Diagnostic value of thromboelastography parameters on sepsis-induced coagulopathy in patients with sepsis in Intensive Care Unit, Dr. Hasan Sadikin General Hospital Bandung

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Abstract
***Objective*: Sepsis is related to impaired hemostasis, starting with a subclinical coagulation activation known as hypercoagulability. The term for the coagulopathy process that occurs during the pathogenesis of sepsis is sepsis-induced coagulopathy (SIC). Appropriate information can be obtained using thromboelastography (TEG) to identify hemostatic disorders. This study aimed to assess the TEG parameter's diagnostic value for SIC in septic patients.**
***Design*: An analytical observational study with a cross-sectional design was conducted on septic patients treated in the Intensive Care Unit (ICU) of Dr. Hasan Sadikin General Hospital Bandung. TEG examinations were performed with TEG® 5000 Thrombelastograph® Hemostasis Analyzer. The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic result's accuracy and to calculate the discriminatory value of the area under the curve (AUC).**
***Setting*: Dr. Hasan Sadikin General Hospital Bandung.**
***Patients and participants*: The participants were patients aged between 18-65 years old, treated in the ICU, with a diagnosis of sepsis established with Sequential Organ Failure Assessment (SOFA) score criteria. The minimum sample size was calculated with a one-sample sensitivity-based formula with type 1 error or α set at 10%, type 2 or β error set at 20%, resulting in a minimum sample size of 35 patients.**
***Results*: It was revealed that patients with SIC had higher abnormal mean parameter TEG and SOFA scores than patients without SIC (p<0.001). α angle sensitivity was 85.7% with a specificity of 78.6%, while maximum amplitude (MA) had a sensitivity of 80.9% with a specificity of 78.6%. The coagulation index (CI) was 90.5% sensitive and 85.7% specific. The AUC diagnosis value of CI and MA was 0.876 and 0.886, respectively.**
***Conclusion*: It is concluded that TEG parameters had an average to strong diagnostic value for SIC and could be used as routine examination for intervention in septic patients.**

Key words: Coagulopathy, diagnostic value, SIC, thromboelastography, coagulation index, maximum amplitude.

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Background

According to the 2021 Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock, sepsis is defined as life-threatening organ dysfunction due to dysregulation of the host response to infection. (1) The body's response to sepsis, which is characterized by excessive activation of immune cells, changes in the coagulation state, inflammatory reactions, and changes in the immune system, has become a particular concern in the medical field. (2) A previous study in Dr. Cipto

Mangunkusumo General Hospital Jakarta, one of the referral hospitals in Indonesia, showed the prevalence of sepsis ranged from 1.5 to 3.72% with a septic shock mortality rate ranging from 37.09 to 80%. (3) Sepsis is associated with coagulation disorders that begin with subclinical activation of the coagulation called hypercoagulable state, from the spontaneous formation of thrombin and fibrin, leading to the formation of a microvascular thrombus. (4)

The existence of a new concept of sepsis-induced coagulopathy (SIC) shows the importance of the coagulopathy process occurring in the pathogenesis of sepsis. (5) Diagnostic criteria for SIC are important in clinical practice, especially as an early diagnosis and as a guide for the establishment of disseminated intravascular coagulation (DIC) diagnosis. Thus, it can be concluded that SIC is an early stage of DIC. (5) Dysregulation of the hemostatic system in sepsis that is further developed in DIC will result in hypoperfusion states, major organ dysfunction, and death. (6,7) Early diagnoses of DIC is an important point of sepsis management and are associated with better outcome. (8)

In patients with sepsis, there is a deterioration of organ function due to prolongation of prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR). There is another measurement tool, namely thromboelastography (TEG) which can describe the overall hemostatic profile. Thromboelastography is used to examine the different stages of coagulation and fibrinolysis to provide accurate information to detect bleeding disorders in less than 60 minutes. (9,10) Previous studies on the role of TEG in sepsis have reported that TEG was useful in identifying abnormalities in coagulation function and found that TEG parameter was associated with clinical prognosis. (2) However, there is still a lack of data on using TEG to predict SIC in septic patients. This study aimed to find TEG's diagnostic value (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], positive likelihood ratio [PLR], negative likelihood ratio [NLR], accuracy value, and area under the curve [AUC] values) for diagnosing SIC in septic patients at ICU of Dr. Hasan Sadikin General Hospital, Bandung.

Method

This study was an analytic observational study with a cross-sectional design. Patients that met the inclusion and exclusion criteria were consecutively selected for inclusion as research subjects. Data were taken primarily. This study was conducted from October to December 2022 after obtaining ethical clearance from The Research Ethics Committee of Dr. Hasan Sadikin General Hospital (No. LB.02.01/X/6.5/303/2022) and research permission approval from Human Resources, Education, and Research Division, Dr. Hasan Sadikin General Hospital.

Participant

The participants in this study were patients aged between 18-65 years old, treated in the ICU, with a diagnosis of sepsis established with Sequential Organ Failure Assessment (SOFA) score criteria. Patients with trauma, malignancy, prior known coagulation disorder, history of anticoagulant use, and patients who were deceased during the first 24 hours of treatment were excluded from this study. Samplings were conducted under a nonprobability sample with consecutive sampling methods.

Sampling size

The minimum sample size was calculated with a one-sample sensitivity-based formula with type 1 error or α set at 10%, type 2 or β error set at 20%, resulting in a minimum sample size of 35 patients.

Instrument

Data regarding age, sex, and SOFA score were obtained. Blood sampling was conducted once the SOFA score criteria for sepsis were fulfilled and was performed once during the stay within the first 24 hours. Patients with SOFA scores of 2 or more were included in this study, and there was no cut-off for patients with higher SOFA scores to be excluded. Diagnosis of SIC was established with criteria listed in **Table 1**. At the same time, blood samples for TEG examination were transferred in a citrate tube and were then processed by TEG® 5000 Thrombelastograph® Hemostasis Analyzer (manufactured by Haemoscope Corporation USA) in Central Laboratory, Clinical Pathology Department, Dr. Hasan Sadikin General Hospital Bandung. Blood for hemostasis profile examination was delivered in a citrate tube and was processed under mechanical viscosity-based methods with a Stago analyzer. Devices were calibrated prior to use. Data from TEG consisted of R-time (time of latency from start of test to initial fibrin formation), K-time (time taken to achieve a certain level of clot strength), α angle (slope of line between R and K), maximum amplitude (MA) (represents the ultimate strength of the fibrin clot), and coagulation index (CI) (calculation of -0.2454R + 0.0184K + 0.1655MA - 0.0241a - 5.0220).

Statistical analysis
Data acquired was then inputted in a special case form and was processed by SPSS 24.0 for Windows. Statistical significance was considered as $p<0.05$. Data distribution was then revealed with the one-sample Kolmogorov-Smirnoff test. The difference between numeric variables was tested with an independent t-test if it was well distributed and was tested with the Mann-Whitney test should the data was not well distributed. Differences between categorical variables were tested with the chi-square test or Fisher's exact test alternatively. Correlation tests were performed with the Pearson test should the data was distributed and alternatively with the Spearman Rank test should it was not well distributed.

Results
As many as 35 subjects with a diagnosis of sepsis treated in the Intensive Care Unit of Dr. Hasan Sadikin General Hospital Bandung between October 2022 to December 2022 were enrolled in this study. No subject was excluded during the research period. Subjects were then grouped into patients with SIC (n=21, 60% of the population) and patients without SIC (n=14, 40% of the population).
Kolmogorov-Smirnoff tests revealed that the subject's age was well distributed and SOFA score was not well distributed. Only SOFA scores showed statistical significance among SIC and non-SIC groups. The study subject's characteristics can be seen in **Table 2**. Fisher's exact analysis on K-time, α angle, maximum amplitude, and coagulation index showed statistical significance between SIC and non-SIC groups. The highest prevalence rate was seen on the coagulation index with prothrombin ratio of 6.3. The association between the TEG parameter of SIC and non-SIC groups can be seen in **Table 3**.
Distribution tests among thromboelastography parameters were found to be well distributed on R-time and K-time, while distribution test on hemostatic parameter was found to be well distributed on PT, INR, and fibrinogen. Prolongation of R-time, K-time, α angle, MA, CI, PT, and aPTT were noted in the SIC group. Fibrinogen was found to be elevated and thrombocytes were found to be depleted in patients with SIC. There were statistical significances on all thromboelastography parameters, hemostatic profile, and SOFA scores between subjects who developed SIC and those who did not develop SIC. Analysis can be seen in **Table 4**.
K-time, α angle, and coagulation index were found to be the parameters with good accuracy (defined as accuracy >80%). The coagulation index was found to be the most sensitive parameter to establish the diagnosis of SIC, while K-time was found to be the most specific one. PPV was found to be the best on K-time, while the coagulation index was found to be the parameter with the best NPV. Diagnostic values among TEG parameters can be seen in **Table 5**. On the other hand, the receiver operating characteristic (ROC) and the area under the curve (AUC) analysis were found to be highest in maximum amplitude and coagulation index (with AUC of 0.886 and 0.876, respectively). The cut-off point used in this study and ROC-AUC analysis can be seen in **Table 6** and **Figures 1-6**.

Discussion
In patients with sepsis, systemic inflammation occurs and activates the coagulation system, resulting in the consumption of various coagulation factors, leading to coagulopathy, and in 35% of patients with severe sepsis, leading to DIC. (4) Patients who meet DIC scoring criteria also meet SIC criteria, and SIC criteria can predict DIC in patients with sepsis. (5) TEG is used to examine the different phases of coagulation and fibrinolysis, thus providing accurate information to detect hemostatic disorders that reflect changes in coagulation factors, platelets, fibrin, and fibrinolysis at different stages of coagulation and overall function in the process of blood coagulation. (9,11,12)
In this study, age and sex did not show significant differences between the SIC and non-SIC groups. Other studies have also shown that there were no significant differences in the age and sex variables. On the contrary, the SOFA score variable was statistically significant. (2,8,13) In this study, the SOFA score of our subjects only ranged between 2-4 with a median difference of 3:2 between the SIC and non-SIC groups, despite its statistical significance. Findings in this study also showed that TEG parameters with abnormal values were higher in the patients with SIC, and also significant differences in all TEG parameters and hemostasis between the SIC and non-SIC groups. Several other studies on the role of TEG in sepsis and coagulopathy have shown similar results. (2,8,11,14,15)
Each TEG parameter has a certain distinct evaluation interpretation. R-time measures the time elapsed from the onset of blood clot formation, which can be prolonged in case of clotting factor deficiency or use of heparin. MA measures the strength of blood coagulation, in which abnormal MA indicates platelet dysfunction, as well as decreased fibrinogen concentration state. (16) K-time and the α angle provide similar information on the rate of blood clot formation, in which this process is

affected by the fibrinogen level and slightly influenced by platelets. (17) Hypercoagulability is an early feature of DIC; whereas other study has shown that MA in TEG had the potential to be used to monitor patients at risk of hypercoagulability. (9) In sepsis, whereas inhibition of fibrinolysis by plaminogen activator inhibitor-1 was noted, in addition to clotting formation and systemic coagulation factor activation, will lead to SIC that is marked by shortening K-time and R-time with increasing α angle and MA as well. R-time is shortened as platelet function is diminished in SIC, while K-time is shortened due to fibrinolysis inhibition. Increased MA and α angle show increased blood clot formation which concludes hypercoagulability in SIC.

Essentially, it can be observed that the TEG parameter had a sensitivity and specificity greater than 70%, with the exception of R-time. In line with this finding, previous studies on the role of TEG as a diagnosis of coagulopathy among septic patients discovered a sensitivity in K-time of 91.2% and a specificity of 92.0%. Analysis of other parameters, moreover, showed similar results, with MA (sensitivity and specificity of 96.0% and 81.4%, respectively) and for the α angle, (sensitivity and specificity of 92.0% and 88.1%, respectively). (2) Other reference studies that evaluated the diagnostic value of CI showed a sensitivity of 75.95% and specificity of 74.42%. (8) Other research has claimed that TEG could predict thrombin production and total thrombus formation, which was obtained by estimating the number of platelets, fibrinogen, levels of factor XIII, and the rate of blood clot formation proportional to the rate of thrombin formation. The use of thromboelastography performed to be advantageous for a better assessment of complete blood clotting. (18)

The accuracy value in the TEG diagnostic study has been reported to be greater than 60%. (2,8,11) Several studies have indicated that the performance of α-angle was considered good with an AUC cut-off point of >0.7. (2,3) ROC analysis in this study set the cut-off point for AUC of >0.8 for its good performance. Parameters in this study with AUC>0.8 were only MA and CI, for the other parameters (R-time, K-time, and α angle) described moderate AUC values with AUC ranging from 0.7-0.8. Contrary to our findings, the previous investigation showed results of K-time AUC 0.910% which was considered as very good performance, while α angle and MA had good performance with AUC of 0.895% and 0.882%, respectively. (2,8)

Several factors might interfere with TEG measurement, for instance, the sampling process and severity of the sepsis. Therefore, the timing of sampling can greatly influence TEG results as septic coagulopathy is a dynamic process that develops from subclinical coagulation activation to progression to DIC. (14,19) Serial measurement is best considered, which may provide a better understanding of how coagulopathy develops in sepsis. (14,19) In addition, the small sample size of this study due to the low number of septic patients treated during the study limited its statistical power.

It is concluded that TEG can precisely monitor coagulation progression in septic patients and differentiate between hypercoagulability and hypocoagulability states. Evaluation of coagulation dysfunction in patients with sepsis using TEG can assist in the assessment of sepsis severity and prediction of patient outcomes. It can be concluded that TEG examination is advantageous in the management of patients with sepsis.

Table 1. Scoring system for DIC and SIC diagnosis

Item	Score	ISTH overt DIC criteria	SIC criteria
Platelet count (-10^9/l)	2	<50	<100
	1	≥50, <100	≥100, <150
FDP/D-dimer	3	Strong increase	-
	2	Moderate increase	-
Prothrombin time (PT ratio)	2	≥6 s	(>1,4)
	1	≥3 s, <6 s	(>1,2, ≤1,4)
Fibrinogen (g/ml)	1	<100	-
SOFA score	2	-	≥2
	1	-	1
Total score for DIC or SIC		≥5	≥4

Reproduced from Iba et al. (5)

Legend: DIC=disseminated intravascular coagulation; SIC=sepsis-induced coagulopathy; FDP=fibrin degradation products; SOFA=Sequential Organ Failure Assessment; ISTH=International Society on Thrombosis and Haemostasis.

Table 2. Study subjects' characteristic

Variable	Total (n=35)	SIC group (n=21)	Non-SIC group (n=14)	p-value
Age (year) - Mean±SD - Min-max	 50±18 18-87	 52±20 18-87	 46±16 21-64	0.599^{a}
Sex, n (%) - Male - Female	 22 (62.9) 13 (37.1)	 13 (61.9) 8 (38.1)	 9 (64.3) 5 (35.7)	0.886^{b}
SOFA score - Median - Min-max	 3 2-4	 3 2-4	 2 2-2	0.001^{c*}

Legend: SD=standard deviation; SOFA=Sequential Organ Failure Assessment; SIC=sepsis-induced coagulopathy.
Statistical significances were tested with [a]independent t-test, [b]chi-square test, and [c]Mann-Whitney test.
*Significance on the level of $p<0.05$.

Table 3. Association between thromboelastography parameter and SIC events, stratified with device normal reference

Thromboelastography parameter	Total (n=35) n (%)	SIC (n=21) n (%)	Non-SIC (n=14) n (%)	p-value	PR (95% CI)
R-time (min) - Abnormal (<5, >7) - Normal (5-7)	 19 (54.3) 16 (45.7)	 14 (73.7) 7 (43.8)	 5 (26.3) 9 (56.3)	0.072	1.7 (0.9-3.1)
K-time (min) - Abnormal (<1, >3) - Normal (1-3)	 17 (48.6) 18 (51.4)	 16 (94.1) 5 (27.8)	 1 (5.9) 13 (72.2)	0.001*	3.4 (1.6-7.2)
α angle (degree) - Abnormal (<53, >67) - Normal (53-67)	 21 (60.0) 14 (40.0)	 18 (85.7) 3 (21.4)	 3 (14.3) 11 (78.6)	0.001*	4.0 (1.4-11.0)
MA (mm) - Abnormal (<50, >68) - Normal (50-68)	 21 (60.0) 14 (40.0)	 17 (81.0) 4 (28.6)	 4 (19.0) 10 (71.4)	0.002*	2.8 (1.2-6.7)
Coagulation index - Abnormal (<-3, >3) - Normal (-3 - 3)	 21 (60.0) 14 (40.0)	 19 (90.5) 2 (14.3)	 2 (9.5) 12 (85.7)	0.000*	6.3 (1.7-23.0)

Legend: SIC=sepsis-induced coagulopathy; MA=maximum amplitude; PR=prothrombin ratio; CI=confidence interval.
R-time=time of latency from start of test to initial fibrin formation; K-time=time taken to achieve a certain level of clot strength; α angle=slope of line between R and K; maximum amplitude=the ultimate strength of the fibrin clot; coagulation index=calculation of -0.2454R + 0.0184K + 0.1655MA - 0.0241a - 5.0220.
Statistical significances were tested with Fisher exact test. *Significance on the level of $p<0.05$.

Table 4. Mean comparison of thromboelastography parameter and hemostatic profile between SIC group and non-SIC group

Parameter	Normal reference	SIC (n=21) Mean±SD	Non-SIC (n=14) Mean±SD	p-value
Thromboelastography				
- R-time (min)	5-7	8.5±2.0	6.9±1.3	0.022[a*]
- K-time (min)	1-3	3.2±0.9	2.2±0.6	0.002[a*]
- α angle (degree)	53-67	70.9±5.9	64.6±6.5	0.012[b*]
- MA (mm)	50-68	72.9±5.2	64.4±5.8	0.001[b*]
- Coagulation index	-3 - 3	3.5±0.9	2.2±0.8	0.001[b*]
Hemostasis				
- PT (sec)	12-16	19.6±1.2	13.7±0.9	<0.001[a*]
- PTT (sec)	21-41	39.8±4.6	29.6±3.5	<0.001[b*]
- INR	0.8-1.2	1.47±0.05	0.98±0.07	<0.001[a*]
- Fibrinogen (mg/dl)	200-400	592±100	331±51	<0.001[a*]
- Thrombocytes ($x10^3/mm^3$)	150-450	135±69	379±36	<0.001[b*]
SOFA score	<2	3 (2-4)	2 (2-2)	<0.001[b*]

Legend: SIC=sepsis-induced coagulopathy; MA=maximum amplitude; PT=prothrombin time; PTT=partial thromboplastin time; INR=international normalized ratio; SOFA=Sequential Organ Failure Assessment Score; SD=standard deviation.
Statistical significances were tested with [a]independent t-test and [b]Mann-Whitney test.
*Significance on the level of $p<0.05$.

Table 5. Diagnostic value of thromboelastography parameter on SIC diagnosis establishment

Thromboelastography parameter	Accuracy	Sensitivity	Specificity	PPV	NPV	PLR	NLR
R-time (min)	65.7	66.7	64.3	73.7	56.3	1.87	0.52
K-time (min)	80.0	76.2	92.9	94.1	72.2	10.7	0.26
α angle (degree)	82.9	85.7	78.6	86.9	77.5	4.00	0.18
MA (mm)	77.1	80.9	71.4	81.3	70.8	2.83	0.27
Coagulation index	88.6	90.5	85.7	91.4	84.6	6.33	0.11

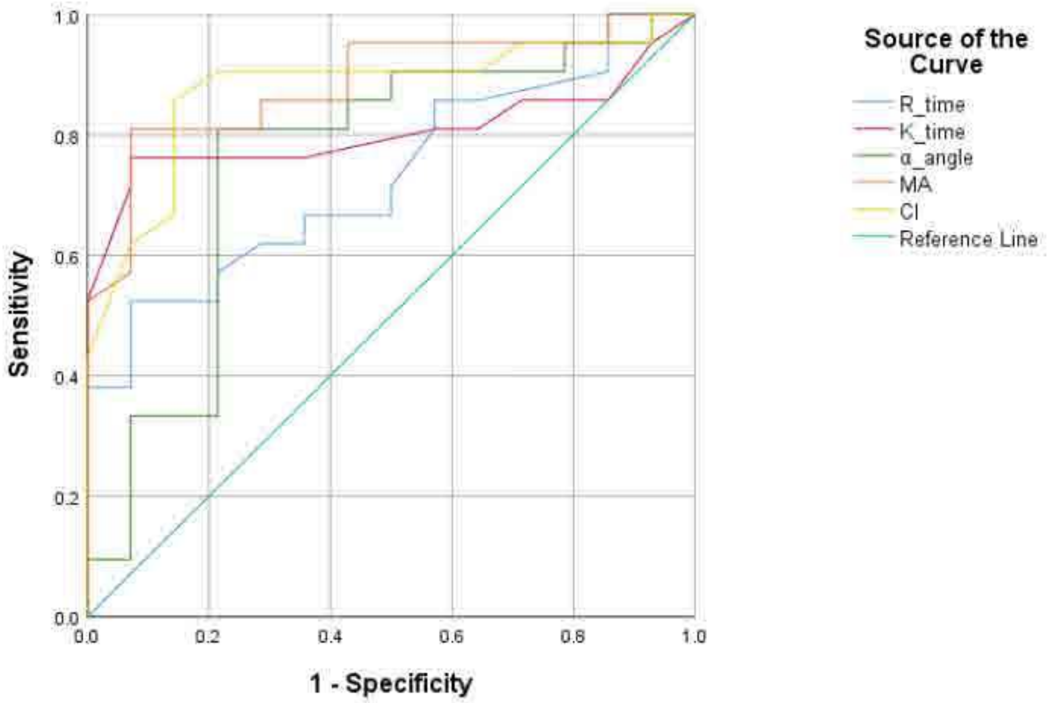
Legend: SIC=sepsis-induced coagulopathy; MA=maximum amplitude; PPV=positive predictive value; NPV=negative predictive value; PLR=positive likelihood ratio; NLR=negative likelihood ratio.
R-time=time of latency from start of test to initial fibrin formation; K-time=time taken to achieve a certain level of clot strength; α angle=slope of line between R and K; maximum amplitude=the ultimate strength of the fibrin clot; coagulation index=calculation of $-0.2454R + 0.0184K + 0.1655MA - 0.0241a - 5.0220$.

Table 6. ROC analysis of thromboelastography parameter on SIC diagnosis

Thromboelastography parameter	AUC (95% CI)	Cut-off point
R-time (min)	0.767 (0.594-0.893)	>7.2
K-time (min)	0.794 (0.624-0.912)	>2.9
α angle (degree)	0.728 (0.551-0.864)	>65.2
MA (mm)	0.886 (0.733-0.968)	>71.5
Coagulation index	0.876 (0.720-0.963)	>2.9

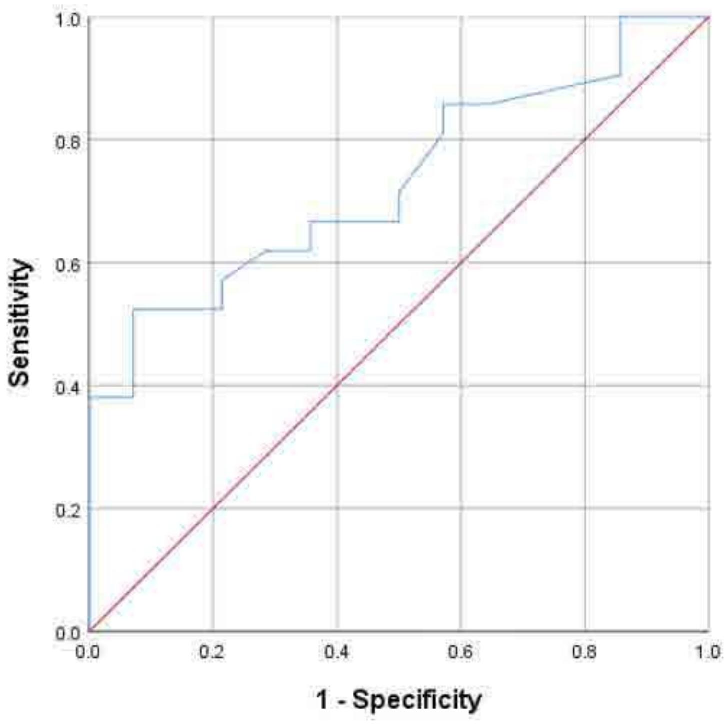
Legend: ROC=receiver operating characteristic; SIC=sepsis-induced coagulopathy; MA=maximum amplitude; AUC=area under the curve; CI=confidence interval.
R-time=time of latency from start of test to initial fibrin formation; K-time=time taken to achieve a certain level of clot strength; α angle=slope of line between R and K; maximum amplitude=the ultimate strength of the fibrin clot; coagulation index=calculation of -0.2454R + 0.0184K + 0.1655MA - 0.0241a - 5.0220.

Figure 1. Combined TEG parameters diagnostic value in SIC ROC diagram



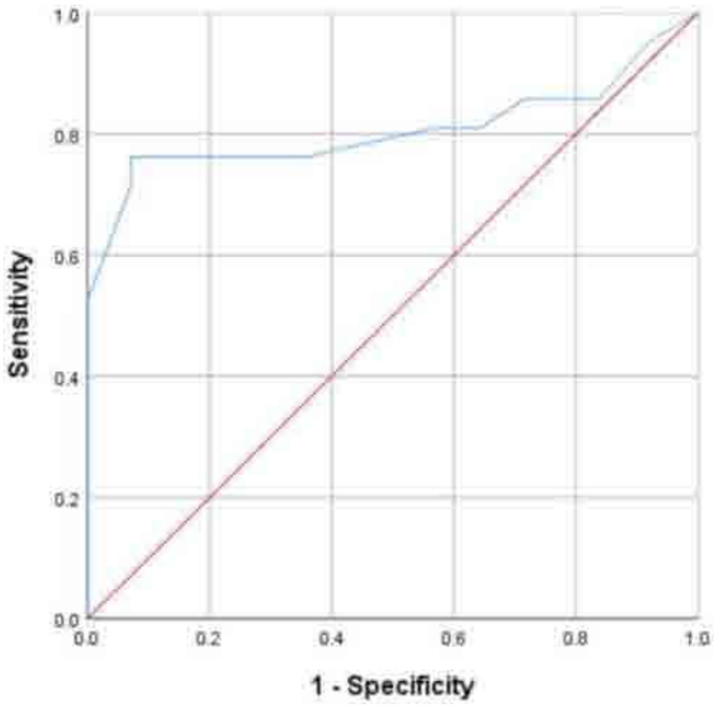
Legend: TEG=thromboelastography; SIC=sepsis-induced coagulopathy; ROC=receiver operating characteristic.

Figure 2. R-time diagnostic value in SIC ROC diagram



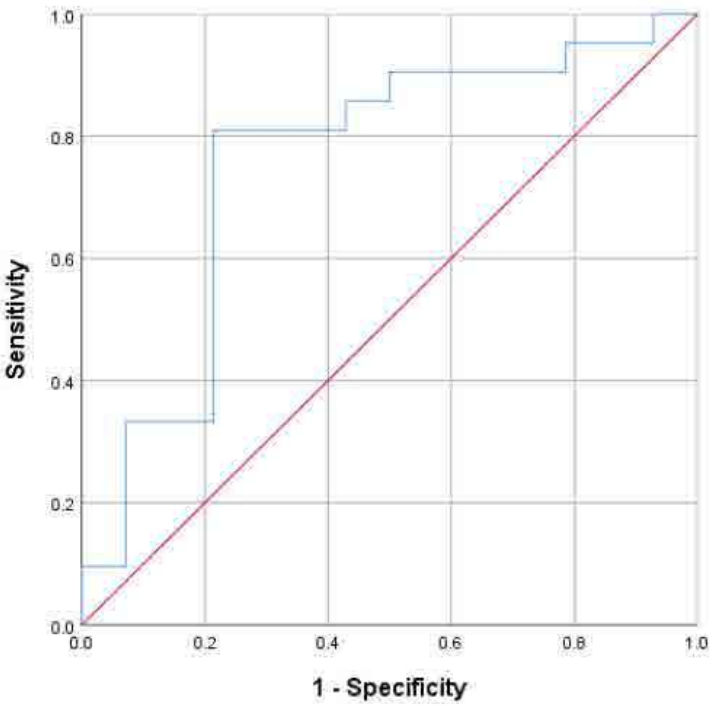
Legend: SIC=sepsis-induced coagulopathy; ROC=receiver operating characteristic.

Figure 3. K-time diagnostic value in SIC ROC diagram



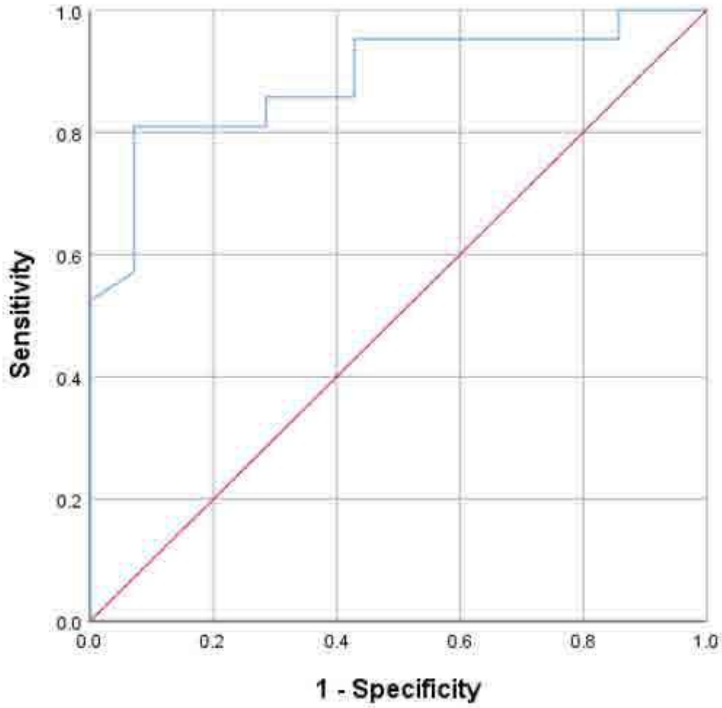
Legend: SIC=sepsis-induced coagulopathy; ROC=receiver operating characteristic.

Figure 4. α angle diagnostic value in SIC ROC diagram



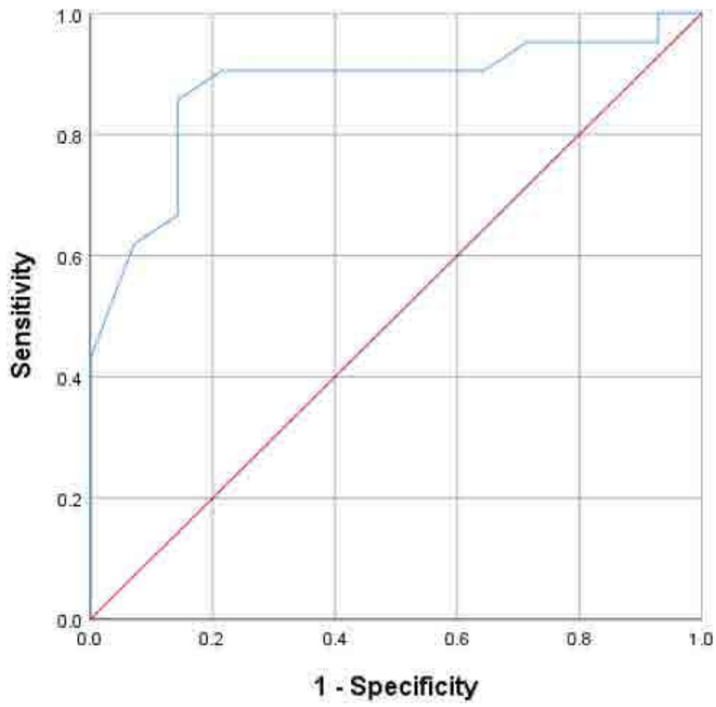
Legend: SIC=sepsis-induced coagulopathy; ROC=receiver operating characteristic.

Figure 5. Maximum amplitude diagnostic value in SIC ROC diagram



Legend: SIC=sepsis-induced coagulopathy; ROC=receiver operating characteristic.

Figure 6. Coagulation index diagnostic value in SIC ROC diagram



Legend: SIC=sepsis-induced coagulopathy; ROC=receiver operating characteristic.

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