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Letter to the Editor

Prevalence of proximal deep vein thrombosis in hospitalized COVID-19 patients

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Letter to the editor

Severe acute respiratory syndrome coronavirus 2(SARS-COV-2) is a novel virus that has spread worldwide since the end of 2019. Although a proportion of patients remains asymptomatic, the virus may be responsible for coronavirus disease 2019 (COVID-19), characterized by a variety of symptoms, with respiratory symptoms at the forefront. The usual manifestations of COVID-19 include fever, cough, fatigue, myalgia, dyspnea, and radiographic evidence of pneumonia. Most SARS-COV-2 infections are not severe, but severe illness is characterized by marked dyspnea and hypoxemia requiring hospitalization. These symptoms may progress to acute respiratory distress syndrome, multi-organ dysfunction and ultimately death.

Besides pneumonia which is the most frequent serious manifestation of COVID-19, a variety of other manifestations have been described (1). Increasing evidence supports that patients hospitalized for COVID-19 are at increased risk of venous thromboembolism (VTE), particularly those requiringintensive care unit (ICU) admission(2-8). The suspected underlying mechanism of this increased risk of VTE involves factors related to COVID-19 such as disturbed coagulation with prothrombotic state and endothelial damage, along with classical risk factors of VTE such as older age, obesity, dehydration, immobilization, and mechanical ventilation, which are often present in severe COVID-19. This situation has led several scientific societies to recommend thromboprophylaxis or, if indicated, full-intensity anticoagulation in hospitalized COVID-19 patients.Available clinical studiesmainly describe the incidence of VTE in COVID-19 patients hospitalized in the ICU or general ward(3-7, 9-13). By contrast, data on the prevalence of VTE are still limited.

The authors of this letter performed a cross-sectional study aimed to report the prevalence of proximal deep vein thrombosis (DVT) detected by ultrasonography (US) in patientshospitalized for COVID-19. We prospectively performed lower-limb proximal US screening in all COVID-19 patients hospitalized in our hospital in the ICU or general ward,over a short period of time. Here, we report the results of this screening.

During the pandemic, COVID-19 patients requiring hospitalization in our hospital were admitted to dedicated areas, in the ICU (3 different ICUs) orgeneral ward (7 different facilities, including a ward devoted to the geriatric population). For patients hospitalized for COVID-19, the general policy at our institution was to recommend anticoagulant therapy based on low-molecular-weight heparin or unfractionated heparin, the intensity ranging from low-prophylactic doses (enoxaparin 4000 UI x 1or equivalent) to curative treatment via high–prophylactic doses (enoxaparin 4000 UI x 2 or equivalent) according to the severity of the respiratory condition and/or the presence of risks factors of VTE.

In April 2020, to obtainechographic signs of proximal DVT, regardless of the presence or not of symptoms, all hospitalized COVID- 19 patients in the ICU or general ward underwent systematic Doppler US screening of the lower-limb veinsover a short period of time. Refusal to participate in the study was the only non-inclusion criterion.The screening was performed at the bedside by two radiologists (GR and LS) who performed bilateral venous US of the lower limb, from the ilio-femoral axis to popliteal vein. For practical reasons related to the number of patients to be tested in a short period of time, the screening was performed over 7days(from April 24 to April 30, 2020).For each tested patient, clinical signs suggestinga diagnosis of DVT were noted (excluding events detected by leg screening).

Besides this prospective US evaluation of the presence of lower-limb DVT, we retrospectively retrieved and analyzed clinical, imaging, and biological data from patient files. In particular, we retrieved demographic data;presence of comorbidities; history of previous VTE; use of anticoagulant therapy (and if applicable the type of anticoagulant therapy);results of D-dimer, fibrinogen, and C reactive protein measurements from samples obtained within 48 hr before or after venous US in the ICU and within 5 days before or after venous US in the general ward.

The studyreceived approvalfrom the ethics committee of our hospital [Comitéd'Evaluation de l'Ethique des projets de RechercheBiomédicale Paris Nord (Institutional Review Board -IRB 00006477- of HUPNVS, Paris 7 University, AP-HP)]Data are presented as median [interquartile

Abbreviation: COVID-19, coronavirus disease 2019; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; VTE, venous thromboembolism; DVT, deep vein thrombosis; US, ultrasonography; ICU, intensive care unit; GW, general ward; BMI, body mass index; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenator; CRP, C-reactive protein; LDH, lactate dehydrogenase.

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range] or number (percentage) as appropriate. Patients with and without DVT were compared by Mann-Whitney U test or chi-square test, for quantitative and categorical variables, respectively. D-dimer levels of patients hospitalized in the ICU and general ward were compared by Mann-Whitney U test. $P < 0.05$ was considered statistically significant. From April 23 to April 28, 2020,107 hospitalized COVID-19 patients (24 in the ICU and 83 in the general ward) underwent venous US of the lower limb to search for signs of proximal DVT. No patient refused the US evaluation. Overall, 99% of patients received anticoagulant therapy (at least low-prophylactic doses) at the time of venous US (100% and 99% of patients in the ICU and general ward, respectively). Of the 107 patients, 15 (14%) showed DVT, including 3 in the ICU and 12 in the general ward, corresponding to an incidence of 12.5%and 14.5%, respectively. Clinical, imaging, biological, and anticoagulant data for those with and without DVT are in Table 1 and Table 2 (supplementary material).Median age of the COVID-19 patients with proximal DVT was 76.3 [62.8-83.3] years, and 66.7% (n=10) were female. One patient with proximal DVThad history of VTE. Proximal DVT was ilio-femoral, femoral, popliteal, in 2, 1, and 0 ICU patients, respectively, and in 0, 6 and 6 general-ward patients, respectively.No patient had bilateral DVT. Median time between onset of hospitalization and DVT diagnosis was 9 [7-27] days. Among the 15 patients with US identification of proximal DVT,no ICU patients and 3 general-ward patients had clinical symptoms of lower-limb DVT. CT pulmonary angiography (CTPA) was performed in 7 of the 15 patients with DVT, pulmonary embolism was detected in 2 patients. D-dimer levels were significantly higher in ICU than general-ward patients (Figure 1, supplementary material), but did not significantly differ with and without DVT (Figure 2, supplementary material).

Table 1
Clinical characteristics of COVID-19 patients with and without deep vein thrombosis (DVT) hospitalized in the intensive care unit (ICU) or the general ward (GW).

Variable	Total (n=107)	DVT (n=15)	No DVT (n=92)	p
GW patients, n (%)	83 (77.6%)	12 (80%)	71 (77.2%)	
ICU patients, n (%)	24 (22.4%)	3 (20%)	21 (22.8%)	
CLINICAL CHARACTERISTCS				
Age (years)	67.6 [56.4-80.2]	76.3 [62.8-83.3]	67 [55.4-78.1]	0.1694
Female, n (%)	38 (35.5%)	10 (66.7%)	28 (30.43%)	0.0065
BMI (kg/m^2)	25.9 [22.2-30.4]	27.8 [23.3-32.3]	25.7 [22.1-29.9]	0.2337
Obesity (BMI >30 kg/m^2), n (%)	28	6 (40%)	22 (24.4%)	0.2072
Systemic hypertension, n (%)	56	9 (60%)	47 (51.1%)	0.5216
Diabetes, n (%)	33	4 (26.7%)	29 (31.5%)	0.7058
Dyslipidemia, n (%)	14	2 (13,3%)	12 (13%)	0.9754
History of VTE, n (%)	15	1 (6.67%)	14 (15.22%)	0.3764
Active malignancy, n (%)	2	0	2 (2.2%)	0.5643
Smoking status				0.4070
Never smoker, n (%)	87 (81.3%)	14 (93.3%)	73 (79.3%)	
Former smoker, n (%)	15 (14%)	1 (6.7%)	14 (15.2%)	
Active smoker, n (%)	5 (4.7%)	0	5 (5.4%)	
Anticoagulant therapy				
No anticoagulant, n	1	0	1	0.4732
Low-dose prophylaxis, n	18	1	17	
High-dose prophylaxis, n	48	6	42	
Curative dose, n	40	8	32	
Oxygen therapy, n (%)	71 (66.4%)	9 (60%)	62 (67.4%)	0.5743
ICU patients				
Invasive MV, n (%)	21 (87.5%)	3 (100%)	18 (85.7%)	0.484
Dialysis, n (%)	13 (54.2%)	3 (100%)	10 (47.6%)	0.0885
ECMO, n (%)	8 (33.3%)	2 (66.7%)	6 (28.5%)	0.1904
Time between COVID-19 symptom onset and US (days)	17 [12-30]	15 [13-33]	17 [12-29]	0.8887
Time between hospitalization and US (days)	9 [4-19)	9 [7-27]	10 [4-18]	0.8501

Abbreviations: DVT: deep vein thrombosis; GW: general ward; ICU: intensive care unit; BMI: body mass index; MV: mechanical ventilation, US: ultrasound; ECMO: extracorporeal membrane oxygenator

All 15 patients with proximal DVT were receiving anticoagulant therapy (at least low-dose prophylaxis) at the time of DVT diagnosis. For 7 of 15 patients with proximal DVT, the US diagnosis of DVT led to modifying the anticoagulant management (introduction of treatment or augmentation of the daily dose).

There are several limitations to the study. First, a control group of patients hospitalized without COVID-19 is lacking. Second, our study provides only an estimation of the prevalence of VTE because of the cross-sectional design and because of no systematic exploration of distal venous axis or pulmonary circulation. Thus, the presence of distal DVT or pulmonary embolism cannot be excluded.

The salient results of this monocentric observational study are as follows: 1) systematic US screening of the proximal lower-limb veins during a short time (7 days) detected proximal DVT in a substantial number of COVID-19 patients hospitalized in the ICU or general ward; 2) in most cases, DVT was diagnosed while the patients were receiving anticoagulant therapy; and 3) for patients with DVT detected by US, most (80%) did not have clinical symptoms of DVT. Zhang and colleagues also found low rates of symptomatic DVT in their cohort of 143 patients who underwent systematic DVT screening(14) asdid the Dutch study by Middeldorp et al(4). Taken together, these findings raise the question of systematic screening of DVT in this setting.

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Disclosure

GR, VB, DD, LS, NA, XL, BLJ, AD, JG, GW, AK have no conflict of interest to report, JFT reports personal fees from Merck, personal fees from Pfizer, personal fees from Gilead, personal fees from Paratek, personal fees from Medimmune, outside the submitted work; .HM reports grants from Pfizer, and fees from Novartis, and Boehringer.

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HM takes responsibility for the content of the manuscript, including the data and analysis

Author contributions

- HM, VB, AK designed the study, coordinated the study, analyzed and interpreted the results, and wrote the manuscript

- GR, LS, performed the US screening, collected the data and reviewed the manuscript
- DD collected the data and reviewed the manuscript
- NA, JG analyzed the results and critically reviewed the manuscript
- XL, JFT, BLJ, AD collected the data and critically reviewed the manuscript collected the data
- GW performed statistical analysis and critically reviewed the manuscript

Declaration of Competing Interest

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2021.03.034.

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