High prevalence of deep vein thrombosis in mechanically ventilated COVID-19 patients

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High prevalence of deep vein thrombosis in mechanically ventilated COVID-19 patients

Brief title: Venous thrombosis & mechanically ventilated COVID-19

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Abbreviation List: ARDS = acute respiratory distress syndrome; COVID-19 = Coronavirus disease; DVT = deep vein thrombosis; ICU = intensive care unit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus

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SARS-CoV-2 pneumonia patients present with coagulation disorders and marked susceptibility to thrombosis (1,2). However, the exact prevalence of DVT has been poorly investigated while the risk seems increased in ICU patients (3). Therefore, we decided to perform routine duplex ultrasound examination of the lower limb veins systematically, in order to administer appropriate anticoagulation in all intubated and mechanically ventilated patients with SARS-CoV-2 pneumonia.

We conducted a prospective observational study in the medical and surgical critical care departments of Lariboisière University Hospital, Paris, France. Consecutive adults receiving invasive mechanical ventilation for SARS-CoV-2 pneumonia were included. Patients with previously diagnosed DVT or pulmonary embolism were excluded. During the hospital stay, prophylactic anticoagulation was administered as daily subcutaneous 4,000IU enoxaparin and, if glomerular filtration rate <15mL/min, as continuous intravenous infusion of daily 15,000IU unfractionated heparin. Duplex ultrasonography and plasma D-dimer assessment (STA-Liatest-DDI-Plus®, Stago, France) were performed in all patients during the first week of ICU admission. In patients without DVT on the initial ultrasound, a second ultrasound examination was performed ~7 days later. Quantitative variables are expressed as medians [25^{th}-75^{th} percentiles] and categorical variables as percentages. The study was part of the French COVID-19 cohort registry and was approved by our institutional ethics committee (IDRCB, 2020-A00256-33; CPP, 11-20 20.02.04.68737). When possible, signed informed consent was obtained from the patients or the next of kin.

From March 13^{th} to April 3^{rd} 2020, fifty-six patients with SARS-CoV-2 pneumonia were included. Most of the patients were male (75%), with hypertension (46%), diabetes (45%), obesity (30%) and ischemic heart disease (20%). They required vasopressors in 32% of the

cases. Prophylactic anticoagulation using enoxaparin or unfractionated heparin was administered in 41 patients (73%) and eight patients (14%), respectively. Therapeutic anticoagulation was used in seven patients (13%) to treat atrial fibrillation (N=2) and manage extracorporeal membrane oxygenation (N=5).

The initial ultrasound was performed 3 days [2-4] post-intubation, corresponding to 10 days [8-13] after the onset of the first symptoms. Twenty (36%) patients had DVT among which 11 (20%) were proximal (popliteal or femoral) DVT. A second ultrasound examination was performed in 17 patients, 8 days [5-9] post-intubation, corresponding to 14 days [11-15] after the first symptoms. Six patients (35%) acquired DVT, of which two (12%) were proximal despite prophylactic anticoagulation three patients and therapeutic anticoagulation in the other three. Overall, 26 out of 56 patients (46%) were diagnosed with DVT, either proximal (N=13, 23%) or calf (N=13, 23%) (**Figure 1**). DVT patients had significantly higher plasma D-dimer compared with non-DVT patients (7210 ng/mL [3770-13550] v*ersus* 2225 ng/mL [1195-3630], p=0.0002), with no significant difference in plasma fibrinogen (7.4 g/L [5.8-8.9] *versus* 7.6 g/L [5.5-8.5], p=0.7).

Studies have reported a highly variable prevalence of DVT, between 2.0 (2) and 14.8% (3) in ICU patients, most likely due to the absence of consistent screening. To the best of our knowledge, this is the first study performing systematic ultrasound examination for DVT diagnosis, thus providing data free of selection biases. Our data showed a remarkably high DVT prevalence (46%) and revealed the rapid time-course of thrombus formation despite prophylactic anticoagulation. Importantly, 50% of the DVT were popliteal or femoral, these being most often associated with thromboembolic events, consistent with the unexpectedly high number of pulmonary embolisms (21%) reported in SARS-CoV-2 pneumonia patients admitted to the ICU

and occurring within a median time from ICU admission of 6 days (range, 1-18) (4).

Our data suggests that close monitoring of DVT occurrence is necessary in mechanically ventilated SARS-CoV-2 patients, and since ultrasound may not always be available especially in epidemic settings, larger studies may investigate the diagnostic performance of D-dimers for DVT diagnosis in these patients. Moreover, the intensity of anticoagulation may need to be reconsidered based on future investigations to ensure more effective prevention (1).

In conclusion, we demonstrated a very high DVT prevalence including a high proportion of potentially life-threatening proximal DVT in mechanically ventilated SARS-CoV-2 patients despite standard prophylactic anticoagulant treatment, suggesting the need for close DVT monitoring and assessment of the risks/benefits of more intense anticoagulation regimens in this population.

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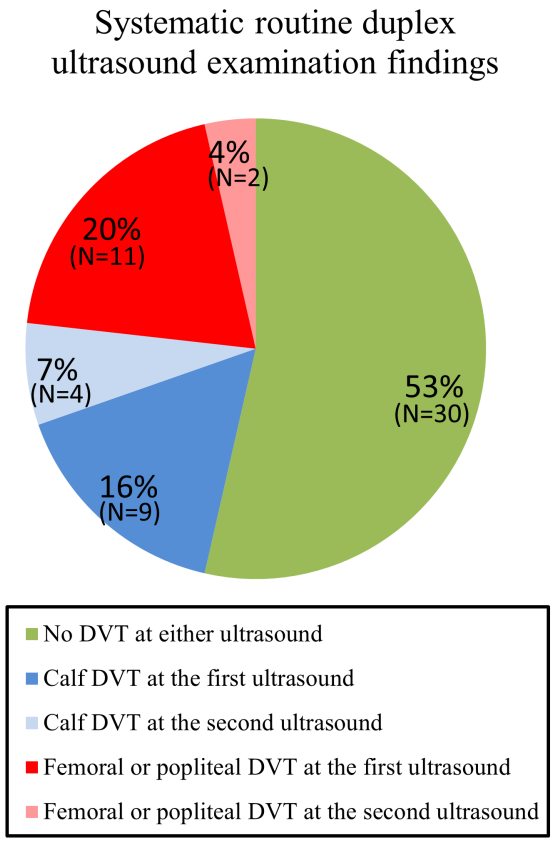
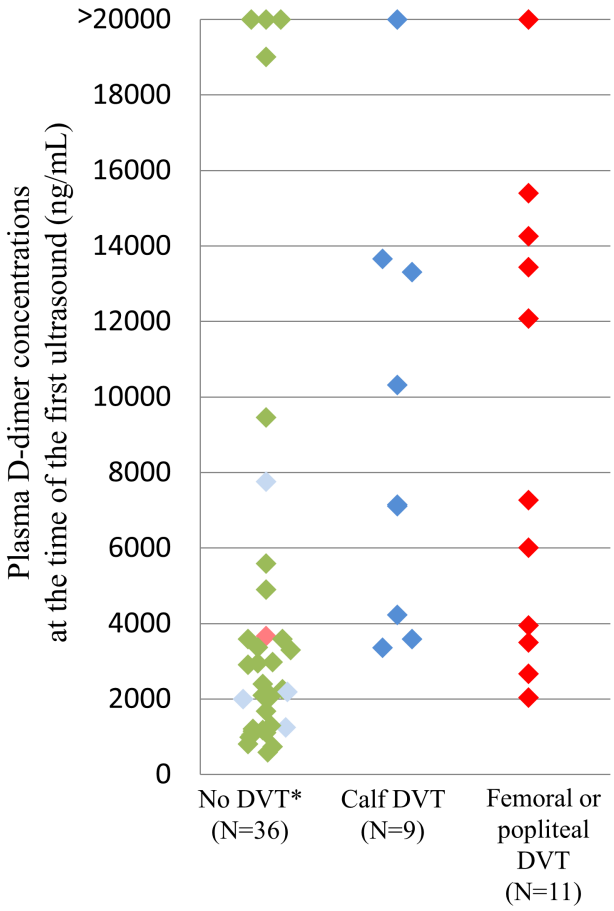
Figure Legend

Figure 1: Deep vein thrombosis (left panel) and plasma D-dimer (right panel) in 56 mechanically ventilated SARS-CoV-2 patients. Left: study groups as percentages of the total (numbers) according to the deep vein thrombosis (DVT) presence and site, at the initial and second ultrasound. Color significance is detailed in the figure. Right: lozenges represent individual concentrations of D-dimer at the initial ultrasound, according to the DVT presence and site, with the same color significance as in the left panel. In the "No DVT" group, the salmon lozenge and the light blue lozenges represent D-dimer in patients who developed femoral and calf DVT respectively, at the second ultrasound. *Missing D-dimer in one patient with popliteal DVT at the second ultrasound.


Systematic routine duplex ultrasound examination findings
4% (N=2)
20% (N=11)
7% (N=4)
53% (N=30)
16% (N=9)
No DVT at either ultrasound
Calf DVT at the first ultrasound
Calf DVT at the second ultrasound
Femoral or popliteal DVT at the first ultrasound
Femoral or popliteal DVT at the second ultrasound


Plasma D-dimer concentrations at the time of the first ultrasound (ng/mL)
>20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
No DVT* (N=36)
Calf DVT (N=9)
Femoral or popliteal DVT (N=11)