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ORIGINAL ARTICLE

# Thromboelastography determined dynamics of blood coagulation and its correlation with complications and outcomes in patients with coronavirus disease 2019

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## Abstract

**Background:** Coronavirus disease 2019 (COVID-19) causes abnormalities in the hemostatic system, collectively known as COVID-associated coagulopathy. The dynamics of clot formation are best discerned by whole-blood viscoelastic tests, such as thromboelastography (TEG). We aimed to assess the various abnormalities seen on TEG and explored the predictors of outcomes in these patients.

**Methods:** Thromboelastography was performed for 28 patients with COVID-19 using an automated thromboelastogram. The hemostatic condition was categorized as hypercoagulable in 17 (63%), hypocoagulable in 2 (7%), and normal in 8 (30%) based on TEG variables, such as reaction time , time until clot reaches a fixed strength, alpha angle, maximum amplitude, and clotting index. Laboratory parameters and clinical outcomes were compared between hypercoagulable and normal groups.

**Results:** Twenty-seven patients with a median age of 50 years (interquartile range, 40-60 years), male-to-female ratio of 0.9:1, median C-reactive protein of 25.7 (10.9-108.8) mg/L, serum ferritin of 693 (317-1031) μg/L, and albumin 2.9 (2.6-3.3) g/dL were included. The median prothrombin time/international normalized ratio and activated partial thromboplastin time were within normal range in the hypercoagulable and normal groups. The severity of COVID-19 was mild in 6 (22.2%), moderate in 2 (7.4%), and severe in 19 (70.4%) patients. Twenty-eight-day mortality among patients with hypocoagulable and hypercoagulable states was higher than normal coagulation status. (log-rank test, $P = .002$).

**Conclusions:** Hypercoagulable state, together with a severe inflammatory state, is common in patients with COVID-19, despite thromboprophylaxis. TEG assesses coagulation status better than conventional coagulation tests. Coagulation abnormalities are associated with poor outcomes.

KEYWORDS
coagulopathy, COVID-19, hypercoagulable, outcome, thromboelastography

Essentials

- Coronavirus disease 2019 (COVID-19) is frequently associated with blood-clotting abnormalities and inflammation.
- Thromboelastography assesses coagulati`on abnormalities better than conventional tests.
- Excessive blood clot formation is common despite treatment with heparin (anticoagulant).
- Patients with COVID-19 with clotting abnormalities are less likely to survive than those without clotting abnormalities.

## 1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for coronavirus disease 2019 (COVID-19).[1] It predominantly causes pulmonary disease, including pneumonia, acute respiratory distress syndrome (ARDS), and respiratory failure.[1] COVID-19 infection may also have extrapulmonary manifestations. The hemostatic pathway abnormalities are referred to as COVID-19–associated coagulopathy (CAC).[1,2] In contrast to disseminated intravascular coagulation (DIC) due to bacterial sepsis or trauma, CAC causes minimal prolongation of the activated partial thromboplastin time (aPTT) and prothrombin time (PT); thrombocytopenia is mild (platelet count ≈100 × $10^9$/L), and laboratory results supporting microangiopathy are infrequent.[3] Serum concentrations of D-dimer, a fibrin degradation product (FDP), are significantly higher (three- to fourfold increased) in patients with severe COVID-19.[4] D-dimer concentrations might be helpful to rapidly identify patients with COVID-19 with a higher risk of pulmonary complications and venous thromboembolism (VTE), facilitating early initiation of effective therapies.[4] In contrast, in DIC, the laboratory abnormalities listed in decreasing order of frequency are thrombocytopenia, elevated D-dimer, prolonged PT and aPTT, and low fibrinogen. In early DIC, the platelet count and fibrinogen levels may remain within the normal range, albeit reduced from the baseline levels.[5]

Thromboelastography (TEG) assesses the global coagulation cascade. Existing studies on TEG in COVID-19 have reported early clot initiation, increased clot strength (due to increased fibrinogen component), and reduced fibrinolysis.[6-8] These changes suggest an underlying hypercoagulable state in patients with COVID-19.[9] This is distinct from the consumptive coagulopathy seen with DIC.

The CAC changes are dynamic and may be affected by multiple factors, including ongoing inflammation, sepsis, anticoagulation, renal failure, and so on. We aimed to assess the abnormalities seen on TEG and derived coagulation index (CI) in admitted patients with COVID-19. In addition, we explored the predictors of outcomes in these patients.

## 2 | METHODS

The study was conducted at the COVID care facility at a tertiary care academic center in India between May 2021 and June 2021. The study was approved by the institutional ethics committee (IEC-556/06.08.2021; RP = 27/2021). Informed consent was waived. Diagnosis of COVID-19 infection was based on a positive real-time polymerase chain reaction for SARS-COV-2. Patients between 18 and 65 years of age with mild/moderate/severe COVID-19 infection admitted to the hospital and who underwent TEG assessment anytime were included. Patients with prior vascular thrombosis, pregnancy, malignancy, and those on any prior antiplatelet drugs like aspirin, clopidogrel, or anticoagulant therapy for non–COVID-related disorders were excluded. Patients with chronic liver disease or chronic kidney disease (estimated glomerular filtration rate [eGFR] <15 mL/min or dialysis dependent) or those who expired within 24 hours of admission were also excluded. Healthy individuals were not included in the study. The criteria for acute kidney injury (AKI) included an increase in serum creatinine by ≥0.3 mg/dL (>26.5 μmol/L) observed within 48 hours; or an increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the past 7 days; or urine volume <0.5 mL/kg/h for 6 hours.[10]

### 2.1 | Evaluation and management of patients

The severity of COVID-19 was graded as per the Ministry of Health and Family Welfare, India guidelines.[11] Asymptomatic patients or those with only upper respiratory tract symptoms and normal oxygen saturation on room air were defined as having a mild disease. Those with lower respiratory tract involvement such as pneumonia and saturation between 90% and 94% at room air and/or respiratory rate (RR) between 24 and 30/min were defined as moderate COVID-19. Patients having saturation <90% on room air and/or a RR >30/min or severe acute respiratory illness were classified as a severe disease.[12] We followed uniform protocol management for all admitted patients.[12] Prophylactic anticoagulation (low-molecular-weight

**TABLE 1** Patient characteristics of the whole cohort, normal and hypercoagulable state

| Characteristics | Whole cohort (n = 27)[a] | Normal (n = 8) | Hypercoagulable (n = 17) | *P* value |
|---|---|---|---|---|
| Age, y (range) | 50 (40-60) | 50 (47-55) | 49 (32-61) | .59 |
| Sex, M:F, n (%) | 13 (48.1):14(51.9) | 4 (50): 4 (50) | 8 (47.1): 9 (52.9) | .61 |
| Diabetes, n (%) | 6 (22.2) | 1 (12.5) | 5 (29.4) | .35 |
| Hypertension, n (%) | 9 (33.3) | 2 (25.0) | 7 (41.2) | .37 |
| COVID severity, n (%) | | | | |
| Mild | 6 (22.2) | 1 (12.5) | 5 (29.4) | .40 |
| Moderate | 2 (7.4) | 0 (0) | 2 (11.8) | |
| Severe | 19 (70.4) | 7 (87.5) | 10 (58.8) | |
| New acute kidney injury | 6 (22.2) | 1(12.5) | 4 (23.5) | .51 |
| Overall mortality | 10 (37.0) | 1 (12.5) | 7 (41.2) | .20 |

[a]All values are in median (interquartile range). For statistical reasons, data from two patients with hypocoagulable state on thromboelastography analysis is not included for comparison.

heparin [LMWH]-enoxaparin) at 40 mg once a day was given to all patients in the moderate and severe categories.

## 2.2 | Protocol for TEG

All patients underwent TEG with kaolin (with heparinase) after enrollment in the study. TEG was done according to the manufacturer's protocol by a single operator. Blood was collected in citrate vials (BD Vacutainer plastic citrate tubes of 2.7 mL [0.109 M, 3.2% buffered sodium citrate]; Becton Dickinson, Franklin Lakes, NJ, USA), and TEG was run within 4 hours of sample collection. It was performed by automated thromboelastogram (Tromboelastometro, Framar Biomedica Srl, Formello [RM], Italia). TEG assessment protocol (kaolin TEG) was as follows: 340 μL of sodium-citrated whole blood and 20 μL of 0.2 mol/L of calcium dichloride were used. The TEG cup contained a 40-μL aqueous solution of kaolin and 2 IU of lyophilized heparinase enzyme. No sample incubation was done before TEG analysis. Disposable cups were placed in the cup wells that were set at a temperature of 37∘C. Normal ranges of various TEG parameters as per manufacturer's protocol are as follows: reaction time (R-time), 2 to 8 minutes; time until clot reaches a fixed strength (K-time), 1 to 3 minutes; alpha angle, 55 to 78 degrees; maximum amplitude (MA): 51–69 mm; clotting index (CI), −3 to 3; and lysis at 30 minutes (LY30), 0% to 8%. The hemostatic condition was defined as hypocoagulable if two or more of the following parameters were observed: increased R-time, increased K-time, decreased alpha angle, and/or decreased MA;[13] and hypercoagulable if two or more of the following parameters were observed: decreased R-time, decreased K-time, increased alpha angle, and/or increased MA.[13] CI, which combines all TEG variables, was used to define the hypercoagulable (CI >3) and hypocoagulable (CI < −3) status. LY30 measures percent lysis 30 minutes after MA and was used to diagnose either primary or secondary fibrinolysis. Primary fibrinolysis was defined when LY30 was higher than the upper limit of the normal reference range, with CI below the lower limit of the normal reference range.[14] Secondary fibrinolysis was defined when LY30 and CI were higher than the upper limit of the normal reference range.[14]

## 2.3 | Follow-up

All patients were followed up for the entire duration of the hospital stay. After discharge from the hospital, patients were followed up telephonically every week for 4 weeks. In case the patient died, the date and cause of death was documented.

## 2.4 | Clinical and laboratory data

The following data of patients were collected: clinical details including comorbidities, COVID severity, and laboratory parameters. White blood cell count (WBC) and platelet count data were obtained from EDTA (BD Vacutainer plastic tubes of 3 mL [buffered K2 EDTA 5.4 mg]) anticoagulated blood samples run on a hematology analyzer (XN-9000; Sysmex Corp., Kobe, Japan). Coagulation tests were performed on STA R Max3 (Diagnostica Stago, Gennevilliers, France) using citrate vials (BD Vacutainer plastic citrate tubes of 2.7 mL [0.109 M, 3.2% buffered sodium citrate]) and included PT (STA NeoPTimal), international normalized ratio (INR), aPTT (STA Cephascreen), fibrinogen (STA Liquid Fib), and D-dimer (STA Liatest D-Dimer). Data of serum creatinine (CREJ2; Roche Diagnostics, Indianapolis, IN, USA), serum urea (Ureal-Roche Diagnostics), total bilirubin (BILT3, Roche Diagnostics), serum albumin (ALB2, Roche Diagnostics), serum aspartate aminotransferase (AST, Roche Diagnostics), serum alanine aminotransferase (ALT, Roche Diagnostics), serum alkaline phosphatase (ALP2, Roche Diagnostics), C-reactive protein (Tina-quant C-Reactive Protein IV, Roche Diagnostics) and serum ferritin (Elecsys Ferritin, Roche Diagnostics) were obtained from serum samples collected in BD Vacutainer SST tubes and run on a Cobas c701 automated chemistry analyzer (Roche Diagnostics).

### 2.5 | Statistical analysis

All continuous variables were expressed as median (interquartile range [IQR]) and categorical variables as numbers and proportions. Mann-Whitney *U* test was used for comparing continuous variables between the groups. The chi-square/Fisher exact test was used for comparing categorical data. A two-tailed *P* value of .05 was considered significant. Cox proportional hazard analysis was done to assess the predictors of 28-day mortality. Statistical calculations were made using the statistical package for social sciences (SPSS version 20.0; (IBM, Armonk, NY, USA). MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Oostende, Belgium) was used to generate Kaplan-Meier curves for 28-day survival.

## 3 | RESULTS

### 3.1 | Baseline parameters

The characteristics of the cohort are presented in Table 1. A total of 28 patients were enrolled in the study. There was an operator error in TEG assessment in one of the patients; hence, this patient was excluded from the analysis. Of the 27 patients included, the median age was 50 years (IQR, 40-60 years), and male-to-female ratio was 0.9:1. The severity of COVID-19 was mild in 6 (22.2%), moderate in 2 (7.4%), and severe in 19 (70.4%) patients. Among the comorbidities, 6 (22%) patients had diabetes, 9 (33%) had hypertension, 2 patients each had coronary artery disease and hypothyroidism. Two patients were post–renal transplants on immunosuppression. New AKI was seen in 6 (22%) patients. Of 10 (37%) patients who died, 7 (70%) were hypercoagulable, and 2 (20%) were hypocoagulable, while 1 (10%) was normal on TEG analysis ($P = .20$).

### 3.2 | Laboratory results

The laboratory results (all values in median) of the cohort are presented in Table 2. Among the inflammatory parameters, WBC was 9.5 × $10^9$/L (7.3-15.6), C-reactive protein (CRP) was 25.7 (10.9-108.8) mg/L, ferritin was 693 (317-1031) µg/L, and albumin was 2.9 (2.6-3.3) g/dL. Hemoglobin was 10.7 (7.9-11.9) g/dL, and platelet count was 160 (124-262) × $10^9$/L. Among the renal function tests, urea was 39 (29-60) mg/dL, and serum creatinine was 0.8 (0.4-1.2) mg/dL. Total bilirubin was 0.5 (0.3-0.8) mg/dL, AST was 34 (23–50) U/L, ALT was 32 (22-67) U/L, and ALP was 115 (95-145) IU/L. Among all the parameters, CRP was found to be statistically significant between normal and hypercoagulable groups of patients ($P = .03$).

### 3.3 | Comparison of characteristics of patients based on coagulation status and TEG parameters

The coagulation profile, including the TEG analysis of the cohort, is shown in Table 3. Median INR was 1.4 (0.9-1.6), aPTT was 31.5 (26.6-39) seconds, fibrinogen was 518.8 (416.3-700) mg/dL, and D-dimer was 922.1 (range, 457.4-1050.0) ng/mL D-dimer units. TEG was done at a median of 10 days from admission (IQR, 4-19). Median follow-up after TEG analysis was 21 (IQR, 2-30) days. Of the 27 patients included, 17 (63%) were hypercoagulable, 8 (30%) were normal, and 2 (7%) were hypocoagulable (Figure 1). The median CI of

**TABLE 2** Laboratory parameters of the whole cohort, normal and hypercoagulable state

| Parameters | Whole cohort (n = 27)[a] | Normal (n = 8) | Hypercoagulable (n = 17) | *P* value |
|---|---|---|---|---|
| Hemoglobin, g/dL) | 10.7 (7.9-11.9) | 11.5 (8.1-12.4) | 10.7 (7.9-11.3) | .45 |
| WBC, ×$10^9$/L | 9.5 (7.3-15.6) | 11.9 (7.5-15.3) | 9.4 (7.3-15.2) | .79 |
| Platelet count, ×$10^9$/L | 160 (124-262) | 156 (106-241) | 167 (140-282) | .45 |
| CRP, mg/L | 25.7 (10.9-108.8) | 7.7 (1.6-25.6) | 43.5 (16.6-120.5) | .03 |
| Ferritin, µg/L | 693 (317-1031) | 371 (177-1026) | 648 (363-861) | .60 |
| Urea, mg/dL | 39 (29-60) | 37 (21-46) | 39 (30-61) | .50 |
| Creatinine, mg/dL | 0.8 (0.4-1.2) | 0.7 (0.4-0.8) | 0.9 (0.4-1.3) | .26 |
| Total bilirubin, mg/dL | 0.5 (0.3-0.8) | 0.6 (0.5-1.3) | 0.5 (0.3-0.8) | .97 |
| AST, U/L | 34 (23-50) | 38 (21-55) | 29 (23-44) | .48 |
| ALT, U/L | 32 (22-67) | 65 (23-105) | 27 (22-47) | .19 |
| ALP, IU/L | 115 (95-145) | 102 (70-167) | 121 (97-140) | .32 |
| Albumin, g/dL | 2.9 (2.6-3.3) | 3.2 (2.3-3.3) | 3.0 (2.8-3.6) | .72 |

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; WBC, white blood cell count.

For statistical reason, data from two patients with hypocoagulable state on thromboelastography analysis is not included for comparison.

[a]All values are in median (interquartile range).

**TABLE 3** Coagulation profile including TEG data of the whole cohort, normal and hypercoagulable state

| Parameters | Whole cohort (n = 27)[a] | Normal (n = 8) | Hypercoagulable (n = 17) | *P* value |
|---|---|---|---|---|
| INR | 1.4 (0.9-1.6) | 1.0 (0.8-1.4) | 1.1 (1.0-1.5) | .48 |
| aPTT, s | 31.5 (26.6-39.0) | 32 (26-50) | 31 (26-35) | .38 |
| D-dimer, ng/mL DDU | 922.1 (457.4-1050.0) | 819 (500-1023) | 882 (335-1050) | .81 |
| Fibrinogen, mg/dL | 518.8 (416.3-700.0) | 437 (117-475) | 569 (421-701) | .02 |
| R-time, min | 5.2 (3.8-7.0) | 6.5 (3.8-7.6) | 5.0 (3.5-6.1) | .04 |
| K-time, min | 1.2 (0.8-1.7) | 1.7 (1.2-2.5) | 0.8 (0.7-1.2) | <.001 |
| Alpha angle, degree | 74 (68-78) | 68.5 (60.4-74.5) | 74.4 (71.7-79.2) | .02 |
| MA, mm | 85.2 (73.8-94.7) | 69.5 (58.2-78.0) | 90.4 (84.9-102.3) | <.001 |
| LY30, n (%) | 0 | 0 (0-3.9) | 0 | .31 |
| CI | 4.8 (1.8-6.0) | 1.1 (−0.7-2.4) | 5.5 (4.8-6.6) | <.001 |

Abbreviations: aPTT, activated partial thromboplastin time; CI, clotting index, DDU, D-dimer units; INR, international normalized ratio; K-time, time until clot reaches a fixed strength; LY30, lysis at 30 min; MA, maximum amplitude; PT, prothrombin time; R-time, reaction time; TEG, thromboelastography.

For statistical reason, data from two patients with hypocoagulable state on TEG analysis is not included for comparison.

[a]All values are in median (interquartile range).

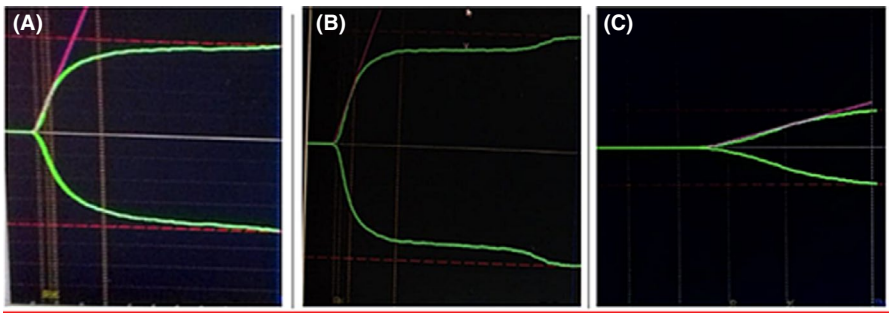


**FIGURE 1** Thromboelastography (TEG) graphs of patients. (A) Normal TEG pattern, (B) hypercoagulability pattern, (C) hypocoagulability pattern

**TABLE 4** Association between anticoagulant status, coagulation markers, and TEG parameters

| Parameters | Anticoagulation[a] (n = 21)[b] | No anticoagulation (n = 6)[b] | *P* value |
|---|---|---|---|
| Platelet count, $\times 10^9$/L | 163 (50-399) | 159 (103-418) | .52 |
| INR | 1.04 (0.6-1.8) | 1.5 (0.9-2.4) | .27 |
| aPTT, s | 31.4 (24.1-97) | 39.8 (22.6-50) | .30 |
| Fibrinogen, mg/dL | 552.3 (116.9-816.2) | 460.7 (72.8-718.3) | .24 |
| D-dimer, ng/mL DDU | 736.3 (253.9-1127.7) | 980.3 (326.2-1100.4) | .31 |
| R-time, min | 5.2 (0.7-30.2) | 4.8 (3.7-7.7) | .66 |
| K-time, min | 1.2 (0.7-11.8) | 0.9 (0.8-2) | .77 |
| Alpha angle, degree | 72.3 (17.2-80.2) | 75.2 (58.1-78.3) | .45 |
| MA, mm | 84.7 (34.7-107.6) | 89 (57.6-108.1) | .68 |
| LY30, n (%) | 0 (0-4.9) | 0 (0-17.8) | .93 |
| CI | 4.8 (−26.6-9.1) | 4.3 (0.5-8.6) | .86 |

Abbreviations: aPTT, activated partial thromboplastin time; CI, clotting index; DDU, D-dimer units; INR, international normalized ratio; K-time, time until clot reaches a fixed strength; LY30, lysis at 30 min; MA, maximum amplitude; PT, prothrombin time; R-time, reaction time; TEG, thromboelastography.

[a]Prophylactic anticoagulation with enoxaparin at 40 mg once a day was given to all moderate and severe category patients.

[b]All values are in median (interquartile range).

the whole cohort was 4.8 (1.8-6.0); it was 1.1 in the normal group, −19.8 in the hypocoagulable group, and 5.5 in the hypercoagulable group ($P < .001$).

### 3.4 | Anticoagulant status, platelet count, coagulation markers, and TEG parameters

The association between anticoagulant status, platelet count, coagulation markers, and TEG parameters is shown in Table 4. Twenty-one (78%) patients in the moderate and severe COVID-19 category received anticoagulation in the form of LMWH, while 6 (22%) patients in the mild COVID-19 category did not receive anticoagulation. There was no statistically significant difference between anticoagulant status, platelet count, coagulation, and TEG parameters.

### 3.5 | Fibrinolysis shutdown

The phenomenon of the fibrinolytic shutdown was observed in four (15%) patients. They were reported as hypercoagulable on TEG analysis. All four patients had high D-dimer levels and LY30 of 0%, with decreased K-time and either increased alpha angle or increased MA. No clinically evident thrombosis was seen in these patients.

### 3.6 | Age-adjusted association of patient characteristics with mortality

The univariate age-adjusted hazard ratios for mortality of various parameters are shown in Table 5. Those who died compared to those who survived were older, had higher inflammatory markers such as WBC ($P < .01$), fibrinogen ($P = .31$), and serum ferritin ($P = .48$). The laboratory parameters such as AST ($P = .08$), ALT ($P = .08$), ALP ($P = .12$) and serum urea ($P = .01$) were higher in those who died. TEG parameters among those who died included an increased MA ($P = .31$) and increased CI ($P = .19$). There were no statistically significant differences between the two groups in the R-time, K-time, alpha angle, MA, LY30, CI, and other biochemical parameters. The 28-day mortality among patients with hypocoagulable and hypercoagulable states was higher than normal coagulation status (log-rank test, $P = .002$; Figure 2).

### 3.7 | Outcomes

At a median follow-up of 21 days (IQR, 2-30), 10 patients (37%) died. All patients died due to ARDS and refractory septic shock due to COVID-19 disease. No patient had clinically evident thrombosis. Mortality occurred at a median of 3.5 days after their TEG test was done. The mortality of the patients in the normal and hypercoagulable groups were 1 of 10 (10%) versus 7 of 10 (70%), respectively ($P = .20$; Table 1).

## 4 | DISCUSSION

In the current study, distinct coagulation abnormalities in patients with COVID-19 were seen. The hypercoagulable state was most common, seen in two-thirds of patients characterized by reduced R-time and reduced K-time and increased alpha angle, increased MA, and increased CI. Patients with abnormal coagulation parameters on TEG had higher mortality compared to those with normal coagulation status.

The proposed theories for CAC center around severe immune dysregulation, impairment of the fibrinolytic system, and/or upregulation of angiotensin-converting enzyme 2 receptors with direct viral invasion and perivascular inflammation leading to endothelial injury.[15] TEG is a global viscoelastic technique that uses whole blood and has various parameters to identify a hypercoagulable state in patients with COVID-19 and at the same time measures fibrinolysis. It fares remarkably better than the conventional coagulation tests.

Our findings of a pronounced hypercoagulable nature of COVID-19 are similar to those reported in the literature on TEG and rotational thromboelastometry.[15-22] Overall, patients in the hypercoagulable group had median conventional coagulation parameters such as INR, PT, aPTT, and platelet levels within reference ranges; however, the levels of fibrinogen, D-dimer, serum ferritin, and CRP were elevated, suggesting a complex inflammatory and hematologic profile distinct from acute DIC.[7,23] These tests are relatively insensitive to measure the thrombotic manifestations of DIC as well as CAC. In the initial stage of DIC (also known as the hypercoagulable state) secondary to an underlying disorder, there is an acute inflammatory response with widespread intravascular deposition of fibrin and downregulation of natural anticoagulants. During this time, TEG changes show decreased R-time and decreased K-time along with increased alpha angle and increased MA. After this stage, there is a secondary fibrinolysis stage in which there is degradation of fibrin and fibrinogen and, hence, accumulation of FDP. FDP compromises clot formation and integrity, causing a decrease in MA. In the final stages of DIC (hypocoagulable state), the patients have severe bleeding due to consumption coagulopathy (ie, depletion of coagulation factors and platelets). TEG changes at this time include increased R-time and K-time with decreased alpha angle and MA (Figure 3).[24]

We observed “fibrinolysis shutdown” (as suggested by LY-30: zero) in our patients (4/27), similar to the observations by Patel et al. and Wright et al.[19,20] All four patients had high D-dimer levels, with decreased K-time and either increased alpha angle or increased MA and LY30 of 0%. They were hypercoagulable on the TEG analysis. Wright et al.[20] reported that fibrinolysis shutdown (elevated D-dimer and LY30 of 0%) predicted VTE events; however, we did not observe any VTE events in our study. The markedly elevated levels of D-dimer in patients with fibrinolysis shutdown might represent local thrombosis in the microvasculature (eg, pulmonary and renal) that are not consistently captured on whole-blood assays.[25] The hypercoagulable state seen in patients with COVID-19 is further exacerbated by a significant state of fibrinolysis shutdown, mediated by overexpression of plasminogen activator inhibitor 1 (PAI-1) and

**TABLE 5** Age-adjusted association of patient characteristics with mortality

| Characteristics | Survived (n = 17) Mean ±SD | Died (n = 8) Mean ±SD | Unadjusted HR (95% CI) | Age-Adjusted HR (95% CI) | *P* value (age-adjusted HR) |
|---|---|---|---|---|---|
| Age, y | 46.41 ± 16.55 | 54.25 ± 14.82 | 0.98 | ... | ... |
| Sex, male:female, n (%) | 8 (47.1):9 (52.9) | 4(50.0):4 (50.0) | 0.79 | 0.99 (0.24-4.16) | .99 |
| Diabetes, n (%) | 3 (17.6) | 3 (37.5) | 2.52 | 1.73 (0.35-8.61) | .49 |
| Hypertension, n (%) | 5 (29.4) | 4 (50.0) | 2.71 | 1.94 (0.41-9.19) | .40 |
| COVID-19 severity, n (%) | | | | | |
| Mild | 6 (35.3) | 0 (0) | 4.25 | 3.38 (0.41-27.79)[a] | .25 |
| Moderate | 1 (5.9) | 1 (10.2) | | | |
| Severe | 10 (58.8) | 7 (87.5) | | | |
| Hemoglobin, g/dL | 10.33 ± 2.41 | 10.12 ± 2.00 | 1.02 | 0.87 (0.57-1.3) | .21 |
| WBC, $\times 10^9$/L) | 10.06 ± 3.96 | 14.38 ± 5.22 | 1.00 | 1.00 (1.00-1.00) | <.01 |
| Platelet count, $\times 10^9$/L) | 209.64 ± 107.70 | 153.75 ± 71.32 | 0.99 | 0.99 (0.98-1.00) | .10 |
| INR | 1.26 ± 0.46 | 1.13 ± 0.17 | 0.31 | 0.43 (0.04-4.76) | .49 |
| aPTT, s | 33.50 ± 8.52 | 32.40 ± 8.60 | 0.98 | 0.99 (0.89-1.11) | .98 |
| D-dimer, ng/mL, DDU | 761.41 ± 321.20 | 719.15 ± 341.94 | 0.99 | 0.99 (0.99-1.00) | .67 |
| Fibrinogen, mg/dL | 448.13 ± 215.79 | 609.05±151.14 | 1.00 | 1.002 (0.99-1.00) | .31 |
| CRP, mg/L | 56.64 ± 74.90 | 56.98 ± 50.27 | 0.99 | 1.00 (0.99-1.01) | .69 |
| Ferritin, µg/L | 609.40 ± 494.53 | 893.40±761.50 | 1.03 | 1.00 (0.99-1.00) | .48 |
| Urea, mg/dL | 35.81 ± 23.74 | 76.25 ± 43.86 | 1.02 | 1.02 (1.00-1.04) | .01 |
| Creatinine, mg/dL | 0.82 ± 0.47 | 1.18 ± 1.09 | 1.54 | 1.32 (0.60-2.89) | .49 |
| Total bilirubin, mg/dL | 0.95 ± 1.14 | 0.58 ± 0.43 | 0.67 | 0.91 (0.27-3.05) | .88 |
| AST, U/L | 29.52 ± 12.92 | 166.25 ± 311 | 1.01 | 1.01 (0.99- 1.03) | .08 |
| ALT, U/L | 40.41 ± 27.70 | 82.37 ± 90.15 | 1.00 | 1.00 (0.999-1.017) | .08 |
| ALP, IU/L | 126.94 ± 67.85 | 149.12 ± 90.22 | 1.00 | 1.01 (0.997-1.02) | .12 |
| Albumin, g/dL | 3.08 ± 0.62 | 2.95 ± 0.33 | 0.82 | 0.44 (0.084-2.35) | .34 |
| R-time, min | 5.55 ± 1.74 | 4.18 ± 2.26 | 0.81 | 0.81 (0.55-1.20) | .30 |
| K-time, min | 1.3 ± 0.68 | 1.07 ± 0.46 | 0.68 | 0.77 (0.16-3.48) | .73 |
| Alpha angle, degree | 72.42 ± 7.33 | 72.7 ± 6.15 | 0.97 | 0.98 (0.87-1.09) | .68 |
| MA, mm | 81.00 ± 17.65 | 90.23± 14.66 | 1.02 | 1.02 (0.97-1.07) | .31 |
| LY30% | 1.74 ± 4.46 | 0 | ... | ... | ... |
| Clot index | 3.50 ± 2.60 | 5.63 ± 2.86 | 1.20 | 1.23 (0.89-1.69) | .19 |

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DDU, D-dimer units; HR, hazard ratio; INR, international normalized ratio; K-time, time until clot reaches a fixed strength; LY30, lysis at 30 min; MA, maximum amplitude; PT, prothrombin time; R-time, reaction time; WBC, white blood cell count.

[a]Mild and moderate cases were combined together to assess severity.

thrombin activatable fibrinolysis inhibitor (TAFI).[25] PAI-1 is the most potent antifibrinolytic mediator produced from endothelial cells and activated platelets. The elevation in PAI-1 levels in COVID-19 can be exacerbated by elevated levels of circulating angiotensin II, which is elevated in COVID -19 infection. These high levels of angiotensin II can subsequently increase the stimulation of PAI-1 production by endothelial cells. Moreover, data from patients with interstitial lung disease have also identified elevated TAFI and protein C inhibitor levels in the alveolar space. Nougier et al.[26] showed markedly elevated circulating tissue-type plasminogen activator (t-PA) and TAFI levels in patients with COVID-19. Despite high t-PA, these patients were hypofibrinolytic, suggesting that the higher levels of PAI-1 and TAFI likely overwhelm the capabilities of t-PA, leading to microvascular fibrin deposition. Other studies have demonstrated persistence of TEG abnormalities at day 7 despite full anticoagulation and at discharge.[21] We did not perform a sequential TEG analysis in our patients.

Maatman et al.[16] found that 50% of their 12 intensive care unit (ICU) patients had a hypercoagulable state on TEG. Hightower et al.[15] reported dysregulation of the fibrinolytic system as a prominent factor for the hypercoagulable state in the TEG profile of 5 patients with COVID-19. Similar to our observations, their patients also had normal platelet counts, normal PT/aPTT values, and elevated

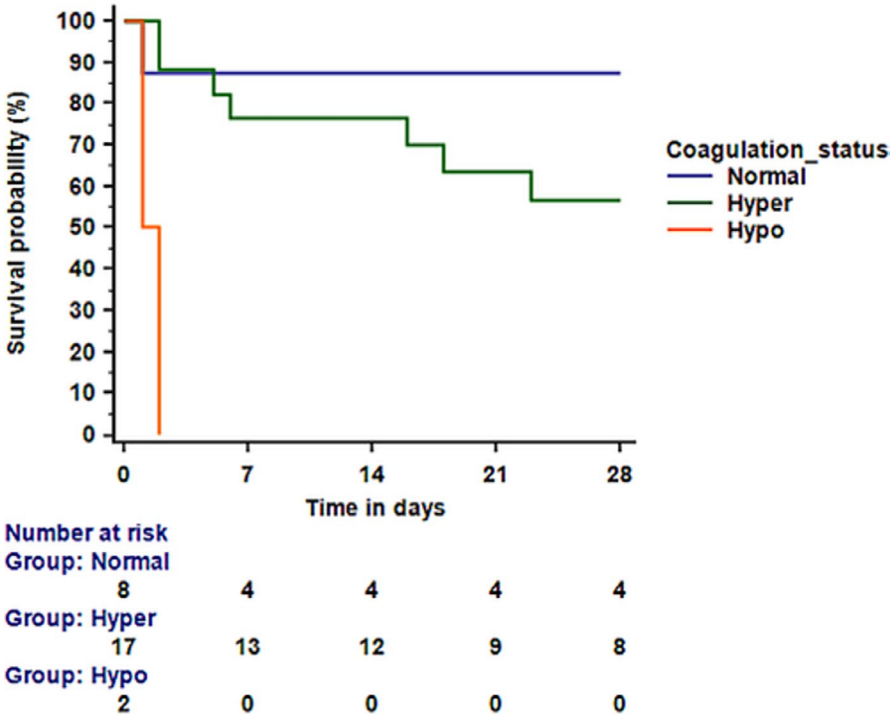


**FIGURE 2** Survival probability among patients with different coagulation status. The 28-day mortality among patients with hypocoagulable and hypercoagulable states was higher than normal coagulation status. (log-rank test, $P = .002$)

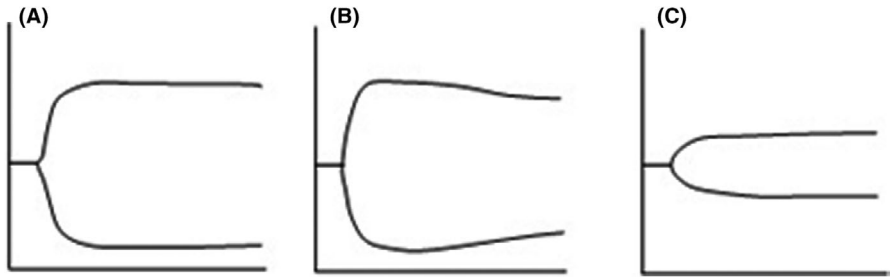


**FIGURE 3** Thromboelastography (TEG) graphs of a patient with disseminated intravascular coagulation. (A) Hypercoagulable state; (B) secondary fibrinolysis; (C) hypocoagulable state

fibrinogen levels. Thus, TEG was able to identify coagulopathic states where conventional laboratory coagulation tests could not. Panigada et al.[17] found hypercoagulability in all 24 ICU patients by TEG as shown by decreased R-time and K-time values and increased values of angle and MA. Yuriditsky et al.[18] reported 50% of their patients had a hypercoagulable state as reflected by CI >3, with 31% of patients having VTE events. In their study, the TEG parameters did not correlate with VTE events. Most TEG studies did not find an association between TEG abnormalities and thrombotic events.[6,22] Similar to our results, a study by Saseedharan et al.[27] found hypercoagulability in 62.5% of their 32 ICU patients, based on CI.

Interestingly, we also observed that in two of our patients with severe COVID-19 disease, increased R-time value even after reversal of prophylactic LMWH with heparin. Increased R-time may be seen in clotting factor deficiencies and anticoagulant therapy.[13] However, PT/INR, aPTT, and platelet count were within normal range in both of these patients, with elevated fibrinogen and D-dimer. Moreover, the anticoagulant therapy was also reversed by heparinase. TEG analysis revealed hypocoagulability identified by increased R-time and decreased alpha angle. This phenomenon may have been due to impending DIC. Unfortunately, both of these patients succumbed to refractory septic shock.

Given the hypercoagulability observed in COVID-19, ISTH guidelines recommend treatment with heparin and heparin adjuvants to reduce patient mortality.[4] As bleeding episodes have been observed in a subset of patients with COVID-19, sequential monitoring of hemostasis through TEG could be particularly important in patients receiving heparin to prevent hemorrhage.[7,20]

We also observed high MA in our patients with hypercoagulable states. It is known that platelets contribute maximally to MA's determination; however, in our analysis, 17 of 27 (63%) patients had elevated fibrinogen levels with normal platelet count, suggesting a significant fibrinogen contribution to clot strength. However, we could not do functional fibrinogen testing by TEG.

Management guidelines of CAC are a work in progress, as only a few randomized trials have been completed. Prophylactic-intensity anticoagulation (over intermediate-intensity or therapeutic-intensity anticoagulation) for patients with COVID-19–related critical illness or acute illness who do not have confirmed or suspected VTE has been suggested.[20,21] Preferred agents are LMWHs or unfractionated heparin (in patients with eGFR <30 mL/min). Vitamin K antagonists are best avoided, and newer oral anticoagulants are second-line agents due to potential drug interactions.[21] Roberts et al. showed from their analysis that COVID-19 hospitalization does not increase

the risk of postdischarge thrombosis compared to other acute medical illnesses, highlighting the current stand of guidelines on postdischarge thromboprophylaxis.[1,28]

Recently, there have been a few studies and trials comparing the outcomes regarding the usage of anticoagulation in patients with COVID-19. Connors et al.[29] randomly assigned 657 symptomatic outpatients with COVID-19 into four groups: aspirin (81 mg once daily), apixaban (2.5 mg twice daily), apixaban (5.0 mg twice daily), or placebo. They found that the rates of composite outcome (all-cause mortality, symptomatic VTE or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause) after 45 days were 0.0%, 0.7%, 1.4%, and 0.0%, respectively, with no significant differences between the active groups and the placebo group. Similarly, in a multiplatform randomized clinical trial by investigators from the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) group; the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-4) group; and the Randomized, Embedded Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) group in 2219 noncritically ill patients with COVID-19, it was concluded that therapeutic-dose anticoagulation with unfractionated heparin or LMWH for the treatment of acute VTE for up to 14 days or until recovery was inferior to usual-care thromboprophylaxis with LMWH.[30] In their study, therapeutic-dose anticoagulation was not associated with a greater probability of survival to hospital discharge or a more significant number of days free of cardiovascular or respiratory organ support than the usual-care pharmacologic thromboprophylaxis in these patients. In yet another study by ATTACC, ACTIV-4a, and REMAP-CAP investigators in 1098 critically ill patients with COVID-19, 534 patients were assigned therapeutic-dose anticoagulation, and 564 patients were assigned usual-care thromboprophylaxis.[31] The median value for organ support-free days was 1 (IQR, −1 to 16) among the patients assigned to therapeutic-dose anticoagulation and was 4 (IQR, −1 to 16) among the patients assigned to usual-care thromboprophylaxis. Thus, they concluded that therapeutic-dose anticoagulation with heparin did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than the usual-care pharmacologic thromboprophylaxis.[31] These results refuted the hypothesis that routine therapeutic-dose anticoagulation benefits critically ill patients with COVID-19.

TEG has been used to guide therapy in a few studies. Bunch et al.[32] reported three cases in which TEG and aPTT facilitated personalized anticoagulation. Hranjec et al.[33] showed that TEG with platelet mapping–guided antiplatelet therapy could decrease mortality by 82%, while non–algorithm-guided anticoagulation leads to 10.3-fold increased mortality risk. In addition, TEG has been shown to help guide transfusions in other diseases.[34-37]

TEG measurements correlate with increased risk of thromboembolism and mortality in patients with COVID-19.[20] TEG may also be critical in accurately identifying patients at increased thrombosis risk and avoiding unwarranted anticoagulation in patients with low thrombosis risk. We found a number of variables (including biochemical parameters and TEG variables) to be significant on univariate analysis for predicting outcomes in patients with COVID-19. While interpreting TEG results, one should remember that TEG was designed to determine the cause of bleeding and guide transfusion algorithms. The definitions of hypercoagulability used in most studies are heterogeneous, and so are the outcome parameters: mortality, thrombotic events, or persistence of abnormalities. Their use to predict thrombosis and guide anticoagulant therapy should be based on more evidence.

Limitations of our study include a small sample size that may limit the widespread applicability of the results. Details regarding body mass index and race/ethnicity were not collected from the patients. We could not perform TEG at a defined interval due to logistic issues. Also, sequential TEG analysis on our patients could have provided an in-depth analysis and understanding of coagulation status in these patients. Role of functional fibrinogen, a quantifier of fibrinogen contribution to clot, was not performed by TEG.

In conclusion, the results of this study support hypercoagulability together with a severe inflammatory state, also called thromboinflammatory state, in patients with COVID-19. Our data show that TEG could better identify and assess hypercoagulability in patients with COVID-19 than conventional coagulation tests such as PT and aPTT.

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The authors have no conflict of interest or financial disclosures.

## AUTHOR CONTRIBUTIONS

All authors contributed substantially to the concept and design, analysis and interpretation of data. TS, MA, and Shalimar contributed to critical writing and revising intellectual content. All authors gave final approval of the version to be published.

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