ORIGINAL ARTICLE

Thromboelastography Parameter and Its Association with Survival of COVID-19 Patients: A Retrospective Cross-Sectional Study

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ABSTRACT

Introduction: Coagulopathy associated with Coronavirus disease 2019 (COVID-19) may cause life-threatening complications, especially in severe or critically ill COVID-19 patients. Thromboelastography (TEG) is an effective, dynamic, and reliable test to assess the complete coagulation process. This study aimed to determine the association between selected TEG parameters and survival in COVID-19 patients. **Methods:** This study was a retrospective observational study using data from medical records of COVID-19 patients who were hospitalized in Dr. Soetomo Hospital, Surabaya, Indonesia. There were 94 COVID-19 patients consisting of 76 survivors and 18 non-survivors. The association between TEG results and certain TEG parameters with survival status was considered significant if the p-value ≤ 0.05. **Results:** Increased coagulation activity had a significant association with the survival status of COVID-19 patients (p=0.04). There were no significant differences in all TEG parameters between COVID-19 patients who survived and those who did not survive (p > 0.05). Based on the TEG analysis tree, the most TEG results found were secondary fibrinolysis (21.3%) and fibrinolytic shutdown (24.5%). No significant association was found between the coagulability and fibrinolysis abnormality with the survival status in COVID-19 patients (p > 0.05). **Conclusion:** There was no significant difference in TEG results between COVID-19 survivors and non-survivors. However, based on the TEG result, an increase in coagulation activity is associated with a lower survival rate. Further study with detailed timing of TEG examination, disease severity and comorbidities stratification in COVID-19 patients may be needed.
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Keywords: COVID-19, Hypercoagulability, Thromboelastography, Fibrinolysis, Survival

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infection caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although COVID-19 infection initially was thought to be a disease that focused on pulmonary disorders, this disease may also cause coagulopathy, such as hypercoagulability and prothrombic state (1,2). This will lead to an increase in the incidence of thrombosis in COVID-19 patients. The incidence of thrombotic events in COVID-19 patients was up to 69% and this incidence remains high (56%) among COVID-19 patients who have received anticoagulation therapy (3). The prothrombotic events found in COVID-19 may lead to death in COVID-19 patients (4). Thus, coagulopathy is a predictor of poor prognosis in COVID-19 patients.

Several coagulation function tests have been used to detect coagulopathy in COVID-19 patients, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and D-dimer. Unfortunately, several studies showed that coagulopathy associated with COVID-19 is causing minimal changes in aPTT and PT values therefore their role in the management of COVID-19 is insignificant (2,4). Previous studies showed that a high D-dimer value had been associated with poor prognosis in COVID-19 patients. However, the performance of the D-dimer test in assessing coagulopathy in COVID-19 patients is highly variable and has not yet been validated. Therefore, these conventional coagulation tests cannot be used as the standard of care in assessing

coagulopathy in COVID-19 patients (4).

Thromboelastography (TEG) is a real-time hemostatic test used to measure the formation and destruction of blood clots. TEG is designed to measure the complete coagulation process including thrombin and fibrin activity, platelet activation and adhesion, and the fibrinolytic system (2,5). TEG results are presented in almost 20 different parameters, including reaction time (R), kinetic time (K), α-Angle, maximum amplitude (MA), and clot lysis at 30 minutes after maximum clot strength (Ly30). TEG could describe all conventional coagulation tests in one graph, making this test superior and more effective in assessing the presence of coagulopathy (6–8). Therefore, this study aimed to assess the association of selected TEG parameters and TEG results with the survival status of COVID-19 patients.

MATERIALS AND METHODS

Study designs and subjects

This retrospective cross-sectional study was conducted at Clinical Pathology Laboratory Dr. Soetomo Hospital, Surabaya, East Java, Indonesia from April 2021 to August 2021. All patients enrolled in this study were aged 18 years or older, tested positive for the SARS-CoV-2 based on a polymerase chain reaction (PCR) test, had moderate to severe COVID-19 infection, and were admitted to the isolation ward for COVID-19 in Dr. Soetomo Hospital during the study period. All COVID-19 patients were included regardless of the comorbidities they had. Demographic data and TEG results were obtained from medical record data. Thus, patients with incomplete TEG data were excluded from this study. This study has been approved by the Health Research Ethics Committee of Dr. Soetomo Hospital, Faculty of Medicine, Airlangga University, Surabaya (0030/KEPK//VII/2020)

Thromboelastography (TEG)

TEG® 5000 was used in this study to assess information regarding the coagulation process in COVID-19 patients in this study. The TEG activator used in our hospital was Citrate Kaolin with or without Heparinase. Since the TEG data were obtained from secondary data, we could not set the specific time of blood collection in our patients. The coagulation, fibrinogen, platelet, and fibrinolysis activity were assessed based on the TEG parameters, such as R time, K time, α-Angle, MA, and Ly30. R time described the initiation phase of fibrin formation (clotting time) which is characterized by a 2 mm amplitude (9). The normal value of R time is 2-8 minutes. K time and α-angle represent the clot kinetics. K time describes the amplification phase of fibrin formation characterized by 20 mm amplitude indicating the fibrin cross-linking (9). The normal value of K time is 1-3 minutes. The α-Angle is used to describe the propagation phase which measures the speed of fibrin build-up and cross-linking (9). The normal value of α-Angle is 55-78o. MA describes the maximum amplitude of fibrin and platelet bonding which represents the clot strength (9). The normal value of MA is 51-69 mm. Ly30 is a measure of the amplitude decreased 30 minutes after the MA which represents the clot stability. The normal value of Ly30 is 0-8%. Thereafter, the TEG result was classified based on the TEG Tree (Figure 1).

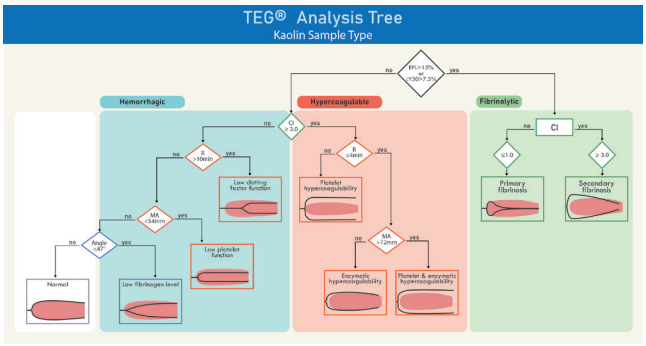

Figure 1: Thromboelastography Analysis Tree (10)

Survival status

Survival of COVID-19 patients was assessed at the end of hospitalization. The patient was considered "survived" if they were alive until they were discharged from the hospital. The patient was considered "not survived" if they died during the hospitalization.

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences (SPSS) version 24.0 for Windows. A normality test was done on all numerical data using the Kolmogorov-Smirnov test. Numerical data were presented as mean ± standard deviation (SD) if the data were normally distributed (age) and presented as median with minimum and maximum value if the data were not normally distributed (R time, K time, α-angle, MA, and Ly30). Meanwhile, categorical data (coagulation activity, fibrinogen activity, platelet activity, and fibrinolysis activity) were presented using frequencies and percentages. Association between TEG parameters and survival status was assessed using the Mann-Whitney test as the TEG parameters value were not normally distributed. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 94 eligible COVID-19 patients were involved in this study. Seventy-six (80.85%) patients were alive at the end of hospitalization. The mean age of the survivor and the non-survivor group were 48.58 ± 11.63 years and 54.44 ± 12.79 years, respectively. Although the non-survivor group had a slightly higher mean age, there was no significant difference in age between the survived and not survived COVID-19 patients in this study ($p > 0.05$). Most COVID-19 patients in both groups were male but there was no significant difference in sex between the two groups. Table I showed that most of the

Table I: Biocharacteristics of COVID-19 Patients

Characteristics	Survival Status		p-value
	Survived (n = 76)	**Not Survived (n = 18)**	
Age (years) Mean ± SD	48.58 ± 11.63	54.44 ± 12.79	0.062*
Sex (n, %)			
Male	57 (60.6)	14 (14.9)	0.805**
Female	19 (20.2)	4 (4.3)	
Coagulation Activity (n, %)			
Increased	21 (22.3)	11 (11.7)	0.04**
Normal	40 (42.6)	2 (2.1)	
Decreased	15 (16.0)	5 (5.3)	
Fibrinogen Activity (n, %)			
Increased	6 (6.4)	0 (0)	0.388**
Normal	62 (66.0)	15 (16.0)	
Decreased	8 (8.5)	3 (3.2)	
Platelet Activity (n, %)			
Increased	42 (44.7)	8 (8.5)	0.648**
Normal	29 (30.9)	8 (8.5)	
Decreased	5 (6.6)	2 (11.1)	
Fibrinolysis Activity (n, %)			
Increased	46 (60.5)	9 (50)	0.637**
Normal	9 (11.8)	2 (11.1)	
Decreased	21 (27.6)	7 (38.9)	

*Independent t test; **Chi-square test

survived COVID-19 patients have normal coagulation activity (42.6%) compared to the not survived patients (11.1%). Fibrinogen activity mostly was normal in survived and not survived COVID-19 patients (52.6% and 83.3%). Both groups mostly had increased platelet and fibrinolysis activity. However, only coagulation activity was significantly associated with the survival status in COVID-19 patients (p = 0.04).

All TEG parameter values were not normally distributed ($p \leq 0.05$). Therefore, the Mann-Whitney test was used to assess the association between the TEG parameters and survival status. The Mann Whitney test results showed that there was no significant difference in all TEG parameters between the survived and not survived COVID-19 patients ($p > 0.05$) (Table II).

Table III showed the classification of TEG results of COVID-19 patients according to the TEG analysis tree. The most common TEG results of COVID-19 patients in this study were secondary fibrinolysis (21.3%) and

Table II: Association of TEG Parameters and Survival of COVID-19 Patients

Characteristics	Survival Status		p-value
	Survived (n = 76)	**Not Survived (n = 18)**	
R time (minutes) Median (min-max)	3.95 (0.2 – 10.9)	4.1 (1.3 – 9.3)	0.371*
K time (minutes) Median (min-max)	1.35 (0.8 – 4.7)	1.45 (1.0 – 11.8)	0.335*
α angle (°) Median (min-max)	69.3 (41.6 – 82.5)	69.35 (21.8 – 5.2)	0.821*
MA (mm) Median (min-max)	70.7 (36.8 – 95)	68.4 (23.2 – 75.7)	0.062*
Ly30 (%) Median (min-max)	5.4 (0 – 99.7)	2.95 (0 – 17.5)	0.231*

*Mann-Whitney test

Table III: The TEG Results According to the TEG Analysis Tree

TEG Results	n	%
Normal	6	6.4
Platelet Hypercoagulability	3	3.2
Enzymatic Hypercoagulability	6	6.4
Enzymatic and Platelet Hypercoagulability	8	8.5
Enzymatic hypercoagulability and decreased fibrinolysis	3	3.2
Enzymatic hypercoagulability and increased fibrinolysis	9	9.6
Enzymatic, platelet hypercoagulability and decreased fibrinolysis	3	3.2
Primary fibrinolysis	9	9.6
Secondary fibrinolysis	20	21.3
Fibrinolysis Shutdown	23	24.5
Decreased Fibrinogen Activity	1	1.1
Decreased MA Activity and fibrinolysis	1	1.1
Decreased coagulation activity and Increased fibrinolysis activity	2	2.1

fibrinolytic shutdown (24.5%). In addition to these 2 results, the third and fourth highest results were primary fibrinolysis and a combination of enzymatic hypercoagulability and increased fibrinolysis, each consisting of 9 subjects (9.6%). Further, we grouped and analyzed the TEG results in Table III into coagulation abnormalities and fibrinolytic abnormalities. Some examples of TEG image from patients with various abnormalities shown in Figure 2.

The relationship between coagulation abnormalities and fibrinolysis with survival status in COVID-19 patients is shown in table IV. In this study, 40 COVID-19 patients had abnormal coagulability. and most of them were hypercoagulability. Seventy COVID-19 patients in this study had abnormal fibrinolysis and most of them were hyperfibrinolysis. However, there was no significant

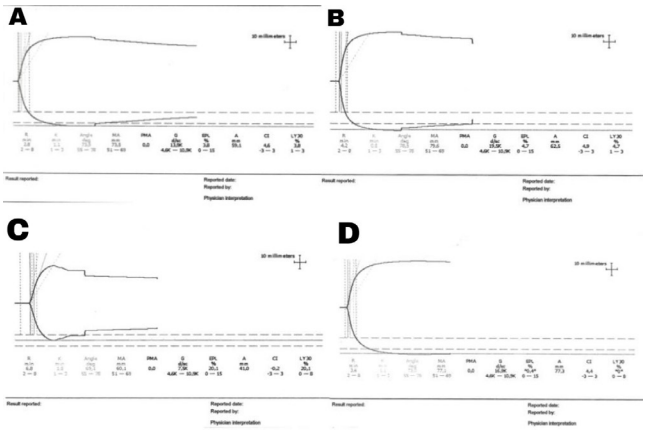

Figure 2: Thromboelastography Image of Patients. (A) Enzymatic Hypercoagulability (B) Platelet Hypercoagulability (C) Primary Fibrinolysis (D) Fibrinolysis Shutdown

Table IV: Association between Coagulability and Fibrinolysis Abnormality with Survival Status in COVID-19 Patients

TEG Abnormality	Survival Status		p-value
	Survived	**Not Survived**	
Coagulability Abnormality (n, %)			
Hypercoagulability	29 (26.4)	7 (6.4)	1.000**
Hypocoagulability	4 (3.6)	0 (5.3)	
Fibrinolysis Abnormality (n, %)			
Hyperfibrinolysis	32 (29.0)	8 (7.3)	0.737*
Hypofibrinolysis	23 (20.9)	7 (6.4)	

*Chi-square test **Fisher's-exact test

association between coagulability and fibrinolysis abnormality with the survival status in COVID-19 patients ($p > 0.05$).

DISCUSSION

Previous studies had shown that a hypercoagulability state was associated with severe COVID-19 infection. Hypercoagulability state in COVID-19 patients may occur in the initial inflammation phase or during the recovery phase. Various mechanisms were proposed to explain this hypercoagulability state found in COVID-19 patients. However, most theories link hypercoagulability in COVID-19 with cytokine storm or massive systemic inflammation which is characterized by increased interleukin (IL)-6, IL-7, tumor necrosis factor , and other inflammatory chemokines. Increased IL-6 produced by monocytes will cause increased fibrinogen levels thus leading to hypercoagulability state. In addition, COVID-19 infection will cause an increase in angiotensin II expression due to the interaction between SARS-CoV-2 with angiotensin-converting enzymes 2 (ACE2) receptor that will lead to endothelial dysfunction. This endothelial damage will increase the von Willebrand factor and activate the intrinsic coagulation cascade. Thus, resulting in a hypercoagulability state (11–13).

This hypercoagulability state may be assessed using TEG. Previous studies stated that hypercoagulability in COVID-19 were characterized by shortened R, shortened K time, increased MA, increased α-angle, and reduced or even absence of Ly30 based on TEG test results (14,15). A hypercoagulability state will increase the risk of thrombotic events which are associated with higher mortality rates in COVID-19 patients. Other studies also showed a high incidence of thrombotic events in critically ill COVID-19 patients which is 1 thrombotic event per 8 cases of critically ill patients (62%). However, this study found no significant differences between PT, aPTT, INR, and platelet count between patients with thrombotic events and without thrombotic events (16). A similar result was obtained by a study were compared the traditional coagulation test with TEG in 40 COVID-19 patients with Acute Respiratory Distress Syndrome (ARDS). The aPTT, INR, and platelet count found to be within the normal limit. Meanwhile, the TEG showed a specific hypercoagulation state (17). Thus, these studies showed that the traditional coagulation test may not be useful in detecting hypercoagulability state in severe COVID-19 patients. Several studies showed that D-dimer may be useful in predicting hypercoagulability state in COVID-19 patients. However, the D-dimer value may not be specific and may be affected by many others conditions, such as pregnancy and heart diseases (1).

There are several parameters of TEG (R time, K time, MA, and Ly30). R time represents the clotting factor coagulability. An R time less than 5 minutes means clotting factor hypercoagulability and an R time greater than 10 minutes means clotting factor hypocoagulability. MA represents the (enzymatic) platelet function in coagulation with MA less than 50 mm meaning enzymatic hypocoagulability and MA greater than 70 mm meaning enzymatic hypercoagulability. Therefore, a combination of R less than 5 minutes and MA greater than 70 mm means clotting factor and enzymatic hypercoagulability. Fibrinolysis can be determined through the parameter Ly30. A high Ly30 value (greater than 7.5%) with normal to low MA indicates primary fibrinolysis, meanwhile a high Ly30 (greater than 7.5%) with normal to high MA indicates secondary fibrinolysis (10). A very low Ly30 (<0.8%) is known as fibrinolysis shutdown (18). Consistent with previous studies, this study showed that coagulation activity (based on TEG result) was significantly associated with the survival state of COVID-19 patients. However, the analysis of TEG result according to the TEG analysis tree showed there was no significant association between the hypercoagulability and hyperfibrinolysis with the survival status of COVID-19 patients.

To our knowledge, this is the first Indonesian study that determined the association between certain TEG parameters and the survival status of COVID-19 patients. TEG could provide a dynamic measurement of coagulation and fibrinolysis status in COVID-19 patients. Decreased R, K, and Ly30 with increased α angle and MA indicating a hypercoagulability state in the TEG test. There was no definite cut-off of TEG parameters in defining the hypercoagulability state. Almost all studies use the normal range of values based on the manual of the TEG analysis tool. For example, some studies used a TEG®6s and stated that hypercoagulability is defined by R time <4.3 minutes, K time < 0.8 minutes, α-angle > 77o, MA > 69 mm, and Ly30 < 1% (19,20). On the other hand, Yuriditsky et al. (2020) used a clotting index (CI) >3 as the hypercoagulability criteria in their study (9). Meanwhile, this study used a TEG® 5000 with slightly different normal ranges (hypercoagulability if R time < 2 minutes, K time < 1 minute, α-angle > 78°, MA > 69 mm, and Ly30 0%). A study by Sehgal et al. (2021) is using the same normal range as our study (2). Therefore, it can be concluded that there is no gold standard regarding the definition of a hypercoagulability state and TEG analysis tree is very useful to help interpret TEG results. Xuan et al. (2021) showed a significantly lower K time, α-angle, and MA in the death COVID-19 patient group

($p < 0.05$), but no significant difference in R time value ($p > 0.05$) (6). Similar results were obtained by Sehgal et al. who showed that higher mortality found was in the patient with abnormal coagulation status based on the TEG parameter than in those with normal coagulation status (2). Blydenstein et al. (2021) found that not all TEG parameters were significantly associated with the survival of COVID-19 patients. A significantly lower α-angle and MA value were found in non-survivor groups. However, there were no significant differences in R time and K time between the survivors and non-survivors (19). A study done by Marvi et al. (2022) found that all TEG parameters were significantly associated with the risk of venous thromboembolism (VTE) in critically ill COVID-19 patients. Therefore, it is suspected significant change in TEG parameter values in COVID-19 patients who died was due to the high incidence of VTE in these patients (18,21).

In contrast, Cordier et al. (2021) showed no significant difference in all TEG parameters between COVID-19 patients who died and those who survived. This study proved that a hypercoagulable state based on TEG parameters was significantly associated with more thrombotic events in severe COVID-19 patients, but not significantly associated with higher mortality (3). A similar result was obtained by Neethling et al. (2021) in their study involving 40 critically ill COVID-19 patients. Neethling et al. (2021) found no significant differences in TEG parameters between 30-day survivors and non-survivors at all time points measurement (1). Our study also showed that there was no significant difference in all TEG parameters between those who survived and those who did not survive. Therefore, the role of TEG parameters in predicting mortality in COVID-19 patient is still questionable and need further research.

Some studies stated that TEG parameters were specific but not sensitive in predicting hypercoagulability and its sensitivity and specificity may vary significantly in different populations (4,8). Among all parameters, K time was the most sensitive parameter (48.96%) and time to MA (TMA) and α-angle were the most specific parameters (94.55% and 87.27%, respectively) in predicting hypercoagulability in COVID-19 patients (6). Combining TEG parameters with other coagulability tests, such as D-dimer may be useful. A low Ly30% value may correctly predict thrombotic events in 40% of COVID-19 patients, but when combined with high D-dimer levels, it may successfully predict thrombotic events in 50% of COVID-19 patients (4). The study also showed that some TEG parameters had a significant correlation with other traditional coagulation tests. Yuriditsky et al. (2020) found that MA correlated with fibrinogen and C-reactive protein (CRP) ($r = 0.453$, $p = 0.001$ and $r = 0.290$, $p = 0.02$), α angle correlated with platelet count and fibrinogen (($r = 0.332$, $p = 0.007$ and $r = 0.309$, $p = 0.021$), and the D-dimer only correlated with R time ($r = –0.362$, $p = 0.003$) (9). Combining TEG with PT, aPTT, fibrinogen, and platelet count will also help in predicting the risk of bleeding for COVID-19 patients that received anticoagulant therapy (22).

One of our study limitation is that we did not stratify the TEG data based on the comorbidities, COVID-19 severity, or specific time of blood sample collection (such as initial or at discharged). Therefore, further studies may be needed to explore the correlation of each parameter with different comorbidities.

CONCLUSION

Certain TEG parameters were not significantly different between the COVID-19 who survived and those who did not survive. There was also no significant association between the hypercoagulability and hyperfibrinolysis with the survival status of COVID-19 patients in this study. However, coagulation activity based on the TEG result showed a significant association with the survival status of COVID-19 patients. Thus, TEG still may be useful for detecting coagulation abnormalities for predicting thrombotic events in severe COVID-19 patients.

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