and VS performed the hemostasis tests and interpretation. SV, VS and BM performed the statistical analyses and drafted the initial version of manuscript. All authors provided critical revision of the manuscript and approved the final draft for publication.

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