Routine Venous Thromboembolism Prophylaxis May Be Inadequate in the Hypercoagulable State of Severe Coronavirus Disease 2019

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Objectives: The aim of this study was to determine the frequency of venous thromboembolism in critically ill coronavirus disease 2019 patients and associate a degree of inflammatory marker elevation to venous thromboembolism development.

Design: An observational study that identified patients with severe coronavirus disease 2019 between March 12, 2020, and March 31, 2020. Data reported are those available through May 6, 2020.

Setting: A multicenter study including three Indianapolis area academic hospitals.

Patients: Two-hundred forty consecutive patients with confirmed severe acute respiratory syndrome coronavirus 2 infection were admitted to one of three hospitals. One-hundred nine critically ill coronavirus disease 2019 patients admitted to the ICU were included in the analysis.

Interventions: All patients received routine subcutaneous chemical venous thromboembolism prophylaxis.

Measurements and Main Results: The primary outcome of this study was to determine the frequency of venous thromboembolism and the degree of inflammatory and coagulation marker elevation associated with venous thromboembolism development. Descriptive statistics outlined the frequency of venous thromboembolism at any time during severe coronavirus disease 2019. Clinical course and laboratory metrics were compared between patients that developed venous thromboembolism and patients that did not develop venous thromboembolism. Hypercoagulable thromboelastography was defined as two or more hypercoagulable parameters.

Main Results: One-hundred nine patients developed severe coronavirus disease 2019 requiring ICU care. The mean ($\pm$ SD) age was 61 ± 16 years and 57% were male. Seventy-five patients (69%) were discharged home, 7 patients (6%) remain in the hospital, and 27 patients (25%) died. Venous thromboembolism was diagnosed in 31 patients (28%) 8 ± 7 days after hospital admission, including two patients diagnosed with venous thromboembolism at presentation to the hospital. Elevated admission D-dimer and peak D-dimer were associated with venous thromboembolism development ($p < 0.05$). D-dimer greater than 2,600 ng/mL predicted venous thromboembolism with an area under the receiver operating characteristic curve of 0.760 (95% CI, 0.661–0.858; $p < 0.0001$), sensitivity of 89.7%, and specificity of 59.5%. Twelve patients (11%) had thromboelastography performed and 58% of these patients had a hypercoagulable study. The calculated coagulation index was hypercoagulable in 50% of patients with thromboelastography.

Conclusions: These data show that coronavirus disease 2019 results in a hypercoagulable state. Routine chemical venous thromboembolism prophylaxis may be inadequate in preventing venous thromboembolism in severe coronavirus disease 2019. (*Crit Care Med* 2020; XX:00–00)

Key Words: deep vein thrombosis; low-molecular-weight heparin; novel coronavirus; pulmonary embolism; venous thromboembolism

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The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a pandemic passing three million worldwide cases of coronavirus disease 2019 (COVID-19) with an associated case-fatality rate of 6.9% (1). The first death from COVID-19 in the state of Indiana was reported on March 16; 65 deaths and 2,565 cases were confirmed by March 31 (2). Severe COVID-19 is

characterized by acute respiratory failure often culminating in the need for mechanical ventilation (3–6). Studies have associated increased acute phase reactants and inflammatory markers with severe COVID-19 (3–5, 7–10). Abnormal coagulation parameters have additionally been associated with severe or fatal COVID-19 (11–13). These reports describe a biochemical profile suspicious for a prothrombotic and hypercoagulable state characterized by significant elevations in fibrinogen and a rapid unexpected ascent of serum D-dimer. This degree of profound systemic inflammation has a well-known association to a hypercoagulable state (14). These findings, and anecdotal clinical experience, have generated the hypothesis that a prothrombotic state may play a dominant pathophysiologic role in severe or fatal COVID-19. Supporting this thesis is a study from China describing decreased mortality in critically ill patients receiving prophylactic anticoagulation with low-molecular-weight heparin (15).

Profound systemic inflammation, critical illness, immobility, and organ failure are documented risk factors for a prothrombotic and hypercoagulable state (16–18). Recent autopsy reports in patients with COVID-19 identified cardiac and pulmonary microvascular thrombosis (19), supporting clinical suspicion for this pathophysiologic mechanism in COVID-19 shared among physicians on preprint platforms and social media. The frequency of venous thromboembolism (VTE) in critically ill patients with COVID-19, including deep vein thrombosis (DVT) and pulmonary embolism (PE), is becoming better understood, ranging from 25% to 27% in recent publications (12, 13). Thromboelastography is a dynamic evaluation of the viscoelastic properties of whole blood throughout the clot formation and lysis process, allowing for quantitative measurement of clot formation kinetics (20, 21). In various clinical circumstances including critical illness, a hypercoagulable thromboelastography profile has been associated with increased thrombotic risk; however, thromboelastography has not been explored in patients with severe COVID-19.

The aim of this study was to determine the frequency of VTE in critically ill COVID-19 patients and associate a degree of inflammatory marker elevation to VTE development.

MATERIALS AND METHODS

Study Population
All patients with laboratory-confirmed SARS-CoV-2 infection admitted to three Indianapolis area hospitals between March 12 and March 31 were evaluated in this study. Patients less than 18 years old, imprisoned patients, pregnant patients, and patients who elected for comfort care on arrival were excluded from analysis. All data available through May 6, 2020, were included.

Two-hundred forty adult patients were admitted; 122 patients had mild/moderate COVID-19 and 118 patients had severe/fatal COVID-19. Definitions of COVID-19 severity are defined in subsequent text. Nine patients with severe COVID-19 elected for comfort care only and were excluded from the analysis, resulting in 109 patients meeting inclusion criteria

(**Fig. 1**). Twelve patients with thromboelastography were included in a subgroup analysis. The Indiana University (IU) Institutional Review Board (IRB) approved the conduct of this study (IRB Study Number 2004134287) and deemed it exempt. Informed consent was waived, and anonymized data were analyzed.

The severity of COVID-19 is defined in subsequent text. All patients admitted with COVID-19 receive VTE chemoprophylaxis including either 5,000 U subcutaneous heparin every 8 hours, 40 mg enoxaparin daily, or 30 mg enoxaparin bid. Mild COVID-19 patients received best supportive treatment. Moderate and severe COVID-19 patients, in addition to best supportive care, were treated with hydroxychloroquine 400 mg orally every 12 hours for two doses, then 400 mg orally daily for four doses and azithromycin 500 mg IV daily for three doses. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin criteria (22). In patients with low pulmonary compliance, similar to traditional ARDS, standard ARDS Network strategy was used (23). Although standardized treatment protocols were applied generally, clinical judgment in individual cases dictated treatment strategies.

Study Definitions
Coexisting medical conditions and medications were recorded according to physician documentation at the time of hospital admission. Individual patient's clinical examination findings, laboratory results, diagnostic imaging, treatment, and outcomes were retrospectively reviewed.

Testing for COVID-19 was obtained in accordance with the Centers for Disease Control and Prevention (CDC) guidelines and clinical specimens were tested using the CDC's assay (24). Testing occurred at the Indiana State Department of Health Laboratory from March 1 to March 19. All testing on and after March 20 was performed at the IU Health Pathology Laboratory.

Per institutional guidelines, mild COVID-19 was defined as Spo_2 greater than 94% on room air with or without radiographic evidence of pneumonia. Moderate COVID-19 was defined as a measured peripheral oxygen saturation (Spo_2) less than or equal to 94% on room air with or without radiographic evidence of pneumonia. Severe COVID-19 was defined as Spo_2 less than or equal to 94% with respiratory rate greater than or equal to 30 breaths per minute and Pao_2/Fio_2 ratio less than or equal to 300 mm Hg. Any patient requiring mechanical ventilation was considered to have severe COVID-19.

Extremity DVT was diagnosed on four-extremity duplex ultrasound performed for clinical suspicion for venous thrombosis and defined as a loss of compressibility of the vein and abnormal or absent blood flow. PE was diagnosed on contrast-enhanced cross-sectional imaging and defined as a filling defect within the lumen of the pulmonary artery or its branches. All patients developing VTE at any time period during their illness were included in this analysis.

Kaolin activated thromboelastography was performed with the TEG5000 hemostasis analyzer (Haemonetics, Braintree, MA) and used heparinase coated cups. Each
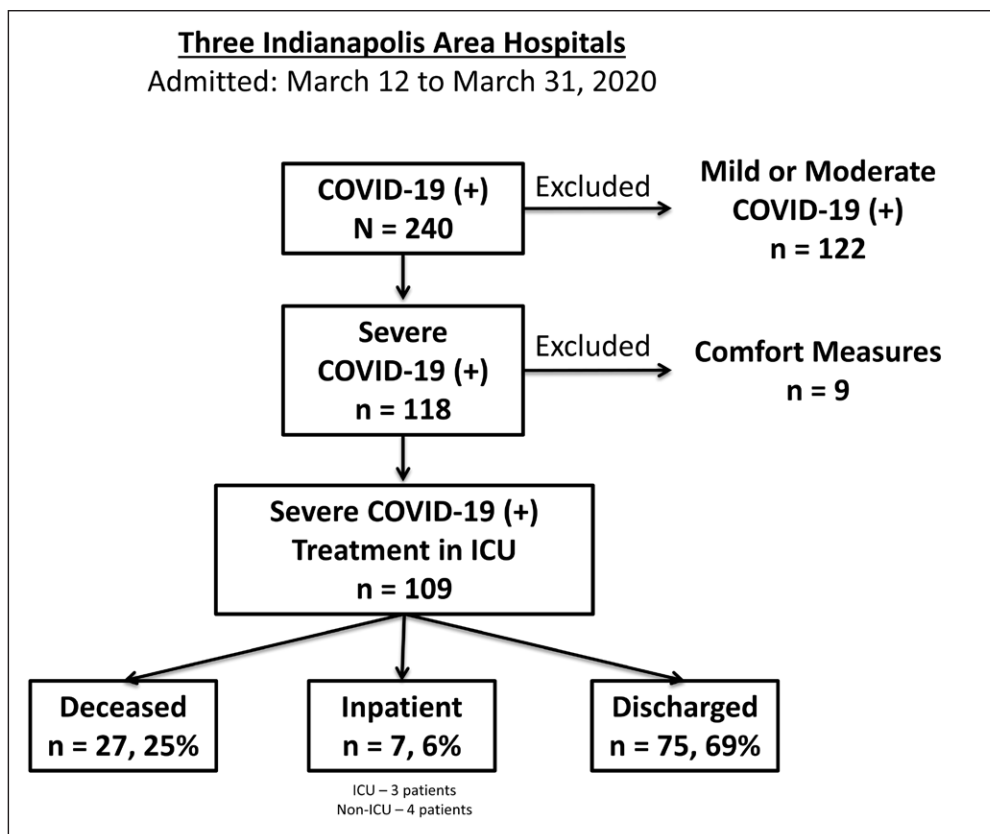
Three Indianapolis Area Hospitals
Admitted: March 12 to March 31, 2020

Figure 1. Flow chart of study patients. COVID-19 = coronavirus disease 2019.

were accepted as statistically significant.

RESULTS

Demographic and Clinical Characteristics

One-hundred nine patients with confirmed SARS-CoV-2 infection were treated for severe COVID-19 requiring intensive care. Demographic and clinical characteristics are shown in **Table 1**. Fifty-five patients (50%) were black, the mean age was 61±16 years, and 57% of patients were male. The mean body mass index was 34.8±11.8 kg/m². Sixty-one patients (56%) were admitted directly to the ICU. The mean duration of symptoms prior to ICU admission was 8±5 days. Respiratory failure requiring mechanical ventilation developed in 103 patients (94%), cardiovascular failure requiring vasopressors developed in 70 patients (64%), and renal failure requiring renal replacement therapy (RRT) developed in 16 patients (15%).

As of May 6, 7 patients (6%) continue to receive inpatient treatment (non-ICU, n = 4; ICU, n = 3), 75 patients (69%) had been discharged from the hospital, and 27 patients (22%) died (Fig. 1). Patients discharged from the ICU had a median duration of 13 days (IQR, 9–17 d) of intensive care. Of the patients discharged from the hospital, the median hospital length of stay was 20 days (IQR, 16–27 d). Death occurred a median of 11 days (IQR, 8–16 d) after hospital admission.

The median time to routine chemical VTE prophylaxis was hospital day 0 (IQR, 0–1 d) and included subcutaneous heparin every 8 hours (n = 61, 56%), enoxaparin daily (n = 26, 24%), or enoxaparin every 12 hours (n = 14, 13%). Seven patients (6%) were treated with full anticoagulation immediately upon admission for existing medical comorbidities (n = 4, 4%) or VTE diagnosed at presentation (n = 2, 2%). One patient was transferred from an outside hospital in which the timing of VTE prophylaxis initiation was unable to be determined.

thromboelastography assay included reaction time (R), kinetics (K), alpha angle (α), maximum amplitude (MA), and fibrinolytic activity 30 minutes after MA (LY30). A hypercoagulable thromboelastography was defined as two or more thromboelastography parameters beyond one sd of the age- and gender-matched controls (25). Of the individual thromboelastography parameters, a decreased R-time and K-time and an increased alpha angle and MA were considered hypercoagulable. A coagulation index (CI) was calculated for each thromboelastography and considered hypercoagulable if elevated beyond the laboratory reference range.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics Version 25.0 with deidentified data (IBM, Armonk, NY). Categorical variables are summarized as number with percentages. Variables with greater than 50% of patients missing data were not reported or included in the analysis. Continuous variables are reported as mean values with sd or median values with interquartile range (IQR). No imputation was made for missing data. As appropriate, the chi-square test and Mann-Whitney U tests were performed to evaluate the bivariate relationship between variables of interest and COVID-19 outcomes. Receiver operator characteristic curves were plotted and Youden Index was used to determine optimal laboratory cutoff points. The discriminatory ability of these cutoff points to predict VTE was assessed by calculating the area under the curve (AUC), sensitivity, and specificity. p values of less than 0.05

Venous Thromboembolism

Of the 109 patients with severe COVID-19, 31 patients (28%) developed VTE. Two patients were diagnosed with VTE upon presentation to the hospital; the remaining 29 patients developed VTE while on routine chemical VTE chemoprophylaxis (n = 26) or on full anticoagulation for medical comorbidities (n = 3). Isolated DVT was diagnosed in 26 patients (84%) and isolated PE was diagnosed in one patient (3%); four patients

TABLE 1. Clinical Characteristics of Patients at Baseline and Laboratory Values at Presentation

Baseline Variables	Cohort ($n = 109$)	No VTE ($n = 78$)	VTE ($n = 31$)
Characteristic			
Mean age (range), yr	61±16 (18–95)	62±15 (18–83)	60±17 (31–87)
Sex, n (%)			
Male	62 (57)	42 (54)	20 (65)
Female	47 (43)	36 (46)	11 (35)
Race, n (%)			
Black	55 (50)	39 (50)	16 (52)
White	44 (40)	33 (42)	11 (35)
Other	10 (9)	6 (8)	4 (13)
Mean body mass index, kg/m^2	34.8±11.8	34.8±11.5	34.7±12.7
Comorbidity			
Hypertension	74 (68)	57 (73)	17 (55)
Hyperlipidemia	59 (54)	46 (59)	13 (42)
Diabetes mellitus	43 (39)	33 (42)	10 (32)
Current smoker (within 30 d)	33 (30)	**28 (36)**	**5 (16)**
Chronic obstructive pulmonary disorder	18 (16)	**17 (22)**	**1 (3)**
Congestive heart failure	17 (15)	14 (18)	3 (10)
Chronic kidney disease	16 (15)	13 (17)	3 (10)
Asthma	16 (15)	13 (17)	3 (10)
Mean duration of symptoms before admission, d	7±5	7±5	7±3
Mean duration of symptoms before ICU admission, d	8±5	9±5	8±4
Laboratory data	n, median (IQR)	n, median (IQR)	n, median (IQR)
WBC count (per mm^3)	109, 7,200 (5,100–9,800)	78, 7,000 (4,875–9,200)	31, 9,000 (5,150–11,450)
Hemoglobin (g/dL)	109, 13.3 (12–14.5)	78, 13.4 (11.9–14.3)	31, 13.0 (12.4–14.8)
Platelet count (per mm^3)	**109, 207,000 (152,000–255,000)**	**78, 189,000 (141,000–252,000**	**31, 224,000 (191,000–261,000)**
Neutrophil-to-lymphocyte ratio	99, 6.5 (4.2–12.2)	71, 6.2 (3.8–11.8)	28, 7.7 (5.6–12.6)
Creatinine (mg/dL)	109, 1.2 (0.9–1.9)	78, 1.30 (0.87–2.13)	31, 1.10 (0.89–1.42)
Alanine aminotransferase (U/L)	103, 24 (18–44)	76, 23.5 (18–38.5)	27, 31 (19.5–47.5)
Aspartate aminotransferase (U/L)	**103, 39 (29.5–63)**	**76, 38 (27–58.5)**	**27, 51 (37–72.5)**
Hemoglobin A1c (%)	78, 6.4 (5.9–7.2)	57, 6.4 (5.9–7.2)	21, 6.1 (5.8–6.9)
Lactate dehydrogenase (U/L)	**91, 437 (348.5–573)**	**66, 426 (332–581)**	**25, 525 (431–568)**
Fibrinogen (mg/dL)	57, 535 (435–651)	36, 535 (425–681)	21, 528 (435–632)
D-dimer (ng/mL)	**84, 506 (321–973)**	**59, 464 (282–755)**	**25, 900 (432–3,570)**
Troponin (ng/mL)	**81, 0.04 (0.03–0.10)**	**61, 0.03 (0.03–0.06)**	**20, 0.10 (0.05–0.22)**
Ferritin (ng/mL)	76, 579 (339–1,057)	52, 579 (339–1,050)	24, 638 (345–1,190)
C-reactive protein (mg/dL)	91, 14.6 (10.1–22.7)	66, 14.8 (8.0–22.8)	25, 14.5 (12.5–21.3)
Procalcitonin (ng/mL)	81, 0.23 (0.12–0.92)	58, 0.20 (0.14–0.58)	23, 0.26 (0.11–1.78)
Interleukin-6 (pg/mL)	55, 14 (7.5–40.5)	39, 14 (7–40)	16, 14 (11–48)

IQR = interquartile range, VTE = venous thromboembolism.

Unless otherwise stated, means values are reported ± SD and median values are reported with IQR.

Bold values represent statistical significance with $p < 0.05$.

had both DVT and PE (13%). Five DVT were associated with central venous catheters (CVCs) in the internal jugular vein ($n = 3$) and femoral vein ($n = 2$); however, in four of these patients, additional DVT were detected in locations remote from the CVC. The number of DVT identified per patient was 3 ± 2. Of the 30 patients with DVT, the location of the DVT was most commonly the lower extremities ($n = 18$, 60%); however, upper extremity DVT and both upper and lower extremity DVT were diagnosed in six each (20%). The mean time from hospital admission to VTE diagnosis was 8 ± 7 days. Initial treatment for VTE included unfractionated heparin IV infusion ($n = 13$, 42%), weight-based enoxaparin subcutaneously bid ($n = 13$, 42%), oral apixaban ($n = 2$, 6%), and unfractionated heparin IV infusion with alteplase infusion ($n = 2$, 6%). In one patient, anticoagulation was contraindicated due to recent cerebrovascular accident.

On univariate analysis, the development of VTE was significantly associated with higher serum platelet count, aspartate aminotransferase, lactate dehydrogenase, D-dimer, and troponin concentrations at admission (Table 1). The frequency of VTE was no different in patients without or with respiratory failure requiring mechanical ventilation (33% vs 28%; $p = 0.785$), cardiovascular failure requiring vasopressors (26% vs 30%; $p = 0.629$), or renal failure requiring RRT (31% vs 12.5%; $p = 0.126$). When comparing the peak serum concentration of laboratory values in patients prior to VTE diagnosis to patients that did not develop VTE, increased D-dimer concentration and decreased platelet counts were observed (**Table 2**).

Admission D-dimer concentration, peak D-dimer concentration, and peak platelet count were plotted on a receiver operating characteristic curve; the AUC, ideal laboratory cutoff points to detect VTE, and associated sensitivity and specificity are shown in **Figure 2**. A serum D-dimer concentration greater than 2,600 ng/mL (normal range, 0–292 ng/mL) was the test with the best discriminatory ability to detect VTE with an AUC of 0.760 ($p < 0.0001$) and a sensitivity and specificity of 89.7% and 59.5%, respectively. Patients developing VTE had

no difference in mortality (8/31, 26%) when compared with patients that did not develop VTE (19/78, 24%; $p = 0.875$).

Thromboelastography

Twelve patients (11%) had thromboelastography analyzed during their hospital stay and the mean value of each thromboelastography parameter is shown in **Figure 3**. Thromboelastography was performed a median of 3.5 days (IQR, 1–6 d) after hospital admission and was performed for significantly elevated D-dimer ($n = 8$, 67%) or as a baseline prior to extracorporeal membrane oxygenation initiation ($n = 3$, 25%). In one patient (8%), thromboelastography was ordered due to persistent clotting of the RRT filter. Hypercoagulable thromboelastography (≥ 2 hypercoagulable thromboelastography parameters) were observed in 58% of patients and at least one thromboelastography parameter was hypercoagulable in 83% of patients. The most common hypercoagulable feature of thromboelastography was a decreased R-time in 67% of patients. The calculated CI was hypercoagulable in 50% of patients. The individual patterns of patients with hypercoagulable and nonhypercoagulable thromboelastography are shown in Figure 3. The mean D-dimer in patients with a hypercoagulable thromboelastography was $2,240 \pm 599$ ng/mL. Three patients (43%) with a hypercoagulable thromboelastography developed VTE; however, one patient with a normal thromboelastography developed VTE.

DISCUSSION

In this series of 109 critically ill COVID-19 patients among three Indianapolis area hospitals, we report an extremely high frequency of VTE despite the prompt initiation of routine chemical VTE prophylaxis. Risk factors associated with VTE development included an elevated D-dimer at hospital presentation and an elevated D-dimer or decreased platelet count during intensive care. Thromboelastography documented hypercoagulability in the majority of patients in which it was

TABLE 2. Peak Inflammatory and Coagulation Markers Prior to Venous Thromboembolism Diagnosis

Laboratory Value	No VTE ($n = 80$), n, Median (IQR)	VTE ($n = 29$), n, Median (IQR)	p
Platelet count (per mm^3)	**78, 383,000 (291,000–472,000)**	**31, 294,000 (223,000–340,000)**	**0.001**
Neutrophil-to-lymphocyte ratio	74, 12.2 (8.6–23.7)	29, 16.0 (9.3–21.0)	0.695
Lactate dehydrogenase (U/L)	75, 541 (401–708)	26, 534 (495–721)	0.870
Fibrinogen (mg/dL)	46, 680 (521–872)	23, 651 (465–771)	0.243
D-dimer (ng/mL)	**74, 1,934 (695–3,573)**	**29, 4,046 (3,071–13,324)**	**0.00004**
Ferritin (ng/mL)	70, 910 (447–1,775)	26, 1,022 (459–1,643)	0.882
C-reactive protein (mg/dL)	73, 24.3 (17.3–32.3)	27, 26.4 (13.6–33.4)	0.877
Procalcitonin (ng/mL)	63, 0.34 (0.20–1.93)	25, 0.66 (0.15–3.98)	0.554

IQR = interquartile range, VTE = venous thromboembolism.
Unless otherwise stated, median values are reported with IQR.
Bold values represent statistical significance with $p < 0.05$.
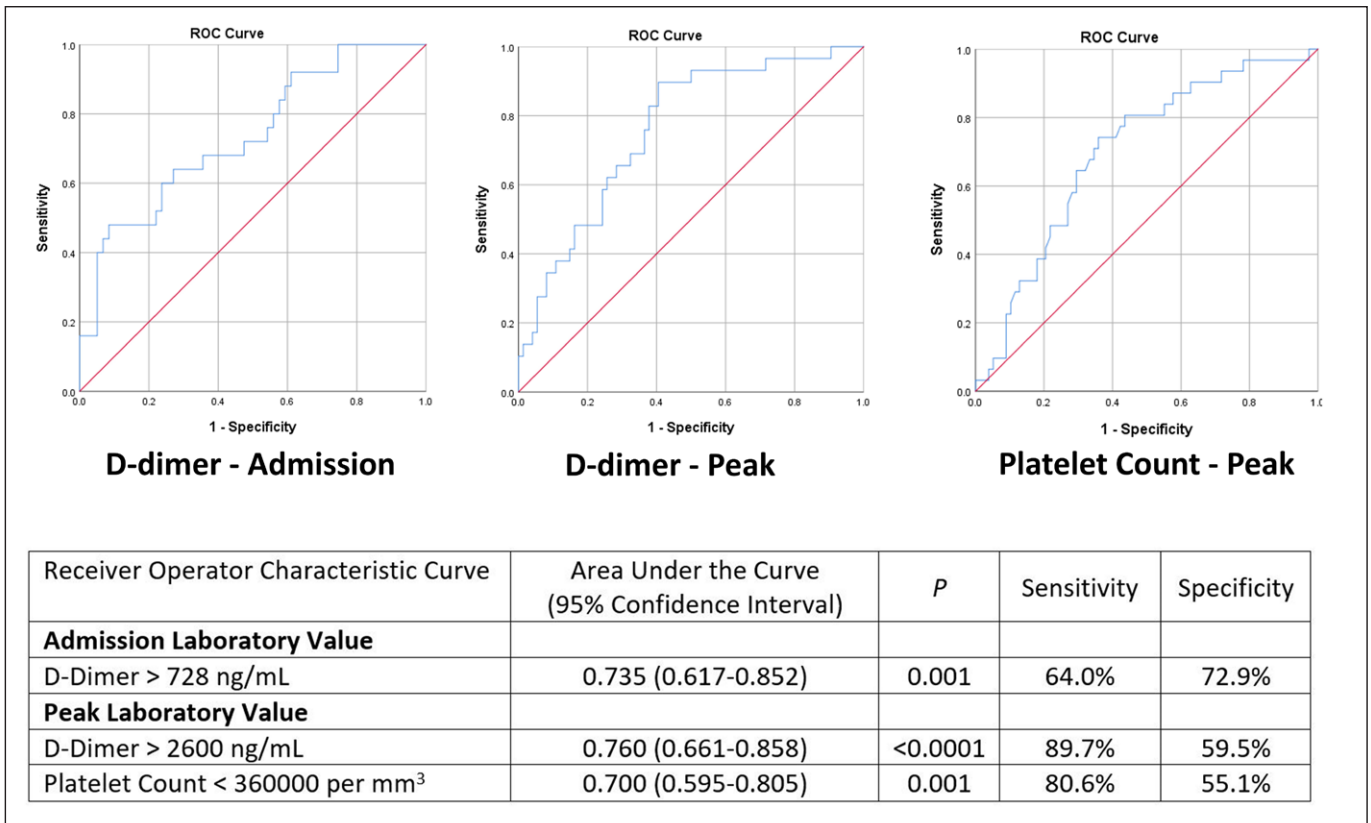
Figure 2. Receiver operator characteristic (ROC) curve, area under the curve, sensitivity, and specificity of ᴅ-dimer and platelet count to detect venous thromboembolism.
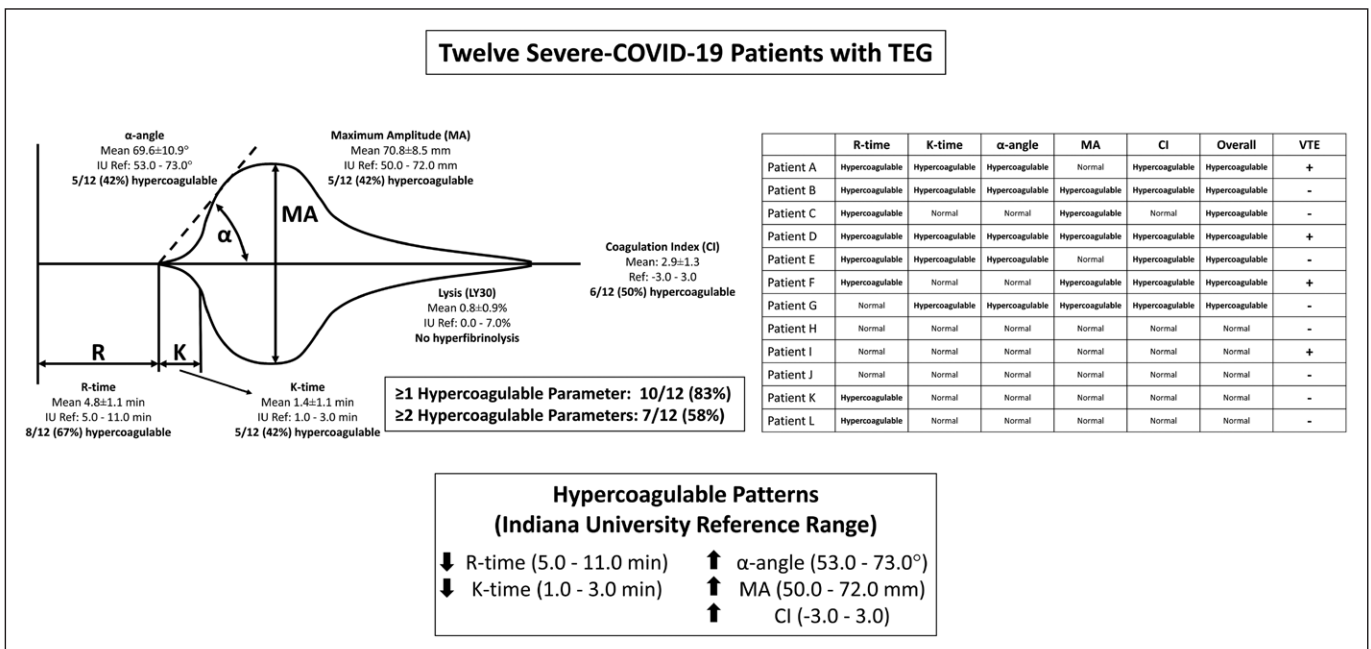
Receiver Operator Characteristic Curve	Area Under the Curve (95% Confidence Interval)	P	Sensitivity	Specificity
Admission Laboratory Value				
D-Dimer > 728 ng/mL	0.735 (0.617-0.852)	0.001	64.0%	72.9%
Peak Laboratory Value				
D-Dimer > 2600 ng/mL	0.760 (0.661-0.858)	<0.0001	89.7%	59.5%
Platelet Count < 360000 per mm³	0.700 (0.595-0.805)	0.001	80.6%	55.1%

Figure 3. Thromboelastography in 12 patients with severe coronavirus disease 2019 (COVID-19). Values are reported as mean ± sᴅ. CI = coagulation index, IU = Indiana University, K = kinetics, LY30 = fibrinolytic activity 30 minutes after maximum amplitude, MA = maximum amplitude, R = reaction time, TEG = thromboelastography, VTE = venous thromboembolism, α = alpha angle.

performed. Mortality was not significantly different in patients developing VTE when compared with patients who did not develop VTE.

We report a frequency of VTE of 28% in critically ill patients with COVID-19 and identified an elevated ᴅ-dimer at presentation and an elevated ᴅ-dimer or thrombocytopenia

during intensive care as risk factors for VTE development. About 5–10% of critically ill patients develop VTE; thus, the risk for VTE in critically ill patients with COVID-19 is about 2.5–5 times higher than the general ICU population (26, 27). The frequency of VTE identified in the current study is similar to that reported in two recent studies from China (25%) and the Netherlands (27%) (12, 13) and similar to that reported in critically ill patients with severe acute respiratory syndrome (24%) during the outbreak in the early 2000s (28). COVID-19 is associated with a profound systemic inflammatory response, hypercoagulable serum coagulation profile, organ failure, and immobility; thus, it is no surprise that the frequency of VTE is significant and higher than expected despite prompt initiation of routine chemical VTE prophylaxis. This study likely underestimates the true frequency of VTE in this population, as diagnostic evaluation for VTE was deferred to prevent untoward risk to healthcare workers and inpatients.

The mechanism by which critically ill patients with COVID-19 develop VTE at a higher frequency than the general ICU population remains unclear, specifically whether a hypercoagulable state is induced by the degree of viremia and the virus itself, or if this is simply in response to the profound systemic inflammation and critical illness, which are known risk factors for VTE development (14, 16, 26, 27). The association between elevated D-dimer and VTE development is likely representative of both the degree of systemic inflammation in critically ill COVID-19 patients and inappropriate activation of the coagulation cascade; however, the degree to which each of these components contribute to VTE development was not possible to determine in this study. The frequency of VTE in severe COVID-19, its risk factors, and outcomes warrant ongoing worldwide investigation, as COVID-19 will likely continue to contribute to worldwide morbidity and mortality for some years. Given the documented hypercoagulability and frequency of VTE in this population, consideration should be given to an escalated dose of chemical VTE prophylaxis using either weight-based or anti-factor-Xa guided dosing in COVID-19 patients with D-dimer greater than 728 ng/mL at presentation. In addition to this increased dosing of chemical VTE prophylaxis, critically ill patients with a D-dimer greater than 2,600 ng/mL (or > 10 times the upper limit of laboratory normal) should be evaluated with four-extremity duplex ultrasound; empiric anticoagulation in the setting of elevated D-dimer and presumptive diagnosis of VTE should be made on a case-by-case basis. Early detection of VTE and prevention of PE in patients with severe COVID-19 is paramount given the mounting clinical and autopsy evidence of lung microvascular and macrovascular thrombosis (12, 13, 19, 29), which plausibly may be contributing to the progressive and fatal hypoxemic respiratory failure in these patients without prompt initiation of adequate anticoagulation.

In this series of 12 patients with severe COVID-19 undergoing thromboelastography analysis, 58% met objective criteria for hypercoagulability and 83% of patients had at least one hypercoagulable thromboelastography parameter. The most common hypercoagulable parameter was the reaction (R) time

in 67% of patients. This suggests that SARS-CoV-2 infection and the associated systemic inflammation, in the most severe cases, results in activation of the coagulation cascade. Three of seven patients with a hypercoagulable thromboelastography went on to develop VTE; thus, larger volume, prospective studies may be warranted to evaluate this association further and define the utility of thromboelastography in COVID-19. Given the degree of inflammatory and coagulation marker elevation in severe COVID-19, serial thromboelastography analysis may provide useful insights as to which patients are at highest risk for microvascular and macrovascular thrombosis, potentially offering a window for improved and effective microvascular and macrovascular thrombosis prophylaxis. Our study corroborates a recently published study that reported hypercoagulable thromboelastography in COVID-19 patients (30). Thromboelastography represents an objective metric (thromboelastography) to describe the hypercoagulability encountered in COVID-19 and provides a more complete picture of the coagulation cascade compared with traditional laboratory values. Large, prospective studies evaluating thromboelastography could provide detailed insight into the abnormal coagulation in COVID-19. Further, the potential role of platelet activation and aggregation in VTE development can be evaluated with thromboelastography, providing an additional target for improved VTE prophylaxis with antiplatelet therapy. The current study and the study published by Panigada et al (30) were unable to evaluate platelet function in COVID-19, as thromboelastography with platelet mapping was not routinely performed. A multi-institutional observational study evaluating the utility of serial thromboelastography in COVID-19 is currently underway. Future investigation may evaluate for an association between thromboelastography parameters and anti-factor Xa guided VTE prophylaxis, as thromboelastography may not be available at all institutions treating COVID-19 patients.

Given the gravity and scope of the COVID-19 pandemic, rapid dissemination of significant clinical observations is paramount to improving patient outcomes; however, several limitations of this study deserve mention. Although this is a relatively large series, it is an observational study and the inherent bias introduced by a retrospective evaluation of any patient population is a limitation. The retrospective nature of this study precludes the ability to establish any causal relationship between D-dimer concentration or platelet count and VTE development. Critically ill COVID-19 patients often had multiple CVCs simultaneously and/or at different time points throughout their treatment and the location of CVC as a risk factor for VTE development was unable to be evaluated. Measurement of prothrombin time was not included in the institutional protocol at the time of this study and not routinely performed, thereby preventing the ability of this study to evaluate disseminated intravascular coagulation. Only critically ill COVID-19 patients were included in this study; therefore, this study lacked a comparator group of ICU patients without COVID-19 in which to compare VTE frequency. The current study did not evaluate the degree of viremia as a risk factor for

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VTE and this should be considered in future studies. The small number of patients with thromboelastography analysis may not accurately reflect the trends of the entire cohort and more detailed analysis is warranted. Given the number of patients with thromboelastography data, we were unable to associate thromboelastography parameters to VTE. The number of comparisons was intentionally kept to a minimum to avoid the introduction of type II error. Finally, Patients with sudden clinical deterioration and death were not evaluated postmortem for the development of VTE.

CONCLUSIONS

These data show that SARS-CoV-2 infection results in systemic hypercoagulability resulting in VTE. Although current data on outcomes in patients receiving therapeutic anticoagulation in COVID-19 are lacking, it is apparent that routine chemical VTE prophylaxis may be inadequate in preventing thrombotic complications in severe COVID-19.

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