CLINICAL RESEARCH STUDIES

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Incidence and effects of deep vein thrombosis on the outcome of patients with coronavirus disease 2019 infection

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ABSTRACT

Background: Deep vein thrombosis (DVT) has been reported to occur at different rates in patients with coronavirus disease 2019 (COVID-19). Limited data exist regarding comparisons with non–COVID-19 patients with similar characteristics. Our objective was to compare the rates of DVT in patients with and without COVID-19 and to determine the effect of DVT on the outcomes.

Methods: We performed a retrospective, observational cohort study at a single-institution, level 1 trauma center comparing patients with and without COVID-19. The 573 non–COVID-19 patients (age, 61 ± 17 years; 44.9% male) had been treated from March 20, 2019 to June 30, 2019, and the 213 COVID-19 patients (age, 61 ± 16 years; 61.0% male) had been treated during the same interval in 2020. Standard prophylactic anticoagulation therapy consisted of 5000 U of heparin three times daily for the medical patients without COVID-19 who were not in the intensive care unit (ICU). The ICU, surgical, and trauma patients without COVID-19 had received 40 mg of enoxaparin daily (not adjusted to weight). The patients with COVID-19 had also received enoxaparin 40 mg daily (also not adjusted to weight), regardless of whether treated in the ICU. The two primary outcomes were the rate of deep vein thrombosis (DVT) in the COVID-19 group vs that in the historic control and the effect of DVT on mortality. The subgroup analyses included patients with adult respiratory distress syndrome (ARDS), pulmonary embolism (PE), and intensive care unit patients (ICU).

Results: The rate of DVT and PE for the non–COVID-19 patients was 12.4% (71 of 573) and 3.3% (19 of 573) compared with 33.8% (72 of 213) and 7.0% (15 of 213) for the COVID-19 patients, respectively. Unprovoked PE had developed in 10 of 15 COVID-19 patients (66.7%) compared with 8 of 497 non–COVID-19 patients (1.6%). The 60 COVID-19 patients with ARDS had had an incidence of DVT of 46.7% (n = 28). In contrast, the incidence of DVT for the 153 non–COVID-19 patients with ARDS was 28.8% (n = 44; *P* = .01). The COVID-19 patients requiring the ICU had had an increased rate of DVT (39 of 90; 43.3%) compared with the non–COVID-19 patients (33 of 123; 33.3%; *P* = .01). The risk factors for mortality included age, DVT, multiple organ failure syndrome, and prolonged ventilatory support with the following odd ratios: 1.030 (95% confidence interval [CI], 1.002-1.058), 2.847 (95% CI, 1.356-5.5979), 4.438 (95% CI, 1.973-9.985), and 5.321 (95% CI, 1.973-14.082), respectively.

Conclusions: The incidence of DVT for COVID-19 patients receiving standard-dose prophylactic anticoagulation that was not weight adjusted was high, especially for ICU patients. DVT is one of the factors contributing to increased mortality. These results suggest a reevaluation is necessary of the present standard-dose thromboprophylaxis for patients with COVID-19. (J Vasc Surg Venous Lymphat Disord 2022;10:803-10.)

Keywords: COVID-19; Deep vein thrombosis; Infection; Outcome

As of April 2021, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), also known as coronavirus disease 2019 (COVID-19) has affected >31 million people and caused >560,000 deaths in the United States.[1] The

major risk factors for morbidity and mortality include older age and the presence of multiple comorbid conditions.[2] Although respiratory compromise—from either pneumonia and/or acute respiratory distress syndrome (ARDS)—has remained the cardinal feature of the disease, recent autopsy studies have additionally demonstrated that elevated circulating D-dimer levels and the associated prothrombotic abnormalities accompanying the presence of fibrin thrombi within small vessels, are also associated with mortality.[3,4] Although a multicenter retrospective study of 400 COVID-19 patients receiving standard-dose prophylactic anticoagulation radiologically confirmed an incidence of venous thromboembolism (VTE) of only 4.8%, a recent meta-analysis documented an incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) of 14.8% and 16.5%, respectively.[5] Another systematic review reported an overall rate of

VTE of 21%, with a rate of 5% for patients not in the intensive care unit (ICU) and 31% for ICU patients, with the odds of mortality increasing by as much as 74% with VTE.[6] Because of the various rates of DVT reported by previous studies, the association of elevated D-dimer levels with an increasing severity of COVID-19, and the extent to which the development of DVT in patients with COVID-19 can increase mortality, we designed the present study to investigate the rate of DVT, relationship of D-dimer levels with DVT, and disease severity and their effects (ie, DVT, D-dimer levels) on mortality by comparing COVID-19 patients to a historical cohort without COVID-19.

METHODS

The institutional review board approved the present retrospective record review and waived the requirement for written informed consent. The present study included 786 patients divided into two groups: 213 COVID-19 patients who had been admitted from March 20 to June 30, 2020 and 573 non—COVID-19 patients who had been admitted from March 20 to June 30, 2019. All the patients had undergone screening for DVT using duplex ultrasound (US). Because of our medical center's logistic changes resulting from the need to admit COVID-19 patients, all elective medical and surgical admissions had been cancelled starting in March 2020. Therefore, the cohort group of non—COVID-19 patients could not be concurrent, because the vast majority of hospital beds were reserved for COVID-19 patients. The data acquired included demographics, diagnosis, service admission, admission to the ward or ICU, laboratory data (including prothrombin time, international normalized ratio, activated partial thromboplastin time, and D-dimer levels on admission [DD-Adm] and at compression US [DD-CUS]), DVT prophylaxis, the presence of COVID-19 pneumonia (PNA), ARDS (defined by the Berlin criteria[7]), the need for mechanical ventilation (MV), the occurrence of DVT, multiple organ failure syndrome (MOFS), PE, and mortality. Critical PNA (Crit-PNA) was defined by the presence of >50% lung infiltrates on the computed tomography (CT) scan of the chest of patients with arterial oxygen saturation <90% on room air with an arterial partial pressure of oxygen/fraction of inspired oxygen ratio of <300 breathing at a respiratory rate >30 breaths/min. PE was identified using CT pulmonary angiography (CTPA) in both groups. Patients with a diagnosis of PE underwent CTPA according to the presence of symptoms (sinus tachycardia, unexplained hypotension, worsening respiratory status). The medical patients who were not in the ICU and did not have COVID-19 had received subcutaneously administered unfractionated heparin 5000 U 3 times daily for thromboprophylaxis. The medical ICU, surgical, and trauma patients had received enoxaparin at a dose of 40 mg once daily (not adjusted to body weight). All COVID-19 patients, both ICU and non-ICU, had received enoxaparin at 40 mg once daily.

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center, retrospective cohort study
- **Key Findings:** The rate of deep vein thrombosis (DVT) and pulmonary embolism in coronavirus disease 2019 (COVID-19)—positive patients was higher than the rate in those without COVID-19. The COVID-19 patients in the intensive care unit had an increased rate of DVT. The risk factors for mortality included age, DVT, multiple organ failure syndrome, and prolonged ventilatory support.
- **Take Home Message:** The incidence of DVT in the COVID-19 patients receiving standard prophylactic anticoagulation was high, especially for patients in the intensive care unit.

The regimen did not change during the study period. Patients with DVT were treated with enoxaparin at 1 mg/kg/day every 12 hours. All the COVID-19 patients had undergone weekly DVT surveillance. In contrast, the 573 patients without COVID-19 had undergone duplex US scans according to the presence of symptoms and clinical risk factors for VTE.

Statistical analysis. Continuous variables are reported as the mean ± standard deviation and were analyzed using an unpaired t test. The parametric data are presented as the median and interquartile range (IQR). Categorical variables were analyzed using the χ^2. The variables that were predictive of the outcome are reported as odds ratios (ORs) with 95% confidence intervals (CIs) and were identified with stepwise logistic regression analysis. The strength of the association between the categorical and scale variables was determined using the eta (η) coefficient test. The subgroup analyses included patients admitted to the ICU and stratified by DVT, ARDS, and PE. Statistical significance was accepted to correspond to a P value < .05.

RESULTS

Of the 3934 non—COVID-19 patients admitted from March 20 to June 30, 2019, 603 (15.3%) had undergone CUS for DVT in accordance with the clinical criteria and risk factors. Of these 603 patients, 456 had been admitted to medicine, 69 to general surgery, and 78 to the trauma service. A total of 34 patients, 30 in the non—COVID-19 group and 4 in the COVID-19 group, were removed from the analysis because they had developed chronic DVT, leaving 573 patients without COVID-19 (age, 61 ± 17 years; 257 men [44.9%]) for comparison with the 213 COVID-19 patients (age, 61 ± 16 years; 130 men [61.0%]), who had undergone weekly DVT surveillance. The comparison of the 573 non—COVID-19 patients with the 213 COVID-19 patients is presented in Table I.

Table I. Comparison of patients with and without COVID-19

	COVID-19		
Variable	No (n = 573)	Yes (n = 213)	*P* value
Age, years	61 ± 17	61 ± 16	1.0
Male sex	257 (44.9)	130 (61)	.001
Comorbid conditions			
DM	92 (16)	76 (35.7)	.001
HTN	138 (24.1)	105 (49.3)	.001
BMI, kg/m^2	30.5 ± 14.2	33.5 ± 18.5	.015
BMI ≥30 kg/m^2	288 (50.3)	129 (60.6)	.010
Smoking	199 (34.7)	96 (45)	.01
CKD	45 (8)	20 (9.4)	.32
CVD	80 (14.5)	36 (16.9)	.30
Clinical outcome			
MV	39 (0.5)	86 (40.4)	.001
DVT	71 (12.4)	72 (33.8)	.001
PE	19 (3.3)	15 (7)	.029
Unprovoked PE[a]	8/497 (1.6)	10/141 (7)	.01
Mortality	23 (4)	50 (23.5)	.001

BMI, Body mass index; *CKD,* chronic kidney disease; *COVID-19,* coronavirus disease 2019; *CVD,* cardiovascular disease; *DM,* diabetes mellitus; *DVT,* deep vein thrombosis; *HTN,* hypertension; *PE,* pulmonary embolism.
[a]PE without DVT preceding it.

Although no differences were found in patient age, more male patients and a greater incidence of diabetes mellitus, hypertension, smoking, and a body mass index >30 kg/m^2 were found in the COVID-19 group. Most of the 456 non–COVID-19 medical patients had undergone duplex CUS for leg pain, leg tenderness and/or swelling, and documentation of the source of PE. The non–COVID-19 surgical (n = 69) and trauma (n = 78) patients had undergone scanning for clinical symptoms. The incidence of DVT was 12.4% (71 of 573) in the non–COVID-19 patients compared with 33.8% (72 of 213) in the COVID-19 group (*P* = .0001). The incidence of PE doubled as a result of COVID-19: 3.3% (19 of 573) for the non–COVID-19 patients vs 7.0% (15 of 213) for the COVID-19 patients (*P* = .02). More patients in the COVID-19 group had developed unprovoked PE: 10 of 141 (7.0%) vs 8 of 502 (1.6%) in the non–COVID-19 group (*P* = .0006). The patients with unprovoked PE were younger than were those whose PE could be linked to DVT: 49 ± 11 years and 62 ± 10 years, respectively. However, other than age, no other difference was found—including mortality—between the 10 with unprovoked and 5 with DVT-related PE (Table II). No difference was found in the mortality of patients with and without PE: 3 of 15 (20.0%) vs 47 of 198 (23.7%), respectively. In the COVID-19 group, the median DD-Adm was 1.50 µg/mL (IQR, 0.51-6.54 µg/mL), and the median DD-CUS was 2.26 µg/mL (IQR, 0.84-5.13 µg/mL; *P* = .29). A subgroup analysis of the 72 COVID-19 patients with DVT showed a nonsignificant difference between the DD-Adm and DD-CUS: median, 1.63 µg/mL (IQR, 0.48-7.41 µg/mL) and median, 3.49 µg/mL (IQR,

1.90-8.82 µg/mL), respectively (*P* = .58). The mean change between the DD-Adm and DD-CUS was 0.40 µg/mL (range, −0.71 to 2.89), indicating increases and decreases in the level of DD-Adm to CUS. In 42 patients, the DD-CUS was greater than the DD-Adm. In contrast, in 32 patients, the opposite had occurred. The patients with DVT-related PE had had greater levels of DD-CUS compared with those with unprovoked PE (median, 9.75 µg/mL; IQR, 5.41-31.25 µg/mL; vs median, 2.55 µg/mL; IQR, 1.32-5.24 µg/mL). The difference, however, did not achieve statistical significance. The median DD-CUS for the 198 patients without PE was 1.48 µg/mL (IQR, 0.51-5.84 µg/mL) and was 5.10 µg/mL (IQR, 1.53-6.38 µg/mL) for the 15 patients with PE (*P* = .47).

In contrast to the COVID-19 group, the 19 cases of PE in the non–COVID-19 patients were more frequently associated with DVT. Eight cases of PE had occurred in 502 patients without DVT (1.6%) vs 11 cases of PE in the 71 patients with DVT (15.5%). The mortality of the COVID-19 patients was 23.5% vs 4.0% (23 of 573) for the non–COVID-19 group. Of the deaths in the non–COVID-19 group, 18 had occurred in the medicine, 4 in the trauma, and 1 in the general surgery service. Patients with DVT had greater mortality in both groups: 16 of 502 without DVT (3.2%) and 7 of 71 with DVT (9.9%) in the non–COVID-19 group and 21 of 141 without DVT (14.9%) and 29 of 72 patients with DVT (40.3%) in the COVID-19 group.

Analysis of COVID-19 patients stratified by outcome

Of the 213 patients with COVID-19, 50 (23.5%) had died of COVID-19 complications. The 50 patients who died

Table II. Subgroup analyses of COVID-19 patients stratified by ARDS, DVT, PE, and ICU

Variable	Total	With	Without	P value
ARDS	213	ARDS (n = 60)	No ARDS (n = 153)	
Age, years	61 ± 16	56 ± 14	63 ± 17	.005
Male sex	130 (61)	42 (70)	88 (57.5)	.11
DVT	72 (33.8)	28 (46.7)	44 (28.8)	.01
DD-Adm, µg/mL	1.50 (0.51-6.54)	0.96 (0.46-3.46)	2.70 (0.55-7.27)	.5
DD-CUS, µg/mL	2.26 (0.83-5.12)	2.05 (0.66-5.12)	2.37 (1.07-4.92)	.5
PE	15 (7)	2 (3.3)	13 (8.5)	.24
COVID-PNA	89 (41.7)	8 (13.3)	81 (52.9)	.0001
Crit-PNA	90 (43.2)	56 (93.3)	34 (22.2)	.0001
MOFS	96 (45)	41 (68.3)	55 (35.9)	.0001
MV	86 (40.4)	54 (90)	32 (20.9)	.0001
Mortality	50 (23.4)	21 (35)	29 (18.9)	.0001
PE	15	PE (n = 5)	No PE (n = 10)	
Age, years	52 ± 15	62 ± 10	49 ± 11	.04
Male sex	13 (86.7)	3 (60)	10 (100)	.09
DD-Adm, µg/mL	6.62 (5.41-13.26)	5.51 (1.89-8.46)	2.55 (1.32-5.24)	.5
DD-CUS, µg/mL	5.15 (1.88-8.46)	5.00 (5.41-13.26)	2.54 (1.32-5.24)	.01
COVID-PNA	7 (46.7)	4 (80)	3 (30)	.11
Critical-PNA	5 (33.3)	1 (20)	4 (40)	.60
MOFS	3 (20)	1 (20)	2 (20)	1.00
MV	5 (33.3)	1 (20)	4 (40)	.60
Mortality	3 (20)	1 (20)	2 (20)	1.00
DVT	213	DVT (n = 72)	No DVT (n = 141)	
Age, years	61 ± 16	60 ± 14	60 ± 17	1.00
Male sex	130 (61)	49 (68)	81 (57.4)	.14
DD-Adm, µg/mL	1.50 (0.51-6.54)	1.63 (0.48-7.41)	1.51 (0.54-4.15)	.49
DD-CUS, µg/mL	2.26 (0.83-5.12)	3.49 (1.90-8.82)	1.41 (0.63-3.49)	.01
COVID-PNA	89 (41.7)	32 (44.4)	57 (40.4)	.65
PE	15 (7)	5 (6.9)	10 (7)	1.00
Critical-PNA	90 (43.2)	40 (55.6)	50 (35.5)	.01
MOFS	96 (45)	41 (56.9)	55 (39)	.01
MV	86 (40.4)	39 (40.2)	47 (33.3)	.004
Mortality	50 (23.4)	29 (40.3)	21 (14.9)	.02
ICU	213	ICU (n = 90)	No ICU (n = 123)	
Age, years	61 ± 16	58 ± 14	64 ± 17	1.00
Male sex	130 (61)	58 (64.4)	72 (56.7)	.14
DD-Adm, µg/mL	1.50 (0.51-6.54)	2.77 (0.63-7.58)	1.15 (0.50-4.31)	.03
DD-CUS, µg/mL	2.26 (0.84-5.13)	2.45 (1.13-5.15)	1.85 (0.64-4.78)	.01
DVT	72 (33.8)	30 (43.3)	33 (26)	.013
PE	15 (7)	5 (5.6)	10 (7.9)	1.00
COVID-PNA	89 (41.7)	32 (35.6)	57 (40.4)	.65
Crit-PNA	90 (43.2)	80 (88.9)	10 (7.9)	.01
MV	86 (40.4)	86 (95.6)	0 (0.0)	.004
Mortality	50 (23.5)	50 (55.6)	0 (0.0)	.001

ARDS, Acute respiratory distress syndrome; *COVID-19*, coronavirus disease 2019; *COVID-PNA*, coronavirus disease 2019-associated pneumonia; *Crit-PNA*, critical pneumonia; *DD-Adm*, D-dimer level at admission; *DD-CUS*, D-dimer level at compression ultrasound; *DVT*, deep vein thrombosis; *ICU*, intensive care unit; *MOFS*, multiple organ failure syndrome; *MV*, mechanical ventilation; *PE*, pulmonary embolism.
Data presented as mean ± standard deviation, number (%), or median (interquartile range).

Table III. Analysis of COVID-19 patients stratified by outcome

Variable	Total (n = 213)	Alive (n = 163)	Dead (n = 50)
Age, years	61 ± 17	60 ± 16	63 ± 19
Sex			
Male	130	95	35
Female	83	68	15
DVT	72 (33.8)	43 (26.4)	29 (58)[a]
PE	15 (7)	12 (7.4)	3 (6)
Crit-PNA	90 (42.3)	54 (33.1)	36 (72)[a]
ARDS	60 (28.2)	39 (23.9)	21 (42)[a]
MOFS	96 (45)	57 (34.9)	39 (78)[a]
DD-Adm, μg/mL	1.50 (0.51-6.54)	1.39 (0.53-6.39)	2.16 (0.51-12.7)
DD-CUS, μg/mL	2.26 (0.84-5.13)	1.72 (0.66-3.65)	4.37 (1.97-7.85)[a]
Progression to ARDS	56/90 (62.2)	18 (11)	38 (76)

ARDS, Acute respiratory distress syndrome; *COVID-19*, coronavirus disease 2019; *Crit-PNA*, critical pneumonia; *DD-Adm*, D-dimer level at admission; *DD-CUS*, D-dimer level at compression ultrasound; *DVT*, deep vein thrombosis; *MOFS*, multiple organ failure syndrome; *PE*, pulmonary embolism.
Data presented as mean ± standard deviation, number, number (%), or median (interquartile range).
[a]$P < .05$.

had had higher DD-Adm and DD-CUS levels and a greater incidence of DVT (58.0% vs 26.4%). Additionally, the nonsurvivors had had a greater incidence of Crit-PNA, ARDS, MOFS, and progression from Crit-PNA to ARDS. The mortality had increased from 12.9% (13 of 101) to 25.9% (15 of 58), 37.0% (10 of 27), and 44.4% (12 of 27) with a DD-CUS level of 0 to 1.99, 2.0 to 4.99, 5.0 to 10.0, and >10.0 μg/mL, respectively. The median level of DD-CUS for the survivors was lower (median, 1.7 μg/mL; IQR, 0.7-3.7 μg/mL) than that for the nonsurvivors (median, 4.4 μg/mL; IQR, 2.0-7.8 μg/mL). However, the higher DD-Adm and DD-CUS levels were not predictive of mortality on multivariable analysis. The variables predictive of mortality included increasing age (OR, 1.030; 95% CI, 1.002-1.058), DVT (OR, 2.847; 95% CI, 1.356-5.597), MOFS (OR, 4.438; 95% CI, 1.973-9.985), and MV (OR, 5.321; 95% CI, 1.973-14.082) (Table III).

Analysis of COVID-19 patients stratified by DVT. Of the 213 COVID-19 patients, 72 (33.8%) had developed lower extremity DVT. Compared with the patients without DVT, the patients with DVT had had higher DD-CUS and DD-Adm levels ($\eta = 0.750$; $\eta^2 = 0.562$). Additionally, they had had a greater incidence of MOFS, which was associated with a 63% increased relative risk of mortality: 14.9% (21 of 141) without DVT to 40.3% (29 of 72) with DVT ($P = .02$; Table II). The incidence of PE was 7.0% (15 of 213) for the patients with COVID-19, with 10 cases of unprovoked PE. Although the DD-CUS level was significantly different statistically between the patients with and without DVT on univariate analysis, the difference did not retain statistical significance on multivariable analysis. The presence of DVT was associated with an absolute 25.4% increase in mortality (14.9% [21 of 141] for patients without DVT vs 40.3% [29 of 72] for those with DVT). The median

interval from admission to the diagnosis of DVT in the COVID-19 group was 10 days (IQR, 4-15 days) compared with 14 days (IQR, 12-20 days) in the non–COVID-19 group ($P = .62$).

Patients stratified by ARDS. Of the 213 patients with COVID-19, 60 (28.2%) had developed ARDS, with 56 of the 60 patients progressing from Crit-PNA to a typical form of ARDS. The patients with ARDS were younger and more frequently male, with a higher incidence of DVT (28 of 60 [46.7%] vs 44 of 153 [28.8%]), and were more likely to have started with Crit-PNA (93.3% vs 22.2%; Table II). The higher rate of DVT in the patients with ARDS was associated with lower DD-Adm and DD-CUS levels (Table II). The presence of ARDS increased the mortality of the COVID-19 patients from 18.9% to 35.0%, a 16.1% increase. We found a moderate association between DVT and ARDS ($\eta = -0.615$; $\eta^2 = -0.378$).

Incidence of DVT in patients admitted to the ICU. A total of 131 patients, 90 of 213 with COVID-19 (42.3%) and 41 of 573 without COVID-19 (7.2%) were admitted to the ICU (Table IV). No difference was found in age and sex between the two groups. The incidence of DVT for the non–COVID-19 ICU patients was lower than that for the ward patients (3 of 41 [7.3%] vs 68 of 532 [12.8%]). In contrast, the incidence of DVT was higher for the COVID-19 patients in the ICU than for the COVID-19 patients on the ward (39 of 90 [43.3%] vs 33 of 123 [26.8%]). Although all the COVID-19 patients in the ICU had died, only 9 (4 medicine, 4 trauma, and 1 general surgery) of 23 non–COVID-19 patients in the ICU had died, with 14 patients dying of myocardial infarction and PE in the ward.

DISCUSSION

The cardinal feature of COVID-19 disease has been the respiratory compromise from the involvement of the

Table IV. Subgroup analysis of patients admitted to the ICU

Variable	ICU group (n = 131)	COVID-19 (n = 90)	Non−COVID-19 (n = 41)	*P* value
Age, years	61 ± 16	58 ± 14	50 ± 18	1.00
Male sex	84 (64.1)	58 (64.4)	26 (63.4)	.14
DVT	42 (33)	39 (43.3)	3 (7.3)	.001
PE	5 (3.8)	5 (5.6)	0 (0.0)	1.00
MV	125 (95.4)	86 (95.6)	39 (95.1)	1.00
Mortality	59 (45)	50 (55.6)	9 (21.9)	.01

COVID-19, Coronavirus disease 2019; *DVT,* deep vein thrombosis; *ICU,* intensive care unit; *MV,* mechanical ventilation; *PE,* pulmonary embolism.
Data presented as mean ± standard deviation or number (%).

pulmonary endothelium, with the resulting two time-dependent phenotypes of COVID-19 pneumonia as described by Gattinoni et al.[8] Early studies had documented elevated circulating D-dimer levels associated with prothrombotic hypercoagulable states, reported to be as high as 20%, with a 25% rate of VTE, despite conventional pharmacologic prophylaxis.[9,10] Two studies suggested that the D-dimer levels are associated with the severity of COVID-19 disease and mortality.[11,12] Because of the various rates of DVT reported by previous studies, in the present study, we investigated the rate of DVT and the relationship between the D-dimer levels and DVT—in the context of disease severity—through comparisons of mortality between a COVID-19 cohort and a cohort without COVID-19.

The rate of DVT in the COVID-19 group was 33.8%, despite conventional pharmacologic prophylaxis, which was greater than the 14.5% reported by Baccellieri et al[13] and the 20% reported by Malas et al.[6] The rate of DVT in the 90 critically ill ICU patients was 43.3%, which was also higher than the rate of 27% of VTE reported Klok et al.[14]

The relative rate of DVT for the patients with COVID-19 was 63.3% higher than the rate of DVT in the cohort of patients without COVID-19 admitted in 2019. Although some of the increased rate could be attributed to the weekly surveillance protocol implemented in the COVID-19 patients, the magnitude of the difference cannot be ascribed solely to the intensity of surveillance. Also, although the rate of DVT in the COVID-19 ICU patients was higher than that in the non-ICU patients (43.3% vs 26.8%, respectively), we observed a low incidence of DVT in the non−COVID-19 ICU patients (7.3% vs 12.8% for the patients in the ward). We believe that the lower rate of DVT in the non−COVID-19 ICU patients (compared with a mean rate of 12.7% of DVT in 1783 ICU patients reported in a meta-analysis of seven studies) might be—in part—the result of the small sample of ICU patients compared with the other studies.[15] Additionally, the lower rate of DVT for the non−COVID-19 ICU patients was likely attributable to the increased compliance with effective DVT prophylaxis for these patients; effective DVT prophylaxis has been associated with a low incidence of VTE.[16,17]

Patients with DVT had a higher level of DD-CUS compared with the patients without DVT, without a considerable overlap in the peak D-dimer values, as documented by others.[18] A moderately strong association was found between the D-dimer levels and the occurrence of DVT. However, we were unable to replicate the findings of other investigators, suggesting that a correlation exists between the D-dimer levels and the severity of COVID-19. Although mortality increased with increasing D-dimer levels, we could not reproduce the findings of Soni et al[19] with respect to the ability of a D-dimer value of ≥2.01 μg/mL to predict for mortality. Furthermore, we failed to demonstrate a correlation between the D-dimer levels and the presence of either severe pneumonia and/or ARDS. Although a significant difference was found in the DD-CUS level between the survivors and nonsurvivors on univariate analysis, the significance was not retained after stepwise logistic regression analysis. Therefore, we could not corroborate the negative effects of elevated D-dimer levels on survival, as previously reported.[12]

The incidence of PE in the COVID-19 cohort was 7.0%, consistent with the range of rates reported in previous studies.[20] Ten of the 15 cases of PE (66.7%) were diagnosed in patients without DVT, consistent with the findings of Helms et al.[21] The rate of unprovoked PE in the non−COVID-19 group was 1.6% (8 of 502 patients). Based on the high rate of DVT in our study, we believe that the prevalence of DVT in the COVID-19 group was not underestimated. We, therefore, propose that—at least in some cases—pulmonary thrombosis, rather than embolism, is the pulmonary pathologic entity associated with COVID-19. Other than a younger age for the patients with unprovoked PE, we could not document any differences, including the D-dimer level, that could help identify the risk factors for unprovoked PE. No difference was found in mortality between patients with unprovoked and DVT-related PE. All the cases of PE in the COVID-19 patients were not fatal. The mortality for 3 of 15 patients with PE was attributable to MOFS. In contrast to the reported higher ICU mortality in patients with PE, the mortality of the patients with PE was not greater than that

experienced by patients without PE (20.0% vs 23.7%, respectively).[22]

The 28.2% rate of ARDS was lower than the reported rate (range, 61%-81%) for patients requiring intensive care reported by other investigators.[23,24] The rate of DVT for the patients with ARDS was almost double the rate of patients without ARDS (43.3% vs 28.8%), without a significant difference in the D-dimer levels. The higher rate of DVT in the patients with ARDS, despite chemoprophylaxis, could be, in part, explained by the presence of more risk factors for DVT in this group, including prolonged MV, protracted immobilization, and a longer length of ICU stay. We believe that—notwithstanding the previously stated risk factors—failure to monitor anti-factor Xa (anti-FXa) activity in patients receiving conventional, not weight-adjusted, enoxaparin prophylaxis was likely the main reason that patients with ARDS had a greater rate of DVT because it has been shown that patients requiring MV will fail to achieve adequate anti-FXa activity if they received a dose of enoxaparin similar to the dose administered to the patients in the ward.[4] The 3.3% incidence of PE in this group was lower than the rate of 17% in a group of 92 patients with COVID-19 ARDS reported by Contou et al.[22] Although others have shown that older age is associated with a greater risk of developing ARDS because of a potentially compromised immune response, the patients with ARDS in our study were younger than those without it. However, as reported by others, they had significantly higher mortality.[25]

Of the 90 patients with Crit-PNA, 56 (62.2%) experienced progression to ARDS. The progression to ARDS increased the fatality rate from 18.9% to 35.0%, confirming the findings of other investigators with respect to the rate of progression to ARDS from severe pneumonia and the associated increased fatality rate.[26]

The results of a retrospective study of 26 patients with severe COVID-19 in two French ICUs, 8 (31%) of whom had received conventional VTE prophylaxis and 18 (69%) had received therapeutic anticoagulation, suggested that early therapeutic anticoagulation might reduce the rate of VTE in ICU patients with severe COVID-19.[27] The reduced rate of major thrombotic events and DVT in patients receiving therapeutic dose anticoagulation has been documented; however, it has not translated into a reduced rate of death for critically ill patients with COVID-19.[28] Therapeutic anticoagulation with heparin for COVID-19 patients not requiring ICU level care has been shown to be superior to the usual care thromboprophylaxis from the standpoint of reducing the need for organ support and mortality, with a more limited benefit for thrombotic events (from 3.2% to 1.9%).[29] In contrast, intermediate-dose prophylaxis of enoxaparin 1 mg/kg/d compared with standard-dose prophylaxis of 40 mg/d has been shown to be ineffective in reducing venous and arterial thrombosis in COVID-19 patients admitted to the ICU.[30]

Although our findings have corroborated the high incidence of VTE in COVID-19 patients, our study had many limitations, including its retrospective design and the comparison of a nonconcurrent group of patients who could not be properly matched. The non–COVID-19 patients had undergone symptom-driven DVT screening, with the possibility of missing asymptomatic events, and, thus, underestimating the incidence of DVT compared with the COVID-19 group who had undergone weekly surveillance. Because of the high proportion of obese patients in both groups, the absence of weight-adjusted dosing of enoxaparin prevented us from identifying whether conventional dosing might be the cause of some of the DVT prophylaxis failure. An additional limitation included the CTPA protocol without CT venography of the pelvis, limiting the evaluation of the iliac and pelvic veins not easily accessible for duplex CUS assessment, potentially overestimating the rate of unprovoked PE by failing to detect iliac and pelvic veins thrombosis, especially in patients who had received femoral vein catheters.

CONCLUSIONS

Based on our results, we have concluded that—despite conventional DVT prophylaxis—patients with COVID-19 will have a greater incidence of DVT and unprovoked PE compared with patients without COVID-19. The incidence of DVT was increased in patients requiring ICU care and MV despite conventional DVT prophylaxis with either subcutaneous administered heparin (5000 U three times daily) or nonweight-adjusted enoxaparin 40 mg once or twice daily. We believe that although the development of DVT increases the risk of mortality, it is unclear whether DVT contributes directly to mortality or is a marker of more severe disease. Because the course of COVID-19 is characterized by a progression from the asymptomatic incubation period (days 1-5) to symptomatic (days 6-11) to the early and late pulmonary phases (days 11-14 and 14 to >30 days), it is likely that effectiveness of thromboprophylaxis or full anticoagulation depends of the timing and dose of its administration in relation to the symptoms and severity of the disease associated with the course of COVID-19.[31] The following questions could not be answered by our study. In view of the high incidence of DVT in COVID-19 patients, the question remains whether—despite the conventional prophylaxis with either unfractionated heparin or enoxaparin—non-ICU patients with rapidly increasing D-dimer levels after admission and no contraindications should receive a higher prophylactic dose of low-molecular-weight heparin such as enoxaparin 0.5 mg/kg twice daily or 1 mg/kg once daily instead of the conventional dose. Another question is whether weight-adjusted low-molecular-weight heparin thromboprophylaxis with anti-FXa—guided dose adjustment to achieve target levels of anticoagulation would be more

appropriate. In addition, it is unknown whether the dosing should be different for COVID-19 patients in the ICU compared with COVID-19 patients not requiring the ICU according to the phase of pulmonary compromise, early vs late, and the D-dimer level. Additionally, it remains to be determined whether a relationship exists between the specific treatment a patient is receiving, such as antiviral vs anti-inflammatory and/or antimicrobial, and the effectiveness of the thromboprophylaxis or anticoagulation therapy. We believe that—pending the results from additional randomized clinical trials that address the potential effects of the timing and dose of thromboprophylaxis in relation to COVID-19 progression—a single-dose static approach might be inferior to one that tailors the dose to the specific phase of COVID-19 according to the timing and symptoms and, possibly, the D-dimer level.

AUTHOR CONTRIBUTIONS

Conception and design: CM, JM
Analysis and interpretation: CM, EL, PP, JM
Data collection: CM, AZ, ZL, AR
Writing the article: CM, EL, PP
Critical revision of the article: CM, EL, PP, AZ, ZL, AR, JM
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