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

**Running title:** Venous thromboembolic events in anticoagulated COVID-19 patients

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**Essentials:**

- Coagulopathy is a common abnormality in patients with COVID-19.
- The incidence of venous thromboembolism (VTE) in anticoagulated COVID-19 patients is unknown

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- 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

## **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 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<sup>th</sup> to April 11<sup>th</sup> of 2020, 26 consecutive patients with severe COVID-19 were screened for VTE. 8 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 to the other group (100% vs. 56%, respectively,  $p=0.03$ ). 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

## **Introduction**

The coronavirus disease 2019 (COVID-19) pandemic is responsible for high intensive care unit (ICU) admission rate 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 (LMWH) 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.

## **Methods**

From March 19<sup>th</sup> to April 11<sup>th</sup> of 2020, we performed a retrospective study in two French ICU 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 complete duplex ultrasound 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 (LMWH) or unfractionated heparin (UH) with anti-Xa monitoring, with therapeutic levels of 0.3-0.7 U/mL of anti-Xa activity. Pulmonary embolism was systematically researched in case of persistent or secondary respiratory failure by CT 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's Chi-square test or the Fisher's exact test as appropriate. According to French law, this study was registered (MR141210420) and patients were informed at ICU discharge.

## 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 previous history of arterial hypertension (n=22, 85%) and had an increased body mass index (median=30.2 kg/m<sup>2</sup>, 25<sup>th</sup>-75<sup>th</sup> IQR: 25.5 – 33.5). The median value of fibrinogen at admission was 7 g/L (25<sup>th</sup>-75<sup>th</sup> IQR: 6.4 – 7.4) and the median D-dimer value was 1750 ng/mL (25<sup>th</sup>-75<sup>th</sup> 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) of prophylactic anticoagulation and 69% (n=18) of therapeutic anticoagulation (**table 1**). We found a cumulative incidence of peripheral VTE of 69% (n=18) and pulmonary embolism was diagnosed in 6 patients (23%). The overall mortality was 12 %, 16 patients were discharged from ICU and 7 continued to receive mechanical ventilation. The proportion of VTE was significantly higher in patients treated with prophylactic anticoagulation when compared to the other group (100% vs. 56%, respectively, p=0.03). However, we found a high rate of thromboembolic events in COVID-19 patients treated with therapeutic anticoagulation, with 56% of VTE and 6 pulmonary embolisms.

## 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 ARDS 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 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

Role and contribution of the authors: JFL designed the study, collected data and wrote the manuscript. ML, CC, JMM, MA, RM and KM collected data and wrote the manuscript.

Characteristics	All (n=26)	Prophylactic anticoagulation at admission (n=8)	Therapeutic anticoagulation at admission (n=18)	p
<b>Characteristics at baseline</b>				
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 TVE	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 prior to admission	7 (27)	0 (0)	7 (39)	0.06
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)	0.06
<b>Laboratory findings at admission</b>				
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)	
Creatininemia, µmol/L	79.5 (55.7 - 100)	86 (81.5 - 97)	94.5 (59.7 - 103)	0.02

#### Management

Worse PaO <sub>2</sub> /FiO <sub>2</sub> 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)	
Veno-venous 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)	0.03
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 *	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)	

#### Table legend

**Main characteristics of the patients at baseline.** SAPSII: simplified acute physiology score II, SOFA: sequential organ failure assessment, VTE: venous thromboembolism, CRP: C-reactive protein, ARDS: Acute respiratory distress syndrome. \*: angio-CT scan in 4 patients and transesophageal echocardiography in 2 patients.