CHEST

Hypercoagulability in ICU Patients With Coronavirus Disease 2019 With Respiratory Failure Results in Increased Prevalence of Venous Thromboembolic Disease

To the Editor:

Many studies indicate that severe coronavirus disease 2019 (COVID-19) infection is associated with a hypercoagulable state, as evidenced by pathologic findings from lung autopsies.[1] Procoagulant antiphospholipid antibodies have also been reported in patients with COVID-19.[2] We sought to determine the prevalence of DVT in patients with COVID-19 and ARDS within our ICUs.

Methods

Institutional review board exemptions were obtained from Tulane Medical Center and the Southern Louisiana Veterans Health Care System for acquisition of data for this study (PROTOCOL#:RO#:2020-0040029RCMS#:692SP#:4212020-538-TU). Inclusion criteria included all patients in respiratory failure in the medical ICU (MICU) who were confirmed positive for COVID-19 by reverse transcriptase-polymerase chain reaction testing. All patients underwent screening ultrasound done within 3 days of either initiation of data collection or admission/transfer to the ICU. Except for patients already receiving anticoagulation for preexisting conditions, all patients included in the study were administered 5,000 units of unfractionated heparin (subcutaneous [SQ] every 12 or 8 h) or enoxaparin (40 mg SQ daily), starting on or before admission to the ICU.[3] Sequential compression devices were not routinely used, based on the recent trial indicating no additional benefit with the use of sequential compression devices in addition to low molecular weight or unfractionated heparin.[4]

Technologists performing the ultrasounds were accredited by the Intersocietal Accreditation Commission (IAC) and studies were performed under the standard IAC lower extremity venous protocol. Interpreters included a combination of radiologists and cardiologists. Data points and risk factors included the following: age; sex; ethnicity; BMI > 40; smoking history; history of prior DVT or pulmonary embolism (PE); comorbidities including cancer, diabetes mellitus, hypertension, coronary artery disease, and chronic liver disease; ongoing sex hormone use; steroid use within the last 3 months; requirement for renal replacement therapy; presence of femoral vein central venous catheter placement; symptom onset before admission; hospital day if the patient was intubated; VTE prophylaxis regimen; use of a paralytic agent; date of admission to hospital for COVID-19-related illness; and D-dimer on admission and the day of the ultrasound. Patients were fully anticoagulated with a continuous infusion of IV unfractionated heparin or SQ enoxaparin at 1 mg/kg every 12 h if a DVT was identified.

Statistical Analysis

Descriptive statistics such as means and frequencies were generated to describe our sample. Continuous variables included mean and categorical variables. Numbers with percentages were used for categorical variables. χ^2 tests and Fisher exact tests were used to test for differences in groups of categorical variables, and unpaired *t* tests were used to test for differences in groups of continuous variables. We evaluated the effectiveness and diagnostic accuracy of D-dimer to predict DVT, using receiver operating characteristic with areas under the curves. *P* values < .05 were considered statistically significant. All data were statistically analyzed with SPSS 26.0 (IBM) and Prism 6 (GraphPad Software).

Results

Seven cases of VTE were discovered via ultrasound screening in 29 patients with COVID-19 admitted to the Tulane Medical Center MICU (24.1%). Six cases were diagnosed in the Veterans Affairs MICU out of 17 patients screened (35.3%). In total there were 13 VTEs detected in 46 patients (28.3%). Eleven of 46 patients had proximal DVTs (23.9%). We performed statistical analysis from combined Tulane Medical Center and Veterans Affairs patients for the presence of DVT vs D-dimer level, BMI, age, and length of hospital stay before the date of the screening ultrasound (Fig 1). The D-dimer receiver operating characteristic curve from values obtained the day of the ultrasound showed an area under the curve of 0.71 (95% CI, 0.54-0.87). Placing a premium on sensitivity in these critically ill patients, a D-dimer level of 1.42 afforded 92% sensitivity, but only 32% specificity. The sensitivity was 100% and the specificity was 6.2%, using a D-dimer value at the upper limit of normal. No patients with VTE had a normal D-dimer level.

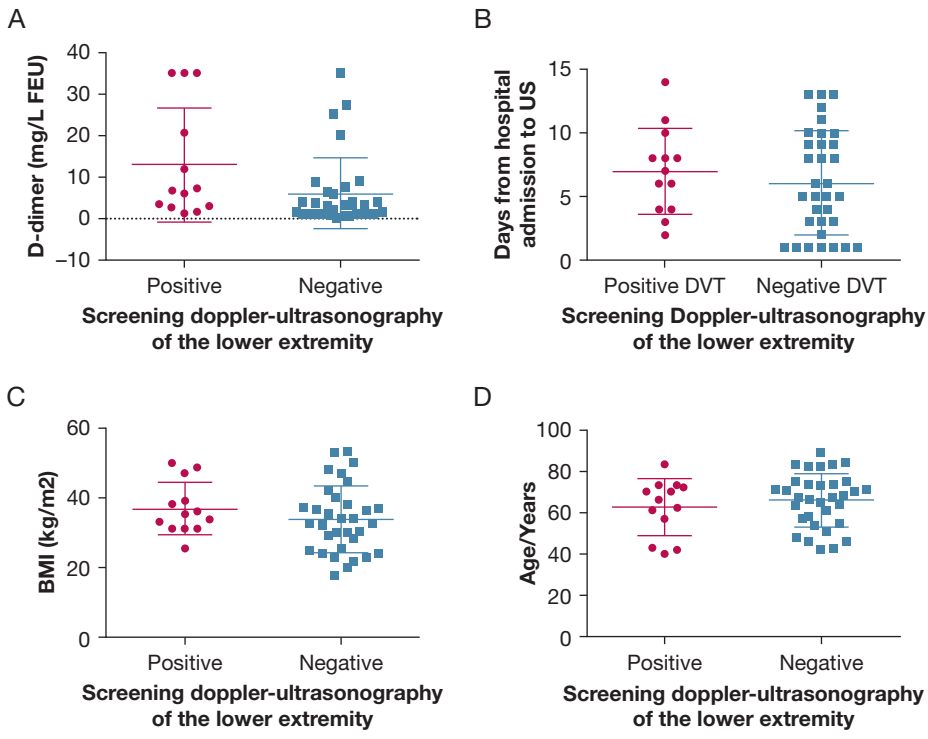

Figure 1 – *A-D, Comparisons between patients with and without DVT in relation to D-dimer level (A), length of stay in hospital before ultrasound screening (B), BMI (C), and age (D). Only D-dimer levels showed a statistically significant difference between the two groups with* $P < .05$. *FEU = fibrinogen equivalent unit; US = ultrasound.*

Discussion

This report is a descriptive screening survey demonstrating the prevalence of DVT in 46 patients with severe COVID-19 infection admitted to two ICUs in New Orleans, Louisiana. The finding of a 28% VTE prevalence is approximately five times higher than that reported in the May 2006-June 2010 multicenter randomized Prophylaxis of Thromboembolism in Critical Care Trial (PROTECT), in which VTE rates ranged from 5.1% (96 of 1,873 for dalteparin) to 5.8% (109 of 1,873 for unfractionated heparin [UFH]).[5] However, in septic patients, Kaplan et al[6] found an overall proximal plus distal DVT prevalence of 37.2%, and 11.5% for proximal lower extremity DVTs.

There are two other reports that increase our confidence in our findings. A recent report by Xu et al[1] indicates that, using the Padua Prediction Score for Risk of VTE, 16.7% of patients in China with COVID-19 were at high risk for VTE. Although retrospective, 20% of these patients were reported to have venous thrombosis. Analogously, Avnon et al[7] reported 25% of 20 patients admitted to the ICU with severe influenza A/H1N1 had thrombotic events. The presence of pulmonary thrombi in autopsy studies and the presence of elevated D-dimers has also been noted.[8]

There are multiple known risk factors for VTE.[9] All of the patients had several of these, including stasis and obesity. VTE risk factors were obtained from the chart history, and physical and laboratory values, as shown in Table 1. The relatively low number of patients assessed does not afford the opportunity to be confident in excluding that there may be a small but significant link to any of these other factors for VTE in patients with COVID-19. The racial demographics of our study are in keeping with the preponderance of Black patients in New Orleans.

All of the patients in this report were treated with SQ UFH or low-molecular-weight heparin from the day of admission to hospital. In light of our findings, one suggestion is to proactively screen for DVTs, and advance anticoagulant therapy as appropriate. Another option is to administer full-dose UFH to patients with COVID-19 and ARDS admitted to ICUs. An observational cohort study in an analogous setting demonstrates H1N1-infected patients with ARDS with a 23.3-fold higher risk for PE and 17.9-fold higher risk for VTE.[10] Empirical anticoagulation in H1N1-infected patients conferred significant protection from thrombotic events during the ICU stay, as patients without empirical systemic anticoagulation were 33 times more likely to have VTEs compared with those

TABLE 1] Baseline Characteristics and VTE Risk Factors and DVT Screening Results, Combined Tulane Hospital and Southern Louisiana Veterans Health-Care System

	Positive DVT Study (n = 13)	Negative DVT Study (n = 33)	*P* Value	All Subjects (N = 46)
Age, mean (SD), y	62.5 (3.8)	65.9 (2.2)	0.42	64.9 (12.8)
Sex, No. (%)				
Male	7 (25.9)	20 (74.1)	…	27 (58.7)
Female	6 (31.6)	13 (68.4)	…	19 (41.3)
Ethnicity, No. (%)				
Black	13 (100.0)	30 (90.9)	…	…
White	0 (0.0)	3 (9.1)	…	…
BMI, mean (SD), kg/m^2	37.0 (2.1)	33.8 (1.7)	0.30	34.7 (9.0)
D-dimer on the day of screening, mean (SD)	13.0 (3.8)	5.9 (1.5)	0.04	6.7 (9.0)
Days to screening ultrasound, mean (SD)	7.0 (0.9)	6.1 (0.7)	0.48	6.3 (3.8)
History of VTE, No. (%)	1 (7.7)	2 (6.1)	1.00	3 (6.5)
History of cancer, No. (%)	1 (7.7)	7 (21.2)	0.66	8 (27.4)
History of liver disease, No. (%)	1 (7.7)	1 (3.0)	0.49	2 (4.3)
Chronic kidney disease, No. (%)	3 (23.1)	10 (30.3)	0.73	13 (28.3)
Recent sex hormone use, No. (%)	1 (7.7)	0 (0.0)	0.28	1 (2.2)
Recent steroid use, No. (%)	2 (15.4)	12 (36.4)	0.29	14 (30.4)

treated with empiric systemic anticoagulation.[10] In a publication from Wuhan, daily SQ treatment with 40 to 60 mg of low-molecular-weight heparin or 10,000 to 15,000 units of UFH was associated with a 20% reduction in mortality in patients with COVID-19 who demonstrated a D-dimer level greater than 3 μg/mL.[11] In an observational study by Paranjpe et al[12] with 395 patients with COVID-19 requiring mechanical ventilation, in-hospital mortality was 29.1% for those treated with full-dose anticoagulation compared with 62.7% in those who were not. The authors did not specify what pharmaceuticals were used for full-dose anticoagulation and commented that prospective randomized trials are needed to determine whether systemic anticoagulation confers a survival benefit in hospitalized patients with COVID-19.

The impact of our findings on our practice has been to order ultrasound screening in patients with COVID-19 in our ICUs, and to treat those with positive test results with full-dose IV UFH. Recognition of the high frequency of DVT in MICU patients with COVID-19 could conceivably reduce the incidence of PE. The majority of MICU patients with COVID-19 have severe ARDS, with Pa_{O_2}/F_{IO_2} ratios of less than 150, and have little reserve to tolerate PE.

Our intent is to draw attention to VTE consequences of the hypercoagulable state seen in patients with severe COVID-19. It is our hope that heightened awareness of this hypercoagulable state and the high prevalence of VTE shown herein will lead to increased DVT screening of patients with severe COVID-19 admitted to MICUs, to prevent life-threatening VTEs.[13]

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