Utility of Thromboelastography and velocity curve derivative in diagnosing COVID-19 associated coagulopathy

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Abstract

**Background:** COVID-19 associated coagulopathy (CAC) can either be localized or systemic hypercoagulable state with increased risk of thromboembolism. This study looked into the usefulness of Thromboelastography (TEG) and the velocity curve (V-curve) derivative from TEG in diagnosing and differentiating different stages of CAC.

**Materials and Methods:** A prospective single cohort study of RT-PCR confirmed COVID-19 patients was carried out for 2 weeks. Severe COVID-19 patients in the adult critical care units with a TEG report were recruited for the study. Citrated kaolin TEG was performed on the day of admission before anticoagulation. TEG parameters included were R and K time, alpha angle, maximum amplitude, lysis at 30 min. The first-degree velocity curve of TEG is plotted as V-curve which extrapolates thrombus generation potential. Parameters analyzed were the maximum rate of thrombus generation as well as thrombus generated (TG).

**Results:** The study included 43 patients with an average age of 58.34 (±15.35). TEG as well as V-curve of all the patients were hypercoagulable compared with age-matched reference range. We had 79.06% of patients in hypercoagulable stage. The mortality rate was 32.56% and 30.23% developed thrombotic incidents. Patients who succumbed to death had prolonged PT, aPTT, MA, Ly30, with a reduced TG (p < .05). The presence of fibrinolysis was associated with thromboembolism (OR = 6.76, CI = 1.48–25.82). Repeat TEG was done randomly in 11 patients and revealed a persistent hypercoagulable stage with increasing fibrinolysis activity.

**Conclusion:** TEG is a useful tool in diagnosing and categorizing Coagulopathy associated with COVID-19.

**KEYWORDS**
coagulopathy, COVID-19, fibrinolysis, mortality, Thromboelastography, thromboembolism, viscoelastic tests

1 | INTRODUCTION

COVID-19 associated coagulopathy (CAC) is characterized by a hypercoagulable state with a predilection for thromboembolism (TE). Inflammation on type II pneumocytes leads to extensive macrophage recruitment and activation which leads to vessel wall damage and tissue factor expression. This triggers entry of procoagulants and pro-inflammatory mediators into pulmonary vasculature eventually resulting in pulmonary immunethrombi formation mediated by macrophages.1 Breakdown of these microthrombi confined in the lungs...
leads to an elevated D-Dimer.\textsuperscript{2,3} Coagulopathy in COVID-19 progresses from an initial pulmonary microthrombi to a systemic hypercoagulable state with widespread activation of coagulation and then to a hypocoagulable picture seen in later phases of the disease.\textsuperscript{4} The second stage with a systemic hypercoagulability is most commonly observed in severe cases with a high propensity to develop TE.\textsuperscript{5}

The most important findings in CAC are highly elevated D-Dimer levels, elevated fibrinogen levels, modest reduction in platelet count, a mild prolongation of Prothrombin time (PT) together with a reduced fibrinolysis activity which is different from what we observe either in sepsis induced coagulopathy (SIC) or disseminated intravascular coagulation (DIC).\textsuperscript{4,5} COVID-19 patients suffer from thromboembolic complications more common than other conditions requiring critical care.\textsuperscript{6} The widespread activation of the coagulation system leading to a profound prothrombotic state was the basis of recommending anti-coagulation in patients requiring hospital admission.\textsuperscript{7–9} In view of the increasing number of severe COVID-19 admission to our hospital in 2021, we studied the role of Thromboelastography (TEG) in the diagnosis and monitoring of coagulation status, TEs, and patient outcome.

\section{METHODOLOGY}

A prospective single cohort study of the patients admitted with severe COVID-19 infection in a tertiary care hospital was carried out in evaluating CAC. All adult patients with a confirmed COVID-19 by RT-PCR admitted to the severe acute respiratory infection (SARI) ICU in our hospital and with a TEG report after informed consent were included. Table 1 presents the Thromboelastography parameters of all COVID-19 cases, comparing them to the normal reference range developed in our centre.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|}
\hline
 & Reference value\textsuperscript{a} & Overall COVID-19 (n = 43) & \textbf{p} \\
 & Mean (SD) & Range & Mean (SD) & Range \\
\hline
R & 6.22 (1.77) & 3.3–10.6 & 3.53 (2.2) & 0.8–14 & <.001 \\
K & 2.00 (.44) & 1.2–3.2 & 1.39 (1.26) & .6–9.0 & .001 \\
Angle & 61.26 (5.9) & 54.9–72 & 72.80 (5.67) & 58.2–82.0 & <.001 \\
MA & 55.45 (5.93) & 51.2–62.6 & 64.48 (8.53) & 36.0–74.0 & <.001 \\
CI & 1.17 (1.47) & 2.1–3.2 & 2.79 (2.69) & 9.0–5.4 & <.001 \\
LY 30 & 3.14 (3.17) & 0–10 & 12.92 (19.37) & 0–79 & <.001 \\
MRTG & 14.26 (2.98) & 7.8–19.5 & 18.33 (5.42) & 7.7–33.4 & <.001 \\
TMRTG & 6.05 (2.98) & 3.33–8.83 & 4.49 (2.35) & 1.42–16.0 & .002 \\
TG & 577.83 (93.75) & 637.6–843.9 & 759.23 (109.13) & 421–893.2 & <.001 \\
\hline
\end{tabular}
\caption{Thromboelastography parameters of all COVID-19 cases comparison with normal reference range\textsuperscript{a}}
\end{table}

\textsuperscript{a}The patient samples were compared to the reference range values that was developed in our centre.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{FIGURE_1.png}
\caption{COVID-19 associated coagulopathy diagnosed in Thromboelastography. Out of 43 patients, 6 had a normal TEG tracing at admission, 34 had a hypercoagulable picture, and 3 had a hypocoagulable picture. Secondary fibrinolysis was noted in 13/34 (38.23%) with a hypercoagulable picture. Primary fibrinolysis was noted in four patients. Physiological lysis activity was seen in six patients. Three patients who had Stage 3 coagulation status died within 3 days of hospital admission.}
\end{figure}
Tests were interpreted based on the algorithm provided by the manufacturer into either normal or hypercoagulable state. Hypocoagulable state was defined as CI<3 with either one of the following: prolonged R and K time, decreased alpha angle and MA. Hypercoagulable picture was defined as CI>3 with either one of the following: normal or shortened R and K time, increased alpha angle and MA. Fibrinolysis was defined as Ly30>8% and primary fibrinolysis when CI<3 with a hypocoagulable picture and secondary when CI>3 with a hypercoagulable picture. V-curve parameters used to assess the rate and strength of thrombus formation.

Coagulopathy had been defined as Stages 1, 2, and 3 for the study purpose representing a normal or upper normal TEG tracing, hypercoagulable picture and hypocoagulable TEG tracing, respectively. Data on the patient’s clinical status, TEG parameters, new onset TEs, laboratory parameters, length of ICU stay, and mortality was collected. Complete blood count (Beckman Coulter DxH 800, Pasadena, CA), PT, aPTT (Sysmex CS 2500), and D-Dimer was collected from laboratory software. Both arterial and venous thromboembolic events that occurred during the hospital stay were included. Acute coronary syndrome was diagnosed in patients showing clinical/ECG evidence of cardiac ischemia, along with rise in cardiac biomarker Troponin. Acute ischemic stroke was confirmed using CT/MRI as clinically indicated. Deep vein thrombosis and pulmonary embolisms were diagnosed by imaging evidence using venous Doppler and CT pulmonary angiography respectively. Analysis was performed using measures of central tendency, ANOVA, correlation, and regression tests. Data were captured in MS Excel and analysis was performed using SPSS v.20 (IBM).

3 | RESULTS

We had 46 patients with TEG reports during the study duration and three did not meet inclusion criteria (n = 43). Average age of the
population was 58.34 (±15.35) years with a male to female ratio of 2.54:1. Patients were admitted to the ICU for a mean duration of 7.04 (range of 1 to 19) days. The TEG parameters were analyzed and compared with age matched normal reference range (Table 1). All parameters were showing a hypercoagulable picture when compared with reference values. TG was significantly increased in such patients.

### TABLE 3 Comparison of Thromboelastography parameters between survivors and non-survivors (ANOVA and linear regression)

| Parameter | Survivors (n = 29) | Non-survivors (n = 14) | ANOVA | Regression |
|-----------|--------------------|------------------------|--------|------------|
| R         | 3.18 (1.45)        | 4.26 (3.21)            | 2.34   | .134       |
| K         | 1.45 (1.51)        | 1.27 (4.44)            | .189   | .666       |
| Angle     | 73.37 (5.28)       | 71.62 (6.45)           | .897   | .349       |
| MA        | 66.40 (5.65)       | 60.51 (11.46)          | 5.149  | .029       |
| Cl        | 3.26 (1.68)        | 1.78 (3.8)             | 3.185  | .082       |
| LY 30     | 8.51 (11.2)        | 22.54 (28.06)          | 5.532  | .024       |
| MRTG      | 18.83 (5.47)       | 17.28 (5.33)           | .775   | .384       |
| TMRTG     | 4.23 (1.7)         | 5.23 (3.43)            | 1.642  | .207       |
| TG        | 796.96 (64.93)     | 732.68 (131.43)        | 4.668  | .037       |

*aRegression analysis—Adjusted $R^2 = .048$, $F = 1.252$, $p = .296$. 

**FIGURE 2** Repeat Thromboelastography of 11 patients
We observed a mortality rate of Though one might observe an ele-
We have observed a mortality rate of within 72 h of hospital admission (Figure 1). These three patients did not receive anticoagulation as they were already in a hypercoagulable stage. The different stages of CAC as seen in TEG is given in Figure S1.

Hyperfibrinolysis activity (Ly30>8%) was present in 39.53% (17/43) patients. Physiological fibrinolysis activity (1%-8%) was observed in 13.95% (6/43) patients while 47.05% (16/34) patients had no evidence of fibrinolysis activity. Comparing across the stages of coagulation status, we had observed that most of the parameters were significantly altered in three stages and overall analysis was also significant ($r = .320$, $p = .007$, Table 2).

Mortality rate among the study population was 32.56% (14/43) and the MA, LY 30 and TG had a significant difference among survivors and non-survivors whereas other parameters were comparable (Table 3). We have observed that 7/14 patients had septic shock on admission with a Pearson correlation of .675 ($p < .001$) with mortality. The mean duration of ICU stay (7.07 vs. 7) as well as platelet count were comparable between these two groups (Table S1). The platelet range was $8-470 \times 10^3/\mu L$ and $97-512 \times 10^3 cells/\mu L$ among those who succumbed to death and survived respectively with three patients among non-survivors developing severe thrombocytopenia ($<50,000/\mu L$). Levels of D-Dimer were also comparable among these two groups while prolonged PT and aPTT was observed among non-survivors (Table S1).

During the ICU stay, 13 (30.23%) developed TEs while they were on heparin, but no hemorrhagic events reported. The events in decreasing order of incidence were acute coronary syndrome ($n = 10$), deep venous thrombosis (DVT) with pulmonary thromboembolism (PTE) ($n = 2$) and middle cerebral artery (MCA) infarction ($n = 1$). One patient with PTE and another patient with MCA infarct was discharged after recovery while all others had succumbed to death (11/13). The TEG parameters did not show any difference between patients who developed TEs and those who did not (Table S2). Logistic regression showed that the presence of fibrinolysis had a more risk of TE (OR = 6.76, CI = 1.48-25.82, $r = .170$, $p = .012$) and a correlation coefficient of .40.

Out of 43 patients, repeat citrated kaolin TEG was done randomly for 11 patients (Figure 2) to assess the coagulation status. The median time gap was 5 days (IQR = 7 days) between the first and second test. All the patients were in the ICU at the time of second TEG and the comparison between the first and the second test showed that these patients were still having a hypercoagulable picture (Figure 2) with increased fibrinolysis activity ($F = 5.64$, $p = .028$). At the end of study period, 14 (32.55%) patients succumbed to death in the hospital, 28 (63.04%) patients were discharged, and one patient was shifted to general ward.

### DISCUSSION

CAC results from an interplay of various factors such as endothelial cells, neutrophils, platelets, inflammatory mediators, coagulation factors, and complement system. Though one might observe an elevated D-Dimer both in COVID-19 and SIC/sepsis DIC, the D-Dimer levels in CAC are much higher compared with SIC. Similarly, the degree of thrombocytopenia is very severe in SIC/sepsis DIC unlike a normal or low normal platelet count in CAC, normal or mild prolongation of PT/aPTT in CAC as opposed to a severe prolongation in SIC and finally high levels of fibrinogen in CAC whereas we might observe either normal or low levels of fibrinogen in sepsis/DIC.

The changes seen in COVID-19 are increase in the levels and activity of von Willebrand factor (vWF) and a reduction in ADAMTS13, elevated Factor VIII, reduced antithrombin, elevated Fibrinogen levels, increased Plasminogen activator inhibitor (PAI 1) and an increased endogenous thrombin generation potential early in the disease which later get reduced in the ICUs. Based on the severity of the disease, decrease in the levels of protein C and anti-thrombin was found in severe COVID-19 (SOFÄ>10). We observed a general shift toward a prothrombotic state in our study group (Table 1) which was evident in clot initiation, clot dynamics, clot strength, and resolution (Figure S1). An Australian critical care team evaluated coagulation status in COVID-19 patients in the ICU using TEG and V-curve and they had observed a similar hypercoagulable picture in the clot initiation, amplification, and propagation. The prothrombotic state is mainly contributed by coagulation factors and its inhibitors as shown by Panigada as well as Boccì et al. 2020. We have observed in the current study that MA was significantly elevated (MA 55.45 vs. 64.48, $p<.0001$) in the absence of thrombocytosis. The role of platelets in modulating the CAC can be critical as platelets get activated in the presence of excess thrombin seen in COVID-19 and release pro coagulant factors.

As the severity of COVID-19 increases, a hypercoagulable picture appear which is similar to other consumptive coagulopathies. Lower thrombus generation has been seen in patients admitted to ICU during the later stages of the disease implying as the disease progresses, patients develop an overt coagulopathy which might be associated with septic shock. Sepsis with a refractory septic shock and severe metabolic acidosis tend to reduce the thrombin generation potential in the ICU. We have observed a mortality rate of 32.55% among the study population. Mortality correlated with MA, LY 30 and TG among TEG parameters (Table 3). The laboratory profile comparison revealed that non-survivors had a prolonged PT/aPTT at admission and it could be due to the fact that 50% of them (7/14) already were in septic shock (Table S1). Abnormal coagulation parameters have been associated with a poor outcome in COVID-19 cases as disease progresses into an irreversible stage with cellular shut down.

CAC is associated with a hypercoagulable condition which puts the patients at risk of TEs. The cumulative incidence of TE in COVID-19 patients admitted to ICU is around 30% and systemic anticoagulation has been recommended to patients requiring ICU...
admission.\textsuperscript{7,8} Even while on anticoagulation patients develop TEs.\textsuperscript{25,26} We have observed that 79\% of our patients had a hypercoagulable TEG tracing at the time of admission and 30.23\% (13/43) had a documented TE during ICU stay even when they were on therapeutic doses of anticoagulants. The high incidence of TE in CAC might be due to the widespread inflammation and severity of the infection which in turn causes widespread clot formation.\textsuperscript{6,27} Majority of them had arterial thrombosis and two patients developed PTE following DVT.

Among the 34 hypercoagulable tracings, 13 had secondary fibrinolysis activity (Figure 1) and six of them had physiological lysis activity. Fibrinolysis activity plays a crucial part in the lungs where pulmonary microthrombi breakdown early in the disease phase is supposed to cause the elevated D-Dimer levels seen in COVID-19.\textsuperscript{2,5,11,21} The high prevalence of TE even while on anticoagulation is believed to be due to the hypercoagulable state with a reduced fibrinolysis activity, however, this particular feature is not proven yet.\textsuperscript{21,28} ROTEM based studies had a reduced lysis activity in TEs whereas TEG based study revealed that 94\% of the included COVID-19 patients had either physiological or hyper fibrinolysis activity.\textsuperscript{19,29,30} The fibrinolysis shutdown observed in COVID-19 is attributed to increased PAI-1 levels which inhibit the clot resolution and puts the patients at risk of TEs.\textsuperscript{20,21} Even though suppressed fibrinolysis activity might be a risk factor for TEs or a poor outcome, current study revealed that presence of fibrinolysis had more risk with a positive correlation to develop a TE. These findings could be due to a possible difference in population genetics, food, and culture which might affect the coagulation system and does the coagulopathy due to B.1.617 (Delta variant) differ from the CAC with an absence of fibrinolysis activity we have so far seen in other parts of the world.\textsuperscript{31–33}

We had repeated TEG in 11/46 patients before discharging from ICU and the repeat TEG (Figure 2) showed that they were still having a hypercoagulable stage even after anticoagulation (median—5 days, IQR—7 days). Interestingly the fibrinolysis activity was more in the repeat TEG compared with their first report and the clinical significance of this might be worth looking into. The increase in fibrinolysis activity on the second TEG might probably be due to a result of reduction in disease severity and inflammation as compared with the day of admission. We were not able to follow up these patients once they were discharged from the hospital. Thrombotic complications including central retinal artery occlusion (CRAO), pulmonary thromboembolism, and mesenteric ischemia have been reported even after being discharged from hospital.\textsuperscript{34–36} Coagulopathy in COVID-19 has been said to be profound and prolonged even after discharge.\textsuperscript{29,30,37} There is still a paucity of evidence as to how long one should continue anticoagulants if they are at risk of TE following CAC.

\section*{5 | LIMITATIONS}

The study cohort lacked platelet function, fibrinogen, and other coagulation factors data. On the hindsight, it would have been better if we had these data for comparison with TEG and analysed the role played by different coagulation factors. It would have been ideal if we could correlate the disease severity and coagulopathy to the genotype of the SARS CoV2 virus in these patients. Repeat evaluation also revealed that these patients had a pro thrombotic stage after 5 days of thromboprophylaxis. In resource limited settings where a well-defined national clinical management protocol is lacking, we are left with unanswered questions like whether to continue thromboprophylaxis or not. The chances of missing out asymptomatic DVTs might be higher in our study population as all the TEs recorded were symptomatic ones.

\section*{6 | CONCLUSIONS}

Current study looked into the applicability of TEG in CAC and most of the TEG had a hypercoagulable picture in clot initiation, propagation, and clot strength at the time of admission while very few had a hypocoagulable coagulation status representing the characteristic of a refractory septic shock stage. Fibrinolysis activity was noted along with a hypercoagulable picture in a fraction of the patients, but, as COVID-19 inflammation reduced, fibrinolysis activity was found to be increasing. TEG helped to diagnose and differentiate stages of coagulopathy associated with COVID-19 and played a useful part in deciding on anticoagulation in COVID-19 patients. We declare that the manuscript has been reviewed and accepted by all authors for publication.

\section*{AUTHOR CONTRIBUTIONS}

The study was conceptualized by Ganesh Mohan and Prithvishree Ravindra. The study was designed by Ganesh Mohan and Shamee Shastri. Data collection and analysis were done by Bemma Paonam and Ashwinkumar Vaidya. Data interpretation was done by Ganesh Mohan and William Wilson. Manuscript preparation was done by Ganesh Mohan. Shwethapriya Rao, Jayaraj Mymbil Bigakrishnan, William Wilson, Prithvishree Ravindra and Souvik Chaudhuri were managing study participants in ICU. Shamee Shastri and Shwethapriya Rao had critically reviewed the manuscript and approved it.

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\section*{CONFLICT OF INTERESTS}

We declare that we do not have any conflicts of interests among ourselves.

\section*{DATA AVAILABILITY STATEMENT}

Data available on request due to privacy/ethical restrictions.
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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.