Thromboelastography Parameters do not Discriminate for Thrombotic Events in Hospitalized Patients With COVID-19

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is associated with a prothrombotic state; leading to multiple sequelae. We sought to detect whether thromboelastography (TEG) parameters would be able to detect thromboembolic events in patients hospitalized with COVID-19.

Methods: We performed a retrospective multicenter case–control study of the Collaborative Research to Understand the Sequelae of Harm in COVID (CRUSH COVID) registry of 8 tertiary care level hospitals in the United States (US). This registry contains adult patients with COVID-19 hospitalized between March 2020 and September 2020.

Results: A total of 277 hospitalized COVID-19 patients were analyzed to determine whether conventional coagulation TEG parameters were associated with venous thromboembolic (VTE) and thrombotic events during hospitalization. A clotting index (CI) >3 was present in 45.8% of the population, consistent with a hypercoagulable state. Eighty-three percent of the patients had clot lysis at 30 min (LY30) = 0, consistent with fibrinolysis shutdown, with a median of 0.1%. We did not find TEG parameters (LY30 area under the receiver operating characteristic [ROC] curve [AUC] = 0.55, 95% CI: 0.44-0.65, P value = .32; alpha angle [α] AUC = 0.58, 95% CI: 0.47-0.69, P value = .17; K time AUC = 0.58, 95% CI: 0.46-0.69, P value = .67; maximum amplitude (MA) AUC = 0.54, 95% CI: 0.44-0.64, P value = .47; reaction time [R time] AUC = 0.53, 95% CI: 0.42-0.65, P value = .70) to be a good discriminator for VTE. We also did not find TEG parameters (LY30 AUC = 0.51, 95% CI: 0.42-0.60, P value = .84; R time AUC = 0.57, 95% CI: 0.48-0.67, P value .07; α AUC = 0.59, 95% CI: 0.51-0.68, P value = .02; K time AUC = 0.62, 95% CI: 0.53-0.70, P value = .07; MA AUC = 0.65, 95% CI: 0.57-0.74, P value < .01) to be a good discriminator for thrombotic events.

Conclusions: In this retrospective multicenter cohort study, TEG in COVID-19 hospitalized patients may indicate a hypercoagulable state, however, its use in detecting VTE or thrombotic events is limited in this population.

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COVID-19, TEG, hypercoagulable state, VTE, fibrinolysis shutdown

**Introduction**

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). As of October 2022, COVID-19 has infected more than 626 million people and led to more than 6.5 million deaths. While the majority of COVID-19 cases are mild, approximately 5% to 32% of infected patients were admitted to the intensive care unit (ICU) in the United States (US). The hallmark symptom of COVID-19 is acute respiratory distress, ranging from pneumonia to acute respiratory distress syndrome (ARDS). Studies have shown that COVID-19 is also associated with a prothrombotic state; leading to multiple sequelae. In the European and Chinese studies, 20% to 30% of COVID-19 patients were found to have thrombotic complications, consisting mostly of venous thromboembolic (VTE) disease, while a US study showed that the overall thrombosis rate was found to be 9.5%. Elevated D-dimer, a marker of increased fibrin formation and degradation, is associated with thrombosis and higher mortality in COVID-19 patients.

Thromboelastography (TEG, Haemonetics) is a whole-blood coagulation assay that measures the dynamics of clot formation, clot strength, and clot dissolution. It is commonly used to guide transfusion of hemostatic products in hemorrhaging patients. It is also used to identify hypercoagulable patients at risk for thrombosis. A study of 44 COVID-19-positive patients showed that a TEG lysis at 30 min (LY30) of 0% and D-dimer value greater than 2600 ng/mL were associated with a markedly elevated risk of renal failure, VTE and thrombotic events. However, another study of 64 COVID-19-positive patients was not able to show a correlation between TEG parameters and VTE. The objective of our study was to evaluate the association between TEG parameters and other common coagulation parameters and thromboembolic events in hospitalized COVID-19 patients. We sought to detect whether TEG parameter would be able to detect thromboembolic events in patients hospitalized with COVID-19.

**Patients and Methods**

**Study Design**

This was a retrospective case–control study of 277 patients hospitalized with COVID-19. These patients were abstracted from the multicenter Collaborative Research to Understand the Sequelae of Harm in COVID (CRUSH COVID) registry of patients admitted between March 2020 and September 2020. Eight tertiary centers, The George Washington University Hospital, University of Arkansas, Mayo Clinic, University of Southern California, University of Maryland Medical Center, Wake Forest Baptist Medical Center, University of Mississippi Medical Center, and Northeast Georgia Health System, contributed data to the registry. This was managed with the Research Electronic Data Capture (REDCap) application. The study was reviewed and approved by the Institutional Review Board at the University of Maryland Medical Center, Baltimore (IRB HP-00084946), which served as the central IRB for all sites. The requirement for written informed consent was waived by the IRB.

**Study Population**

All adult patients admitted to the 8 participating hospitals from March 2020 to September 2020 diagnosed with COVID-19 were eligible for the study. Patients were included if they had laboratory confirmed COVID-19 as measured from a polymerase chain reaction test. Patients were excluded if they did not have a TEG measurement performed during their hospitalization.

**Data Collection**

Demographic variables collected included age, race, sex, past medical history, body mass index (BMI), and a history of smoking or vaping (both active and former). Comorbidity variables abstracted included hypertension, diabetes mellitus (DM), end-stage renal and liver diseases (ESRD and ESLD), cancer, HIV, cardiovascular disease (CVD), cerebrovascular accident (CVA), and coronary artery disease (CAD). VTE surveillance, detection, and diagnosis were done at the discretion of the clinicians and practice may slightly differ across the different institutions. Kaolin TEG values and other laboratory values were obtained at clinicians’ discretion and TEG measurements were done based on each institutions’ policy. Heparinase was used to measure TEG values in patients on heparin based on each institution’s policy. In the event of multiple TEG or laboratory samples, analysis was done based on the initial values. Since TEG measurements were obtained at the discretion of the clinician, the time to TEG measurement from initial hospital admission is not uniform.

**Case Definitions**

The study’s primary outcome was the area under the receiver operating characteristic (ROC) curve for VTE. The secondary outcome was the ROC for the composite endpoint of VTE, ischemic stroke, and myocardial infarction, herein defined as “thrombotic events”. TEG indices utilized in the analysis included reaction time (R time), alpha angle (α), K time, maximum amplitude (MA), and LY30. In addition, the clotting index (CI), which is computed as CI $= -0.2454 R + 0.0184 K + 0.1655 MA - 0.0241 α - 5.0220$, was assessed in order to provide an overall assessment of coagulation. Additional
coagulation factors evaluated were D-dimer and fibrinogen levels measured at the time of hospital admission.

Statistical Analysis

Data analysis was performed using STATA (Version 14, StataCorp). This was a nested case-control study of COVID-19-positive patients whereby the patient was stratified based on whether they experienced the primary or secondary outcome. Demographic and laboratory values were compared using Student’s t-test or the Wilcoxon–Mann–Whitney test for continuous variables, depending on the normality of the distribution. A chi-square test or Fisher’s exact test was utilized for categorical variables depending on the sample size. The ROC curves were generated for each outcome of interest for all TEG parameters, the initial D-dimer and fibrinogen level. Delong’s test was performed to examine whether the area under the ROC curve (AUC) was statistically different from 0.5. Using Youden’s J statistic, the optimal threshold for each value in detecting each outcome was identified, and the sensitivity and specificity were calculated. Statistical significance was defined by \( p < .05 \) for all analyses.

Results

Study Population

In total, 277 hospitalized COVID-19 patients met study inclusion criteria. Sixty percent (\( n = 165 \)) of patients were male and 80% (\( n = 223 \)) of patients had a BMI \( \geq 25 \) kg/m\(^2\). Outside of being overweight, the most common preexisting conditions were hypertension (\( n = 165; 59.6\% \)) and DM (\( n = 125, 45.1\% \)). One hundred and seventy-nine (65%) patients were admitted to the ICU, and their hospital length of stay was considerably longer with the median days of 24 days (Q1 = 11, Q3 = 41). The median length of stay among those who were not admitted to ICU was 5 days (3, 8). In-hospital mortality occurred in 25.6% (\( n = 71 \)) of patients. The median qSOFA (quick Sepsis Related Organ Failure Assessment) score for these patients was 1 (0, 2). Twenty-eight patients (10.1%) developed VTE and 43 patients (15.7%) developed renal failure requiring hemodialysis. The median day from admission to VTE diagnosis was 15 days (8, 29). The composite secondary outcome of thrombotic events was detected in 22.4% (\( n = 62 \)) of patients. Fibrinolysis shutdown (Ly30 = 0) was observed in 83.8% (\( n = 232 \)) of the population.

A hypercoagulable state (CI > 3.0) was observed in 54.2% of the sample (\( n = 150 \)) (Table 1). The median time to TEG measurement was 4 days (inter quartile range [IQR]: 0-20). Thirty-nine percent (\( n = 108 \)) of patients received therapeutic level heparin dosing and 8.3% (\( n = 23 \)) received therapeutic level enoxaparin dosing. Nine percent (\( n = 25 \)) received no prophylactic or therapeutic anticoagulation and the rest received prophylactic dosing.

Conventional Coagulation Tests and Ability to Differentiate VTE and Thrombotic Events

The median values of the conventional coagulation parameters were outside the reference range for most conventional coagulation tests except for platelet count (Tables 2 and 3). The median D-dimer concentration in our population was 1140 ng/mL, (605-3670) which is much higher than the reference range (\( \leq 250 \) ng/mL). The median fibrinogen was 590 mg/dL (443-730). When comparing patients with VTE to those without, the median D-dimer concentration was 3790 ng/mL (1032.5-4660) compared to 1090 ng/mL (576-2470) (\( P = .9 \)). When comparing fibrinogen concentration between patients with VTE to those without, the median fibrinogen concentration was 686 mg/dL (446-800) compared to 580 mg/dL (441.5-728) (\( P = .09 \)) (Table 2).

When comparing patients with thrombotic events to those without, the median D-dimer concentration was 1770 ng/mL.
Viscoelastic index

| Coagulation parameters, median (IQR) | All patients | No VTE | VTE | P value |
|-------------------------------------|--------------|--------|-----|---------|
| Platelet count, 10^9/L              | 210 (162–277) | 210 (163–275) | 197 (143–295) | .08     |
| Prothrombin time, s                | 14.7 (13.3–15.65) | 15.1 (13.5–15.8) | 13.8 (12.1–14.7) | .58     |
| Activated partial thromboplastin time (aPTT), s | 29.95 (27–33.5) | 29.9 (27–33.5) | 30.9 (28–33.5) | .69     |
| Fibrinogen, mg/dL                  | 590 (443–730) | 580 (441.45–728) | 686 (446–800) | .09     |
| D-dimer, ng/mL                     | 1140 (605–3670) | 1090 (576–2470) | 3790 (1032.5–4660) | .90     |
| International normalized ratio (INR) | 1.18 (1.1–1.3) | 1.18 (1.1–1.1) | 1.12 (1.1–1.1) | .97     |
| C-reactive protein (CRP) level     | 11 (4.66–22.75) | 10.25 (4.19–21) | 20.35 (10.1–34.2) | .34     |

Viscoelastic index

- Reaction time (R time) (min): 5.4 (4.4–6.9) vs. 5.4 (4.4–6.9) vs. 5.3 (4.25–6.75) (.72)
- K time (min): 1.4 (1.1–1.8) vs. 1.4 (1.1–1.8) vs. 1.2 (1.05–1.75) (.60)
- α°: 69.8 (65–74.2) vs. 69.6 (63.9–73.9) vs. 72.05 (66.1–75.25) (.35)
- Maximum amplitude, mm: 68.5 (61.3–74) vs. 68.8 (61.4–74.3) vs. 67.8 (60.15–72.05) (.45)
- Clot lysis at 30 min (LY30), %: 0.1 (0–1) vs. 0.1 (0–1) vs. 0.25 (0–1.15) (.29)
- Clotting index (CI): 3.26 (2.03–4.21) vs. 3.26 (2.02–4.23) vs. 3.10 (2.10–4.13) (.04)

Abbreviations: IQR, interquartile range; α, alpha angle.

Table 3. Coagulation Markers and Thrombotic Events.

| Coagulation parameters, median (IQR) | Total (n = 277) | No thrombotic (n = 215) | Thrombotic (n = 62) | P value |
|-------------------------------------|----------------|------------------------|--------------------|---------|
| Platelet count, 10^9/L              | 210 (162–277) | 226 (181–283) | 148 (100–207) | .29     |
| Prothrombin time, s                | 14.7 (13.3–15.65) | 14.4 (13.2–15.2) | 15.3 (13.9–16.17) | .34     |
| Activated partial thromboplastin time (aPTT), s | 29.95 (27–33.5) | 29.2 (27–32.1) | 33 (28.1–38.35) | .27     |
| Fibrinogen, mg/dL                  | 590 (443–730) | 603 (470–744) | 480 (372–699) | .26     |
| D-dimer, ng/mL                     | 1140 (605–3670) | 1043 (554–2330) | 1770 (820–4000) | .66     |
| International normalized ratio (INR) | 1.18 (1.1–1.3) | 1.18 (1.08–1.28) | 1.2 (1.1–1.4) | .61     |
| C-reactive protein (CRP) level     | 11 (4.66–22.75) | 11.25 (4.51–21.55) | 9.61 (5.21–24.6) | .30     |

Viscoelastic index

- Reaction time (R time) (min): 5.4 (4.4–6.9) vs. 5.3 (4.3–6.6) vs. 5.8 (4.6–8.1) (.70)
- K time (min): 1.4 (1.1–1.8) vs. 1.3 (1.1–1.8) vs. 1.65 (1.2–2.5) (.01)
- α°: 69.8 (65–74.2) vs. 70.5 (65.5–74.5) vs. 68 (60.7–73.1) (.61)
- Maximum amplitude, mm: 68.5 (61.3–74) vs. 69.7 (63.5–75.1) vs. 62.7 (58–71.2) (.36)
- Clot lysis at 30 min (LY30), %: 0.1 (0–1) vs. 0.1 (0–1) vs. 0.1 (0–1) (.52)
- Clotting index (CI): 3.26 (2.03–4.21) vs. 3.50 (2.26–4.31) vs. 3.23 (1.28–3.66) (.50)

Abbreviations: IQR, interquartile range; α, alpha angle.

When comparing fibrinogen concentration between patients with thrombotic events to those without, the median fibrinogen concentration was 480 mg/dL (372-699) compared to 603 mg/dL (470-744) (P = .66). When comparing fibrinogen concentration between patients with thrombotic events to those without, the median fibrinogen concentration was 480 mg/dL (372-699) compared to 603 mg/dL (470-744) (P = .66). When comparing fibrinogen concentration between patients with thrombotic events to those without, the median fibrinogen concentration was 480 mg/dL (372-699) compared to 603 mg/dL (470-744) (P = .26) (Table 3).

When examining the ability of D-dimer or fibrinogen to discriminate VTE, our AUC analysis found that D-dimer had only a fair ability to discriminate (D-dimer AUC = 0.66, 95% CI: 0.54-0.78, P value = .004). Fibrinogen was not able to discriminate VTE well (fibrinogen AUC = 0.57, 95% CI: 0.45-0.69, P value = .21) (Figure 1a and b). Calculation of the optimal point for the detection of VTE for D-dimer was 1642 ng/mL, which was associated with a sensitivity of 53% and specificity of 69% (Figure 1c).

D-dimer and fibrinogen were able to detect thrombotic events with fair discrimination (D-dimer, AUC=0.57, 95% CI: 0.48-0.67, P value = .05; fibrinogen, AUC = 0.61, 95% CI: 0.52-0.70, P value = .01) (Figure 2a and b). Calculation of the optimal point for the detection of thrombotic event for D-dimer was 3090 ng/mL and for fibrinogen level was 487 mg/dL resulting in sensitivities and specificities of 61% and 77% for D-dimer and 53% and 68% for fibrinogen, respectively (Figure 2c).

TEG Measurements and VTE

All median TEG coagulation values were within the reference range except for LY30. The median LY30 value in our population was 0.1% (0-1.1), which is below the lower range of normal of 0.8%. The median CI in our population was 3.26 (2.03-4.21), indicating a hypercoagulable state. The median α was 69.8° (65.0-74.2); the median K time was 1.4 min (1.1-1.8); the median MA was 68.5 mm (61.3-74.2); and the median R time was 5.4 min (4.4-6.9). Among patients with a VTE, the median LY30 was 0.25% (0-1) compared to patients without a VTE whose median LY30 was 0.1% (0-1) (Table 2). This difference was not statistically significant.
Similarly, when comparing the $\alpha$ ($P = .35$), MA ($P = .45$), and R time ($P = .72$) among patients with and without a VTE, these differences were not statistically significant.

When examining the ability of any TEG parameter to detect VTE, the AUC analysis found that none of the TEG parameters were able to accurately discriminate for VTE (LY30 AUC = 0.55, 95% CI: 0.44-0.65, $P$ value = .32; $\alpha$ AUC = 0.58, 95% CI: 0.47-0.69, $P$ value = .17; K time AUC = 0.58, 95% CI: 0.46-0.69, $P$ value = .67; MA AUC = 0.54, 95% CI: 0.44-0.64, $P$ value = .47; R time AUC = 0.53, 95% CI: 0.42-0.65, $P$ value = .70) (Figure 1a and b).

### TEG Measurements and Thrombotic Events

When comparing TEG values in patients with and without thrombotic events, there were no differences in TEG values. The median LY30 of patients without thrombotic events was 0.1% and the median LY30 for patients with thrombotic events was 0.1% (0-1.1) ($P = .52$) (Table 3). Similarly, when comparing the $\alpha$ ($P = .61$), MA ($P = .36$), and R time ($P = .70$) among patients with and without thrombotic events, these differences were not statistically significant. However, when comparing patients with thrombotic events to those without, the median K time was 1.65 min (1.2-2.5) compared to 1.3 min (1.2-2.5) ($P = .01$).
When examining the ability of any TEG parameter to discriminate thrombotic events, the AUC analysis found that LY30 and R time were not able to accurately discriminate for thrombotic events (LY30 AUC = 0.51, 95% CI: 0.42-0.60, P value = .84); R time AUC = 0.57, 95% CI: 0.48-0.67, P value .07). The $\alpha$, K time, and MA had fair discrimination for thrombotic events ($\alpha$ AUC = 0.59, 95% CI: 0.51-0.68, P value = .02; K time AUC = 0.62, 95% CI: 0.53-0.70, P value = .07; MA AUC = 0.65, 95% CI: 0.57-0.74, P value < .01) (Figure 2a and b). Calculation of the optimal point for the detection of thrombotic event for $\alpha$ level was 69.50°, with sensitivities and specificities of 68% and 49%. The optimal point for the detection of thrombotic event for K time was 1.4 min, with sensitivities and specificities of 65% and 53% (Figure 2c).

**Discussion**

Patients with COVID-19 have been reported to have a 20% to 30% incidence of thrombotic and thromboembolic events.\(^5\,\text{6}\) Autopsies performed on COVID-19 decedents have revealed higher VTE (58%) and microscopic thrombi in observed
lungs (53%) than those detected in live COVID-19 patients. COVID-19 associated hypercoagulability is associated with multiple changes in traditional coagulation tests and viscoelastic coagulation parameters. The most significant change in traditional coagulation parameters is reported to be D-dimer, which is commonly elevated in cases of severe disease. Given the number of patients with COVID-19 with a D dimer over 2600 ng/mL without any identifiable DVT/PE, it is not surprising that D dimer is neither a sensitive nor specific marker for VTE. However, we may not be able to see microthrombi, which are part of the ARDS pathophysiology seen after autopsy but cannot be detected in live patients. In this multicenter study, we report coagulation and TEG profiles of hospitalized COVID-19 patients and analyze the utility of TEG in discriminating VTE and thrombotic events. We did not find that either traditional coagulation tests or TEG parameters were able to discriminate VTE events or other thrombotic events with a high degree of accuracy. To our knowledge, this is the largest study to date examining TEG in hospitalized COVID-19 patients.

Previous studies suggested that TEG may be used to identify patients at risk for VTE or other thrombotic events. A study by Wright et al suggested that D-dimer and LY30 could be used to predict of VTE. Their study reported that patients with LY30 = 0 and D-dimer > 2600 ng/mL had a VTE rate of 50% compared with 0% for patients with neither risk factor. Our results are not consistent with their finding. We found that TEG, as a whole, was not able to discriminate patients who had VTE to those who did not.

We also found that only α and MA were able to discriminate thrombotic event with fair accuracy, which resulted in fairly low sensitivities and specificities. D-dimer also had a fair ability to discriminate for VTE with low sensitivity and specificity. As for thrombotic events, D-dimer and fibrinogen both had a fair ability to discriminate thrombotic events with low sensitivities and specificities. Overall, our findings do not support the use of TEG parameters, D-dimer or fibrinogen to discriminate for patients who are at increased risk for VTE or thrombotic events. Both TEG and traditional coagulation tests have some limitations that may account for these findings. For example, TEG and traditional coagulation assays do not measure primary hemostasis and cannot readily demonstrate enhanced platelet adhesion that occurs in COVID-19 from elevated von Willebrand factor. TEG parameters also may not reflect changes in native endothelium that creates a procoagulant state in COVID-19.

Our population had similar coagulation parameters when compared to other cohorts. We found that, despite prophylactic anticoagulation, our VTE rate was 10.1%, which is similar to what is previously reported in the literature. Based on TEG measurements, we found that 83.8% of our patients was in fibrinolysis shutdown with a median LY30 of 0.1%, which is consistent with multiple previous studies that investigated the TEG parameters in hospitalized COVID-19 patients. Fibrinolysis shutdown may occur in COVID-19 patients because patients have increased release of plasminogen activator inhibitor-1. In our study, median R time, the speed of fibrin polymerization (α), and the MA were all within the normal range, which is generally consistent with prior studies.

Our study also demonstrated that 22.4% of hospitalized COVID-19 patients met the composite endpoint of having a thrombotic event. Fifty-four percent of the population had a hypercoagulable profile as defined by CI greater than 3. Despite these findings suggestive of a hypercoagulable state; TEG parameters, D-dimer and fibrinogen level were not found to effectively discriminate VTE or thrombotic events in COVID-19 patients.

Although this study benefits from its multicenter design and sample size, it has several limitations. First, this is a retrospective observational study with limitations that are inherent in observational studies including residual confounding. Some of our patients may have active cancer, may have been pregnant or have other anticoagulation abnormalities that may affect the TEG values, D-dimer and fibrinogen level used in this analysis. Next, as a retrospective study, there was no uniformity in the timing of TEG measurement within the patients’ disease course. VTE surveillance and detection were done at the discretion of the clinicians and the diagnosis of VTE and thrombotic event may not follow exactly the same criteria across the different institution. Additionally, there is no uniformity among the patients in receiving therapeutic anticoagulation, which would alter the results of coagulation measurements.

Conclusion
In this multicenter retrospective case–control study, TEG parameters in hospitalized patients with COVID-19 were suggestive of a hypercoagulable state, however, were not accurate discriminators of VTE or thrombotic events in this population. The role of TEG in screening for VTE and other thrombotic events in COVID-19 patients remains unclear and randomized controlled trials will ultimately be needed to confirm the utility of viscoelastic testing. However, we do not recommend the use of TEG to predict VTE and thrombotic events in COVID-19 patients.

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Supplemental Material

Supplemental material for this article is available online.

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