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# Characteristics of Venous Thromboembolism in COVID-19 Patients: A Multicenter Experience from Northern Italy

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**Background:** The liability of patients affected by novel coronavirus disease (COVID-19) to develop venous thromboembolic events is widely acknowledged. However, many particulars of the interactions between the two diseases are still unknown. This study aims to outline the main characteristics of deep venous thrombosis (DVT) and pulmonary embolism (PE) in COVID-19 patients, based on the experience of four high-volume COVID-19 hospitals in Northern Italy.

**Methods:** All cases of COVID-19 in-hospital patients undergoing duplex ultrasound (DUS) for clinically suspected DVT between March 1st and April 25th, 2020, were reviewed. Demographics and clinical data of all patients with confirmed DVT were recorded. Computed tomography pulmonary angiographies of the same population were also examined looking for signs of PE.

**Results:** Of 101 DUS performed, 42 were positive for DVT, 7 for superficial thrombophlebitis, and 24 for PE, 8 of which associated with a DVT. Most had a moderate (43.9%) or mild (16.9%) pneumonia. All venous districts were involved. Time of onset varied greatly, but diagnosis was more frequent in the first two weeks since in-hospital acceptance (73.8%).

Most PEs involved the most distal pulmonary vessels, and two-thirds occurred in absence of a recognizable DVT.

**Conclusions:** DVT, thrombophlebitis, and PE are different aspects of COVID-19 procoagulant activity and they can arise regardless of severity of respiratory impairment. All venous districts can be involved, including the pulmonary arteries, where the high number and distribution of the thrombotic lesions without signs of DVT could hint a primitive thrombosis rather than embolism.

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## INTRODUCTION

Novel coronavirus pneumonia (COVID-19) has rapidly spread worldwide, affecting more than 15 million people and killing over 600,000.<sup>1</sup> Although several reports and reviews have been published so far concerning its pathogenic activity and related morbidity and mortality, much still remains unknown, especially regarding its effects on the vascular system. In fact, like in other respiratory infections, important alterations in the hemostatic functions, namely a procoagulant effect, have been described in critically ill COVID-19 patients, yielding to an increased incidence of venous thromboembolism (VTE) that has been estimated between

**Table I.** DVT in COVID-19 patients (1st March, 2020, to 25th April, 2020)

Severity (CRP range)	N (%)	Median age (IQR)	M:F	Median DUS day since acceptance (IQR)	Median D-dimer value at the diagnosis (mcg/L)	PE
Mild (0–4.9 mg/L)	8 (19.6)	65 (15)	5:3	15.5 (8.5)	7,083	2
Moderate (5–29.9 mg/L)	18 (43.9)	63.5 (9)	13:5	7.5 (11)	12,173	2
Severe (30–99 mg/L)	9 (21.9)	72 (10)	6:3	5 (2)	7,300	3
Critical (>100 mg/L)	6 (14.6)	66.5 (7.5)	5:1	12 (9)	14,092	1
Tot.	42	65 (14.5)	29:12	11 (8)	9,300 (13,059)	8

25% and 29% among those hospitalized in intensive care unit (ICU).<sup>2,3</sup> However, although the higher liability of COVID-19 patients to develop VTE is widely acknowledged, many aspects of this frequent and worrisome complication have not been investigated yet: the most pressing questions that need to be addressed concern its time of onset, if and how it relates with the severity and progression of the pneumonia, and whether it affects in particular some venous districts.

The present study conducted across four high-volume hospitals for COVID-19 patients in Lombardy, the Italian region that was affected the most by the pandemics, aims to offer a contribution to address those questions.

## METHODS

The vascular surgery units of the four participating centers reviewed all the duplex ultrasound (DUS) that were demanded for COVID-19 patients suspected for VTE between March 1st and April 25th, 2020. Demographics (age and sex) and clinical conditions of patients that turned out positive for DVT were recorded, including pneumonia severity and respiratory assistance, day of DVT diagnosis since hospital admittance, significant risk factors for DVT, and venous district affected, along with D-dimer levels. Categorical variables were expressed with numbers and percentages on the total and continuous variable as median and interquartile range (IQR). The severity assessment was based on c-reactive protein (CRP) levels, stratified as shown in [Table I](#), which has been demonstrated a valuable marker of the extent of pulmonary involvement.<sup>4</sup> Meanwhile, the computed tomography pulmonary angiography (CTPA) of the COVID-19 patients screened for DVT were reviewed searching for signs of pulmonary embolism (PE). All patients found positive for DVT were prescribed anticoagulant doses of low molecular weight heparin (LMWH) and followed up by DUS after ten days. Three patients were already receiving oral anticoagulant

therapy and one anticoagulant dosage of heparin treatment because of atrial fibrillation (3 cases) and a previous DVT.

## RESULTS

A total number of 101 DUS was performed across the four participating centers on COVID-19 patients, 42 of them being found positive for DVT and 7 for superficial thrombophlebitis. Among those found positive for DVT, male sex was largely predominant (29 males and 13 females), reflecting the gender gap existing among in-hospital COVID-19 patients, and median age was 65 years (range: 49–83, IQR: 14.5). Most significant risk factor for DVT were the presence of a central venous catheter in the affected vein (6 cases), overweight and obesity (4 patients), malignancy (2 cases), and pregnancy (1 case). Three patients in the ICU were already under anticoagulant therapy, whereas the rest were receiving prophylactic dosages of EBPM. Only 11 patients were in the ICU, the rest being hospitalized in infectious diseases, pneumology, and general medicine units, where administration of prophylactic heparin treatment was adopted at physician discretion, based on a case-by-case evaluation. Among those patients, four had had a previous episode of DVT or PE in their life, based on the available medical reports, but only one within the previous year. Most frequent respiratory support was continuous positive airway pressure (C-PAP, 20 patients), followed by orotracheal intubation (8 patients) and noninvasive ventilation (7 patients); 6 patients had no respiratory support and 1 had a tracheostomy. Although median CRP was high (45 mg/L, IQR: 82), severity assessment of the patients based on CRP showed that all grades of intensity could be affected by VTE, with a predominance of the moderate grade, which reflects most in-hospital patients ([Table I](#)). Median levels of D-dimer were 9.3 mg/L (IQR: 13.06). Most cases were diagnosed within the first two weeks since hospital admittance, with even distribution between the first and the second ([Table II](#)), and most

**Table II.** Time of DVT diagnosis by week

Week of diagnosis	Patients (N)
1st (days 0–7)	16
2nd (days 8–14)	15
3rd (days 15–21)	6
Later than 4th (>21)	5

common reason why the DUS was asked was sudden pain of the target limb, followed by edema and/or redness, as reported in [Table III](#). One patient was diagnosed with a DVT of the common femoral vein after PE was observed at CTPA. Most frequently affected sites were the lower limbs, especially the femoral and popliteal veins, together or separately, and the brachial-axillary vein ([Tables III–V](#)). Three patients with upper limb thrombosis had jugular central venous catheter (CVC) and one a peripherally inserted central catheter. Five more cases of femoral vein thrombosis arose from a femoral CVC.

Concerning PE, among the COVID-19 patients referred to vascular surgery units for suspected DVT, 24 cases were positive at the CTPA: 8 with a recognized DVT and 3 with a concomitant thrombophlebitis. The rest were negative for lower and upper limb DVT. The median diagnosis time was 12 days since admission (range: 4–20).

## DISCUSSION

A procoagulant role of COVID-19 has been confirmed both by laboratory and clinical findings, as well as the high risk of VTE in critically ill in-hospital COVID-19 patients.<sup>2,3</sup> Outlining the existing relationship between those two diseases is of the utmost importance, not only to recognize and treat promptly this dangerous and frequent complication, but also because VTE is probably associated with poor prognosis and is said to predict systemic disseminated intravascular coagulation.<sup>5</sup> Most evidence reporting on the incidence of DVT in COVID-19 patients focuses on critically ill ICU patients, although some reports have involved non-ICU cases also with mild or moderate pneumonia.<sup>5–7</sup> This case series clearly shows that VTE can affect in-hospital COVID-19 patients regardless of grade and extent of their disease or other risk factors. In fact, the distribution of VTE events showed no predilection for critical and severe patients, as expected, but 46% of patients that were positive for DVT had a moderate pulmonary involvement, as shown by the CRP levels. This consideration is also

supported by the fact that most patients were not under mechanical ventilation with orotracheal tube, but were ventilated with C-PAP, so their respiratory impairment was only partial. The predilection of VTE events for male sex and age groups ranging between 50 and 80 years reflects the characteristics of the population examined. The fact that only 11 patients were hospitalized in ICU and 15 had a severe or critical illness is probably due to the fact that most of ICU patients receive anticoagulant therapy from the beginning, as a result of the existing evidence, whereas heparin is not routinely administered to noncritical, non-ICU hospitalized patients. Therefore, the first conclusion that can be drawn from these data is that administration of anticoagulant or at least prophylactic doses of LMWH should be considered for non-ICU patients also. Moreover, a discussion on whether a DUS screening program should be organized or not in all COVID-19 in-hospital patients, as suggested for ICU patients, should be started, based on the evidence available so far.<sup>3,5</sup>

The second consideration regards the timing of onset of DVT: it has been claimed that DVT is an early complication of COVID-19 pneumonia and that it can often be diagnosed directly at the time of hospitalization. This study shows conflicting findings on the matter, as displayed in [Table II](#): it is true, in fact, that 16 cases of 42 (38%) were found on the first week since hospital admission, six of whom at first medical contact, on the first day, but, on the other hand, almost as many patients showed the first symptoms only the following weeks, and a lesser, but considerable, number of cases were diagnosed even later, on the third and fourth week, which should lead to conclude that DVTs can arise in any phase of COVID-19, although there seems to be some predilection toward the early phase, when the first respiratory symptoms appear.

Concerning the DVT site, the lower limbs is confirmed as the most frequently affected, although the upper limb are affected as well, and even the jugular veins and vena cava, consistently with the systemic endothelial activation hypothesis.

The last, perhaps most interesting observation regards PE: its high rate in COVID-19 has already been observed and discussed, with an incidence reported as high as 20.4% in ICU patients.<sup>7</sup> This study found 24 cases of PE only among those patients who were referred to vascular surgery units for suspected DVT, but only 8 of them had a concomitant DVT. Some had superficial thrombophlebitis, and 16 were negative for ultrasound signs of DVT in all explorable districts. Although the sensitivity of the US for iliac and caval thrombosis is limited, it is possible that most cases of PEs without DVT were

**Table III.** Chief complaint or findings justifying DUS

Complaint or finding	DVT	Thrombophlebitis
Pain of the limb	22	3
Edema/redness of the limb	17	4
High D-dimer (>15 mg/L)	2	
Primary PE	1	

**Table IV.** Site of DVT and thrombophlebitis

Site of DVT	N (%)	Site of thrombophlebitis	N (%)
Femoral veins	13	GSV	1
Popliteal veins	8	LSV	1
Femoropopliteal axis	6	Basilic vein	3
Calf veins	4	Cefalic vein	1
Brachial-axillar axis	9		
Jugular vein	1		
Inferior vena cava	1		

GSV, great saphenous vein; LSV, lesser saphenous vein.

**Table V.** DVT, thrombophlebitis, and PE across the four participating centers

Center	Total DUS performed in COVID-19 pts	DVT	Thrombophlebitis	PE
IRCCS Policlinico S. Matteo, Pavia	53	22	6	15 (4 with DVT) (3 with thrombophlebitis)
Istituto di Cura Città di Pavia, Pavia	14	4	-	1 (with DVT)
Ospedale Maggiore, Lodi	32	13	0	6 (2 with DVT)
Ospedale Maggiore, Crema	4	3	1	2 (1 with DVT)
Tot.	101	42	7	24 (8 with DVT)

the result of primary pulmonary thrombosis instead of peripheral embolism. In fact, the aspect of the pulmonary tree visible at most CTPAs showed microembolism of the most distal branches, or embolism of the subsegmentary and segmentary pulmonary arteries, meaning that the vascular lesions had a marked tendency to locate in the vessels of lesser caliber. That could mean either that they are extremely small fragment detached from small peripheral thrombi that were not visible by US scan, or that multiple disseminated thrombosis occurs directly in the pulmonary arteries, as a result of the infection or the inflammatory response, as hypothesized by Lodigiani et al.<sup>8</sup> In other words, DVT, thrombophlebitis, and PE are probably different and often independent manifestations of the inflammatory process that arise as a consequence of the infection. Like DVT, PE also can arise

in ICU and non-ICU patients equally, and time of diagnosis is greatly variable.

The limits of this study include its retrospective nature and the lack of incidence and prevalence data of DVT in COVID-19 patients because it is only based on those cases that were referred to the vascular surgeons for suspected DVT, and cannot offer a whole panorama of the whole population of COVID-19 in-hospital patients. Therefore, it is possible that silent, undiagnosed DVT makes the total number of in-hospital COVID-19 patients with DVT considerably larger than that examined here and the same can be said for PE because the CTPAs analyzed were also limited to the same sample of patients: having shown that most cases are negative for DVT, the number of PE among in-hospital COVID-19 patients is expected to be even higher than those of DVTs. However, this is not a

prevalence study, and its aim is to describe the most important and most peculiar characteristics of VTE in COVID-19, which is already acknowledged as a common and severe complication of this disease. In this respect, the observations made previously should be useful in learning how to manage it, both in terms of early recognition and treatment, even in its most insidious forms and presentations, namely primitive PE. The lack of a control group to compare the results reported is also an important shortcoming, but to conduct a full controlled study in the present situation of health emergency would have delayed the publication of these results too much, and we think it in the best interest of the readers to be provided with the present data, albeit partial, as soon as possible. Another limit is the lack of information regarding the general prognosis and disease progression, which require a longer follow-up period to be available. Once they are collected and reviewed, they will provide a more complete picture of the course of VTE in COVID-19, especially concerning its response to anticoagulation, which still needs further explanation, as suggested by the cases, reported here and by Llitjos et al., of VTE onset under anticoagulation.<sup>2</sup>

## CONCLUSIONS

COVID-19 causes a diffuse procoagulant status that can be due to endothelial direct activation by the virus or by the inflammatory response, which can be manifested as DVT, thrombophlebitis, and PE, each of them either in association or isolated.

The main characteristics of VTE in COVID-19 are the capacity to affect all in-hospital patients, regardless of ICU or non-ICU stay, severity of pneumonia, and degree of respiratory failure. Age and sex prediction reflect the in-hospital population of these patients. Unlike previously reported, the timing of

onset is variable, ranging from the first day of hospitalization to the fifth week, although early onset seems slightly more frequent.

Moreover, PE is common, often affects the most distal branches of the pulmonary arteries and can arise without concomitant DVT, suggesting the possibility of primary pulmonary thrombosis.

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