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BRIEF REPORT

Incidence of deep vein thrombosis among non-ICU patients hospitalized for COVID-19 despite pharmacological thromboprophylaxis

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Abstract

Background: A remarkably high incidence of venous thromboembolism (VTE) has been reported among critically ill patients with COVID-19 assisted in the intensive care unit (ICU). However, VTE burden among non-ICU patients hospitalized for COVID-19 that receive guideline-recommended thromboprophylaxis is unknown.

Objectives: To determine the incidence of VTE among non-ICU patients hospitalized for COVID-19 that receive pharmacological thromboprophylaxis.

Methods: We performed a systematic screening for the diagnosis of deep vein thrombosis (DVT) by lower limb vein compression ultrasonography (CUS) in consecutive non-ICU patients hospitalized for COVID-19, independent of the presence of signs or symptoms of DVT. All patients were receiving pharmacological thromboprophylaxis with either enoxaparin or fondaparinux.

Results: The population that we screened consisted of 84 consecutive patients, with a mean age of 67.6 ± 13.5 years and a mean Padua Prediction Score of 5.1 ± 1.6. Seventy-two patients (85.7%) had respiratory insufficiency, required oxygen supplementation, and had reduced mobility or were bedridden. In this cohort, we found 10 cases of DVT, with an incidence of 11.9% (95% confidence interval [CI] 4.98-18.82). Of these, 2 were proximal DVT (incidence rate 2.4%, 95% CI −0.87-5.67) and 8 were distal DVT (incidence rate 9.5%, 95% CI 3.23-5.77). Significant differences between subjects with and without DVT were D-dimer > 3000 μg/L ($P < .05$), current or previous cancer ($P < .05$), and need of high flow nasal oxygen therapy and/or non-invasive ventilation ($P < .01$).

Conclusions: DVT may occur among non-ICU patients hospitalized for COVID-19, despite guideline-recommended thromboprophylaxis.

KEYWORDS

COVID-19, deep vein thrombosis, thromboprophylaxis, venous thromboembolism

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1 | INTRODUCTION

Since the beginning of 2020, the infectious disease caused by coronavirus 2 (SARS-CoV-2), named COVID-19, has spread around the world becoming a global emergency.[1,2] In the last few months there has been increasing appreciation that venous thromboembolism (VTE) might contribute to acute respiratory failure in COVID-19 patients and affect clinical outcome. Indeed, subjects hospitalized for COVID-19 are the prototypical example of acutely ill medical patients at increased risk of VTE, as they suffer from an acute infection; may have acute respiratory failure; and often are bedridden, or have reduced mobility, because they need oxygen supplementation and/or are isolated in their room due to hospital restrictions. The concomitant presence of these conditions substantially increases the risk of VTE, and this risk may be even higher if other factors, such as cancer, history of previous VTE, and age ≥70 years, exist.[3] In addition, some COVID-19 patients may have significant abnormalities of coagulation parameters, including D-dimer levels above >1000 μg/L,[4] and this further supports the concept that VTE needs to be properly prevented in these patients.

A remarkably high incidence of VTE has been recently reported among COVID-19 patients assisted in the intensive care unit (ICU), although all patients were receiving at least thromboprophylactic doses of anticoagulants.[5,6] Also, there are autopsy data indicating that deep vein thrombosis (DVT), pulmonary embolism (PE), and various types of microvascular pathology may be found in patients deceased for COVID-19, although such findings have not been confirmed in other autopsy series.[7-9] Based on this and other anecdotal reports, many physicians are advocating the empiric use of therapeutic anticoagulation even in patients who do not have a documented diagnosis of VTE.[10] On the other hand, the current position of the majority of medical societies still is to use standard prophylactic doses of anticoagulation for hospitalized COVID-19 patients, as is recommended for other acutely ill medical patients.[11,12]

In this study, we performed a systematic screening for the diagnosis of DVT in non-ICU consecutive patients hospitalized for COVID-19 that were receiving pharmacological thromboprophylaxis.

Essentials

- The incidence of deep vein thrombosis (DVT) among patients hospitalized for COVID-19 is unknown.
- A screening for DVT was performed in COVID-19 patients that were receiving thromboprophylaxis.
- The incidence of DVT was 11.9% (95% confidence interval 4.98-18.82). Most DVTs were asymptomatic.
- DVT may occur in COVID-19 patients despite guideline-recommended thromboprophylaxis.

2 | METHODS

All the patients affected by COVID-19 and hospitalized at the Fondazione Policlinico Universitario A. Gemelli IRCCS (Rome, Italy) between 3 April 2020 and 10 April 2020 were included in the study, with the exception of those younger than 18 years, those assisted in the ICU, and those receiving full-dose anticoagulant therapy for conditions such as atrial fibrillation and/or previous VTE. All patients had an established diagnosis of infection by SARS-CoV-2, confirmed by a positive molecular assay on oral/nasopharyngeal swabs. All patients were receiving a prophylactic dose of anticoagulant (either enoxaparin 40 mg once daily or fondaparinux 2.5 mg daily) since the first day of hospitalization, in keeping with the internal guidelines of our University Hospital for the prevention of VTE.

Venous compression ultrasonography (CUS) of the legs was performed on all enrolled patients during hospital stay, using a Philips CX50 portable ultrasound system, and consisted in the assessment of the proximal and distal deep venous system of both legs. The distal veins included in the study were the posterior tibial, fibular, gastrocnemius (internal and external), and soleal veins. All venous segments were examined in real-time B-mode using color Doppler in transverse and longitudinal views. Lack of compressibility, or direct identification of an endoluminal thrombus, were the criteria used for the diagnosis of DVT, as established in the literature.[13]

Demographic data, clinical characteristics, and laboratory results were collected from the medical charts of our hospital. Respiratory insufficiency was defined as PaO2 <60 mm Hg and/or PaCO2 >50 mm Hg in room air, or need for oxygen supplementation. Complete blood tests were available for all patients, including D-dimer levels, which were assessed by using a latex agglutination test. The Padua Prediction Score (PPS) was calculated for all patients.

Data are presented as means ± standard deviation (SD), or number and percentage when appropriate. *T* test or Mann-Whitney *U* test were used to assess differences between groups of patients. $P < .05$ was defined as statistically significant. Statistical analysis was conducted using SPSS software version 21.0 (IBM).

The study was approved by the Ethics Committee of the Fondazione Policlinico Universitario A. Gemelli IRCCS (Rome, Italy; ID number 3149). Due to the nature of the study, the Ethics Committee waived the need for informed consent.

3 | RESULTS

A total of 84 hospitalized COVID-19 patients were studied. The demographic, clinical, and laboratory data of the studied population are presented in Table 1. The mean age was 67.6 ± 13.5 years. There were 61 males (72.6%) and 23 females (27.4%). The following comorbidities were present at the time of hospital admission: hypertension

TABLE 1 Demographic, clinical, and laboratory characteristics of the 84 patients hospitalized for COVID-19 who underwent CUS

Characteristic	Number (%) or mean (±SD)
Mean age, years ± SD	67.6 ± 13.5
Men, n (%)	61 (72.6)
Obesity, n (%)	15 (17.9)
Hypertension, n (%)	45 (53.6)
Type 2 diabetes mellitus, n (%)	18 (21.4)
CAD and/or CVD, n (%)	11 (13.1)
Cancer (previous or current), n (%)	14 (16.7)
Previous VTE, n (%)	3 (3.6)
Trauma or recent surgery, n (%)	8 (9.5)
Acute infectious disease, n (%)	84 (100.0)
Reduced mobility, n (%)	72 (85.7)
Acute respiratory failure with oxygen supplementation, n (%)	72 (85.7)
High flow nasal oxygen therapy or NIV	15 (17.8)
Mean hemoglobin level, g/L ± SD	12.9 ± 13.0
Mean white blood cell count, $10^9 \times L \pm SD$	5831 ± 2825
Mean platelet count, $10^9 \times L \pm SD$	266 ± 120
Mean D-dimer level, μg/L ± SD	4108 ± 7098
D-dimer >1500 μg/L, n (%)	46 (54.8)
D-dimer >3000 μg/L, n (%)	23 (27.4)
Mean fibrinogen level, mg/dL ± SD	499 ± 170
Mean PT, seconds ± SD	11.2 ± 0.7
Mean length of hospital stay, days ± SD	24.0 ± 13.5
Deaths, n (%)	8 (9.5)

Abbreviations: CAD, coronary artery disease; CUS, compression ultrasonography; CVD, cardiovascular disease; NIV, non-invasive ventilation; PT, prothrombin time; SD, standard deviation; VTE, venous thromboembolism.

in 45 patients (53.6%), type 2 diabetes mellitus in 18 patients (21.4%), obesity in 15 patients (17.9%), history of coronary artery disease (CAD) and/or cardiovascular disease (CVD) in 11 patients (13.1%), cancer (current or previous) in 14 patients (16.7%). Three patients (3.6%) had history of previous VTE. Recent trauma and/or recent surgery were found in eight patients (9.5%). The mean length of hospital stay of this cohort was 24.0 ± 13.5 days. There were eight deaths, with a mortality rate of 9.5%. At the time of CUS examination, 72 patients (85.7%) had respiratory insufficiency, required oxygen supplementation, and had reduced mobility or were bedridden. High flow nasal oxygen therapy and/or non-invasive ventilation (NIV) was required in 15 patients (17.8%). The mean platelet count was 266 ± 120 × 10^9/L. The mean D-dimer level was 4108 ± 7098 μg/L. Forty-six patients (54.8%) had D-dimer level >1500 μg/L. Twenty-three patients (27.4%) had D-dimer level >3000 μg/L. The mean prothrombin time (PT) was 11.2 ± 0.7 seconds.

Table 2 presents information on the PPS and the type of prophylactic anticoagulation used in the enrolled patients. It also

TABLE 2 Padua Prediction Score (PPS), type of pharmacological thromboprophylaxis, and incidence of thrombosis among patients hospitalized for COVID-19 who underwent CUS

Characteristic	Number (%) or mean (SD)
PPS = 4, n (%)	44 (52.4)
PPS = 5, n (%)	17 (20.3)
PPS > 5, n (%)	23 (27.4)
PPS, mean ± SD	5.1 ± 1.6
Pharmacological thromboprophylaxis, n (%)	84 (100.0)
Enoxaparin 40 mg once daily	82 (97.6)
Fondaparinux 2.5 mg once daily	2 (2.4)
DVT, n (%), (95% CI)	10 (11.9) (4.98-18.82)
Proximal DVT, n (%), (95% CI)	2 (2.4) (−0.87-5.67)
Distal DVT, n (%), (95% CI)	8 (9.5) (3.23-15.77)
Bilateral DVT, n (%), (95% CI)	4 (4.7) (0.17-9.23)
Symptomatic DVT, n (%), (95% CI)	2 (2.4) (−0.87-5.67)
Mean length of hospital stay at the time of CUS, days ± SD	5.8 ± 2.2

Abbreviations: CUS, compression ultrasonography; DVT, deep vein thrombosis; PPS, Padua Prediction Score; SD, standard deviation.

presents the data in the incidence rate of DVT. The PPS was 4 in 44 patients (52.4%), 5 in 17 patients (20.3%), and >5 in 23 patients (27.4%). The mean value of PPS was 5.1 ± 1.6. All patients (100.0%) were on anticoagulant thromboprophylaxis since the first day of hospitalization, in the majority of cases with enoxaparin and in a small number of cases with fondaparinux. CUS was performed 5.8 ± 2.2 days after hospital admission. In five cases, it was performed within the first 48 hours from hospital admission. In none of these cases a diagnosis of DVT was performed. A DVT was found in 10 patients, with an overall incidence of 11.9% (95% confidence interval [CI] 4.98-18.82). In eight cases, they were distal DVT (located in veins below the knee: peroneal, posterior, anterior tibial, and muscular veins), with an incidence rate of 9.5% (95% CI 3.23-15.77). There were two proximal DVT, with an incidence rate of 2.4% (95% CI −0.87-5.67). In four cases, DVT was bilateral. Signs or symptoms of DVT (such as pain, swelling, warmth, redness, cramps, bluish or whitish skin discoloration at the level of the lower limb) were present only in 2 of the 10 patients with DVT.

Subjects with DVT did not differ from those without DVT in terms of age, sex, and frequency of obesity, hypertension, type 2 diabetes mellitus, and CAD/CVD. Also, their PPS was similar to that displayed by subjects without DVT. Likewise, mean D-dimer levels, PT, and platelet count were similar between the two groups. However, the number of subjects with D-dimer level >3000 μg/L was significantly higher in the DVT group than in the non-DVT group ($P < .05$). In addition, subjects with DVT had higher incidence of cancer (either current or previous; 40.0% versus 13.5%, $P < .05$) and more frequently required high flow nasal oxygen therapy and/or NIV, compared with subjects without DVT (60.0% versus 8.1%, $P < .01$). These data are summarized in Table 3.

TABLE 3 Comparison between subjects with and without DVT

Characteristic	DVT (n = 10)	No DVT (n = 74)	*P*
Mean age, years ± SD	72.0 ± 11.3	67.0 ± 13.8	n.s.
Men, n (%)	7 (70.0)	54 (73.0)	n.s.
Obesity, n (%)	2 (20.0)	13 (17.5)	n.s.
Hypertension, n (%)	6 (60.0)	39 (52.7)	n.s.
Type 2 diabetes mellitus, n (%)	1 (10.0)	17 (22.9)	n.s.
CAD and/or CVD, n (%)	0 (0.0)	11 (14.8)	n.s.
Cancer (previous or current), n (%)	4 (40.0)	10 (13.5)	<.05
Previous VTE, n (%)	1 (10.0)	2 (2.7)	n.s.
Trauma or recent surgery, n (%)	0 (0.0)	8 (10.8)	n.s.
Acute infectious disease, n (%)	84 (100.0)	74 (100.0)	n.s.
Reduced mobility, n (%)	10 (100.0)	62 (83.7)	n.s.
Acute respiratory failure/ oxygen supplementation, n (%)	10 (100.0)	62 (83.7)	n.s.
High flow nasal oxygen therapy or NIV	6 (60.0)	9 (8.1)	<.01
Mean haemoglobin level, g/L ± SD	13.5 ± 1.8	12.8 ± 2.1	n.s.
Mean white blood cell count, 10^9xL ± SD	6892 ± 3111	5688 ± 2776	n.s.
Mean platelet count, 10^9xL ± SD	218 ± 106	272 ± 121	n.s.
Mean D-dimer level, μg/L ± SD	6009 ± 8218	3840 ± 6950	n.s.
D-dimer > 1500 μg/L, n (%)	8 (80.0)	38 (51.3)	n.s.
D-dimer > 3000 μg/L, n (%)	6 (60.0)	17 (22.9)	<.05
Mean fibrinogen level, mg/dL ± SD	560 ± 151	491 ± 171	n.s.
Mean PT, seconds ± SD	11.4 ± 1.0	11.3 ± 0.7	n.s.
PPS, mean ± SD	5.5 ± 1.1	5.1 ± 1.7	n.s.
Mean length of hospital stay at the time of CUS, days ± SD	6.2 ± 2.3	5.7 ± 2.2	n.s.

Abbreviations: CAD, coronary artery disease; CUS, compression ultrasonography; CVD, cardiovascular disease; DVT, deep vein thrombosis; NIV, non-invasive ventilation; PPS, Padua Prediction Score; PT, prothrombin time; VTE, venous thromboembolism.

4 | DISCUSSION

This study provides information on the incidence of DVT among non-ICU patients hospitalized for COVID-19 that receive guideline-recommended thromboprophylaxis. We found 10 cases of DVT among the 84 patients included in the study, with an overall incidence of 11.9%. Our findings are consistent with those of Demelo-Rodriguez et al, who recently reported an incidence of DVT of 14.7% among 156 patients hospitalized in non-ICUs with diagnosis of COVID-19 pneumonia.[14] The incidence of DVT that we found is high, compared with the results of the randomized double-blind MEDENOX trial, which is the landmark study that assessed the incidence of DVT among acutely ill hospitalized medical patients receiving pharmacological thromboprophylaxis. Indeed, in the MEDENOX Study, 16 DVT were found among 291 patients treated with enoxaparin, with an incidence of 5.5%.[15] However, it is important to point out that the increased incidence of DVT that we found in our study was mainly due to a relatively high number of distal DVT, while the incidence of proximal DVT was not substantially different from that observed in the MEDENOX trial. In particular, the incidence of distal DVT in our study and in the MEDENOX trial was 9.5% and 3.8%, respectively, while the incidence of proximal DVT in our study was 2.4% and in the MEDENOX study was 1.7%. Nonetheless, it should be noted that in the MEDENOX study the diagnosis of DVT was done by venography, while we used CUS, which is known to have lower sensitivity for the diagnosis of DVT in asymptomatic patients.[16,17] Therefore, it is possible to hypothesize that in our study the number of COVID-19 patients with DVT could have been higher if venography had been used. Another important randomized placebo-controlled study that assessed the incidence of DVT among acutely ill hospitalized medical patients receiving pharmacological thromboprophylaxis is the PREVENT trial.[18] In this study, subjects treated with dalteparin displayed a 2.7% incidence of proximal DVT, which is similar to what we found in our study. Of note, in the PREVENT trial, the diagnosis of DVT was done by CUS, as it was done in our study. A difference is that distal DVT were not assessed in the PREVENT trial, based on the concept that their clinical relevance is not well established. We decided instead to search for distal DVT, because we believe that the risk of extension of thrombosis to proximal veins may be high in COVID-19 patients. Whether the incidence of DVT is higher in COVID-19 patients than in subjects affected by other acute viral respiratory infections remains to be determined. Indeed, high rates of thrombotic complications have been reported also during the H1N1 influenza virus pandemic and the various outbreaks of SARS-CoV infection.[19-23]

Of note, the patients that had DVT in our study did not differ from those without DVT in terms of age, male sex, and comorbidities. Also mean PPS, D-dimer levels, PT, and platelet count were similar between patients with and without DVT. There were, though, some statistically significant differences. One was that patients with DVT more often had D-dimer levels >3000 μg/L, compared with subjects without DVT. This is interesting, because a D-dimer cut-off value of 3000 μg/L has been recently associated with mortality in non-ICU COVID-19 patients treated with heparin.[24] Instead, we did not find a difference between DVT and non-DVT patients when subjects with D-dimer level >1500 μg/L were considered, although this D-dimer value has been recently proposed as a cut-off to predict thrombosis in COVID-19 patients assisted in the ICU.[25]

Our study has some limitations. First, the number of patients is relatively small and therefore our findings need to be confirmed in

larger samples. Second, CUS was performed relatively early during hospitalization and not at the same time point for all patients; therefore, it is possible that DVT that developed at later stages during the hospital stay were not identified. Also, CUS was never performed at the moment of hospitalization. Therefore, we cannot exclude that some patients had developed DVT before hospitalization, when they were not yet receiving anticoagulant prophylaxis. Third, we have no data on the clinical outcome of patients with DVT compared to subjects without DVT. Finally, we did not look for PE and this is an important issue that needs to be addressed by additional studies in the future.

In conclusion, our study shows that DVT is not uncommon among non-ICU patients hospitalized for COVID-19, despite the use of guideline-recommended thromboprophylaxis. The best thromboprophylactic strategy to use in COVID-19 patients remains to be determined.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

A. Santoliquido and A. Porfidia: concept and design, analysis and interpretation of data, critical writing, and final approval of the version to be published. A. Nesci, G. De Matteis, G. Marrone, E. Porceddu, and G. Cammà: analysis and interpretation of data; final approval of the version to be published. I. Giarretta: analysis and/or interpretation of data, critical writing and revising the intellectual content, and final approval of the version to be published. M. Fantoni, F. Landi, and A. Gasbarrini: concept and design, critical writing or revising the intellectual content, and final approval of the version to be published. R. Pola: concept and design, analysis, and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published.

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