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BRIEF REPORT

High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients

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Abstract

Background: Coagulopathy is a common abnormality in patients with COVID-19. However, the exact incidence of venous thromboembolic event is unknown in anticoagulated, severe COVID-19 patients.

Objectives: Systematic assessment of venous thromboembolism (VTE) using complete duplex ultrasound (CDU) in anticoagulated COVID-19 patients.

Patients and methods: We performed a retrospective study in 2 French intensive care units (ICU) where CDU is performed as a standard of care. A CDU from thigh to ankle at selected sites with Doppler waveforms and images was performed early during ICU stay in patients admitted with COVID-19. Anticoagulation dose was left to the discretion of the treating physician based on the individual risk of thrombosis. Patients were classified as treated with prophylactic anticoagulation or therapeutic anticoagulation. Pulmonary embolism was systematically searched in patients with persistent hypoxemia or secondary deterioration.

Results: From March 19 to April 11, 2020, 26 consecutive patients with severe COVID-19 were screened for VTE. Eight patients (31%) were treated with prophylactic anticoagulation, whereas 18 patients (69%) were treated with therapeutic anticoagulation. The overall rate of VTE in patients was 69%. The proportion of VTE was significantly higher in patients treated with prophylactic anticoagulation when compared with the other group (100% vs 56%, respectively, $P = .03$). Surprisingly, we found a high rate of thromboembolic events in COVID-19 patients treated with therapeutic anticoagulation, with 56% of VTE and 6 pulmonary embolisms.

Conclusion: Our results suggest considering both systematic screening of VTE and early therapeutic anticoagulation in severe ICU COVID-19 patients.

KEYWORDS

SARS-CoV-2, COVID-19, anticoagulation, venous thromboembolism, pulmonary embolism, critical care

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is responsible for high intensive care unit (ICU) admission rates and high mortality.^{1,2} Apart from respiratory failure, coagulopathy is a common abnormality in patients with COVID-19, with elevated levels of both fibrinogen and D-dimers.³ Therefore, experts have recently published a statement on the management of coagulopathy in COVID-19 patients suggesting to consider prophylactic doses of low molecular weight heparin in all COVID-19 patients.⁴ However, the evidence is scarce and we found only two studies reporting the incidence of venous thromboembolism (VTE) in severe COVID-19 patients. One study report a 27% rate of VTE in COVID-19 patients, but without systematic assessment.⁵ Another recent study report a 25% incidence rate of VTE using systematic assessment in COVID-19 patients, but without thromboprophylaxis.⁶ We here report our experience with systematic assessment of VTE using complete duplex ultrasound (CDU) in severe ICU COVID-19 patients.

2 | METHODS

From March 19 to April 11, 2020, we performed a retrospective study in two French ICUs where CDU is usually performed upon admission as a standard of care. The COVID-19 diagnosis was confirmed by RNA detection of SARS-CoV-2 in patients with respiratory failure. Characteristics at baseline, biological findings, and CDU results were extracted from electronic hospital medical records. Independent certified specialists in vascular medicine performed CDU between day 1 and day 3 after admission. In patients without VTE during the first CDU, a second CDU was performed at day 7. According to guidelines, a CDU is performed from thigh to ankle at selected sites with Doppler waveforms and images. Anticoagulation dose was left to the discretion of the treating physician based on the individual risk of thrombosis and patients were classified as treated with prophylactic anticoagulation or therapeutic anticoagulation. Patients treated with therapeutic anticoagulation received either low molecular weight heparin or unfractionated heparin with anti-Xa monitoring, with therapeutic levels of 0.3 to 0.7 U/mL of anti-Xa activity. Pulmonary embolism was systematically researched in case of persistent or secondary respiratory failure by computed tomography pulmonary angiogram or transesophageal echocardiography when patients were not transportable. Continuous variables were expressed as median (interquartile range) and categorical variables as numbers (percentages) and were compared by the Pearson chi-squared test or Fisher exact test as appropriate. According to French law, this study was registered (MR141210420) and patients were informed at ICU discharge.

3 | RESULTS

During the study period, 26 COVID-19 patients were admitted in our ICUs. Main clinical characteristics at baseline and biological findings are reported in Table 1. Patients were mostly men (n = 20, 77%), had a

Essentials

- Coagulopathy is a common abnormality in patients with COVID-19.
- The incidence of venous thromboembolism (VTE) in anticoagulated COVID-19 patients is unknown.
- Using a systematic VTE screening strategy, we found 69% of VTE in anticoagulated COVID-19 patients.
- We suggest considering VTE screening and therapeutic anticoagulation in severe COVID-19 patients.

previous history of arterial hypertension (n = 22, 85%), and had an increased body mass index (median = 30.2 kg/m², 25th-75th interquartile range [IQR]: 25.5, 33.5). The median value of fibrinogen at admission was 7 g/L (25th-75th IQR: 6.4, 7.4) and the median D-dimer value was 1750 ng/mL (25th-75th IQR: 1130, 2850). All patients underwent mechanical ventilation, with prone positioning in 16 patients (62%). All patients were anticoagulated from admission, with 31% (n = 8) with prophylactic anticoagulation and 69% (n = 18) with therapeutic anticoagulation (Table 1). We found a cumulative incidence of peripheral VTE of 69% (n = 18), and pulmonary embolism was diagnosed in six patients (23%). The overall mortality was 12%, 16 patients were discharged from the ICU, and seven continued to receive mechanical ventilation. The proportion of VTE was significantly higher in patients treated with prophylactic anticoagulation when compared with the other group (100% vs 56%, respectively, P = .03). However, we found a high rate of thromboembolic events in COVID-19 patients treated with therapeutic anticoagulation, with 56% of VTE and six pulmonary embolisms.

4 | DISCUSSION

Using a systematic VTE screening strategy, we found a 69% incidence rate of VTE in severe ICU anticoagulated COVID-19 patients. Whether a recent study reports a lower rate of VTE,⁵ our results differ by two major points: (1) other authors did not perform systematic CDU and therefore may underestimate the rate of VTE and (2) all patients in our cohort are mechanically ventilated with a high proportion of acute respiratory distress syndrome, whereas patients from the other reports are less ill. In another recent study, authors report a 25% incidence rate of VTE using systematic assessment in COVID-19 patients, but without thromboprophylaxis. Moreover, the exact time point of the venous Doppler ultrasound and whether a certified specialist performed it are unclear in this study. Nevertheless, these two studies underline the importance of venous thromboembolic events in severe COVID-19 patients. Surprisingly, we found that VTE even occur in patients treated with therapeutic anticoagulation from admission, highlighting the thrombogenicity of COVID-19. Moreover, 23% of patients were diagnosed with pulmonary embolism, pointing out the importance of considering VTE complications in COVID-19 patients. This study is limited in the small number of patients and

TABLE 1 Main characteristics of the patients at baseline

Characteristics	All (n = 26)	Prophylactic Anticoagulation at Admission (n = 8)	Therapeutic Anticoagulation at Admission (n = 18)	P
Characteristics at baseline				
Age (years)	68 (51.5-74.5)	68 (45-72.7)	67.5 (53.5-76.2)	
Male sex	20 (77)	6 (75)	14 (78)	
Chronic medical condition				
Active cancer	0 (0)	0 (0)	0 (0)	
Previous VTE	1 (4)	0 (0)	1 (6)	
Arterial hypertension	22 (85)	7 (87)	15 (83)	
Tobacco	7 (27)	2 (25)	5 (28)	
Surgery < 3 months	1 (4)	0 (0)	1 (6)	
Anticoagulation before admission	7 (27)	0 (0)	7 (39)	.06
Days between symptom onset and admission	7 (3.2-8.7)	7 (6.2-9.2)	5.5 (3-8)	
SOFA score	3 (2-4.7)	2.5 (2-3.2)	3.5 (3-5)	.06
Laboratory findings at admission				
D-dimers, ng/mL	1750 (1130-2850)	2330 (1495-3165)	1750 (1245-2850)	
Fibrinogen, g/L	7 (6.4-7.4)	7.1 (6.9-8.3)	6.8 (6.4-7.3)	
Platelets count, G/L	234 (169-306)	261 (159-316)	234 (185-293.5)	
CRP, mg/L	187 (147-279)	197 (155-287)	177 (147.5-258.5)	
Hematocrit, %	37.7 (35.9-41.9)	41.2 (39.2-42.3)	36.5 (34.8-40.2)	
Creatinemia, μmol/L	79.5 (55.7-100)	86 (81.5-97)	94.5 (59.7-103)	.02
Management				
Worse PaO ₂ /FiO ₂ ratio	86.5 (74-116)	106 (82-115)	78 (70-117)	
Mechanical ventilation	26 (100)	8 (100)	18 (100)	
Prone positioning	16 (62)	5 (62)	11 (61)	
Venovenous extracorporeal membrane oxygenation	2 (8)	1 (12)	1 (5)	
Renal replacement therapy	4 (15)	0 (0)	4 (22)	
Vasoconstrictive agent	23 (88)	8 (100)	15 (83)	
Antibacterial treatment	25 (96)	7 (87)	18 (100)	
Complete duplex ultrasound findings				
Venous thromboembolism	18 (69)	8 (100)	10 (56)	.03
Superficial	4 (22)	2 (25)	3 (30)	
Deep	14 (78)	6 (75)	7 (10)	
Bilateral	10 (55)	5 (63)	5 (50)	
Outcome				
ARDS	21 (81)	7 (87)	14 (78)	
Pulmonary embolism ^a	6 (23)	0 (0)	6 (33)	
Acute kidney injury	9 (35)	2 (25)	7 (39)	
Liver dysfunction	4 (15)	1 (12)	3 (17)	
Death	3 (12)	1 (12)	2 (11)	

Abbreviations: ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; SAPSII, simplified acute physiology score II; SOFA, sequential organ failure assessment; VTE, venous thromboembolism.

^aAngio-computed tomography scan in 4 patients and transesophageal echocardiography in 2 patients.

the retrospective design of the study. However, given the systematic VTE screening strategy and the severity of the anticoagulated patients, our results support to consider routine screening of VTE

in severe ICU COVID-19 patients in the pandemic context and suggest taking into consideration early therapeutic anticoagulation in this setting.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Jean-François Llitjos designed the study, collected data, and wrote the manuscript. Maxine Leclerc, Camille Chochois, Jean-Michel Monsallier, Malika Auvray, Michel Ramakers, and Karim Merouani collected data and wrote the manuscript.

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