Original Article

Prevalence of deep venous thrombosis in ventilated COVID-19 patients: a mono-center cross-sectional study

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Background: COVID-19 patients are related with an elevated risk for deep venous thrombosis (DVT). We evaluated the prevalence of DVT in our intubated and mechanically ventilated COVID-19+ patients at March 29th.

Methods: We performed a Mono-center, investigator-initiated, observational, cross-sectional study. A total of 12 intubated COVID-19+ patients at intensive care unit (ICU) ward C3 of the Jessa Hospital, Hasselt, Belgium at March 29th were included. All patients received a prophylactic dose of low-molecular-weight heparin (LMWH). All intubated and mechanically ventilated patients were screened for the presence of DVT in femoral, popliteal, jugular and inferior caval veins with duplex ultrasound.

Results: In total, 8 from all 12 intubated and ventilated COVID 19+ patients had already developed minimally one DVT. No relevant correlations could be detected.

Conclusions: The prevalence of DVT in critically ill ICU patients with COVID-19 is over 60% despite adequate treatment with a prophylactic dose of LMWH. We suggest the use of graduated compression (elastic) stockings (GCS) and intermediate-dose LMWH for thrombosis prophylaxis in all COVID-19 patients. Since there were no clinical signs of DVT, we suggest to routinely screen all COVID-19 patients admitted to ICU for DVT via ultrasound. Future research should focus on the mechanisms underlying these observations.

Keywords: COVID-19; venous thrombosis; intensive care unit (ICU); catheterization; central venous; respiration; artificial

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Introduction

The spectrum of illness severity of COVID-19 is very wide: mild infection (no signs of lung involvement) is reported in approximately 80 percent, severe illness (e.g., with dyspnea or hypoxia) is reported in approximately 15 percent and critical disease (e.g., with respiratory failure, shock, or multiorgan dysfunction) is reported in 5 percent (1,2). The clinical manifestations of this disease may suggest that SARS-CoV-2 predominantly targets the respiratory tract. Consequently, respiratory failure due to severe bilateral pneumonia and/or acute respiratory distress syndrome (ARDS) has been reported as a major cause of death (1). Therefore, initial supportive therapy at our intensive care unit (ICU), Jessa Hospital, Hasselt, Belgium, focused mainly at respiratory support with (non)-invasive ventilatory support with oxygen- and positive end-expiratory pressure (PEEP).

On the 13th of March, the first COVID-19 patient was admitted to the ICU in our hospital. Within a few days the admissions at our COVID-19 ICU unit grew exponential. During the placement of a dialysis catheter in the femoral vein in one patient, we noticed a large deep vein thrombosis (DVT) proximal in both common femoral veins. This patient had no clinical signs of DVT. We hypothesised that thrombo-embolic phenomenon's may be another (at the time of writing) less-well known deadly complication of a severe COVID 19 infection. To test this hypothesis, we decided to evaluate the prevalence of deep venous thrombosis (DVT) in our intubated and mechanically ventilated COVID-19+ patients. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jeccm-20-62).

Methods

This mono-center, investigator-initiated, observational, cross-sectional study is performed at the ICU of the Jessa Hospital, Hasselt, Belgium. All intubated and mechanically ventilated COVID-19+ patients treated at ICU ward C3 on March 29th were included in the study. Selection bias was countered by inclusion of all intubated and mechanically ventilated COVID-19. There is no information bias since the collected information was objective. Confounding was not excluded in our analysis. The study was approved by the ethical committee of the Jessa Hospital, Hasselt, Belgium (Chairperson Dr. Koen Magerman, registration number 20.35_LEC_retrospectief) on April 10th 2020 and is executed based on the Declaration of Helsinki (as revised in 2013). The study is registered on clinicaltrials.gov (NCT04338932). Written informed consent was waived in light of the urgent need to collect data in the ongoing pandemic.

The primary endpoint of this study was the prevalence of DVT in intubated and mechanically ventilated COVID-19+ patients. All patients were screened for the presence of DVT in femoral, popliteal, jugular and inferior caval vein with duplex ultrasound. A positive diagnosis of DVT was based on a venous duplex ultrasound of the full legs, inferior caval vein and jugular veins.

A possible correlation between the presence of DVT and demographic variables, medical history, symptoms at admission to ICU, laboratory findings, medical treatment and ventilator parameters was also assessed.

All patients included in this study, were treated according to the COVID-protocol of the Jessa Hospital. This protocol was developed at the beginning of March 2020 based on the latest insights on COVID-19 at that time point, mainly focusing on the pulmonary involvement of the disease. According to this protocol, all patients admitted to our ICU received an IV-infusion with glucose 5% at 60 mL/h as maintenance fluid, stress ulcer prophylaxis with Pantoprazole 40 mg intravenously daily and thrombosis prophylaxis with Nadroparin subcutaneously 0.3 mL (2850 IE) daily. Prophylactic antibiotic therapy was initiated for 5 days, using Amoxicillin-clavulanic acid 1 g intravenously 4 times a day or moxifloxacin 400 mg intravenously once daily in case of known allergy to penicillin. The protocol also comprised the administration of hydroxychloroquine orally starting with a loading dose of 400 mg twice on the first day, followed by 200 mg twice a day, for 4 days, with daily monitoring of the QTC-interval by ECG. This therapy was interrupted if the QTC-interval exceeded 500 ms since QTC-interval prolongation is one of the well-known important side-effects of hydroxychloroquine potentially causing severe cardiac arrythmias. Ventilatory support was initiated with a high-flow nasal canulla or non-invasive mechanical ventilation as long as the patient was cooperative to this treatment. In case of respiratory fatigue, patients were sedated and intubated and invasive mechanical ventilation was started according to the ARDS-network guidelines that included a protocol based on low-oxygen and high-PEEP. This was based on the first reports that the viral pneumonia caused by SARS-CoV-2 mimics an ARDS-like pattern. Sedation was performed by a combination of propofol, midazolam

and piritramide aiming for the lowest level of sedation by which the patient would tolerate the mechanical ventilation. Adjustments were made guided by spO_2-levels, which are continuously monitored and arterial blood gasses taken every 4 hours. In case of hypotension due to vasoplegia, norepinephrine was used as first choice vasopressor.

Descriptive statistics were presented as frequencies and percentages, while numerical variables were presented as mean ± SD. A one-way ANOVA with Bonferroni correction for multiple testing was used to calculate differences between the groups. A P value <0.05 was considered statistically significant. All analyses are conducted using the statistical software Graphpad Prism version 5.1.

Results

In total, 8 from all 12 intubated and ventilated COVID 19+ patients treated at ICU-C3 in the Jessa Hospital, Hasselt, Belgium on march 29th had already developed minimally one DVT (*Table 1*).

Demographic data, underlying medical conditions and symptoms at admission of all intubated and mechanically patients with COVID-19 admitted at ICU on 2020/03/29 are presented in *Table 1*, stratified according to the presence of DVT.

Laboratory data, stratified according to the presence of DVT, are presented in *Table 2*. Platelet count and coagulation test values were not significantly different. Treatment, ventilator parameters and outcomes, stratified according to the presence of DVT, are presented in *Table 3*. We could not detect statistically significant differences between two groups. Location of DVT per patient is shown in *Table 4* and the relation of DVT with deep venous catheter is shown in *Table 5*.

Discussion

In this mono-centre cross-sectional study, assessment of the presence of DVT in intubated and mechanically ventilated COVID-19+ patients revealed a prevalence of DVT of more than 65%. No relevant correlations between the presence of DVT and demographic variables, medical history, symptoms at admission to ICU, laboratory findings, medical treatment and ventilator parameters could be detected. Presumably, patient groups were too small to demonstrate relevant correlations.

Virchow's triad describes the major DVT risk factors in three categories: venous stasis, vessel injury and activation of blood coagulation. Consequently, every ICU patient is at risk for thrombo-embolic events. The incidence of DVT during ICU stay has been reported between 10% and 30% (3). Our results however suggest that COVID-19 ICU patients are at two- or even three-fold increased relative risk of developing thrombo-embolic complications.

Our results are in line with recent literature. Klok *et al.* found an incidence of symptomatic acute pulmonary embolism (PE), DVT, ischemic stroke, myocardial infarction or systemic arterial embolism of 31% despite systematic thrombosis prophylaxis in 184 COVID-19 patients treated admitted to ICU (4). Wang *et al.* reported temporary improvement in the P/F ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen concentration) after off-label usage of alteplase for COVID-19 patients suffering from ARDS and respiratory failure (5). Tang *et al.* found improved mortality in severe COVID-19 patients, meeting sepsis induced coagulopathy criteria or with markedly elevated D-dimer, who received anticoagulant therapy (6).

Multiple studies have proposed that SARS-CoV-2 induces a hyper-inflammatory state (7-9). It has been suggested that systemic inflammation induces endothelial injury. The injury activates the coagulation cascade and impairs fibrinolysis with disruption of endothelial barrier and loss of physiologic antithrombotic factors. This process elevates the risk for venous thrombo-embolism (VTE) significantly (10).

Application of neuromuscular blocking agents (NMBA) to facilitate oxygenation and ventilation in severe ARDS (acute respiratory distress syndrome) may be another precipitating factor for the development of DVT due to patient immobilization (11). Boddi *et al.* already concluded that administration of NMBA is the strongest independent predictor for DVT (12). In this study, all 8 patients who developed a DVT received intermittent NMBA boluses to optimize oxygenation and ventilation and to facilitate prone-ventilation.

Prolonged mechanical ventilation (>7 days) is another well-known risk factor for the development of DVT (13). In this study, mean length of mechanical ventilation was 8 days. Furthermore, mechanical ventilation with high PEEP reduces blood flow to the heart. This may facilitate stasis of venous blood and can promote formation of a DVT despite adequate prophylaxis (12,14,15). A high PEEP-strategy was applied in all our mechanically ventilated patients, according to the local COVID-protocol. Theoretically, these ventilator settings may have additionally increased

Table 1 Demographic data, underlying medical conditions and clinical manifestations of patients with COVID-19 admitted at ICU on 2020/03/29

Variable	DVT (n=8)	No DVT (n=4)	P value
Age (years)	62.4±5.6	65.5±14.7	0.59
>65, n (%)	3 (37.5)	3 (75.0)	
Gender (male), n (%)	7 (87.5)	2 (50.0)	
BMI (kg/m^2), n (%)	28.5±5.0	28.0±5.2	0.89
<20.0	0 (0)	0 (0.0)	
20.0–24.9	3 (37.5)	2 (50.0)	
25.0–29.9	2 (25.0)	1 (25.0)	
30.0–39.9	3 (37.5)	1 (25.0)	
≥40.0	0 (0.0)	0 (0.0)	
Co-morbidities, n (%)			
Cardiovascular disease	0 (0.0)	2 (50.0)	
Hypertension	3 (37.5)	2 (50.0)	
Diabetes	0 (0.0)	0 (0.0)	
Respiratory disease	4 (50.0)	0 (0.0)	
Malignancy	0 (0.0)	0 (0.0)	
Chronic renal disease	1 (12.5)	0 (0.0)	
Chronic liver disease	0 (0.0)	0 (0.0)	
Chronic bowel disease	1 (12.5)	0 (0.0)	
Chronic nerve disease	0 (0.0)	0 (0.0)	
Cerebrovascular disease	0 (0.0)	1 (25.0)	
HIV/AIDS	0 (0.0)	0 (0.0)	
Haematological disease	2 (25.0)	0 (0.0)	
Obesity	3 (37.5)	1 (25.0)	
Rheumatological disease	0 (0.0)	0 (0.0)	
Dementia	0 (0.0)	0 (0.0)	
Symptoms at hospital admission, n (%)			
Fever	8 (100.0)	2 (50.0)	
Cough	8 (100.0)	4 (100.0)	
Dyspnoea	6 (75.0)	3 (75.0)	
Sputum production	2 (25.0)	0 (0.0)	
Myalgia	4 (50.0)	3 (75.0)	
Headache	3 (37.5)	0 (0.0)	
Diarrhoea	1 (12.5)	0 (0.0)	
Rhinorrhoea	3 (37.5)	0 (0.0)	
Pharyngalgia	1 (12.5)	0 (0.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	DVT (n=8)	No DVT (n=4)	P value
Dizziness	1 (12.5)	0 (0.0)	
Nausea/vomiting	3 (37.5)	0 (0.0)	
Thoracic pain	2 (25.0)	0 (0.0)	
Palpitations	0 (0.0)	0 (0.0)	
Length of hospital stay up till ICU admission (days)	3.1±2.5	1.0±1.4	0.15
Length of ICU stay[A]	9.0±4.0	7.8±5.1	0.65
Vital signs at ICU admission			0.11
Temperature (℃)	37.2±0.9	38.4±0.3	
Breathing rate (#/min)	28.7±8.5	26.3±6.6	
Systolic blood pressure (mmHg)	142.9±32.7	137.5±20.0	
Mean arterial blood pressure (mmHg)	87.1±19.7	75.0±101	
Heart rate (#/min)	85.4±19.9	97.5±14.5	
Glasgow Coma Scale, n (%)			
3/15	3 (37.5)	1 (25.0)	
15/15	5 (62.5)	3 (75.0)	

Data are n (%) or mean ± standard deviation. [A], up until 2020/03/29. DVT, deep venous thrombosis; BMI, body mass index (kg/m^2); HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

Table 2 Laboratory findings of patients with COVID-19 admitted at ICU on 2020/03/29

Variables	Submission at ICU			2020/3/29		
	DVT (n=8)	No DVT (n=4)	P value	DVT (n=8)	No DVT (n=4)	P value
pH	7.44±0.1	7.47±0.0	0.44			
pCO_2 (mmHg)	35.0±8.6	31.5±3.9	0.46			
pO_2 (mmHg)	81.0±69.5	52.5±20.7	0.45			
Oxygen saturation (%)	89.4±9.0	93.0±1.0	0.85			
Potassium (mmol/L)	3.7±0.3	3.7±0.2	0.51			
Sodium (mmol/L)	133.5±3.8	133.8±3.0	0.87			
Calcium (mmol/L)	1.1±0.5	1.1±0.0	0.56			
Bicarbonate (mmol/L)	22.6 ±2.2	22.3±2.6	0.79			
Base excess (mmol/L)	−1.1±2.6	−0.5±1.8	0.69			
Lactate (mmol/L)	2.0±1.4	3.0±2.1	0.34			
Glucose (mg/dL)	113.6±16.3	139.5±25.0	0.05			
Haemoglobin (mg/dL)	12.5±1.7	12.5±1.9	1.00	9.3±1.3	9.5±1.0	0.81

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Submission at ICU			2020/3/29		
	DVT (n=8)	No DVT (n=4)	P value	DVT (n=8)	No DVT (n=4)	P value
Basophiles (%)	0.1±0.3	0.0±0.0	–			
Eosinophils (%)	0.6±1.6	0.0±0.0	–			
Monocytes (%)	3.7±3.8	2.5±1.6	0.55			
Neutrophils (%)	87.0±12.2	89.2±4.6	0.73			
Haematocrit (%)	37.2±4.3	37.5±5.4	0.93	29.7±2.7	29.8±3.4	0.97
Red blood cells ($\times10^{12}$/L)	4.3±0.9	4.1±0.5	0.70			
White blood cells ($\times10^{9}$/L)	8.5±3.0	8.4±3.7	0.97	13.1±7.0	7.1±1.2	0.12
Platelets ($\times10^{9}$/L)	228.9±74.7	262.5±95.1	0.51	225.3±91.1	253.0±73.2	0.61
PT (%)	87.1±15.1	89.8±19.2	0.79	83.7±15.5	83.0±14.2	0.94
aPTT (s)	35.9±5.9	39.1±8.1	0.47	48.1±9.1	42.3±8.2	0.31
Fibrinogen (g/L)	4.1±0.1[A]	N/A	–	N/A	N/A	
D-dimers (mg/L)	0.6±0.0[B]	1.39±0.0[B]	–	N/A	N/A	
PT (INR) (ratio)	1.1±0.1	1.1±0.1	0.85	1.1±0.2	1.1±0.1	0.95
Ureum (mg/dL)	41.1±14.6	46.8±31.5	0.67	61.6±27.3	41.3±23.0	0.23
Creatinine (mg/dL)	1.1±0.4	1.0±0.4	0.85	1.6±0.7	1.1±0.9	0.30
eGFR	77.6±22.9	73.3±32.9	0.79			
Total bilirubin (mg/dL)	0.8±0.9	0.4±0.1	0.34	2.1±1.7	0.6±0.4	0.21
AST (U/L)	55.7±21.1	83.5±79.9	0.35			
ALT (U/L)	38.1±11.2	53.8±53.9	0.42			
Lactate dehydrogenase (U/L)	400.0±96.3[C]	505.0±163.8	0.20			
Troponin T (ng/L)	15.6±7.1	32.2±16.4[D]	0.03*	56.8±74.8	20.2±16.4	0.36
CRP (mg/L)	208.9±142.3[C]	252.5±58.5	0.57	320.0±74.8	307.5±90.7	0.73
Ferritin (mg/L)	1,840±720.1	1,833.0±850.5[D]	0.99			

Data are mean ± standard deviation. [A], n=2; [B], n=1; [C], n=7; [D], n=3. *, P<0.05 is considered statistically significant. DVT, deep venous thrombosis; N/A, not available; pCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein.

Table 3 Treatment and outcomes of patients with COVID-19 admitted at ICU on 2020/03/29

Variables	DVT (n=8)	No DVT (n=4)	P value
Treatment, n (%)			
Antiviral treatment	0 (0.0)	0 (0.0)	
Antibiotic treatment	8 (100.0)	4 (100.0)	
Antifungal treatment	0 (0.0)	0 (0.0)	
Corticosteroid treatment	1 (12.5)	1 (25.0)	
CRRT	2 (25.0)	1 (25.0)	
IVIg treatment	0 (0.0)	0 (0.0)	
Plaquenil treatment	6 (75.0)	4 (100.0)	
Oxygen therapy			
Invasive mechanical ventilation, n (%)	8 (100.0)	4 (100.0)	
FiO_2 (mmHg)	67.4±19.5	71.3±23.2	
PEEP	16.8±3.2	17.3±6.1	
Length of ventilation[A]	8.0±2.7	7.0±5.6	0.76
ECMO, n (%)	0 (0.0)	0 (0.0)	0.83
Invasive mechanical ventilation + ECMO, n (%)	0 (0.0)	0 (0.0)	0.67
Vasopressor/inotropic support, n (%)	8 (100.0)	3 (75.0)	
Neuromuscular blocking agents, n (%)	8 (100.0)	2 (50.0)	
Prone ventilation, n (%)	5 (62.5)	2 (50.0)	
Complications, n (%)			
ARDS	8 (100.0)	3 (75.0)	
Acute kidney failure	3 (37.5)	1 (25.0)	
Acute heart failure	2 (25.0)	0 (0.0)	
Septic shock	1 (12.5)	0 (0.0)	
Secondary infection	7 (87.5)	4 (100.0)	
Seizure	2 (25.0)	0 (0.0)	
Stroke	0 (0.0)	0 (0.0)	
Hyperglycemia	0 (0.0)	0 (0.0)	
Hypoglycemia	0 (0.0)	1 (25.0)	

Data are n (%) or mean ± standard deviation. [A], number of days. DVT, deep venous thrombosis; CRRT, continuous renal replacement therapy; IVIg, intravenous immunoglobulin; ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome.

Table 4 Location of DVT per patient

Patient	Jugular	Inferior caval vein	Femoral	Popliteal	Gastrocnemius
1	1	0	0	0	0
2	0	0	1	0	0
3	1	0	0	0	0
4	0	0	0	0	1
5	0	0	2	0	0
6	0	0	2	0	0
7	0	0	2	1	0
8	1	0	0	1	1

DVT, deep venous thrombosis.

Table 5 Location of DVT and relation to central venous catheter

Position of DVT	Central venous catheter related	Non-central venous catheter related
Internal jugular vein	4	0
Axillary vein	1	0
Femoral vein	1	2
Popliteal vein	1	1
Gastrocnemius vein	0	1

DVT, deep venous thrombosis.

patient's intra-thoracic pressure and impaired venous return. However, a positive correlation between high PEEP and development of upper extremity DVT's could not be demonstrated (16).

Central venous catheterization is another well-known risk factor for DVT due to the vessel injury and venous stasis (17). In this study, 63.6% (7/11) of the proved DVT's were associated with an indwelling catheter (*Table 5*).

Obesity is another risk factor for DVT (18). This might be explained by blood stasis due to the impaired venous return caused by the chronic increased intra-abdominal pressure. Furthermore, a relative hypercoagulability state may be present within the obese population due to an elevation of pro-thrombotic factors and impaired fibrinolysis (19). In this study, 58% (7/12) of included patients were overweight and 33% (4/12) were obese.

Dehydration has also been proposed to elevate the risk of DVT since a higher viscosity of the blood may decrease venous return (20). In total, 40% of COVID-19+ patients report dehydration prior to hospitalization (1). Furthermore, according to the surviving sepsis guidelines for COVID-19 patients, we also applied a fluid restrictive policy (17). These two factors may have led to relative dehydration of our patients and an elevated risk of developing DVT's.

Last but not least, SARS-CoV-2 itself may induce coagulopathy and an increased risk of VTE's. Multiple viruses have been associated with thrombo-embolic events (21). Several mechanisms have been proposed to explain this association: alteration of the level of a variety of coagulation proteins, viral platelet binding with subsequent platelet activation, viral induction of endothelial injury resulting in activation of coagulation and fibrinolysis impairment, due to increased levels of plasminogen activator inhibitor-1 (21). Very recently, The American Association of Hematology also recognizes the possibility that a severe COVID-19 infection may elicit a fulminant activation of coagulation (22).

This study also contains some limitations. First, due to cross-sectional design of the study, there is a lack of temporal relationship between the development of DVT and the different risk factors that were evaluated. Second, due to the small sample size, the prevalence of DVT may be overestimated in this study. Third, for small sample sizes, it is unrealistic to look for correlations across large number of parameters. Fourth, patients in this study only received a prophylactic dose of low-molecular-weight heparin (LMWH). A follow-up study would be interesting to assess the effect of the measures taken to lower the risk of DVT's. Finally, the generalisability of these results may be questioned due to the single-centre design.

In conclusion, our results suggest that the prevalence of

DVT in critically ill ICU patients with COVID-19 treated with a prophylactic dose of LMWH is more than 60%. Consequently, the risk of VTE complications in this patient group is very high. In the light of these considerations, we suggest the use of thigh-high graduated compression (elastic) stockings (GCS) and intermediate-dose LMWH for thrombosis prophylaxis in all COVID-19 patients with daily anti-Xa-activity monitoring to provide adequate therapy since an important interpatient variability has been reported. Furthermore, we suggest to routinely screen all COVID-19 patients admitted to ICU for DVT twice weekly via venous duplex ultrasound.

Future research should focus on the mechanisms underlying these observations.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jeccm-20-62

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the ethical committee of the Jessa Hospital, Hasselt, Belgium (Chairperson Dr. Koen Magerman, registration number 20.35_LEC_retrospectief) on April 10th 2020 and is executed based on the Declaration of Helsinki (as revised in 2013). The study is registered on clinicaltrials.gov (NCT0433893). Written informed consent was waived in light of the urgent need to collect data in the ongoing pandemic.

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