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Rotational thromboelastometry in patients with acute respiratory distress syndrome owing to coronavirus disease 2019: Is there a viscoelastic fingerprint and a role for predicting thrombosis?

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ABSTRACT

Objectives: We evaluated rotational thromboelastometry tracings in 44 critically ill coronavirus disease 2019 patients, to determine whether there is a viscoelastic fingerprint and to test the hypothesis that the diagnosis and prediction of venous thromboembolism would be enhanced by the addition of rotational thromboelastometry testing.

Results: Rotational thromboelastometry values reflected an increase in clot strength for the EXTEM, INTEM, and FIBTEM assays beyond the reference range. No hyperfibrinolysis was noted. Fibrinolysis shutdown was present but did not correlate with thrombosis; 32% (14/44) of patients experienced a thrombotic episode. For every 1 mm increase of FIBTEM maximum clot formation, the odds of developing thrombosis increased 20% (95% confidence interval, 0–40%, $P = .043$), whereas for every 1,000 ng/mL increase in D-dimer, the odds of thrombosis increased by 70% (95% confidence interval, 20%–150%, $P = .004$), after adjustment for age and sex (AUC 0.96, 95% confidence interval, 0.90–1.00). There was a slight but significant improvement in model performance after adding FIBTEM maximum clot formation and EXTEM clot formation time to D-dimer in a multivariable model ($P = .04$).

Conclusions: D-dimer concentrations were more predictive of thrombosis in our patient population than any other parameter. Rotational thromboelastometry confirmed the hypercoagulable state of coronavirus disease 2019 intensive care unit patients. FIBTEM maximum clot formation and EXTEM clot formation time increased the predictability for thrombosis compared with only using D-dimer. Rotational thromboelastometry analysis is most useful in augmenting the information provided by the D-dimer concentration for venous thromboembolism risk assessment when the D-dimer concentration is between 1,625 and 6,900 ng/dL, but the enhancement is modest. Fibrinolysis shutdown did not correlate with thrombosis.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the etiologic agent of coronavirus disease 2019 (COVID-19). The severe phenotype of this disease manifests as progressive hypoxic respiratory failure and acute respiratory distress syndrome (ARDS).

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Our understanding of the pathogenesis of COVID-19 is still evolving, but elevated concentrations of fibrinogen, an acute-phase reactant, and D-dimer, a marker of activation of coagulation, have been associated with increased mortality from COVID-19.[1]

Critically ill COVID-19 patients have a high prevalence of venous thromboembolism (VTE).[2] Tang et al demonstrated that the degree of activation of coagulation (as measured by circulating D-dimer concentration) was significantly greater amongst nonsurvivors.[3] However, recent data indicate that, because the prevalence and magnitude of elevated D-dimer concentrations in COVID-19 critical illness are so high, relatively elevated D-dimer concentrations of up to 3,000 ng/mL may not have probative value for the diagnosis of thrombosis.[4]

Anticoagulant prophylaxis is ideal for these patients,[5–9] but for some patients full therapeutic anticoagulation has been recommended,[10–12] with a demonstrable salutary effect on mortality in critically ill, mechanically ventilated patients.[13] Although empiric therapeutic anticoagulation has been advocated,[10–13] there is also a substantial (~20%) risk of bleeding[14]; routine anticoagulant prophylaxis is recommended for these patients at this time.[15]

Better elucidation of the coagulopathic phenotype and risk profile of these patients is needed. Viscoelastic testing offers an alternative, rapid functional assessment of hemostatic and thrombotic potential. Rotational thromboelastometry (ROTEM) (Instrumentation Laboratory, Bedford, MA) is being explored for the prediction of bleeding and clotting across multiple disease states. Among hypercoagulable states, ROTEM has been used to assess the risk of VTE in patients with cancer,[16,17] after major noncardiac surgery,[18] and recently for COVID-19 infection.[19] We used ROTEM analysis to test the hypothesis that the diagnosis and prediction of VTE would be enhanced by addition of ROTEM testing.

Methods

This study was approved by the Institutional Review Board (#20-03021671) of Weill Cornell Medicine with a waiver of informed consent. All critically ill, nonbleeding COVID-19 patients receiving intensive care unit (ICU) care who had ROTEM testing ordered by the clinical service were included in this study. ROTEM testing was ordered based on a clinical indication (clinical suspicion that the patient was at high risk of thrombosis) during the first peak of the pandemic in New York City in March and April 2020. All laboratory tests were ordered based on the clinical discretion of the patients' providers. Patients were screened for deep venous thrombosis after ICU admission with duplex ultrasound examinations when indicated clinically. Thrombotic events were defined as either deep or superficial venous thrombosis, arterial thromboembolic events, or observed clotting of dialysis access catheters, delaying or preventing renal replacement therapy.

Anticoagulation was ICU- and patient-specific. Anticoagulant prophylaxis in COVID-19 patients utilized enoxaparin 0.5 mg/kg q12h subcutaneously (SC) if glomerular filtration rate (eGFR, estimated by the Cockroft-Gault equation) was $\geq$30 mL/min. If eGFR was <30 mL/min, then unfractionated heparin (UFH) 5,000 U q8h SC was used. For therapeutic anticoagulation, if eGFR was $\geq$30 mL/min, then enoxaparin 1 mg/kg q12h SC was used. If eGFR was <30 mL/min, a bolus of UFH was given followed by a titrated continuous infusion. Activated partial thromboplastin time was monitored at steady-state during infusion of UFH, and appropriateness of dosing was confirmed by measurement of anti-Xa. ROTEM specimens were collected after prophylactic doses of heparinoid anticoagulants were administered, but before any patient was put on therapeutic doses of heparinoids.

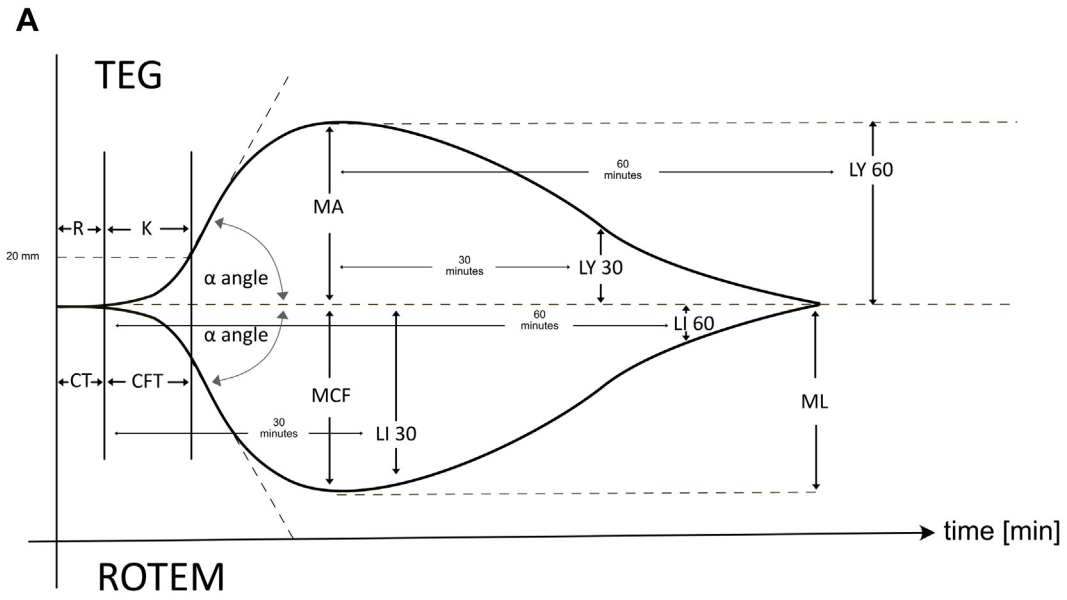
ROTEM defines various parameters to describe clot dynamics and kinetics, the size and the firmness of clot during formation, and clot lysis (Figure 1, *A*). Clotting time (CT) defines the initial period until the onset of clot formation (when a 2-mm amplitude is reached). The alpha angle is the angle between the center line and a tangent to the curve at the 2-mm amplitude point. Clot formation time (CFT) is determined by the time elapsed from the CT until an amplitude of 20 mm is reached, whereas the maximum amplitude defines the maximum clot firmness (MCF). A10 refers to the amplitude at 10 min after the clotting time. The clot lysis index at 60 min (LI60) describes the ratio of the amplitude at 60 min after CT to the maximum clot firmness and provides information about fibrinolysis.

ROTEM tests were performed per standard clinical protocols: INTEM (ellagic acid [a contact activator] -activated intrinsic pathway), EXTEM (tissue factor [derived from rabbit brain] -triggered extrinsic pathway), and FIBTEM (EXTEM with platelet inhibitor [cytochalasin D] added to evaluate the contribution of fibrinogen to CF). Parameters measured in this study were CT, CFT, MCF, alpha angle, A10, and LI60 (the inverse value of the maximum lysis [ML] value at 60 min after CT).

The ROTEM reference range was established previously for quality assurance and clinical validation purposes using 26 specimens from healthy adult volunteers representing diverse ethnic, race, and age backgrounds. Before testing patient specimens, the ROTEM device was calibrated according to quality standards and underwent required quality control testing. All measurements were performed immediately after blood was hand-delivered to the laboratory to avoid spurious results.

Statistical analyses were performed using Stata version 16 (StataCorp LLC, College Station, TX) and R version 4.0.2 (R Project for Statistical Computing, Vienna, Austria). Categorical variables, counts, and percentages of patients were analyzed by the Fisher exact test or χ^2 test as appropriate. Continuous variables were analyzed by 2-sample *t* test or Wilcoxon rank-sum test, as appropriate. ROTEM values and standard laboratory test results were compared with the reference ranges (median value) using the Wilcoxon rank-sum test. Linear regression analysis was performed for detecting associations among ROTEM variables and laboratory test results, and analysis of variance (ANOVA) was performed to determine whether the associations were different between thrombosis and nonthrombosis groups.

Stepwise backward elimination was applied as the variable selection method for the logistic regression model. CT, CFT, alpha angle, A10, MCF, and LI60 for EXTEM, FIBTEM, and INTEM were entered into the selection process. Multiple logistic regression was conducted to detect the independent effect of selected variables on thrombotic outcome after adjustment of age and sex. The probability of a thrombosis event was derived using maximum likelihood ratios. To detect whether including ROTEM variables increased the performance of prediction for thrombosis over D-dimer alone, both logistic regression with only D-dimer and confounders and logistic regression with D-dimer, confounders, and selected ROTEM variables were performed. The 2 models were compared through ANOVA to determine whether there was a significant improvement in model performance by adding ROTEM variables. To determine the optimal cutoff point for numeric values (model discrimination), receiver-operating characteristic (ROC) curve analysis was performed. To determine whether there was a significant difference between areas under the ROC curves (AUC) for the 2 models, testing was performed using the method of Delong.[20] ROC curve analysis was also applied to measure the performance of prediction of multiple logistic regressions. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios were calculated according to methods described by Pepe.[21] The Hosmer-Lemeshow goodness-of-fit test was used to evaluate



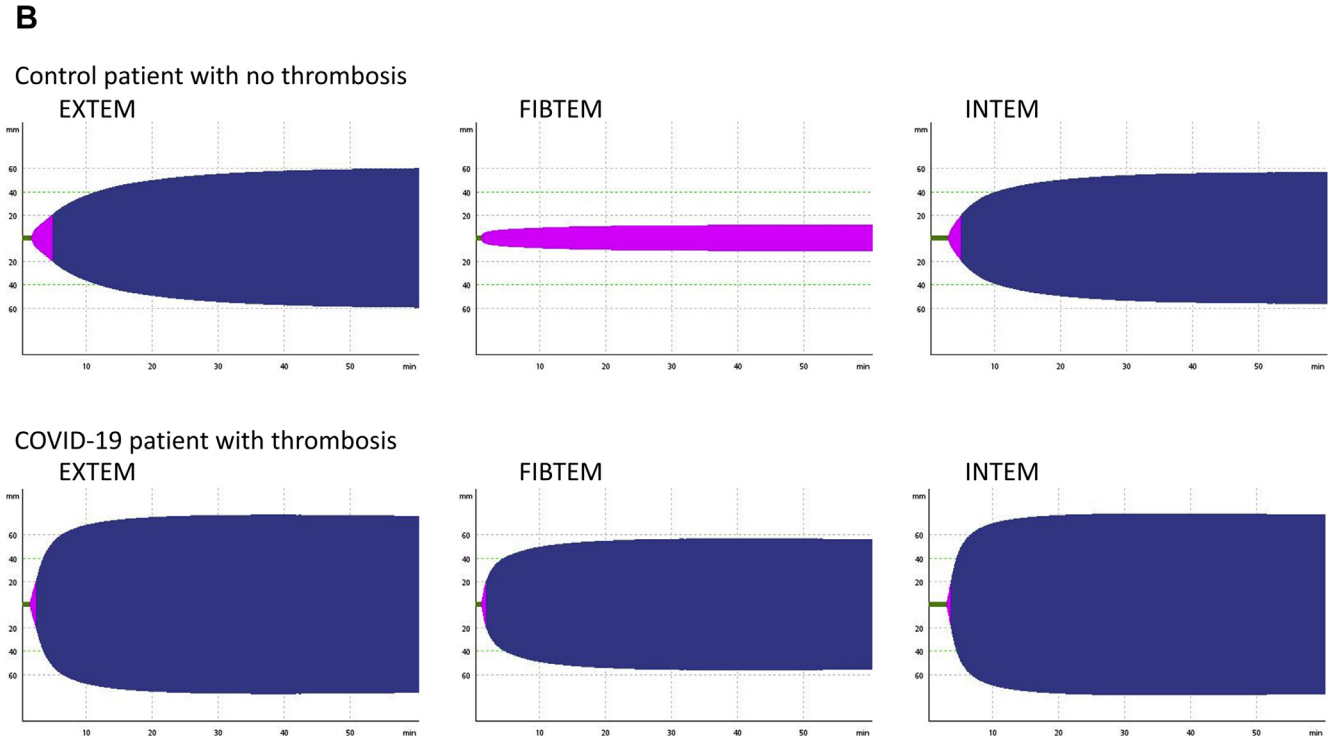


Figure 1. (*A*) ROTEM and TEG parameters comparison. (*B*) Prominent increase in MCF reflects a hypercoagulable state in COVID-19 patients. Please note absence of fibrinolysis. *TEG*, thromboelastography; *R*, reaction time; *K*, K time; *MA*, maximum amplitude; *LY30/LY60*, 30/60 minute fibrinolysis; *ROTEM*, rotational thromboelastometry; *CT*, clotting time; *CFT*, clot formation time; *A10*, amplitude at 10 min after the clotting time; *MCF*, maximum clot firmness; *LI30*, the clot lysis index at 30 minutes; *LI60*, the clot lysis index at 60 minutes; *ML*, maximum lysis.

model calibration. Change in pseudo R^2 when the variable is added to the model last was used to determine variable importance.

Results

Demographic and clinical data were collected and analyzed for 44 SARS-CoV-2 reverse transcriptase-polymerase chain reaction (rtPCR)-positive patients who had ROTEM testing in an ICU and summarized in Table I. No patients were bleeding at the time of sample collection. During this time period, 133 individuals were treated for COVID-19 in our ICUs, among whom 44 (33%) had ROTEM at the time of ICU admission.

Forty of 44 samples for ROTEM analysis were collected after ICU admission; 4 samples were collected en route to the ICU. ROTEM samples were collected within 48 hours of admission to the ICU. Summary data are presented in Table II. Overall, the COVID-19 population's ROTEM results were statistically different (all, $P < .001$) than the reference range population for all values except EXTEM and INTEM LI60, and INTEM CT (Table II and Figure 1, *B*).

Table I
Demographics of patients undergoing rotational thromboelastometry testing

	Total (Percent)*	Thrombotic events		P
		No	Yes	
		N = 30 (68.2)	N = 14 (31.8)	
COVID-19-positive	44 (100)	30 (68.2)	14 (31.8)	
Age*	63 (15)	62 (16)	64 (11)	.72
Sex				
Male	32 (72.7)	8 (66.7)	4 (33.3)	.58
Female	12 (27.3)	22 (68.8)	10 (31.3)	
Race				.02
White	13 (29.6)	9 (69.3)	4 (30.8)	
African American	6 (13.7)	1 (16.7)	5 (83.3)	
Asian	12 (29.6)	11 (69.3)	1 (30.8)	
Other/Unknown	13 (27.3)	9 (91.7)	4 (8.3)	
Comorbidities				
Cancer	5 (11.4)	2 (40.0)	3 (60.0)	.31
Hypertension	24 (54.6)	14 (58.3)	10 (41.7)	.20
Anticoagulation				.72
Prophylactic	31 (70.5)	22 (61.5)	9 (38.5)	
Therapeutic	13 (29.5)	8 (71.0)	5 (29.0)	

* Mean and standard deviation were reported for age and length of stay.

Table II
Rotational thromboelastometry in COVID-19 patients compared with reference range

ROTEM	[Reference range]	Abnormal (%)*	Median (IQR)	Range	P†
EXTEM CT	[43–82 s]	13 (30)	73.0 (67.5–86.5)	51–134	<.001
EXTEM CFT	[48–127 s]	20 (45)	48.5 (43.0–61.5)	32–168	<.001
EXTEM alpha	[65–80 deg]	19 (43)	80 (78–81)	59–84	<.001
EXTEM A10	[46–67 mm]	27 (63)	70 (63–74)	38–79	<.001
EXTEM MCF	[52–70 mm]	32 (7)	76 (70–79)	46–82	<.001
EXTEM LI60	[85%–100%]	0	97% (94%–98%)	85%–100%	.930
FIBTEM A10	[7–22 mm]	41 (93)	37 (30.5–43.5)	18–50	<.001
FIBTEM MCF	[7–24 mm]	42 (95)	39 (31.5–47.5)	20-56	<.001
FIBTEM LI60	[85%–100%]	0	99% (97%–100%)	88%–100%	<.001
INTEM CT	[122–208 s]	7 (16)	167 (150–188)	114–273	.477
INTEM CFT	[45–110 s]	18 (41)	45 (42–54.5)	33–175	<.001
INTEM alpha	[70–81 deg]	10 (23)	81 (79–81)	58–83	<.001
INTEM A10	[46–67 mm]	25 (57)	68.5 (65–73)	37–78	<.001
INTEM MCF	[51–72 mm]	26 (59)	73 (71–78)	45–82	<.001
INTEM LI60	[85%–100%]	1% (2%)	96% (94%–98%)	84%–100%	.344

s, seconds, *alpha*, alpha angle; *deg*, degrees, *CT*, clotting time, *CFT*, clot formation time, *A10*, amplitude after 10 minutes, *MCF*, maximum clot firmness; *min*, *LI60*, Lysis Index at 60 minutes.
* Total N = 44. Abnormal (%) above reference range except below reference range for EXTEM CFT and INTEM CFT.
† By 2-sample Wilcoxon rank-sum test compared with a reference range control group.

During ICU admission, 32% (14 of 44) of patients with ROTEM specimens experienced thrombosis, including deep venous thrombosis ($n = 10$), arterial occlusion ($n = 2$), or dialysis catheter occlusion ($n = 2$). No pulmonary emboli were diagnosed. The D-dimer concentration that was collected closest to the ROTEM specimen collection predicted thrombotic episodes by univariate logistic regression analysis (odds ratio [OR] 1.58, 95% confidence interval [CI], 1.12–2.23, $P < .009$ per every 1,000 ng/mL increase), consistent with findings by Choi et al.[22] The time between ROTEM specimen collection and diagnosis of thrombosis was no greater than 7 days. The *C*-statistic for D-dimer and thrombosis was 0.93 (95% CI, 0.81–0.98) at a calculated optimal threshold of 2,818 ng/mL (Supplementary Table S2). Based on the thrombosis prevalence of 31.8%, sensitivity is 92.9% (95% CI, 68.5%–98.7%), specificity is 80.0% (95% CI, 62.7%–90.5%), positive predictive value is 68.4%, and negative predictive value is 96.0%. For D-dimer concentration below 1,625 ng/mL the sensitivity is 100%, and above 6,900 ng/mL the specificity is 100%. The 2,818 ng/mL D-dimer threshold is consistent with the D-dimer threshold value of 3,000 ng/mL that was published recently by our group.[4]

The rate of thrombosis in ICU patients who did not have ROTEM specimens was lower (15.7%) ($P = .032$). The median maximum D-dimer concentration was also lower in this group (6,550 ng/mL [IQR 2,138–15,534]) compared with the median maximum D-dimer concentration in ROTEM patients (26,664 ng/mL [IQR 11,548–41,424]) ($P = .02$). Similarly, the median maximum fibrinogen concentration was also lower in the non-ROTEM group 709 mg/dL ([IQR 594–873]) vs 1,000 (IQR 908–1000, $P = .003$) in the ROTEM group.

There was no significant association between ROTEM parameters and thrombosis outcomes by the Wilcoxon rank-sum test (Table II, Supplementary Figures S1–S6). Backward stepwise regression selected D-dimer, EXTEM CFT, and FIBTEM MCF as predictive of a thrombosis episode. Multiple logistic regression showed that for every 1 mm increase of FIBTEM MCF, the odds of developing thrombosis increased 20% (95% CI, 0–40%, $P = .043$), whereas for every 1,000 ng/mL increase in D-dimer, the odds of thrombosis increased by 70% (95% CI, 20%–150%, $P = .004$), after adjustment for age and sex (AUC = 0.96, 95% CI, 0.90–1.00) (Figure 2). There was no significant independent effect detected for

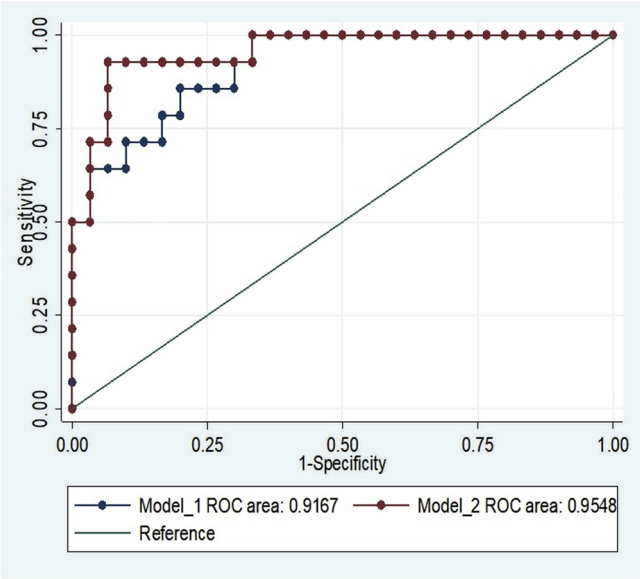


Figure 2. Comparison of receiver-operating characteristic (ROC) curves for 2 models predicting thrombotic events.

Model 1 for thrombosis correlated with D-dimer, controlled for age and sex

Variable:	Odds ratio	[95% CI]	*P*
D-dimer (per 1,000 ng/dL)	1.6	1.1–2.3	.007
Age (years)	1	0.9–1.0	.205
Sex (male/female)	2.2	0.2–19.4	.761

Number of observations = 44.
Pseudo R^2 = 0.47, Model $P < .0001$; area under ROC curve = 0.917; Hosmer-Lemeshow $\chi^2 = 1.81$, $P = .178$.

Model 2 for thrombosis with D-dimer, FIBTEM MCF, and EXTEM CFT controlled for age and sex

Variable:	Odds ratio	[95% CI]	*P*
D-dimer (per 1,000 ng/dL)	1.7	1.2–2.5	.004
FIBTEM MCF (mm)	1.2	1.0–1.4	.045
EXTEM CFT (s)	1	1.0–1.1	.193
Age (years)	0.9	0.9–1.0	.163
Sex (male/female)	2.5	0.2–27.9	.451

Number of observations = 44.
Pseudo R^2 = 0.58, Model $P < .0001$.
Area under ROC curve = 0.955; Hosmer-Lemeshow $\chi^2 = 5.24$, $P = .154$.

EXTEM CFT (adjusted OR = 1.0 [95% CI, 1.0–1.1, $P = .193$]). There was a significant improvement in overall model performance after adding FIBTEM MCF and EXTEM CFT in the model (difference in deviance, −6.32, $P = .04$). However, the increase in AUC was not a significant (increase of 0.04, $P = .20$). D-dimer made the largest change in pseudo R^2 when added to the model last (change of $R^2 = 0.48$), and FIBTEM MCF made the second largest change (change of $R^2 = 0.20$).

In patients with thrombosis, FIBTEM MCF correlated inversely with D-dimer by linear regression (coefficient −0.57, 95% CI, −0.84 to −0.28; R^2 0.62, $P < .001$). Conversely, in the nonthrombosis group, the regression slope was positive but not significantly correlated (coefficient 0.45, 95% CI, −1.10 to 2.00; R^2 0.01, $P = .556$) (Figure 3), with a significant difference (ANOVA, $P < .001$) in the slopes of the 2 curves. All 7 patients with D-dimer >7,000 ng/mL had thrombosis. Interestingly, the FIBTEM MCF amplitude was diminished when D-dimer concentrations exceeded 7,000 ng/mL, possibly owing to ROTEM assay interference from fibrin degradation products (FDP), including D-dimer.[23] After excluding such patients owing to possible assay interference, a significant association ($P = .034$, Wilcoxon rank-sum test) between FIBTEM MCF and thrombosis was observed.

Similarly, EXTEM CFT correlated with D-dimer concentration in the thrombosis group by linear regression (coefficient 1.80, 95% CI 0.68–2.93; R^2 0.51, $P = .004$). The EXTEM CFT was shorter than the reference range when D-dimer concentration was less than 7,000 ng/mL for the majority of patients. However, when D-dimer was greater than 7,000 ng/mL, CFT was prolonged, once again possibly owing to assay interference from FDP.

The EXTEM LI60 and INTEM LI60 were within the normal range in 100% and 98% of tests, respectively. Hyperfibrinolysis was not noted in any patient. The median EXTEM LI60 was 97% (IQR, 94–99) for patients who had a thrombosis event and similar to the median for those who did not (96; IQR, 93–97) ($P = .258$). Fibrinolysis shutdown (FSD), defined here as EXTEM ML <3.5% at 60 min after CT based on a previous publication,[24] was present in 50% (22/44) of patients in the EXTEM assay. Of those with FSD, 8 (18%) had thrombotic events and 14 (32%) did not. Contrary to a previous report,[24] FSD was not associated with thrombosis (χ^2; $P = .53$).

Discussion

During ICU admission, 32% (14/44) of patients experienced a thrombotic episode. D-dimer concentration aptly predicted

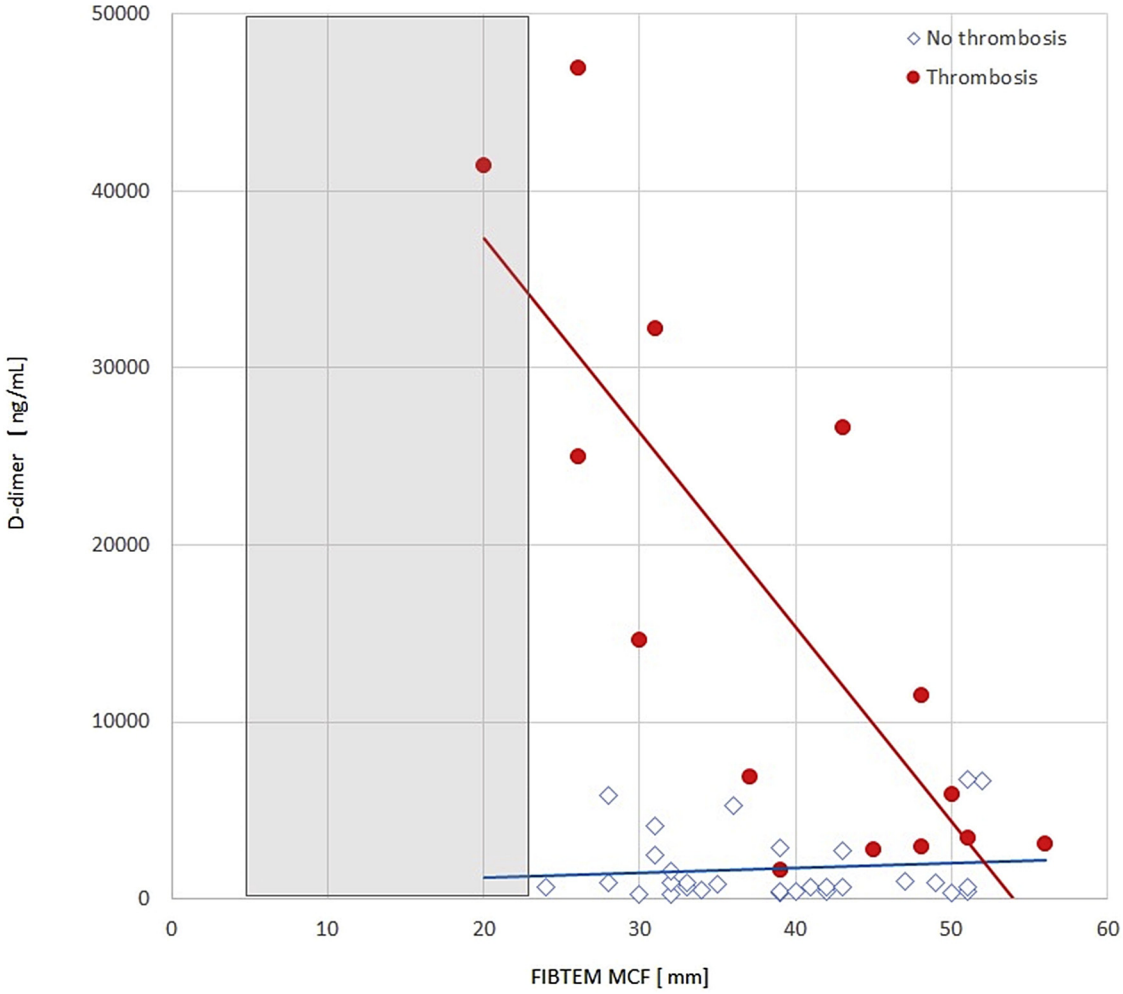


Figure 3. In patients with thrombosis FIBTEM MCF correlates inversely with D-dimer.
Shaded gray area indicates the FIBTEM MCF reference range (7–24 mm). *MCF*, maximum clot firmness.

episodes of thrombosis, and the calculated optimal threshold for D-dimer concentration and thrombosis was 2,818 ng/mL. No hyperfibrinolysis was noted in any patient, and overall lysis was minimal in all assays. FSD was present but did not correlate with thrombosis. Although ROTEM values reflected an increase in clot strength for the EXTEM, INTEM, and FIBTEM assays beyond the reference range, there was no significant association between ROTEM parameters and thrombosis outcomes by the Wilcoxon rank-sum test. However, there was a significant improvement of thrombosis prediction model performance after adding FIBTEM MCF and EXTEM CFT to D-dimer concentrations.

The ICU patients with COVID-19 in this cohort tended to have a distinct ROTEM fingerprint, most having a FIBTEM, EXTEM, and INTEM MCF above the normal range, but other parameters seemed to vary by the specific patient scenario. A normal level of fibrinolysis associated with increased D-dimer concentrations (a main product of fibrinolysis) in patients who presented with clinical thrombosis is an interesting and notable finding of our study, given recent publications on impaired fibrinolysis as it pertains to COVID-19.[24,25]

FDPs, including D-dimer, are produced by thrombus degradation, principally by plasmin. ROTEM assay interference from FDPs seemed to occur when D-dimer concentrations were extremely high.[23] Concentrations of D-dimer greater than 7,000 ng/mL interfered with CFT and MCF in EXTEM, FIBTEM, and INTEM. The most pronounced decrease in MCF with very high D-dimer concentrations was observed with FIBTEM (Figure 3), with an inverse linear correlation (R^2 0.62, $P = .001$). This same inverse correlation was recently reported in a similar study of ROTEM in 30 severely ill COVID-19 patients.[26] Our study corroborates this effect, but we offer an alternate explanation for this observation: interference of ROTEM assay by exquisitely high FDPs.

Data regarding fibrinolysis evaluation in COVID-19 using viscoelastic testing are sparse and often conflicting. Wright et al[25] performed citrated kaolin thromboelastography (TEG) in 44 COVID-19 ICU patients, demonstrating increased maximum amplitude (MA) and low lysis at 30 min (LY30). Complete FSD was observed in 57% of patients and was a modest predictor of VTE (C-statistic, 0.742). Pavoni et al[27] showed no evidence of hyperfibrinolysis in ROTEM analysis of 40 patients.

Fibrinolysis parameters cannot be compared directly between ROTEM and TEG.[28] As noted in Figure 1, *A*, the lysis parameter is calculated differently for TEG than ROTEM. With TEG, the timing begins at the MA of the curve and ROTEM timing begins at the CT. In addition, ROTEM may be more sensitive than TEG for detecting fibrinolysis, owing to differences in activation by tissue factor (ROTEM) versus kaolin (TEG). Thus, our study results cannot be directly compared with the Wright et al study,[25] but they are similar to those of Pavoni et al.[27]

Creel-Bulos et al[24] used ROTEM to evaluate for the presence and implications of “acute fibrinolytic shutdown” in COVID-19 ICU patients, noting that 44% (11/25) had FSD, and 78% of those

(8/11) had a thrombotic event. They defined FSD as having EXTEM ML <3.5%, consistent with the definition provided for trauma patients by Gomez-Builes et al,[29] and they asserted that the high rate of FSD correlated significantly with thrombosis. We did not confirm this finding. By way of explanation, the ML value evolves over time with viscoelastic testing and reflects the process of clot degradation. If a test is run longer, more lysis occurs until the clot is degraded completely. Thus, it is imperative to compare lysis values at a similar time point in the assay, underscoring the utility of LI60 to ensure that the degree of lysis is always evaluated at the same point in the life of the clot. Earlier in the assay, there is less clot lysis, calling the findings of Creel-Bulos et al[24] into question because their assays were apparently run for different amounts of time and for <60 min (see Creel-Bulos et al, Figures 1 and 2, *B*).[24] In their Figure 1, 2 cases are shown where the ML value at 60 min (inverse of LI60) is not present in the images because the assay was not run until the 60-min point. Indeed, in their Figure 2, *B*, the assay appears to have run for only 35 minutes. To ensure a standardized comparison of lysis between patients we used only LI60 <3.5% to evaluate FSD. Our cohort demonstrated normal fibrinolysis at 60 min across all tests (INTEM, EXTEM, and FIBTEM), which is a difference from the findings of Creel-Bulos et al.[24] More importantly, no correlation between FSD and thrombosis was found in our study.

D-dimer concentrations were more predictive of thrombosis in our patient population than any other single parameter. FIBTEM MCF had a weaker predictive role for thrombosis, but adding FIBTEM MCF and EXTEM CFT in a regression model increased the predictability for thrombosis compared with only using D-dimer, age, and sex. This information may be useful to build a model to predict thrombotic events and determine anticoagulant treatment, but the additive benefit is modest. Based on the data in hand, we recommend that ROTEM testing may be beneficial for patients with a D-dimer concentration between 1,625 ng/mL and 6,900 ng/mL. Below, the incidence of VTE is so low that there may not be signal, and above the range the presence of FDP may interfere with the ROTEM assay accuracy.

Strengths of this study include the homogeneous severely ill COVID-19 patient population at the beginning of the ICU stay; ICU providers with greater than 4 years' experience with ROTEM ordering and interpretation; ROTEM testing performed by licensed, trained technologists in the blood bank; standardized definitions of and monitoring for thrombosis amongst a small, closely aligned group of critical care specialists in our institution; and a standardized treatment approach for anticoagulation/prevention of thrombosis. Limitations of this study include a small sample size that was not powered to detect minor differences in outcome, the retrospective and observational nature of the study, no control population in whom ROTEM was not performed, and potential bias in patient selection based on clinician decision-making when deciding to order a ROTEM, and physician discretion for initiating thrombosis investigation. That ROTEM was not performed on all ICU patients with COVID-19 during this time period is also a limitation, and it is unclear whether ROTEM may have been more or less useful had all patients been included.

A larger study will be needed to examine the predictive nature of ROTEM for thrombosis for patients with a D-dimer concentration between 1,625 ng/mL and 6,900 ng/mL. In addition, further investigation of the D-dimer or FDP threshold at which ROTEM measurements may become inaccurate owing to assay interference is warranted.

In conclusion, ROTEM confirmed the hypercoagulable state of COVID-19 ICU patients. FIBTEM MCF and EXTEM CFT increased the predictability for thrombosis compared with only using D-dimer, corrected for age and sex. ROTEM analysis is most useful in augmenting the information provided by the D-dimer concentration for VTE risk assessment when the D-dimer concentration is between 1,625 and 6,900 ng/dL, but the enhancement is modest. FIBTEM MCF and EXTEM CFT were the ROTEM parameters found to be most useful in predicting thrombosis within this range. Outside this range, the likelihood of thrombosis is best predicted by D-dimer alone and ROTEM is unlikely to be helpful. Fibrinolytic shutdown did not correlate with thrombosis. Care must be taken when using ROTEM in patients with high levels of fibrin degradation products because assay interference could lead to inaccurate results and misinterpretation.

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Conflict of interest/Disclosure

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [https://doi.org/10.1016/j.surg.2021.08.051].

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