Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation

Russell A. Trigonis, MD[1]; Daniel B. Holt, MD[1]; Rebecca Yuan, MD[2]; Asma A. Siddiqui, MD[3]; Mitchell K. Craft, DO[3]; Babar A. Khan, MD[1]; Rajat Kapoor, MD[3]; Omar Rahman, MD[3]

Objectives: One of the defining features of the novel coronavirus disease 2019 infection has been high rates of venous thromboses. The present study aimed to describe the prevalence of venous thromboembolism in critically ill patients receiving different regimens of prophylactic anticoagulation.

Design: Single-center retrospective review using data from patients with confirmed severe acute respiratory syndrome coronavirus 2 requiring intubation.

Setting: Tertiary-care center in Indianapolis, IN, United States.

Patients: Patients hospitalized at international units Health Methodist Hospital with severe acute respiratory syndrome coronavirus 2 requiring intubation between March 23, 2020, and April 8, 2020, who underwent ultrasound evaluation for venous thrombosis.

Interventions: None.

Measurements and Main Results: A total of 45 patients were included. Nineteen of 45 patients (42.2%) were found to have deep venous thrombosis. Patients found to have deep venous thrombosis had no difference in time to intubation ($p = 0.97$) but underwent ultrasound earlier in their hospital course ($p = 0.02$). Sequential Organ Failure Assessment scores were similar between the groups on day of intubation and day of ultrasound ($p = 0.44$ and $p = 0.07$, respectively). D-dimers were markedly higher in patients with deep venous thrombosis, both for maximum value and value on day of ultrasound ($p < 0.01$ for both). Choice of prophylactic regimen was not related to presence of deep venous thrombosis ($p = 0.35$). Ultrasound evaluation is recommended if D-dimer is greater than 2,000 ng/mL (sensitivity 95%, specificity 46%) and empiric anticoagulation considered if D-dimer is greater than 5,500 ng/mL (sensitivity 53%, specificity 88%).

Conclusions: Deep venous thrombosis is very common in critically ill patients with coronavirus disease 2019. There was no difference in incidence of deep venous thrombosis among different pharmacologic prophylaxis regimens, although our analysis is limited by small sample size. D-dimer values are elevated in the majority of these patients, but there may be thresholds at which screening ultrasound or even empiric systemic anticoagulation is indicated. (*Crit Care Med* 2020; 48:00–00)

Key Words: anticoagulation; coronavirus disease 2019; d-dimer; deep venous thrombosis

The United States has over a million identified cases of the novel coronavirus disease 2019 (COVID-19) infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with over 60,000 total deaths (1). Given the pathophysiology of cytokine storming and excessive complement activation (2), it stands to reason that one of the defining features of COVID-19 has been the increased prevalence of deep venous thrombosis (DVT) (3–5). Based on current data, it is unclear how use of prophylactic anticoagulation prevents development of DVTs in critically ill COVID-19 patients. We conducted an analysis to explore if pharmacologic prophylactic agents are effective for prevention of clinical venous thrombosis in critically ill COVID-19 subjects. We also evaluated different D-dimer value thresholds associated with DVTs that could guide further diagnostic and therapeutic interventions for this patient population.

MATERIALS AND METHODS

Patients hospitalized at IU Health Methodist Hospital with confirmed SARS-CoV-2 requiring intubation and mechanical ventilation between March 23, 2020, and April 8, 2020, were identified through electronic medical records. Methodist Hospital is an 802-bed tertiary-care center with 120 ICU beds, affiliated with Indiana University School of Medicine. A manual chart review was conducted by the primary author (R.T.) on identified COVID-19 patients and all who underwent

[1]Department of Pulmonary and Critical Care Medicine, Indiana University School of Medicine, Indianapolis, IN.

[2]Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN.

[3]Department of Pulmonary and Critical Care Medicine, Indiana University Health Methodist Hospital, Indianapolis, IN.

DOI: 10.1097/CCM.0000000000004472

ultrasound evaluation for DVT were included. Any DVT noted in the lower or upper extremities on ultrasound was recorded as positive (+) for DVT. The study was approved by the institutional review board at Indiana University School of Medicine.

A data collection form was developed for the systematic retrieval of anonymized epidemiologic, historical, diagnostic, and treatment data. Age, race, and body mass index (BMI) were all noted at time of patient admission. Time from admission to intubation as well as time from admission to ultrasound evaluation were calculated in days. Sequential Organ Failure Assessment (SOFA) was calculated for all patients with data provided during the time period immediately prior to intubation as well as on the day of the ultrasound study. D-dimer values were also recorded as the value closest to the date of ultrasound as well as the overall maximum value during the hospitalization. Finally, DVT pharmacologic prophylactic agent and dosing were recorded for all patients at time of the ultrasound.

Baseline variables with normal distributions were described as mean and SD and as median and interquartile ranges for skewed distribution. Continuous measures were compared using Mann-Whitney *U* test and categorical measures through Pearson chi-square test or Fisher exact test. *p* value of less than 0.05 were defined as statistically significant. All analyses were performed using Microsoft Excel (Version 16.38; Microsoft, Redmond, WA).

Using the D-dimers recorded for each patient, we calculated different thresholds including positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity associated with the ultrasound diagnosis of DVT.

RESULTS

Between March 23, 2020, and April 8, 2020, 45 intubated patients with COVID-19 underwent ultrasound evaluation to identify DVT and were subsequently included in our study. Overall incidence of DVT was 19 of 45 or 42.2% with all noted

TABLE 1. Patient Demographics and Clinical Characteristics

Characteristic	Total (*n* = 45)	(+) DVT (*n* = 19)	(–) DVT (*n* = 26)	*p*
Age, yr, mean (SD)	60.8 (14.9)	64.1 (14)	58.3 (15.4)	0.102
Race, *n* (%)				
White	14 (31)	5 (26)	9 (35)	0.830
Black	24 (53)	11 (58)	13 (50)	
Other	7 (16)	3 (16)	4 (15)	
Body mass index (kg/m^2), mean (SD)	33.6 (9.5)	31.8 (5.8)	35.2 (11.3)	0.119
Days from admission to intubation, median (IQR)	1 (0–2)	1 (0–1.5)	1 (0–3)	0.97
Days from admission to DVT ultrasound, median (IQR)	7 (4–9)	6 (3.5–7.5)	9 (6–10)	0.02[a]
Sequential Organ Failure Assessment score, median (IQR)				
Day of intubation	5 (4–6)	6 (4–7)	5 (4–6)	0.44
Day of DVT ultrasound	5 (4–6)	6 (5–7)	5 (3.25–5.75)	0.07
D-dimer value (ng/mL), median (IQR)				
D-dimer (maximum)	4,046 (2,706–8,912)	6,911 (4,156–13,892)	3,148 (1,751–5,309)	< 0.01[a]
D-dimer (date of ultrasound)	3,000 (1,861–5,606)	5,606 (2,937–11,867)	2,274 (1,080–3,430)	< 0.01[a]
DVT prophylaxis, *n* (%)				
LMWH 40 mg every 24 hr	7 (16)	5 (26)	2 (8)	0.35
LMWH 30 mg q12h	16 (35)	6 (32)	10 (38)	
LMWH 40 mg q12h	6 (13)	2 (11)	4 (15)	
UFH 5,000 U q8h	10 (22)	5 (26)	5 (19)	
UFH 7,500 U q8h	2 (4)	0 (0)	2 (8)	
Other	4 (9)	1 (5)	3 (12)	

DVT = deep venous thrombosis, IQR = interquartile range, LMWH = low-molecular-weight heparin, q8h = every 8 hr, q12h = every 12 hr, UFH = unfractionated heparin.

[a]Significance at $p < 0.05$.

Summary of demographics, clinical characteristics, and pharmacologic DVT prophylaxis for patients admitted to the ICU who underwent DVT ultrasound. LMWH and UFH were used for prophylaxis in the majority of cases. One patient who was found to have a DVT was already on a heparin infusion due to recurrent clotting of continuous veno-venous hemofiltration filter and three of the patients in the DVT (–) group were on therapeutic bivalirudin drips for veno-venous-extracorporeal membrane oxygenation.

findings being lower extremity clot. **Table 1** provides the general demographics and diagnostic values.

The mean age was 60.8 years with no significant difference between the DVT and non-DVT groups (64.1 vs 58.3; $p = 0.102$). The mean BMI was 33.6 kg/m^2, again with no significant difference between the groups (31.8 vs 35.2; $p = 0.119$). Patients in the DVT group had the ultrasound earlier in their hospital course compared with non-DVT group (6 vs 9 d; $p = 0.02$).

SOFA scores on the day of intubation were not different between the two groups (6 vs 5; $p = 0.44$). Patients with DVT also had similar SOFA scores on the date of the ultrasound (6 vs 5; $p = 0.07$). D-dimer values were significantly higher in the (+) DVT group, both on the date of ultrasound as well as the overall maximum value ($p < 0.01$ for both).

Table 1 also shows the various pharmacologic DVT prophylaxis in both groups. Low-molecular-weight heparin (LMWH) dosed at 30 mg every 12 hours was the most commonly used medication and dosing. There was no significant difference in anticoagulant regimen between the two groups ($p = 0.35$).

We also used D-dimer values to describe the PPV, NPV, sensitivity, and specificity with respect toward the diagnosis of DVT at different cutoff values (**Table 2**).

DISCUSSION

We found a large proportion of DVTs among our critically ill COVID-19 patients, findings similar to several other studies looking at COVID-19 patient populations (3–5). However, our study results further expand these findings with regards to evaluation of specific anticoagulant regimen. Prophylactic regimens consisting of both LMWH and unfractionated heparin were seen at different doses and frequencies. We found that DVTs occurred in each regimen, and there was no relationship between different prophylactic anticoagulation treatment and diagnosis of DVT.

We found similar age and racial distribution between our two groups and found similar rates of obesity. This is notable as obesity is an independent risk factor in general for venous thromboembolic disease (6) but does not appear to be associated with a higher risk of DVT in COVID-19 subjects. The mean SOFA scores, although not different between the two groups on the date of intubation, trended toward significance on the date of ultrasound (6 vs 5; $p = 0.07$). This raises several questions, primary of which was what drove the provider to order an ultrasound on that specific day? Was it due to generalized worsening clinical course or were there specific examination

TABLE 2. Predictive Values of Different D-Dimer Thresholds

Date of Ultrasound					
D-Dimer Greater Than (ng/mL)	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity	No. of Patients With D-Dimer Greater Than
1,000	0.51	1.00	1.00	0.31	37
1,500	0.53	1.00	1.00	0.35	36
2,000	0.56	0.92	0.95	0.46	32
2,500	0.59	0.88	0.89	0.54	29
3,000	0.59	0.74	0.68	0.65	22
3,500	0.68	0.77	0.68	0.77	19
4,000	0.71	0.75	0.63	0.81	17
4,500	0.73	0.73	0.58	0.85	15
5,000	0.71	0.71	0.53	0.85	14
5,500	0.77	0.72	0.53	0.88	13
6,000	0.82	0.71	0.47	0.92	11
6,500	0.80	0.69	0.42	0.92	10
7,000	0.88	0.68	0.37	0.96	8
7,500	0.88	0.68	0.37	0.96	8
8,000	0.88	0.68	0.37	0.96	8
8,500	0.88	0.68	0.37	0.96	8
9,000	1.00	0.68	0.37	1.00	7
9,500	1.00	0.67	0.32	1.00	6
10,000	1.00	0.67	0.32	1.00	6

Calculated positive predictive value, negative predictive value, sensitivity, and specificity at different D-dimer levels noted on day of ultrasound. All 45 patients had recorded D-dimer values that were used for calculations.

findings that prompted the examination? Although we cannot answer this for each case, clinical patterns indicate that ultrasounds were pursued in these patients due to their severity of illness and elevated inflammatory markers, most notably D-dimer. Given our study's retrospective nature, our patient population was determined by the original provider's digression of ordering a DVT ultrasound. Although this may limit how generalizable our findings are, our incidence of DVT does match what has been found in other larger studies (7). This leads us to believe our observations likely are consistent with this population of critically ill COVID-19 patients.

All of our patients were on some form of chemical prophylaxis from the date of their admission, which does distinguish our study from others (4). In addition, these regimens were personalized based on the patient's renal function and weight at the discretion of the critical care provider caring for the patient. However, given the novel nature of this disease process and the constantly evolving knowledge of its pathophysiology, treatment regimens did deviate from what might be otherwise usual care in the ICU. Due to ongoing case studies as well as likely a component of anecdotal discussion between providers, patients were often placed on regimens at higher dosages or frequencies than what is commonly used. Although our results did not show any significant difference between the regimens, our sample sizes were quite small and further data gathering might begin to suggest a trend.

Patients in the (+) DVT group had markedly higher D-dimer values. D-dimer is a well-known and effective screening tool for venous thromboembolism, although most of its utility lies in its NPV due to its poor specificity (8). D-dimer has also been evaluated specifically in COVID-19 patients as a screening tool with 1,500 ng/mL chosen as a possible screening value (4). However, both of our patient groups had medians higher than this threshold, albeit with very large interquartile ranges. We calculated our own testing characteristics at different D-dimer thresholds as noted in Table 2. Although the data were recorded both as the overall maximum as well as on the date of the ultrasound, we believe that the measurements on the date of ultrasound are likely better suited as a screening value as these results may have prompted the provider to pursue the diagnostic study. From our findings, we recommend ultrasound evaluation if D-dimer is greater than 2,000 ng/mL (sensitivity 95%, specificity 46%) and strongly consider empiric therapeutic anticoagulation if D-dimer is greater than 5,500 ng/mL (sensitivity 53%, specificity 88%). The screening threshold of 2,000 ng/dL was chosen given increased specificity as compared with the 1,500 ng/dL threshold (46% vs 35%) with an acceptable drop in sensitivity (95% vs 100%). Driving this was an effort to minimize exposure for ultrasound technicians. The empiric treatment level of 5,500 ng/dL was chosen for its strong specificity of 88% while retaining a sensitivity of 53% as compared with cutoffs above it showing a sensitivity of less than 50%.

CONCLUSIONS

DVT is common in critically ill patients with COVID-19. Although D-dimer values are elevated in the majority of these patients, there may be thresholds at which screening ultrasound evaluation or even empiric systemic anticoagulation is indicated. Finally, there was no difference in incidence of DVT among different pharmacologic prophylaxis regimens, although our analysis is limited by small sample size.

Dr. Khan's institution received funding from the National Institutes of Health. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Address requests for reprints to: Omar Rahman, MD, 1801 N Senate Ave, Suite 230, Indianapolis, IN 46202. E-mail: orahman@IUHealth.org

REFERENCES

1. Centers for Disease Control and Prevention: Coronavirus Disease 2019 (COVID-19) in the U.S. Centers for Disease Control and Prevention. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html. Accessed April 28, 2020
2. Campbell CM, Kahwash R: Will complement inhibition be the new target in treating COVID-19-related systemic thrombosis? *Circulation* 2020; 141:1739–1741
3. Klok FA, Kruip MJHA, van der Meer NJM, et al: Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020; 191:145–147
4. Cui S, Chen S, Li X, et al: Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 2020; 18:1421–1424
5. Llitjos J-F, Leclerc M, Chochois C, et al: High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020 Apr 22. [online ahead of print]
6. Stein PD, Beemath A, Olson RE: Obesity as a risk factor in venous thromboembolism. *Am J Med* 2005; 118:978–980
7. Klok FA, Kruip MJHA, van der Meer NJM, et al: Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res* 2020; 191:148–150
8. Pulivarthi S, Gurram MK: Effectiveness of d-dimer as a screening test for venous thromboembolism: An update. *N Am J Med Sci* 2014; 6:491–499