

## Original Article

# Thrombelastography and coagulation parameters in septic patients and their clinical significance

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**Abstract:** This study aimed to study the clinical significance of the thrombelastography (TEG) and coagulation parameters in septic patients. 92 septic patients were divided into three groups: sepsis group, sever sepsis group, and septic shock group. At the same time, they were divided into survival group and death group according to their outcomes. Results showed that the difference in days of hospitalization, hemoglobin, CRP and PCT among the three groups was statistically significant ( $P < 0.05$ ). The difference in PT, APTT, TT, FIB, INR and D-Dimer among the three groups was not statistically significant ( $P > 0.05$ ), but D-Dimer in septic shock group was higher than in the other groups. The results of TEG showed that the difference interactiontime (R), K time,  $\alpha$ -angle, maximal amplitude (MA), platelet function, and clot index (CI) among the three groups were statistically significant ( $P < 0.05$ ). K,  $\alpha$ -angle, MA, platelet function and CI in septic shock group were significantly lower than in sepsis group and sever sepsis group ( $P < 0.05$ ). R in sever sepsis group was significantly shorter than in the other groups. And  $\alpha$ -angle, MA, platelet function and CI in sever sepsis group were significantly higher than in sepsis group ( $P < 0.05$ ). The difference in R, K,  $\alpha$ -angle, MA, platelet function and Ctof TEG between survival group and death group was statistically significant ( $P < 0.05$ ). Taken together, TEG contributes to the diagnosis of coagulability and prognosis in sepsis patients.

**Keywords:** Sepsis, coagulation function, thrombelastography

## Introduction

Sepsis refers to the systemic inflammatory response syndrome caused by infection. It is one of the most common diseases in emergency intensive care unit (ICU), and has become the leading cause of death in ICU besides heart disease. Sepsis is a disease with high incidence, high mortality and high treatment cost. It is a serious threat to human health and becomes a huge burden of economic development. The most effective way in treatment and prevention of sepsis is based on its pathogenesis. Pathological changes of sepsis involve excessive inflammatory response, blood coagulation inflammation, immune suppression, and cell apoptosis. The interaction between the excessive inflammatory response and blood coagulation disorder is considered the most basic pathological changes in sepsis. Thrombelastography (TEG) is an indicator reflecting the dynamic changes of blood coagulation (including fibrin formation rate, dissolving

state, robustness of coagulation and elastic degree). It has potential clinical value in the assessment of blood coagulation dysfunction in patients with sepsis. In this article, TEG and routine coagulation parameters were compared, to explore the disease state and blood coagulation function in patients with sepsis, thus providing more convenient and feasible detection means for better interpreting coagulation disorder state in patients with sepsis.

## Materials and methods

### Subjects

92 patients with sepsis treated in emergency department of Renji hospital from January 2014 to December 2014 were selected for this retrospective analysis. There were 52 males and 40 females, aged from 24 to 92, with the average age at  $71.72 \pm 16.15$ . All cases were confirmed by the diagnosis standard of 2008 sepsis classification standard [1]. Based on

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**Table 1.** General clinical parameters in different groups ( $\bar{x} \pm s$ )

Items	Age (y)	Days of hospitalization (n)	WBC ( $10^9/L$ )	HB (g/L)	PLT ( $10^9/L$ )	PLT distribution width (%)	CRP (mg/L)	PCT (ng/L)
Sepsis (n=58)	71.72 $\pm$ 16.15	10.05 $\pm$ 5.28 <sup>b,c</sup>	9.82 $\pm$ 5.22	112.86 $\pm$ 27.87	163.41 $\pm$ 62.44	14.97 $\pm$ 13.53	59.49 $\pm$ 57.28	4.19 $\pm$ 1.21
Sever sepsis (n=28)	69.39 $\pm$ 18.54	15.71 $\pm$ 9.67 <sup>a</sup>	11.45 $\pm$ 6.81	112.21 $\pm$ 23.65	203.82 $\pm$ 62.41 <sup>a,c</sup>	12.01 $\pm$ 2.08	107.09 $\pm$ 107.28 <sup>a</sup>	4.47 $\pm$ 2.91 <sup>a</sup>
Septic shock (n=6)	62.33 $\pm$ 8.45	27.00 $\pm$ 27.12 <sup>a,b</sup>	12.26 $\pm$ 3.53	101.00 $\pm$ 19.04 <sup>a,b</sup>	182.67 $\pm$ 33.16 <sup>a</sup>	12.71 $\pm$ 1.33	115.05 $\pm$ 107.25 <sup>a,b</sup>	4.00 $\pm$ 1.39 <sup>a</sup>
P	0.392	<0.05	0.336	<0.05	<0.05	0.480	<0.05	<0.05

Notes: <sup>a</sup>P<0.05, vs. sepsis group; <sup>b</sup>P<0.05, vs. sever sepsis group; <sup>c</sup>P<0.05, vs. septic shock group. WBC, white blood cell; HB, hemoglobin; PLT, platelets; CRP, C-reactive protein; PCT, procalcitonin.

**Table 2.** Coagulation parameters in different groups ( $\bar{x} \pm s$ )

Items	PT (s)	APTT (s)	TT (s)	FIB (g/L)	INR	D-Dimer
Sepsis (n=58)	13.20 $\pm$ 1.29	36.00 $\pm$ 8.60	15.94 $\pm$ 3.58	3.74 $\pm$ 1.44	1.48 $\pm$ 0.74	1.43 $\pm$ 1.32
Sever sepsis (n=28)	11.90 $\pm$ 1.57	30.51 $\pm$ 5.0	20.90 $\pm$ 4.36	3.48 $\pm$ 1.00	1.08 $\pm$ 0.16	1.36 $\pm$ 1.42
Septic shock (n=6)	14.20 $\pm$ 1.26	28.70 $\pm$ 8.37	15.53 $\pm$ 2.77	3.36 $\pm$ 1.31	1.23 $\pm$ 0.14	2.33 $\pm$ 1.70
P	0.438	0.503	0.268	0.611	0.447	0.179

Notes: PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, plasma fibrinogen; INR, international normalized ratio.

2008 sepsis classification standard [1], the 92 cases were divided into three groups, sepsis group (58 cases, 32 males and 26 females, average age  $71.72 \pm 16.15$ ); severe sepsis group (28 cases, 18 males and 10 females, average age  $69.39 \pm 18.54$ ); and sepsis shock group (6 cases, 2 males and 4 females, average age  $62.33 \pm 8.45$ ). And patients were divided into survival group (70 cases) and death group (22 cases) according to the prognosis. The death group included 16 cases of severe sepsis group (16/28, 55.6%) and 6 cases of sepsis shock group (6/6, 100%).

#### Clinical data

All data were obtained from medical records query system of Renji hospital and had been re-checked. The Sysmex XE2100 automatic blood analyzer was used to determine blood routine indexes. Double antibody sandwich immune luminescence was used to detect the serum procalcitonin (PCT) level in the Rochecobas 6000 automatic electrochemical luminescence analyzer. Serum C-reactive protein (CRP) level was tested using Siemens BNII automatic protein analyzer. ACL TOP700 automatic blood coagulation instrument from IL Company was used to detect the coagulation routine indexes, including prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), plasma fibrinogen (FIB), international normalized ratio (INR) and plasma D-Dimer. The TEG 5000 blood coagulation analyzer was used to test the indexes of TEG, including the reaction time (R), K time (K),  $\alpha$ -angle, the maximal amplitude (MA), platelet function, and clot index (CI).

#### Statistical analysis

SPSS 17.0 software package was used for data processing.  $\bar{x} \pm s$  represented for data accorded with normal distribution and homo-

geneity of variance. One-Way ANOVA was used for comparison between groups, and LSD test was used for comparison between two groups. Data not in conformity with the normal distribution or homogeneity of variance were shown as the median (range). And nonparametric rank sum test was used for comparison between groups. Data in conformity with the bivariate normal distribution was analyze using Pearson correlation analysis, while those not in conformity with the bivariate normal distribution was analyzed using Spearman rank correlation analysis. Multiple variables were analyzed using multiple linear regression analysis.  $P < 0.05$  was considered statistically significant.

## Results

### Basic information

There was significant difference in hospitalization days, hemoglobin, platelet count, CRP and PCT between the three groups ( $P < 0.05$ ). Hemoglobin in sepsis shock group was lower compared with that in sepsis and severe sepsis group ( $P < 0.05$ ). Platelets in sepsis shock group were higher compared with that in sepsis and severe sepsis group, and the difference was statistically significant ( $P < 0.05$ ). PCT in sepsis shock group and severe sepsis group was higher than that in sepsis ( $P < 0.05$ ). There was no significant difference in age, white blood cell count and platelet distribution width ( $P > 0.05$ ). But the number of white blood cells gradually increased in the three groups (Table 1).

### Coagulation status

There was no statistical difference in PT, APTT, TT, FIB, INR and D-Dimer between the three groups ( $P > 0.05$ ). But D-Dimer in sepsis shock group was higher than in the other two groups (Table 2).

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**Table 3.** TEG parameters in different groups (x ± s)

Items	R	K	α-angle	MA	PLT function	CI
Sepsis (n=58)	6.76 ± 2.40	1.93 ± 1.14	71.23 ± 6.58	9704.8 ± 3305.2	64.41 ± 9.23	1.03 ± 3.72
Sever sepsis (n=28)	6.01 ± 1.88 <sup>a,c</sup>	1.77 ± 0.73	72.95 ± 6.24 <sup>a</sup>	10424.0 ± 2965.9 <sup>a,c</sup>	66.85 ± 6.24	1.15 ± 2.26 <sup>a</sup>
Septic shock (n=6)	6.43 ± 1.13	1.41 ± 0.12 <sup>a,b</sup>	64.63 ± 5.80 <sup>a,b</sup>	6819.0 ± 2677.0 <sup>a,b</sup>	55.63 ± 9.09 <sup>a,b</sup>	-0.73 ± 1.73 <sup>a,b</sup>
P	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

Notes: <sup>a</sup>P<0.05, vs. sepsis group; <sup>b</sup>P<0.05, vs. severe sepsis group; <sup>c</sup>P<0.05, vs. septic shock group. R, reaction time; K, K time; MA, the maximal amplitude; PLT function, platelet function; CI, clot index.

**Table 4.** TEG parameters in survival and death group (x ± s)

Items	R	K	α	MA	PLT function	CI
Survival (n=70)	5.92 ± 1.80	1.81 ± 1.08	72.05 ± 6.37	10035.6 ± 3329.5	65.18 ± 8.91	1.26 ± 3.48
Death (n=22)	7.36 ± 2.34	2.34 ± 0.68	67.75 ± 6.36	8780.7 ± 2838.1	56.68 ± 8.07	-0.3 ± 2.18
F	9.18	2.847	7.605	5.540	5.371	3.683
P	<0.05	0.115	<0.05	<0.05	<0.05	<0.05

Notes: R, reaction time; K, K time; MA, the maximal amplitude; PLT function, platelet function; CI, clot index.

**Table 5.** Univariate logistic regression analysis in prediction of death in septic patients

Items	OR	CI	P
R	1.639	0.203-2.233	0.002
K	1.225	0.790-1.899	0.364
α-angle	0.913	0.849-0.981	0.013
MA	1.000	1.000-1.000	0.117
PLT function	0.969	0.919-1.022	0.246
CI	0.862	0.722-1.029	0.100

Notes: R, reaction time; K, K time; MA, the maximal amplitude; PLT function, platelet function; CI, clot index.

**Table 6.** Multivariate logistic regression analysis in prediction of death in septic patients

Items	OR	CI	P
R	1.538	1.068-2.215	0.021
α-angle	0.972	0.890-1.063	0.537

Notes: le R, reaction time.

## TEG

There was statistical difference in R, K, α-Angle, MA, platelet function and CI between three groups (P<0.05). K, α-Angle, MA, platelet function and CI in sepsis shock group were lower than in sepsis group and severe sepsis group, and the difference was statistically significant (P<0.05). R-value in severe sepsis group was lower than that in sepsis group and sepsis shock group (P<0.05). α-Angle, MA, platelet function and CI in severe sepsis group were higher than in sepsis group (P<0.05) (**Table 3**).

## TEG parameters in survival and death group

There was significant difference of R, α-Angle, MA, platelet function and CI between survival and death group (P<0.05), while there was no significance in K (P>0.05) (**Table 4**).

## Predictors of death in septic patients

Univariate logistic regression analysis showed that R and α-angle were predictors of death in septic patients (P<0.05) (**Table 5**), while multivariate logistic regression analysis showed that only R was the predictors of death in septic patients (P<0.05) (**Table 6**).

## Discussion

Blood coagulation system disorder is common in patients with sepsis [2]. Septic systemic inflammatory response leads to release of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6, resulting in blood coagulation activation and fibrinolytic inhibition. The imbalance of intravascular fibrin formation and removal is the symbol of coagulation disorder. Anticoagulation significantly decreases with fibrinolytic inhibition; meanwhile extensive coagulation is activated, eventually leading to out-of-control fibrin formation, causing coagulation factors and coagulation inhibitors being burned out. A large amount of intravascular fibrin formation causes microvascular thrombosis, and eventually progresses to diffuse intravascular coagulation (DIC).

DIC aggravates inflammation, resulting in multiple organ ischemia and necrosis, forming the pathophysiologic process of sepsis [3]. Therefore, effective detection of blood coagulation state changes and timely guidance of individualized intervention treatment are very important to reduce the mortality and shorten hospitalization time of sepsis patients.

In a KyberSept study on 2314 cases of patients with severe sepsis [4], TEG was used to detect sepsis patients and healthy control group. Five measures of TEG suggested sepsis patients were in significant high coagulation state, and after anticoagulation treatment, the data trended towards normal. Results of a subsequent analysis of a subgroup showed that the mortality was lower in patients with heparin treatment than without in 28 days and 90 days of treatment [5]. It has been found that early application of low-dose heparin therapy to patients with sepsis (pre-DIC) did not reduce the 28-day mortality, but it reduced the APACHE II score, shortened the breathing machine ventilation time and ICU hospitalization days, and reduced the complications compared with the control group [6]. A prospective study on continuous TEG testing and 28-day mortality in severe sepsis showed that, the percentage of patients in low coagulation state, normal coagulation state and high coagulation state was 22%, 48% and 30%, respectively. Patients in low coagulation state had higher sequential organ failure possibility and DIC score compared with patients in high coagulation state ( $P<0.05$ ), and they also had higher 28-day mortality compared to normal coagulation group ( $P<0.05$ ) [7]. In an *in vitro* experiment, TEG was sensitive for determination of coagulation state in sepsis patients [8]. Some small clinical researches demonstrated that extending the anticoagulant therapy could improve blood coagulation parameters, effectively prevent the endotoxin-induced leukocyte adhesion to the vascular endothelium, and improve capillary performance. All above changes are very important in the development of organ failure in sepsis patients.

Sepsis includes severe sepsis and septic shock. Severe sepsis is sepsis complicated with acute organ failure, and ultimately refractory hypotension [9, 10]. Organ failure and shock significantly increases risk of death during sepsis [11]. Results of this study showed

that there was significant difference in hospitalization days, hemoglobin, platelet count, CRP and PCT in patients with sepsis between the three groups ( $P<0.05$ ), while there was no statistical significance in age, white blood cell count and platelet distribution width ( $P>0.05$ ). But the number of white blood cells gradually increased in the three groups. Different degree of anemia was observed in sepsis shock groups. Anemia is not conducive for the control of infection, and may also have impacts on blood coagulation changes in patients with sepsis.

Coagulopathy, resulting in formation of microthrombi, play an important role in microvascular alterations in sepsis patients [12, 13]. Plasma source routine coagulation tests are main methods in the clinical evaluation of blood coagulation function [14]. Patients with the PT and APTT level below the normal lower limit value and high FBG and PLT level can be considered in high coagulation state or with thromboembolic diseases [15, 16]. Previous study showed that D-dimer contributed to emergency risk classification of sepsis patients [17]. In the present study, results of routine coagulation analysis showed that there was no statistical difference in PT, APTT, TT, FIB, INR and D-Dimer between the three groups ( $P>0.05$ ). D-Dimer was higher in the sepsis shock group compared with the other two groups. D-Dimer is made up of the fibrin with cross-linked fibrinolytic enzyme degradation. The increase of D-Dimer shows that the organisms in secondary fibrinolytic hyperthyroidism or low coagulation state [18]. In the present study, D-Dimer was higher in the sepsis shock group, indicating that along with the blood coagulation system activation, the fibrinolytic system was also activated. Therefore, detection of routine coagulation function alone has limited clinical significance on the judgment of the blood coagulation state of patients with sepsis.

Previous study showed that on the basis of the traditional routine coagulation tests, combination with TEG would be more accurate to evaluate blood coagulation state and risk classification of patients, thus guiding the clinical risk assessment and treatment [19, 20]. By detecting viscoelasticity changes of blood clots in the coagulation process, TEG records the whole process of blood clots forming fiber dissolution,



and draws the results into curves, to reflect comprehensively the function of platelet clotting factors and the fiber dissolving system. Previous study showed that TEG had high values in evaluating high coagulation state changes and could effectively guide and manage clinical anticoagulant therapy [21]. TEG has also been proved to contribute to detection of blood coagulation state changes in sepsis animal models [22].

In the present study, results of six measures of TEG showed that the comparison analysis between the three groups was statistically significant ( $P < 0.05$ ). R-value reflects the comprehensive function of clotting factors from the start time of blood coagulation system till the fibrin clot formation time. Shortened R-value indicates that patients are in relatively high coagulation state. K time reflects the blood clot netting speed. It shortens with the increase level of fibrinogen. Platelet function shows little influence on K time, while anticoagulants extend K time.  $\alpha$ -Angle reflects coagulation clot formation rate, and is mainly affected by fibrinogen, thrombin and platelet quantity or quality. The larger angle means the higher coagulation state. MA value mainly stands for the platelet aggregation function, and is in line with changes in platelet function. In sepsis shock group, K,  $\alpha$ -Angle, MA, platelet function and CI were significantly decreased compared with the sepsis group and the severe sepsis group, indicating patients with sepsis shock were in low coagulation state with decreased platelet function and fibrinolytic hyperthyroidism. And the mortality of patients with sepsis shock increased significantly. Those results were similar to previous research [7]. R value in the severe sepsis group were lower than in the sepsis group and sepsis shock group ( $P < 0.05$ ), while  $\alpha$ -Angle, MA, platelet function value and CI were higher than in the sepsis group ( $P < 0.05$ ), prompting that patients in severe sepsis group were in higher coagulation state compared with the sepsis group. Comparison analysis of TEG in survival group and death group showed that the difference of R,  $\alpha$ -Angle, MA and platelet function value between the two groups was statistically significant ( $P < 0.05$ ), illustrating that TEG has certain value in judging the prognosis of patients with sepsis.

Taken together, we carried on a correlation analysis of blood coagulation state in patients

with sepsis using TEG and routine coagulation parameters, and found that patients with sepsis were in a state of blood coagulation disorders. With the disease aggravating, patients were in high blood coagulation state at first and than in low blood coagulation state. Since TEG has been shown to be a highly sensitive assay for hypercoagulability, TEG measurements may indicate distinct coagulation changes in septic patients that can not be measured by routine tests. TEG detection in sepsis patients is beneficial to the judgment of blood coagulation state and prognosis, and it contributes to timely guidance of individualized intervention treatment. TEG plays a significant role in reduction the mortality and shortening the hospitalization time of sepsis patients.

### Disclosure of conflict of interest

None.

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