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Deep vein thrombosis in hospitalized patients with coronavirus disease 2019

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ABSTRACT

Objective: The pandemic of coronavirus disease 2019 (COVID-19) has caused devastating morbidity and mortality worldwide. In particular, thromboembolic complications have emerged as a key threat for patients with COVID-19. We assessed our experience with deep vein thrombosis (DVT) in patients with COVID-19.

Methods: We performed a retrospective analysis of all patients with COVID-19 who had undergone upper or lower extremity venous duplex ultrasonography at an academic health system in New York City from March 3, 2020 to April 12, 2020 with follow-up through May 12, 2020. A cohort of hospitalized patients without COVID-19 (non–COVID-19) who had undergone venous duplex ultrasonography from December 1, 2019 to December 31, 2019 was used for comparison. The primary outcome was DVT. The secondary outcomes included pulmonary embolism, in-hospital mortality, admission to the intensive care unit, and antithrombotic therapy. Multivariable logistic regression was performed to identify the risk factors for DVT and mortality.

Results: Of 443 patients (COVID-19, n = 188; and non–COVID-19, n = 255) who had undergone venous duplex ultrasonography, the COVID-19 cohort had had a greater incidence of DVT (31% vs 19%; $P = .005$) than had the non–COVID-19 cohort. The incidence of pulmonary embolism was not significantly different statistically between the COVID-19 and non–COVID-19 cohorts (8% vs 4%; $P = .105$). The DVT location in the COVID-19 group was more often distal (63% vs 29%; $P < .001$) and bilateral (15% vs 4%; $P < .001$). The duplex ultrasound findings had a significant impact on the antithrombotic plan; 42 patients (72%) with COVID-19 in the DVT group had their therapy escalated and 49 (38%) and 3 (2%) had their therapy escalated and deescalated in the non-DVT group, respectively ($P < .001$). Within the COVID-19 cohort, the D-dimer level was significantly greater in the DVT group at admission (2746 ng/mL vs 1481 ng/mL; $P = .004$) and at the duplex examination (6068 ng/mL vs 3049 ng/mL; $P < .01$). On multivariable analysis, male sex (odds ratio [OR], 2.27; 95% confidence interval [CI], 1.06-4.87; $P = .035$), intensive care unit admission (OR, 3.42; 95% CI, 1.02-11.44; $P = .046$), and extracorporeal membrane oxygenation (OR, 5.5; 95% CI, 1.01-30.13; $P = .049$) were independently associated with DVT.

Conclusions: Given the high incidence of venous thromboembolic events in this population, we support the decision to empirically initiate therapeutic anticoagulation for patients with a low bleeding risk and severe COVID-19 infection. Duplex ultrasonography should be reserved for patients with a high clinical suspicion of venous thromboembolism for whom anticoagulation therapy could result in life-threatening consequences. Further study of patients with COVID-19 is warranted to elucidate the etiology of vascular thromboembolic events and guide the prophylactic and therapeutic interventions for these patients. (J Vasc Surg Venous Lymphat Disord 2021;9:597-604.)

Keywords: Deep venous thrombosis; Coronavirus 2019; Venous thromboembolism; Anticoagulation; Pulmonary embolism; Duplex ultrasonography

In late 2019 and early 2020, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a global outbreak of coronavirus disease 2019 (COVID-19). To date, ~6 million people have been affected, with an overall mortality of ~7%.[1] The clinical presentation of COVID-19 ranges from asymptomatic or mild cases of pneumonia to severe acute respiratory distress syndrome, cardiomyopathy, derangements in coagulation, and death.

Although marked hypercoagulability has been observed in many patients with COVID-19, little is understood about the factors associated with deep vein thrombosis (DVT) in COVID-19. Several recent studies have described links between COVID-19 and proinflammatory, hypercoagulable states leading to thromboembolic events. Some studies have suggested that anticoagulation therapy might lower mortality in

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patients with COVID-19. However, others have reported that the increased rates of venous thromboembolism (VTE) in patients with COVID-19 in the intensive care unit (ICU) persist despite prophylactic anticoagulation.[2-5]

Evidence is lacking regarding which risk factors will place particular patients with COVID-19 at increased risk of VTE and which patients might benefit from prophylactic or therapeutic anticoagulation. An exploration of this issue might offer clinicians clearer guidance on the use of anticoagulation therapy as they treat patients during the COVID-19 pandemic. In the present study, we examined the incidence of DVT and associated risk factors among patients with confirmed COVID-19.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective cohort analysis
- **Key Findings:** Of 443 hospitalized patients, patients with coronavirus disease 2019 (COVID-19) had a significantly greater incidence of deep vein thrombosis (DVT; 31% vs 19%; $P = .005$), with a greater proportion of distal (63% vs 29%; $P < .001$) and bilateral (15% vs 4%; $P < .001$) DVTs compared with those without COVID-19. Male sex and markers of a severe inflammatory process such as intensive care unit admission and extracorporeal membrane oxygenation support were independently associated with DVT.
- **Take Home Message:** Given the high incidence of venous thromboembolic events in patients with COVID-19, we support the decision to empirically initiate therapeutic anticoagulation for patients with severe COVID-19 infection. Duplex ultrasonography should be reserved for patients with a high clinical suspicion of venous thromboembolism for whom anticoagulation therapy could result in life-threatening consequences.

METHODS

Study population. From March 3, 2020 to April 12, 2020, all consecutive patients admitted to a single academic medical center in New York City with SARS-CoV-2 pneumonia who had undergone venous duplex ultrasonography of the upper or lower extremities were included. Duplex ultrasound studies were ordered based on the clinical judgment of the treating physicians. All studies were performed by accredited vascular technologists and reviewed and formally read by vascular surgeons with either registered vascular technologist or registered physician in vascular interpretation accreditation in a vascular laboratory accredited by the Intersociety Accreditation Commission. SARS-CoV-2 pneumonia was diagnosed clinically and confirmed by reverse transcription-polymerase chain reaction detection of COVID-19. The clinical outcomes were monitored up to May 13, 2020. A cohort of hospitalized patients admitted without COVID-19 (non–COVID-19) who had undergone venous duplex ultrasonography from December 1, 2019 to December 31, 2019, before the pandemic, was used for comparison. The institutional review board at New York University Langone Health approved the present study before data analysis and waived the need for patient informed consent.

Data collection. The electronic medical records were retrospectively reviewed from hospital admission to the time of discharge, death, or the end of data monitoring period (May 13, 2020). Data, including demographic characteristics, medical history, laboratory and imaging data, antithrombotic therapy, in-hospital mortality, DVT, and pulmonary embolism (PE), were collected for analysis. DVT was classified as proximal if localized to the iliac, femoral, or popliteal vein and distal if in the tibial, gastrocnemius, or soleal vein. Upper extremity DVT was defined as thrombosis of the radial, ulnar, brachial, axillary, subclavian, or internal jugular vein. Patients were categorized as non-ICU or ICU patients. Non-ICU patients were defined as those not in the ICU for their entire hospital stay. All ICU patients had required mechanical ventilation and/or were hemodynamically unstable, requiring a titrating dose of vasoactive infusion in an intensive care setting at some point during their hospitalization. Prophylactic antithrombotic therapy was a part of the standard care for all admitted patients with COVID-19, unless clinically contraindicated and consisted of 5000 U of subcutaneous unfractionated heparin three times daily, 40 mg of subcutaneous low-molecular-weight heparin (LMWH; enoxaparin sodium) daily, or 30 mg LMWH twice daily. Persistent elevation of D-dimer levels after initiation of anticoagulation was defined as an increasing D-dimer value after ≥5 days of anticoagulation compared with the level before the initiation of anticoagulation.

Outcomes. The primary outcome was DVT. The secondary outcomes included PE, in-hospital mortality, admission to the ICU, and antithrombotic therapy.

Statistical analysis. Statistical analysis was performed using SPSS, version 25.0, software (IBM Inc, Armonk, NY). The χ^2 test of independence and Mann-Whitney U test were used for data analysis where applicable, and the Student t test was used to compare normally distributed continuous variables. Continuous variables are presented as the mean ± standard deviation. Discrete variables are presented as absolute numbers with the population percentage. Based on univariate screening of variables with a $P < .2$, logistic regression models for the risk of DVT and in-hospital mortality were created. The effect is expressed by odds ratios

(ORs), with the corresponding 95% confidence intervals (CIs). Statistical significance was accepted at a $P < .05$.

RESULTS

Patient characteristics. A total of 443 patients, 258 men (58%) and 185 women (42%), met our inclusion criteria and were included in final analysis. The COVID-19 and non–COVID-19 cohorts consisted of 188 and 255 patients, respectively. The comparison of baseline characteristics is summarized in Table I. The COVID-19 cohort were more likely to be male (65% vs 53%; $P = .015$) and to have a higher body mass index (30.2 kg/m^2 vs 28.1 kg/m^2; $P = .0002$), with a higher proportion of patients with diabetes mellitus (35% vs 25%; $P = .027$). Coronary artery disease (23% vs 13%; $P = .008$), congestive heart failure (14% vs 5%; $P = .002$), atrial fibrillation (14% vs 7%; $P = .015$), hypercoagulable state (10% vs 4%; $P = .018$), and a history of DVT (18% vs 4%; $P < .001$) were more common in the non–COVID-19 cohort. The COVID-19 cohort had a greater proportion of patients requiring ICU admission (52% vs 18%; $P < .001$), ventilatory support (45% vs 12%; $P < .001$), and dialysis (12% vs 2%; $P < .001$). The mean age was similar at 64 ± 15 years for the COVID-19 and 63 ± 18 years for the non–COVID-19 cohorts ($P = .513$). The mean interval from admission to duplex ultrasonography in the COVID-19 cohort was 7 ± 6 days (range, 0-29 days). The mean length of stay was 21 ± 15 days (range, 1-60 days) for 162 patients(86%) with COVID-19, with 22 patients (14%) remaining hospitalized at the end of the follow-up period.

In-hospital outcomes and thromboembolic characteristics. The results from a comparison of in-hospital outcomes are detailed in Table II. The COVID-19 cohort had a greater incidence of DVT (31% vs 19%; $P = .005$) compared with the non–COVID-19 cohort. However, the incidence of PE was not significantly different statistically between the COVID-19 and non–COVID-19 cohorts (8% vs 4%, respectively; $P = .105$). The distribution of DVTs stratified by COVID-19 status is summarized in Table III. The DVTs in the COVID-19 cohort tended to be distal (63% vs 29%; $P < .001$) and bilateral (15% vs 4%; $P < .001$). In contrast, those in the non–COVID-19 cohort were more likely to occur in the upper extremities (20% vs 7%; $P < .001$). The overall in-hospital mortality was significantly higher in the COVID-19 cohort than in the non–COVID-19 cohort (22% vs 7%; $P < .001$).

DVT vs non-DVT groups in COVID-19 cohort. The comparison of the DVT and non-DVT groups in the COVID-19 cohort is summarized in Table I. The DVT group was more likely to be male (77% vs 60%; $P = .026$) and to require extracorporeal membrane oxygenation (ECMO; 11% vs 2%; $P = .004$) compared with the non-DVT group. The prevalence of patients taking anticoagulants as home medications was greater in the non-DVT group (16% vs 0%; $P < .001$). The rates of in-hospital mortality (19% vs 24%; $P = .7$), ICU admissions (61% vs 49%; $P = .49$), ventilatory support (48% vs 44%; $P = .573$), and dialysis (12% vs 12%; $P = .963$) did not differ significantly between the DVT and non-DVT groups, respectively.

VTE characteristics in the COVID-19 cohort. The VTE characteristics are shown in Table III. Of the 58 cases of DVT, 36 (63%) were distal (soleal, tibial, or gastrocnemius vein), 7 (13%) were proximal (iliac, femoral, or popliteal vein), 10 (18%) were both, and 4 (7%) were in the upper extremity (brachial, internal jugular, or radial vein). Of the 15 cases of PE in the COVID-19 cohort, 11 (73%) had occurred in the setting of concomitant DVT and 4 (27%) without demonstrable DVT. Four patients with DVT underwent inferior vena cava filter placement because of extensive bilateral DVTs with PE in three patients and a contraindication for systemic anticoagulation in one patient.

Antithrombotic regimen in the COVID-19 cohort. A comparison of various antithrombotic therapies before and after duplex ultrasonography in the COVID-19 cohort is detailed in Table IV. Of the 188 patients, 20 (11%) had not received any antithrombotic therapy until duplex ultrasonography had been performed, 12 because of recent or remote gastrointestinal bleeding and 8 because of active intracranial malignancy, recent neurosurgery, or intracranial hemorrhage. Of 37 patients (20%) receiving therapeutic dose anticoagulation at duplex ultrasonography, 21 had received a therapeutic dose since admission and 16 had had the therapy escalated to the therapeutic dose because of a progressive increase in D-dimer before the duplex ultrasound examination. Of the 188 patients, 152 (81%) had received a prophylactic dose on admission to the hospital (unfractionated heparin, n = 39; LMWH, n = 113). Of the 113 patients receiving a prophylactic dose of LMWH, 16 had their does escalated to the therapeutic level, as stated previously. Patients receiving the therapeutic dose before duplex ultrasonography had had a significantly greater mean D-dimer level at admission and duplex ultrasound examination compared with those not receiving a therapeutic dose (3527 ng/mL vs 1467 ng/mL; $P < .001$; and 5823 ng/mL vs 3528 ng/mL; $P = .008$, respectively).

Before duplex ultrasonography, the proportion of prophylactic (62% vs 74%) and therapeutic (26% vs 16%) doses did not differ between the DVT and non-DVT groups, respectively ($P = .231$). However, the results of duplex ultrasonography had a significant effect on the antithrombotic plan; 42 patients (72%) in the DVT group had had their therapy escalated and 49 (38%) and 3 (2%) had had their therapy escalated and deescalated in the non-DVT group, respectively ($P < .001$). Of the 20 patients who had not been receiving any antithrombotic therapy, 7 (35%) were diagnosed with DVT. In contrast, 36 of 132

Table I. Patient characteristics stratified by deep vein thrombosis (*DVT*) status

Characteristic	COVID-19			Non–COVID-19		
	DVT group (n = 58)	Non-DVT group (n = 130)	*P* value	DVT group (n = 49)	Non-DVT group (n = 206)	*P* value
Age, years	62 ± 16	65 ± 14	.235	61 ± 16	63 ± 20	.557
BMI, kg/m^2	30.4 ± 6.9	30.1 ± 7.5	.802	27.7 ± 7.8	27.9 ± 6.6	.83
Obesity (BMI >30 kg/m^2)	29 (52)	60 (46)	.453	12 (32)	54 (37)	.587
Gender			**.035**			.775
Male	44 (76)	78 (60)		24 (58.5)	88 (56)	
Female	14 (24)	52 (40)		17 (41.5)	69 (44)	
HTN	33 (57)	80 (62)	.548			
HLD	27 (47)	68 (52)	.466	21 (43)	96 (47)	.576
DM	16 (29)	50 (38)	.221	17 (35)	47 (23)	.96
CAD	5 (9)	20 (15)	.207	11 (22)	48 (24)	.859
CHF	1 (2)	8 (6)	.189	6 (12)	28 (14)	.776
COPD	5 (9)	11 (9)	.971	2 (4)	24 (12)	.11
Atrial fibrillation	1 (2)	12 (9)	.061	5 (10)	31 (15)	.363
Hypercoagulable state	1 (2)	7 (5)	.251	9 (18)	17 (8)	**.039**
History of DVT	0 (0)	8 (6)	.054	18 (37)	27 (13)	**<.001**
Cancer	5 (9)	14 (11)	.652	11 (22)	28 (14)	.133
Thyroid status			.626			.473
Euthyroid	53 (92)	118 (91)		43 (88)	174 (86)	
Hypothyroid	5 (8)	10 (8)		6 (12)	23 (11)	
Hyperthyroid	0	2 (2)		0 (0)	6 (3)	
Smoking history	13 (22)	28 (22)	.893	10 (20)	45 (23)	
Home medication						
ACE inhibitor	7 (12)	25 (19)	.227	7 (14)	23 (11)	.566
Aspirin	19 (33)	44 (34)	.884	10 (20)	54 (27)	.381
Plavix	3 (5)	7 (5)	.952	4 (8)	12 (6)	.568
Anticoagulant	0 (0)	21 (16)	**<.001**	12 (25)	39 (19)	.382

ACE, Angiotensin-converting enzyme; *BMI*, body mass index; *DM*, diabetes mellitus; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *COVID-19*, coronavirus disease 2019; *HLD*, hyperlipidemia; *HTN*, hypertension.
Data presented as number (%), unless otherwise indicated. Boldface *P* values represent statistical significance.

patients receiving a prophylactic dose had developed DVT. Of 36 patients receiving a therapeutic dose, 15 (42%) had developed DVT. None of the 21 patients receiving a therapeutic dose of antithrombotic therapy because of their comorbidities (atrial fibrillation or history of DVT) had developed DVT.

D-dimer level and association with DVT in the COVID-19 cohort. The comparison of the plasma D-dimer levels at different stages of the hospital stay between the DVT and non-DVT cohorts is summarized in Table II. The D-dimer level was significantly higher in the DVT cohort at hospital presentation (2746 ng/mL vs 1481 ng/mL; $P = .004$) and at the duplex ultrasound examination (6068 ng/mL vs 3049 ng/mL; $P < .001$). The peak D-dimer level was also higher in the DVT cohort (6927 ng/mL vs 4293 ng/mL; $P < .001$). The initiation of therapeutic anticoagulation in the DVT cohort was associated with a significant reduction in the D-dimer level compared with that of the non-DVT cohort (2241 ng/mL vs 2028 ng/mL; $P = .58$). However, 9 patients (16%) in the DVT cohort and 39 (30%) in the non-DVT cohort exhibited persistently elevated D-dimer levels refractory to systemic anticoagulation therapy. This subset of patients was associated with increased in-hospital mortality (46% vs 12%; $P < .001$). The location and extent of DVT did not have a significant effect on the degree of D-dimer elevation (data not shown).

Risk factors for DVT and mortality. On multivariable analysis, male sex (OR, 2.27; 95% CI, 1.06-4.87; $P = .035$), ICU admission (OR, 3.42; 95% CI, 1.02-11.44; $P = .046$), and ECMO (OR, 5.5; 95% CI, 1.01-30.13; $P = .049$) were independently associated with the occurrence of DVT

Table II. In-hospital outcomes stratified by deep vein thrombosis (*DVT*) status

Outcome	COVID-19			Non–COVID-19		
	DVT group (n = 58)	Non-DVT group (n = 130)	*P* value	DVT group (n = 49)	Non-DVT group (n = 206)	*P* value
ICU admission	35 (61)	63 (49)	.132	8 (19)	28 (17)	.462
ECMO	6 (10)	2 (2)	**.006**	2 (4.7)	1 (0.6)	.05
Ventilatory support	28 (48)	57 (44)	.573	7 (14)	17 (8)	.194
Dialysis	7 (12)	16 (12)	.963	2 (4)	2 (1)	.115
Discharge destination			.079			.117
Inpatient	6 (10.3)	26 (20)		0 (0)	0 (0)	
Home	22 (37.9)	58 (44.6)		26 (63.4)	118 (75.2)	
Rehabilitation	19 (32.8)	21 (16.2)		8 (19.5)	28 (17.8)	
Death	11 (19)	31 (23.8)	.79	7 (17)	11 (7)	**<.001**
LOS, days	22 (14)	21 (15)	.533	NA	NA	
Time from admission to DUS, days	8 (6)	6 (6)	.478	NA	NA	
IVC filter	4 (7)	0 (0)	**.002**	3 (7)	5 (3)	.231
D-dimer, ng/mL				NA	NA	
At DUS	6068	3049	**<.001**			
At apex	6927	4293	**<.001**			
At presentation	2746	1481	**.004**			
After anticoagulation	2241	2028	.58			
Persistently elevated after anticoagulation initiation	9 (16)	39 (30)	.053			

DUS, Duplex ultrasonography; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit; *IVC*, inferior vena cava; *LOS*, length of stay; *NA*, not applicable; *PE*, pulmonary embolism; *VTE*, venous thromboembolism.
Data presented as number (%), unless otherwise indicated. Boldface *P* values represent statistical significance.

(Table V). A separate logistic regression analysis was performed to determine the risk factors for in-hospital mortality. The analysis showed that ICU status (OR, 18.55; 95% CI, 2.72-126.55; $P = .003$), persistent D-dimer elevation after initiation of anticoagulation (OR, 13.91; 95% CI, 4.21-46; $P < .001$), smoking status (OR, 3.66; 95% CI, 1.22-11.01; $P = .021$), and diabetes mellitus (OR, 5.34; 95% CI, 1.58-18.11; $P = .007$) were associated with in-hospital mortality among patients undergoing venous duplex ultrasonography. The presence of DVT was not associated with in-hospital mortality (OR, 0.96; 95% CI, 0.31-3.00; $P = .94$).

DISCUSSION

COVID-19 has been associated with hemostatic abnormalities, including mild thrombocytopenia, increased D-dimer levels, and derangement in coagulation.[6-8] However, only a few studies have described the association between DVT and COVID-19. Although thrombosis was observed in other acute infections such as the influenza pandemic in 2009, we observed an unusually high rate (31%) of DVT in patients admitted with SARS-CoV-2 pneumonia. Compared with the prepandemic hospitalized cohorts, the severity of the acute inflammatory response and the prevalence of organ failure were significantly greater in patients with COVID-19, as evidenced by the higher rates of ICU admission, ventilatory support, renal failure requiring hemodialysis, and death. Furthermore, the risk profile associated with COVID-19 appeared to supersede previously known risk factors for DVT such as previous VTE, advanced age, obesity, cancer, and a baseline hypercoagulable disorder. As such, patients with COVID-19 might benefit from empiric therapy, instead of waiting for duplex ultrasonography, which can delay appropriate therapy and, potentially, subject vascular laboratory technicians to unnecessary exposure to COVID-19.

Thromboembolic complications have emerged as a key threat in patients with COVID-19. Although largely unknown, several mechanisms have been proposed to explain the potential cascades by which COVID-19 might promote thrombosis. A metallopeptidase, angiotensin-converting enzyme 2, has been identified as a functional receptor of SARS-CoV-2.[9] Because these receptors are expressed in endothelial cells, COVID-19 might cause hemostatic derangement through direct endothelial involvement.[10] Varga et al[11] performed postmortem histologic examinations of patients with multiorgan failure

Table III. Comparison of venous thromboembolic characteristics stratified by coronavirus disease 2019 (*COVID-19*)

Characteristic	COVID-19 (n = 188)	Non–COVID-19 (n = 255)	*P* value
DVT	58 (31)	49 (19)	**.005**
Location			**<.001**
Proximal (iliac, femoral, popliteal vein)	7 (13)	12 (29)	
Distal (tibial, soleal, gastrocnemius vein)	36 (63)	12 (29)	
Both (proximal and distal)	10 (18)	9 (22)	
Upper extremity	4 (7)	8 (20)	
Bilateral	28 (15)	10 (4)	**<.001**
VTE (DVT + PE)	63 (34)	54 (21)	**.004**
PE	15 (8)	11 (4)	.105

DVT, Deep vein thrombosis; *PE*, pulmonary embolism; *VTE*, venous thromboembolism.
Data presented as number (%), unless otherwise indicated. Boldface *P* values represent statistical significance.

and found extensive endotheliitis, suggesting direct viral infection of the endothelial cells. This direct endothelial involvement might explain why D-dimer elevations has been one of the most consistent findings in COVID-19. Other mechanisms include cytokine storm, hypoxic injury, increased platelet activity, complement cascade activation, and a transient increase in antiphospholipid antibodies, leading to prothrombotic state.[12-14]

Emerging evidence has pointed toward intense vasodilation and endothelial dysfunction as the mechanism leading to severe acute respiratory syndrome in patients with COVID-19.[15] Reports of increased respiratory dead space have suggested the presence of pulmonary vascular thrombosis from thrombotic microangiopathy.[16] We found that ECMO and ICU status were independently associated with DVT among patients undergoing venous duplex ultrasonography. These findings might indicate that the severity of intrapulmonary shunting and microvascular thrombosis could reflect the severity of global endothelial inflammation, predisposing patients to venous thromboembolic events.

A few studies have demonstrated a high incidence of VTE in patients with COVID-19. However, these studies were limited by the small numbers of patients undergoing duplex ultrasonography to confirm and characterize DVT (ie, location, extent, and unilateral vs bilateral).[4,17-21] Of 34 patients with COVID-19 receiving antithrombotic therapy in the ICU, Nahum et al[17] demonstrated a DVT rate of 65%, predominantly bilateral (53%) and proximal (26%) in distribution. In 81 ICU patients in China, Cui et al[18] showed that 25% of patients were diagnosed with DVT. However, the study was biased by patients not having received routine antithrombotic therapy. In European studies of patients receiving prophylactic antithrombotic therapy, the incidence VTE ranged from 18% to 31% and was predominantly PE.[4,19-21] In contrast to our unusually high rate of DVT, the incidence of DVT in these studies was reported at 2% to 13%. This observed difference could also have results from the diagnostic challenges among patients with COVID-19, because the imaging studies used to diagnose DVT might not be pursued owing to the risk of transmitting infection to other patients or healthcare workers and, potentially, because of patient instability. Moreover, the use of duplex ultrasonography could have been limited by patient positioning, because many patients with acute respiratory distress syndrome will require prone positioning, and the prognosis of patients might be grave enough that the diagnosis of an underlying VTE might not alter the course of treatment. Unlike previous studies, we included only patients who had undergone venous duplex ultrasonography. As such, our study had the largest number of positive duplex studies to date, allowing for the most accurate characterization of DVT in patients with COVID-19. The COVID-19 cohort exhibited more distal (63% vs 29%; $P < .001$) and bilateral (15% vs 4%; $P < .001$) DVTs. These findings are consistent with previous studies demonstrating the effect of COVID-19 on small blood vessels, which might explain the unusually high proportion of distal DVTs seen in our study.

At present, the role of empiric therapeutic anticoagulation without a diagnosis of VTE has been controversial. A few single-center studies have suggested the potential benefit of intermediate and therapeutic doses of anticoagulation to prevent microvascular thrombosis.[4,5,22] In a study of 198 patients with COVID-19, Middeldorp et al[21] reported a VTE rate of 20%; however, no VTE was observed in 19 patients who had received maintenance anticoagulant therapy from admission. We observed a similar trend—of 21 patients who had received therapeutic antithrombotic therapy from admission because of comorbidities (ie, atrial fibrillation, history of DVT), none developed VTE. Currently, no validated clinical decision models exist to predict for VTE in patients with COVID-19. Ultimately, the decision to escalate antithrombotic therapy for patients with COVID-19 should be individualized, balancing the anticipated risk of life-threatening hemorrhage and the expected benefit derived from

Table IV. Antithrombotic regimen for coronavirus disease 2019 (COVID-19) cohort

Regimen	DVT group (n = 58)	Non-DVT group (n = 130)	*P* value
Antithrombotic therapy before DUS			.231
None	7 (12)	13 (10)	
Prophylactic	36 (62)	96 (74)	
UFH	12 (21)	27 (21)	
LMWH	24 (41)	69 (53)	
Therapeutic	16 (26)	21 (16)	
UFH	13 (23)	11 (8)	
LMWH	2 (3)	6 (5)	
DOAC	0 (0)	4 (3)	
Antithrombotic therapy after DUS			**<.001**
None	3 (5)	16 (12)	
Prophylactic	2 (3)	50 (38)	
UFH	0 (0)	12 (9)	
LMWH	2 (3)	38 (29)	
Therapeutic	53 (92)	64 (50)	
UFH	31 (54)	32 (25)	
LMWH	17 (29)	26 (20)	
DOAC	4 (7)	4 (3)	
DTI	1 (2)	2 (2)	
Anticoagulation therapy modified after DUS	42 (72)	52 (40)	**<.001**
Escalated	42 (100)	49 (94)	
Deescalated	0 (0)	3 (6)	
Inpatient antiplatelet medication, %			
Aspirin	19	27	.513
Plavix	7	5	.683

DOAC, direct oral anticoagulant; *DTI,* direct thrombin inhibitor; *DUS,* duplex ultrasonography; *DVT,* deep vein thrombosis; *LMWH,* low-molecular weight heparin; *UFH,* unfractionated heparin.
Data presented as number (%), unless otherwise indicated. Boldface *P* values represent statistical significance.

Table V. Multivariable analysis estimating predictors of deep vein thrombosis (*DVT*) and mortality among patients with coronavirus disease 2019 (COVID-19)

Predictor	OR	95% CI	*P* value
DVT			
Male sex	2.27	1.06-4.87	**.035**
ICU status	3.42	1.02-11.44	**.046**
ECMO	5.5	1.01-30.13	**.049**
Atrial fibrillation	0.18	0.02-1.69	.134
History of hypercoagulable state	1.11	0.1-12.61	.935
History of cancer	0.88	0.26-2.92	.831
Ventilatory support	0.33	0.1-1.14	.080
Dialysis	0.77	0.27-2.21	.633
Mortality			
ICU	18.55	2.72-126.55	**.003**
Ventilatory support	0.87	0.16-4.92	.881
Dialysis	2.46	0.58-10.43	.221
DM	5.34	1.58-18.11	**.007**
CAD	0.55	0.09-3.49	.527
Smoker	4.20	1.2-14.75	**.025**
ACE inhibitor	1.52	0.44-5.27	.502
Plavix	1.98	0.18-21.78	.576
Anticoagulation	5.61	0.69-45.59	.107
Age	1.02	0.98-1.07	.341
In-hospital DVT	0.96	0.31-3	.940
BMI	1.04	0.96-1.12	.349
Persistent D-dimer elevation after anticoagulation	13.91	4.21-46	**< .001**

ACE, angiotensin-converting enzyme; *BMI,* body mass index; *CAD,* coronary artery disease; *CI,* confidence interval; *DM,* diabetes mellitus; *ECMO,* extracorporeal membrane oxygenation; *ICU,* intensive care unit; *OR,* odds ratio.
Data presented as number (%), unless otherwise indicated. Boldface *P* values represent statistical significance.

anticoagulation. Because of the difficulty in performing duplex ultrasonography owing to the limited workforce and personal protective equipment and difficulty in completely disinfecting the machine between patients, the clinical practice at our institution changed toward the end of the study period. Duplex ultrasonography was performed more selectively for patients with a high bleeding risk and a high clinical suspicion of PE and/or DVT. In addition, with the increased awareness of VTE developing in patients with COVID-19, therapeutic anticoagulation was pre-emptively initiated without a confirmed diagnosis of VTE in the ICU patients with a low bleeding risk and suspected VTE and/or a high level of serum acute phase reactants reflective of a severe inflammatory process (ie, elevated D-dimer >2000 mg/dL).

Additional studies might be needed to further define the additional risk factors for VTE to help identify those at most risk of VTE. A prospective randomized controlled trial (ClinicalTrials.gov identifier, NCT04359277) is ongoing to compare a lower dose against a higher dose of antithrombotic therapy to reduce the complications of DVT formation in patients hospitalized for COVID-19 infection.

The present study had several limitations. A limited number of patients had undergone venous duplex ultrasonography, largely related to the lack of available resources to scan all patients with elevated D-dimer levels and the competing risk of death. However, to the best of our knowledge, the present study is the largest series to date specifically tailored to characterize DVT and evaluate the incidence of DVT in patients with COVID-19 undergoing venous duplex ultrasonography. Another limitation of the present study was that it was

retrospective in nature, and we were unable to control for such confounders as multiple investigational drugs (ie, clazakizumab, remdesivir, sarilumab).

CONCLUSIONS

Our study has provided the characteristics and incidence of DVT in patients with confirmed COVID-19. Given the high incidence of venous thromboembolic events in this population, we support the decision to empirically initiate therapeutic anticoagulation for patients with a low bleeding risk and severe COVID-19 infection. Duplex ultrasonography should be reserved for patients with a high clinical suspicion of VTE for whom therapeutic anticoagulation could result in life-threatening consequences. Further studies are needed to elucidate the mechanisms leading to venous thromboembolic events to better guide treatment in the COVID-19 cohort.

AUTHOR CONTRIBUTIONS

Conception and design: HC, CR, MB
Analysis and interpretation: HC, CR, GJ, JH, KG, TM, MS, MB
Data collection: HC, GS, WJ, MB
Writing the article: HC
Critical revision of the article: HC, CR, GJ, GS, WJ, JH, KG, TM, MS, MB
Final approval of the article: HC, CR, GJ, GS, WJ, JH, KG, TM, MS, MB
Statistical analysis: HC
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Overall responsibility: HC

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