Thromboelastography Parameters and Platelet Count on Admission to the ICU and the Development of Venous Thromboembolism in Patients With Coronavirus Disease 2019

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OBJECTIVES: Determine if thromboelastography parameters and platelet count on the day of ICU admission are associated with the development of venous thromboembolism in patients with coronavirus disease 2019.

DESIGN: Prospective, observational cohort study.

SETTING: Tertiary-care, academic medical center in Nashville, TN.

PATIENTS: Patients with coronavirus disease 2019 pneumonia and acute respiratory failure admitted to the adult ICU without venous thromboembolism at the time of ICU admission.

INTERVENTION: None.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was development of venous thromboembolism during the index hospitalization. Venous thromboembolism was defined by clinical imaging or autopsy, demonstrating deep vein thrombosis or pulmonary embolism. Forty consecutive critically ill adults with laboratory-confirmed coronavirus disease 2019 were enrolled; 37 (92.5%) were hypercoagulable by at least one thromboelastography parameter at the time of ICU admission and 12 (30%) met the primary outcome of venous thromboembolism during the index hospitalization. Patients who developed venous thromboembolism had decreased measures of clotting (maximum amplitude, alpha angle, shear elastic modulus parameter, and clotting index) on ICU admission thromboelastography compared with patients who did not develop venous thromboembolism ($p < 0.05$ for all measures). For each individual thromboelastography parameter used to dichotomize patients as hypercoagulable, the rate of venous thromboembolism was not higher in those identified as hypercoagulable; in fact, the venous thromboembolism rate was higher in patients who were not hypercoagulable by thromboelastography for maximum amplitude ($p = 0.04$) and alpha angle ($p = 0.001$). Platelet count was positively correlated with maximum amplitude, alpha angle, G parameter, and clotting index, and significantly lower in patients who developed venous thromboembolism than those who did not (median 186 vs 278 $10^3/\mu L$, $p = 0.046$). Venous thromboembolism was associated with inhospital mortality (odds ratio, 6.3; 95% CI, 1.4–29; $p = 0.02$).

CONCLUSIONS: Our data do not support the use of thromboelastography to risk stratify critically ill adults with coronavirus disease 2019 for the development of venous thromboembolism or to guide decisions about anticoagulation. Lower platelet count on ICU admission, which may reflect platelet aggregation, was associated with venous thromboembolism.

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KEY WORDS: coronavirus disease 2019; deep venous thrombosis; platelet count; pulmonary embolism; thromboelastography; venous thromboembolism

Despite prophylactic anticoagulation, 20–80% of critically ill adults with coronavirus disease 2019 (COVID-19) develop venous thromboembolism (VTE), with rates varying based on screening methods (universal vs symptomatic) and definition of VTE (1–3). Thromboelastography that measures the dynamics of clot formation and dissolution utilizing whole blood has been suggested as a tool to identify patients at risk for thromboembolic events (4–6). Each individual thromboelastography parameter has been used to predict thromboembolic events with faster clot initiation and propagation, increased clot strength, or decreased clot breakdown associated with increased rates of thrombotic events in trauma, surgical, critically ill, or hospitalized patients (6). However, despite reports of hypercoagulable thromboelastography parameters in patients with COVID-19, an association between thromboelastography measurements indicating hypercoagulability and increased risk of VTE among patients with COVID-19 has not been established (1, 3, 7–9). Lower peak platelet counts have been associated with the development of VTE in patients with COVID-19, despite the median peak platelet count still being above the lower bound of the reference range (3, 10). Platelets are known to influence thromboelastography measurements with lower platelet counts leading to diminished measures of clot strength (10). This study aims to evaluate the association between thromboelastography parameters and platelet counts at the time of admission to the ICU and the development of VTE among critically ill adults with COVID-19.

MATERIALS AND METHODS

We conducted a single-center prospective cohort study of consecutive adults with COVID-19 pneumonia and hypoxemic respiratory failure admitted to the medical ICU at a tertiary-care academic medical center in Nashville, TN, between April 29, 2020, and July 17, 2020. This work was conducted as public health surveillance as defined in 45 CFR 46.102(l)(2) and was determined to not be research by the Institutional Review Board.

Study Population

Critical illness from COVID-19 inclusion criteria was: 1) age greater than or equal to 18 years old, 2) ICU admission, 3) positive reverse transcriptase polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the index hospitalization, 4) pulmonary infiltrate on chest imaging, and 5) peripheral oxygen saturation (Spo_2) below 90% on room air. Criteria for ICU admission included need for vasoactive medication or oxygen saturation less than 90% on greater than 6 L of oxygen by nasal cannula or fraction of inspired oxygen greater than 50%. Patients were excluded if they had been diagnosed with acute venous thromboembolism (VTE) or arterial thromboembolism on objective imaging (extremity venous duplex ultrasonography, CT pulmonary angiography [CTPA], or CT angiography of the head and neck) prior to enrollment.

Coagulability and Platelet Measurements

Thromboelastography and platelet counts were measured within 48 hours of ICU admission. Viscoelastic testing was performed on the thromboelastography 5000 Thromboelastograph Hemostasis Analyzer System (Haemonetics, Boston, MA) (11). Thromboelastography parameters were defined as outlined by Yuriditsky et al (1): maximum amplitude (MA), α angle (α), reaction time (R), clotting index, and percentage of clot lysis at 30 minutes. The G parameter, reported by thromboelastography software as a calculated measure of complete clot strength, was also analyzed. Each of the thromboelastography parameters has been used independently in prior studies to define hypercoagulability in patients (6). For the primary analysis, thromboelastography parameters were maintained as continuous variables and compared between the patients with and without VTE. To allow for comparison with prior studies that used thresholds in thromboelastography parameters to define hypercoagulability, patients were dichotomized as hypercoagulable or not hypercoagulable for each thromboelastography parameter, and then frequency of VTE was compared between these binary groups. A patient was considered hypercoagulable by a parameter if the measure was above the reference range for MA, α, G, or clotting index measurements and below the reference range for R (6). At our institution, heparinase is only added to thromboelastography if patients

are on therapeutic unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). To remove any possible effect from prophylactic anticoagulation, all thromboelastographies were ordered as citrated kaolin with heparinase. Due to an error in the conversion of orders from the electronic medical record to the operating system for laboratory technicians, 14 of 40 thromboelastographies were run without heparinase following the institutional guidelines. None of the patients who underwent thromboelastography without heparinase were on therapeutic anticoagulation. Platelet counts from routine complete blood count measurements were collected on the day of thromboelastography measurements.

Venous Thromboembolic Events

Testing for VTE was conducted by treating clinicians without influence by the study protocol. Institutional guidelines advised imaging in patients with signs and symptoms of VTE and recommended against routine screening in the absence of symptoms. Patients were classified as having VTE if they were identified as having acute deep venous thrombosis (DVT) or pulmonary embolism (PE) by imaging during the index hospitalization or at autopsy if death occurred during the index hospitalization according to the International Society on Thrombosis and Haemostasis (ISTH) guidelines (12). Imaging modalities included: upper and lower extremity venous duplex ultrasound with compression (identifying distal and proximal DVT) and CTPA (identifying subsegmental and more proximal PE). Patients diagnosed with both a DVT and PE were classified as PE. Clinicians were unblinded to study laboratory results.

Secondary Outcomes

The initiation of renal replacement therapy and extracorporeal membrane oxygenation (ECMO) during the index hospitalization were recorded. All patients were followed to hospital discharge or death. Major bleeding events were recorded as defined by the ISTH guidelines in nonsurgical patients (13).

Anticoagulation and Antiplatelet Treatments

The study protocol did not control any treatment decisions. The treating clinicians, following institutional guidelines, determined all treatments, including anticoagulation and antiplatelet therapies. According to institutional guidelines, patients chronically on direct oral anticoagulants were continued on their home medications. All other patients received prophylactic anticoagulation with UFH or LMWH. Therapeutic anticoagulation with either UFH or LMWH was initiated at the time of diagnosis of a thromboembolic event, initiation of ECMO, or frequent circuit clotting while on renal replacement therapy at the discretion of the treating clinician(s).

Data Collection and Statistical Analysis

During the study, research personnel prospectively collected information from the electronic medical record for direct data entry into an electronic case report form using a research electronic data capture platform (14, 15). Comparisons between the patients with and without VTE were conducted using Mann-Whitney *U* tests for continuous variables and Fisher exact tests for categorical variables. Separate sensitivity analyses were performed excluding patients who underwent thromboelastography without heparinase, patients who did not undergo a clinical evaluation with extremity duplex ultrasonography or CTPA, and patients who were on therapeutic anticoagulation at the time of laboratory analysis. A univariable logistic regression was performed to determine the association between VTE and mortality. The associations between thromboelastography measurements and platelet count were assessed using R squared (R^2). Analyses were conducted with the statistical program Stata/SE, Version 15.1 (StataCorp, College Station, TX).

RESULTS

Study Population

During the enrollment period, 74 patients were admitted to the ICU with a positive SARS-CoV-2 PCR. Of those, 45 met criteria for COVID-19 pneumonia with 40 patients (32 men and eight women) (**Table 1**) enrolled after the exclusion of five patients for a diagnosis of acute VTE prior to enrollment. The median age was 55 years (interquartile range [IQR], 48–62 yr). Seventy percent of the patients had at least one comorbidity. The median body mass index was 33.6 (IQR,

TABLE 1.
Clinical Characteristics and Laboratory Measures on ICU Admission Grouped by Venous Thromboembolism

Laboratory Measures	Reference Range	All Patients *n* = 40	VTE *n* = 12	No VTE *n* = 28	*P*
Age (yr)		56.5 (48–62)	60.5 (55.5–64)	53 (45.0–60.5)	0.10
Sex (male)		32 (75.0)	11 (91.7)	21 (75.0)	0.40
Comorbidities		28 (70.0)	7 (58.3)	21 (75.0)	0.45
Diabetes		21 (52.5)	4 (33.3)	17 (60.7)	0.17
Hypertension		20 (50.0)	5 (41.7)	15 (53.6)	0.73
Heart disease		5 (12.5)	0 (0)	5 (17.9)	0.30
Chronic kidney disease		2 (5.0)	0 (0)	2 (7.1)	1.0
Prior transplant		3 (7.5)	1 (8.3)	2 (7.1)	1.0
Body mass index (kg/m^2) (*n* = 37)		33.6 (29.5–38.2)	34.6 (27.8–36.7)	32.8 (30.1–39.1)	0.49
Anticoagulation					
Prophylactic		34 (85.0)	10 (83.3)	24 (85.7)	1.0
UFH		9 (26.5)	4 (33.3)	5 (17.9)	0.40
LMWH		25 (73.5)	6 (50.0)	19 (67.9)	0.40
Therapeutic		6 (15)	2 (16.7)	4 (14.3)	1.0
UFH		2 (16.7)	1[a] (8.3)	1 (3.6)	0.2
LMWH		1 (16.7)	1[b] (50)	0 (0)	0.2
Direct oral anticoagulant		3 (7.5)	0 (0)	3 (10.7)	0.2
Exposure to antiplatelet agent (aspirin)		5 (12.5)	1 (8.3)	4 (14.3)	1.0
Epoprostenol use		4 (10.0)	2 (16.7)	2 (7.1)	0.57
Extracorporeal membrane oxygenation (venovenous)		2 (5.0)	1 (8.3)	1 (3.6)	0.52
Level of oxygen support					0.07
Mechanical ventilation		14 (35.0)	4 (33.3)	10 (35.7)	
Bilevel positive airway pressure		7 (17.5)	5 (41.7)	2 (7.1)	
High-flow nasal cannula oxygen		14 (35.0)	2 (16.7)	12 (42.9)	
Low-flow nasal cannula oxygen		5 (12.5)	1 (8.3)	4 (14.3)	
Sequential Organ Failure Assessment score		4.5 (4–8)	5 (4–8)	4 (4–7.5)	0.30
Fibrinogen (mg/dL)	188–450	703 (571–865)	757 (473–865)	689 (584–864)	0.72

(*Continued*)

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Clinical Characteristics and Laboratory Measures on ICU Admission Grouped by Venous Thromboembolism

Laboratory Measures	Reference Range	All Patients *n* = 40	VTE *n* = 12	No VTE *n* = 28	*P*
Platelet count (× 10^3/μL)	135–371	263 (179–314)	186 (140–280)	278 (198–342)	0.046
Creatinine (mg/dL)	0.72–1.25	0.8 (0.7–1.1)	0.8 (0.71.0)	0.8 (0.7–1.2)	0.65
International normalized ratio (*n* = 39)		1.1 (1.0–1.2)	1.2 (1.11.2)	1.1 (1.0–1.2)	0.25
Prothrombin time (s) (*n* = 39)	11.9–14.5	14.4 (13.5–15.4)	15.1 (14.1–15.5)	14.2 (13.5–14.9)	0.18
Activated partial thromboplastin time (s) (*n* = 37)	23.5–33.5	32.3 (29.8–35.1)	33.5 (29.3–39.0)	32.2 (29.8–34.5)	0.47
Thromboelastography					
Maximum amplitude (mm)	50–70	68.1 (63.6–72.1)	64.4 (62.0–68.7)	70.4 (64.8–73.2)	0.02
Alpha angle (°)	53–72	72.2 (68.3–75.8)	69.0 (66.7–71.2)	74.4 (70.7–77.1)	0.003
Reaction time (min)	5–10	3.8 (3.2–4.8)	3.9 (3.4–5.5)	3.7 (3.2–4.8)	0.44
Shear elastic modulus (complete clot strength) (dyne/cm^2)[c]	4.5–11	10.7 (8.8–13.0)	9.1 (8.2–11.0)	11.9 (9.2–13.6)	0.02
Clotting index	–3.0 to +3.0	+3.4 (+3.0 to +4.1)	+3.1 (+2.7 to +3.4)	+3.8 (+3.0 to +4.3)	0.02
Percent lysis at 30 minutes (%)	0–8	0.6 (0.0–1.4)	0.9 (0.2–1.5)	0.5 (0.0–1.3)	0.30

LMWH = low-molecular-weight heparin (enoxaparin), UFH = unfractionated heparin, VTE = venous thromboembolism.
[a]The patient developed a PE despite therapeutic anticoagulation for VV extracorporeal membrane oxygenation and was found to have platelet factor 4 antibodies but a negative serotonin release assay that is not consistent with pathogenic heparin-induced thrombocytopenia antibodies.
[b]The patient was initially on therapeutic anticoagulation while awaiting extremity venous duplex ultrasounds, which returned as negative the day of ICU admission labs. The patient was transitioned back to prophylactic dosing of LMWH and developed an acute PE 26 days later.
[c]Shear elastic modulus (complete clot strength) = (5,000 × amplitude)/(100 – amplitude) with a unit of force represented as dyne/cm^2 (1 dyne/cm^2 = 0.1 Pa).
Measures represent number (column percent) or median (interquartile range) as appropriate. *n* = 40 except where noted.
p values from two-sided Mann-Whitney *U* test for continuous variables and Fisher exact test for categorical variables.

29.5–38.2). On the day study laboratory samples were drawn, 14 patients (35%) were on mechanical ventilation, 14 (35%) were on high-flow nasal cannula, seven (17.5%) were on bilevel positive airway pressure, and five (12.5%) were on low-flow nasal cannula. Four patients (10%) were treated with epoprostenol and two patients (5%) were initiated on venovenous ECMO on the same day labs were drawn, but after enrollment. At the time of study laboratory sample collection, all patients were treated with either prophylactic (85%) or therapeutic anticoagulation (15%). The median ICU length of stay was 13 days (IQR, 7–19.5 d) and the median hospital length of stay was 14 days (IQR, 10.5–26.5 d).

VTE Events

Among the 40 enrolled patients, 12 (30%) developed a VTE during the index hospitalization, including seven with PE (one central, four lobar, one segmental, and one subsegmental) and five with DVT without PE (**Table 2**). Among the 40 enrolled patients, 15 patients underwent CTPA and six (40%) were positive for PE; 20 patients underwent extremity duplex ultrasounds and seven (35%) were positive for DVT, all of which were proximal. One patient who was unable to undergo CTPA due to clinical instability was identified as having a PE at autopsy. Two patients were diagnosed with both PE and DVT. The median time from ICU

TABLE 2.
Outcome Data Grouped by Development of Venous Thromboembolism

Outcome Variable	All Patients	VTE	No VTE	*P*
n (%)	40	12 (30%)	28 (70%)	
Venous thromboembolism	12 (30.0)	12 (100)	0 (0)	
Deep venous thrombosis	5 (12.5)	5 (41.7)	0 (0)	
Pulmonary embolism	7 (17.5)	7 (58.3)	0 (0)	
Renal replacement therapy	15 (37.5)	8 (66.7)	7 (25.0)	0.03
Major bleeding[a]	6 (15.0)	4 (33.3)	2 (7.1)	0.06
Extracorporeal membrane oxygenation (venovenous)	4 (10.0)	2 (16.7)	2 (7.1)	0.57
Inhospital death (d)	18 (45.0)	9 (75.0)	9 (32.1)	0.02
ICU length of stay (d)	13 (7–19.5)	15.5 (11–40.5)	10.5 (6–14.5)	0.03
Hospital length of stay (d)	14 (10.5–26.5)	18.5 (13.5–41)	13 (10–21.5)	0.14

VTE = venous thromboembolism.
[a]Classified by International Society on Thrombosis and Haemostasis guidelines (14): includes four intracranial hemorrhages, one retroperitoneal bleed, and one hematoma in the adductor compartment with active arterial extravasation. All six patients were on therapeutic anticoagulation at the time of diagnosis (four patients for VTE, one for ischemic stroke, and one for extracorporeal membrane oxygenation). Measures represent number (column percent) or median (inter-quartile range) as appropriate.

admission to diagnosis of VTE was 9.5 days (IQR, 5.5–20 d). Acute worsening of hypoxemia or circulatory failure were the most common indications for VTE testing. ICU admission Sequential Organ Failure Assessment score was not significantly different between the patients with and without VTE (Table 2) but was significantly higher in patients who died compared with survivors (median 6.5 vs 4, $p = 0.01$). Overall, 18/40 patients (45%) died during the index hospitalization. Inhospital death was more common among patients with VTE (9/12, 75%) than those without VTE (9/28, 32%) (odds ratio, 6.3; 95% CI, 1.4–29; $p = 0.02$).

Association of Thromboelastography Measurements and Platelet Count With the Risk of VTE

Thirty-seven patients (92.5%) were hypercoagulable by at least one thromboelastography parameter on ICU admission, with 42.5% hypercoagulable by MA, 50% by α, 80% by R, 47% by G, and 75% by clotting index. Two patients had normal thromboelastography parameters and both developed a VTE. One patient was hypocoagulable by MA, α, G, and clotting index on thromboelastography with heparinase while receiving prophylactic UFH and did not develop a VTE. No other patients demonstrated a hypocoagulable parameter. Although the majority of patients who developed a DVT were hypercoagulable by at least one parameter on thromboelastography, patients who developed VTE had significantly lower MA, α, G, and clotting index than those who did not develop VTE ($p < 0.05$ for each measurement) (**Fig. 1**). When using thresholds for the thromboelastography parameters to dichotomize patients as hypercoagulable or not, the frequency of VTE was not higher for the group classified as hypercoagulable by any of the parameters; in fact, patients who were classified as hypercoagulable by MA and α had lower frequency of VTE than those not classified as hypercoagulable (**Fig. 2**).

In a sensitivity analysis excluding the 14 patients who underwent thromboelastography without heparinase, decreased measures of clot strength and rate of clot propagation continued to be associated with the development of VTE ($p < 0.01$ for MA, α, G, and clotting index). The associations remained significant for thromboelastography in sensitivity analyses excluding patients on therapeutic anticoagulation at the time of baseline labs

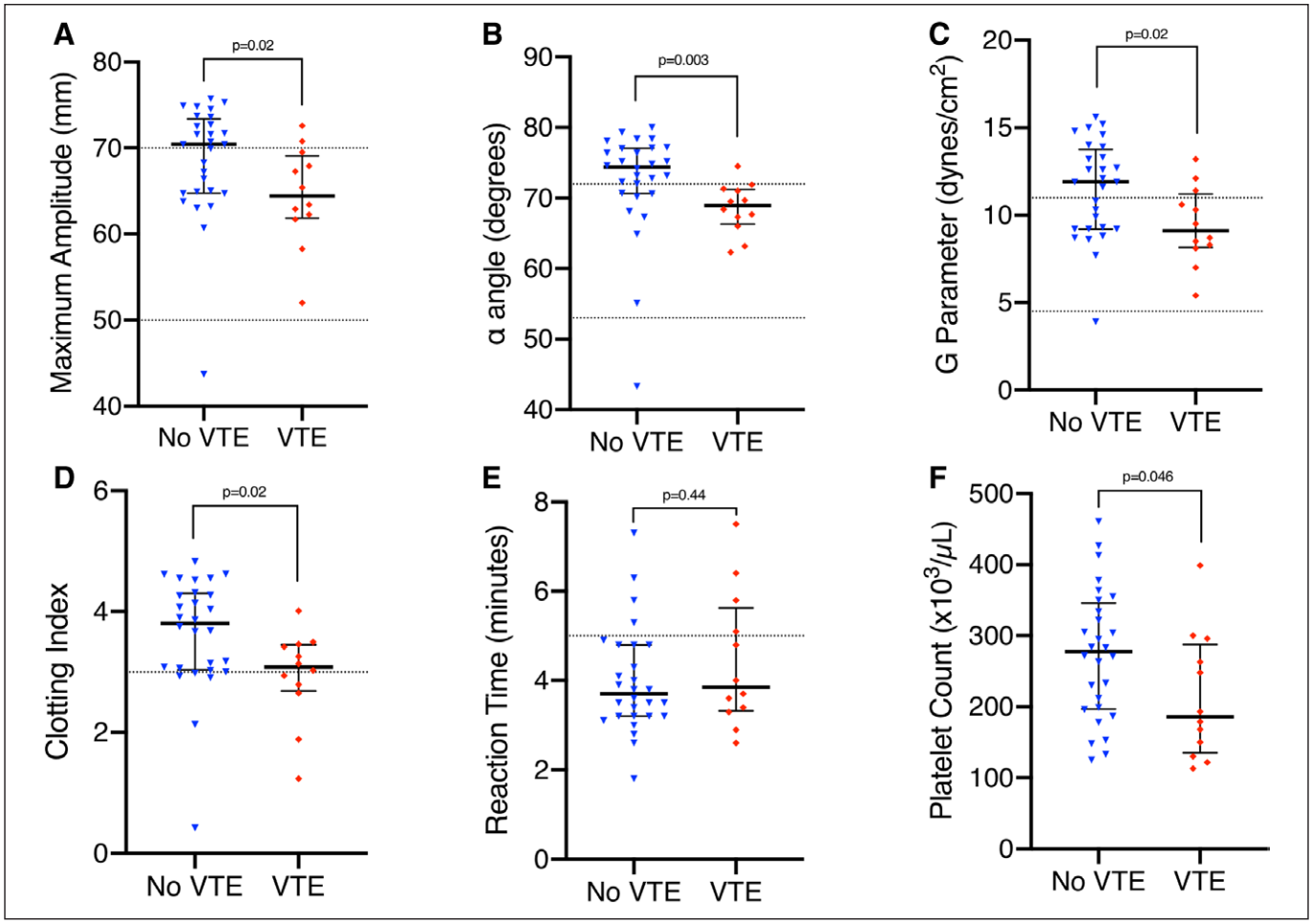

Figure 1. Dot plot of thromboelastography measurements and platelet counts at admission to the ICU grouped by patients who developed venous thromboembolism (VTE, $n = 12$) and those who did not (no VTE, $n = 28$). *Solid bar* represents median values with associated interquartile ranges. *Dotted lines* represent the upper and lower limits of the reference ranges. **A**, Maximum amplitude. **B**, Alpha (α) angle. **C**, Shear elastic modulus (G parameter). **D**, Clotting index, lower limit of the reference range not represented. **E**, Reaction time, upper limit of the reference range not represented. **F**, Platelet count.

($n = 34$, MA: $p = 0.02$; α: $p = 0.02$, G: $p = 0.02$, and clotting index: $p = 0.03$) and including only patients who underwent a clinical evaluation during the index admission ($n = 25$, MA: $p = 0.048$, α: $p < 0.01$, G: $p = 0.046$, and clotting index: $p = 0.049$). The cohort of patients who underwent a clinical evaluation had a high prevalence of events (44% of patients), which may be due to the unit protocol recommending imaging only for patients with signs and symptoms of VTE. Furthermore, all PEs were segmental or more proximal and all DVTs were proximal, suggesting that the events identified were clinically meaningful; the one patient with a subsegmental PE was diagnosed on autopsy and excluded from the sensitivity analysis of patients who underwent a clinical evaluation.

Patients who developed VTE also had lower platelet counts at admission to the ICU compared with patients who did not develop VTE (median 186 vs 278 $10^3/uL$, $p = 0.046$). Platelet count had a positive correlation with MA ($R^2 = 0.41$, $p < 0.001$), α ($R^2 = 0.19$, $p < 0.01$), G ($R^2 = 0.49$, $p < 0.001$), and clotting index ($R^2 = 0.47$, $p < 0.001$), but no correlation with R ($R^2 = 0.01$, $p = 0.58$) (**Fig. 3**). Platelet count was not associated with ICU length of stay ($R^2 = 0.06$, $p = 0.12$) or inhospital death ($p = 0.23$).

DISCUSSION

Among critically ill patients with COVID-19 pneumonia, VTE was commonly observed despite prophylactic or therapeutic anticoagulation. Although thromboelastography values at admission to the ICU demonstrate a hypercoagulable state in the majority of patients, those who developed VTE had decreased

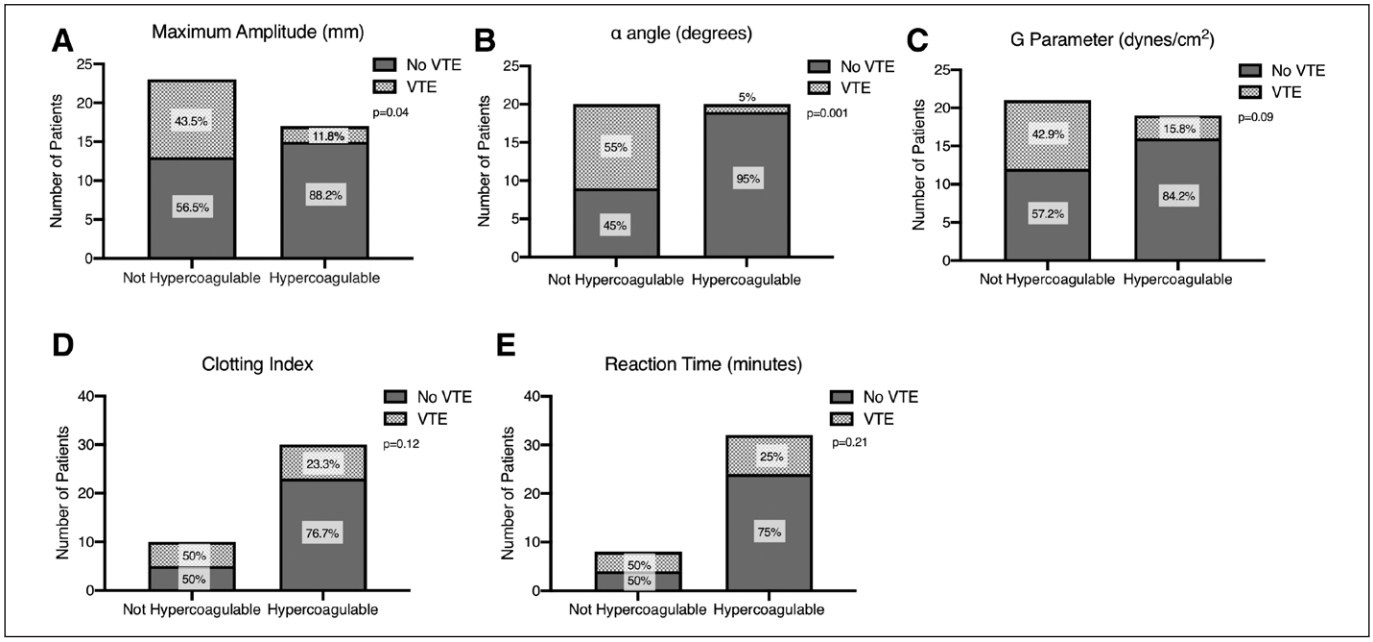

Figure 2. Stacked bar graph with the number of patients who develop venous thromboembolism (VTE) for patients categorized as hypercoagulable or not hypercoagulable by (**A**) maximum amplitude, (**B**) alpha angle (α), (**C**) shear elastic modulus (G), (**D**) clotting index, and (**E**) reaction time. Percentage represents the proportion of patients within each category who developed VTE.

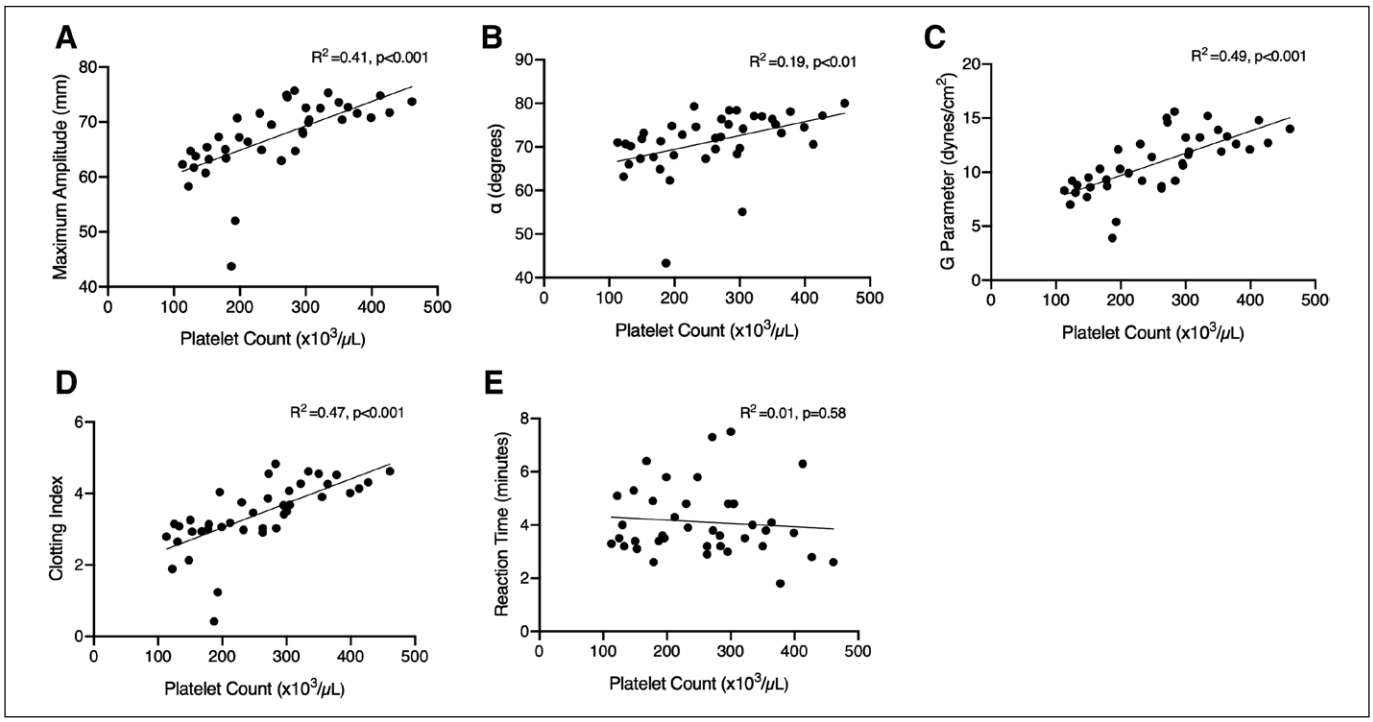

Figure 3. Scatter plot representing the relationship between platelet count and each thromboelastography parameter. **A**, Maximum amplitude (mm). **B**, Alpha angle (α). **C**, Shear elastic modulus (G). **D**, Clotting index, and (**E**) reaction time.

measures of clot strength, slower clot propagation, and lower platelet counts on ICU admission compared with those who did not develop VTE. These findings suggest that thromboelastography measurements are not useful for risk stratifying critically ill adults with COVID-19 for VTE and do not support the use of thromboelastography measurements to guide decisions about anticoagulation in this population.

Consistent with previous findings, our study found a high prevalence of hypercoagulability by

thromboelastography in patients with COVID-19 pneumonia on ICU admission (1, 3, 7). However, increased measures of clotting on thromboelastography were not associated with the development of VTE. In fact, patients who developed clinically significant VTE during their hospitalization had lower MA, α, G, and clotting index at ICU admission than patients who did not. Our findings differ from those of Mortus et al (4), who found an association between increased MA and higher risk of thrombotic events among critically-ill patients with COVID-19. The rate of thrombotic events was higher in the Mortus et al (4) study, which included arterial events, when compared with ours (62% vs 30%); however, 92% of their events were associated with an indwelling device or dialysis filter. Clotting of the dialysis filter was not recorded in our study and only one of the VTEs was associated with an indwelling line. Device-associated thromboses are of unclear significance and may represent a different mechanism of thrombosis development. Nevertheless, the rate of thromboembolic events in our cohort was consistent with other previous studies with similar methods (1, 3, 16).

Although still within the normal range, lower platelet counts at admission to the ICU were also associated with the development of VTE. The decrease in platelet counts may be multifactorial with contributions from critical illness, multiorgan failure, and antibiotics, among others. Patients who developed VTE were exposed to a longer ICU length of stay and experienced higher rates of mortality, suggesting that they might have suffered from an increased severity of illness. Notably, admission platelet count was not associated with ICU length of stay or mortality. However, due to the small sample size, we were unable to account for potential confounders and baseline differences between the groups. Nevertheless, understanding the mechanisms that lead to lower platelet counts in patients who later develop VTE may identify additional therapeutic targets. Increased aggregation from platelet activity provides a potential mechanism for the association between lower platelet counts and VTE beyond the severity of illness. COVID-19 has been shown to induce platelet hyperactivity with altered gene expression leading to increased P-selectin expression and faster aggregation (17). Soluble P-selectin, a marker of platelet activation that has been associated with acute PE, has also been shown to be higher in patients with COVID-19 on day 3 of ICU admission compared with COVID-19-negative patients admitted to the ICU (18–20). Platelet hyperactivity may lead to increased aggregation, which may represent early subclinical clotting, and lower serum platelet counts (21, 22). In patients with dengue virus infections, for example, platelet activation correlated directly with platelet depletion (23). We hypothesize that despite lower counts, the remaining platelets may be hyperactive ultimately resulting in VTE.

If indeed platelet depletion is due to platelet hyperactivity in critically ill patients with COVID-19, antiplatelet therapies may represent an effective strategy for thromboprophylaxis. In a randomized controlled trial, ticagrelor decreased inflammation and platelet aggregation while improving oxygenation in patients with non-COVID-19 pneumonia (24). The decrease in platelet aggregation seen with ticagrelor has also been shown to prevent thrombocytopenia in animal models of sepsis (25). Inhibition of platelet activation prevented platelet depletion by decreasing the clearance of activated platelets by phagocytic cells in an in vitro model of dengue virus infection (23). Ticagrelor and other antiplatelet agents may be potential treatments for mitigating platelet hyperactivity and preventing VTE in critically ill patients with COVID-19.

The paradoxical association of diminished thromboelastography coagulation parameters with VTE may be explained by decreased platelet counts (10, 11). Thromboelastography parameters attempt to measure physiologic clot formation and dissolution. MA measures clot strength with contributions from platelets (80%) and fibrinogen (20%) (26). G parameter is an amplification of MA and has been considered the best measurement of complete clot strength (27). Nevertheless, thromboelastography is influenced primarily by the platelet count, not the activity of platelets (10). In heparin-induced thrombocytopenia, for example, a case report described a patient with normal thromboelastography despite extensive arterial and venous thromboses (28). Kaolin-activated thromboelastography is not a sensitive measure of platelet activity, because it lacks platelet activators and does not measure the interaction between the platelets and the endothelium. The direct contribution of platelet counts to thromboelastography parameters is consistent with our finding that decreasing platelet count is correlated with decreasing MA, α, G, and clotting index and confirmed by previous work in this field (29). R is dependent on clotting factors primarily, which may explain why

R was not correlated with platelet count. Therapeutic anticoagulants (UFH, LMWH, and direct oral anticoagulants) inhibit clotting factors, prolonging the time to clot formation (R) in a dose-dependent manner (10); notably, differences in R time do not appear to be associated with the development of VTE in this cohort.

Our study has several limitations. Patients enrolled were predominantly males that may limit generalizability of the findings, although males have been shown to be at higher risk for severe disease from COVID-19 (30, 31), and the study size was modest. The inclusion of some thromboelastography measurements without the use of heparinase may have affected our results. However, a sensitivity analysis excluding patients who underwent thromboelastography without heparinase demonstrated consistent results. Screening for thromboembolic events was not universally performed, and elevated serum troponin levels were not included, potentially underdiagnosing overall clotting events. The clinician-guided screening for thromboembolic events and the removal of the ambiguity of including elevated serum troponin levels strengthen the study results by focusing on clinically meaningful VTE, which is supported by the association between VTE and mortality. Laboratory measures, including D-dimer and thromboelastography parameters, were visible in the electronic medical record and may have influenced patient care, leading to increased screening and therefore detection of more VTEs. The small number of patients enrolled precluded analyses accounting for the competing risk of death and adjusting for covariates and multiple comparisons. The associations between antiplatelet agents, laboratory measures, and outcomes were unable to be assessed due to the limited number of patients receiving antiplatelets.

Our study also has strengths. The prospective design of this study with consecutive enrollment of eligible patients limited bias by measuring thromboelastography regardless of clinical suspicion for a hypercoagulable state. Exclusion of patients with known prevalent thromboembolism on ICU admission enabled an evaluation for associations between the thromboelastography measurements and the risk of developing VTE, which is more clinically meaningful than evaluating VTE already clinically apparent. The sample size represents one of the larger studies conducted with comprehensive thromboelastography parameters in critically ill patients with COVID-19 pneumonia, and the combination of platelet counts adds information about the interpretation of thromboelastography and potential mechanism of VTE formation.

CONCLUSIONS

Increased measures of clotting and hypercoagulability on thromboelastography were not associated with the development of clinically significant VTE in critically ill patients with COVID-19 pneumonia. These findings do not support the use of thromboelastography to guide the initiation of anticoagulation in this population. The lower platelet counts observed in patients who developed VTE may reflect increased platelet activation and aggregation. Platelet counts may be a potential prognostic tool and antiplatelet agents may have a therapeutic role in patients with severe COVID-19 pneumonia. Future studies evaluating the safety and efficacy of antiplatelet strategies to prevent thromboembolic events in this population are needed.

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REFERENCES

1. Yuriditsky E, Horowitz JM, Merchan C, et al: Thromboelastography profiles of critically ill patients with coronavirus disease 2019. *Crit Care Med* 2020; 48:1319–1326
2. 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
3. Maatman TK, Jalali F, Feizpour C, et al: Routine venous thromboembolism prophylaxis may be inadequate in the hypercoagulable state of severe coronavirus disease 2019. *Crit Care Med* 2020; 48:e783–e790
4. Mortus JR, Manek SE, Brubaker LS, et al: Thromboelastographic results and hypercoagulability syndrome in patients with coronavirus disease 2019 who are critically ill. *JAMA Netw Open* 2020; 3:e2011192
5. Wright FL, Vogler TO, Moore EE, et al: Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. *J Am Coll Surg* 2020; 231:193–203.e1
6. Harahsheh Y, Ho KM: Use of viscoelastic tests to predict clinical thromboembolic events: A systematic review and meta-analysis. *Eur J Haematol* 2018; 100:113–123
7. Pavoni V, Gianesello L, Pazzi M, et al: Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. *J Thromb Thrombolysis* 2020; 50:281–286
8. Iba T, Levy JH, Levi M, et al: Coagulopathy of coronavirus disease 2019. *Crit Care Med* 2020; 48:1358–1364
9. Ng J, Fan BE, Chia YW: In response to "coagulopathy of coronavirus disease 2019". *Crit Care Med* 2020; 48:e1159–e1160
10. Ho KM, Pavey W: Applying the cell-based coagulation model in the management of critical bleeding. *Anaesth Intensive Care* 2017; 45:166–176
11. MacDonald SG, Luddington RJ: Critical factors contributing to the thromboelastography trace. *Semin Thromb Hemost* 2010; 36:712–722
12. Le Gal G, Carrier M, Castellucci LA, et al; ISTH CDE Task Force: Development and implementation of common data elements for venous thromboembolism research: On behalf of SSC subcommittee on official communication from the SSC of the ISTH. *J Thromb Haemost* 2021; 19:297–303
13. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis: Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3:692–694
14. Harris PA, Taylor R, Minor BL, et al; REDCap Consortium: The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; 95:103208
15. Harris PA, Taylor R, Thielke R, et al: Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42:377–381
16. Bilaloglu S, Aphinyanaphongs Y, Jones S, et al: Thrombosis in hospitalized patients with COVID-19 in a New York City Health System. *JAMA* 2020; 324:799–801
17. Manne BK, Denorme F, Middleton EA, et al: Platelet gene expression and function in patients with COVID-19. *Blood* 2020; 136:1317–1329
18. Fraser DD, Patterson EK, Slessarev M, et al: Endothelial injury and glycocalyx degradation in critically ill coronavirus disease 2019 patients: Implications for microvascular platelet aggregation. *Crit Care Explor* 2020; 2:e0194
19. Ferroni P, Martini F, Riondino S, et al: Soluble P-selectin as a marker of *in vivo* platelet activation. *Clin Chim Acta* 2009; 399:88–91
20. Chung T, Connor D, Joseph J, et al: Platelet activation in acute pulmonary embolism. *J Thromb Haemost* 2007; 5:918–924
21. Yang X, Yang Q, Wang Y, et al: Thrombocytopenia and its association with mortality in patients with COVID-19. *J Thromb Haemost* 2020; 18:1469–1472
22. Thachil J: What do monitoring platelet counts in COVID-19 teach us? *J Thromb Haemost* 2020; 18:2071–2072
23. Ojha A, Nandi D, Batra H, et al: Platelet activation determines the severity of thrombocytopenia in dengue infection. *Sci Rep* 2017; 7:1–10
24. Sexton TR, Zhang G, Macaulay TE, et al: Ticagrelor reduces thromboinflammatory markers in patients with pneumonia. *JACC Basic to Transl Sci* 2018; 3:435–449
25. Braun O, Rahman M, Gustafsson D, et al: Ticagrelor reduces neutrophil recruitment and lung damage in abdominal sepsis. *J Am Coll Cardiol* 2013; 61:e70
26. Harr JN, Moore EE, Chin TL, et al: Platelets are dominant contributors to hypercoagulability after injury. *J Trauma Acute Care Surg* 2013; 74:756–762
27. Kashuk JL, Moore EE, Sabel A, et al: Rapid thrombelastography (r-TEG) identifies hypercoagulability and predicts thromboembolic events in surgical patients. *Surgery* 2009; 146:764–772
28. Kline JA, Puskarich MA, Pike JW, et al: Inhaled nitric oxide to control platelet hyper-reactivity in patients with acute submassive pulmonary embolism. *Nitric Oxide* 2020; 96:20–28
29. Kim SY, Gu JY, Yoo HJ, et al: Benefits of thromboelastography and thrombin generation assay for bleeding prediction in patients with thrombocytopenia or hematologic malignancies. *Ann Lab Med* 2017; 37:484–493
30. Klein SL, Dhakal S, Ursin RL, et al: Biological sex impacts COVID-19 outcomes. *PLoS Pathog* 2020; 16:e1008570
31. Sun Y, Dong Y, Wang L, et al: Characteristics and prognostic factors of disease severity in patients with COVID-19: The Beijing experience. *J Autoimmun* 2020; 112:102473