Original Article

Identification of soluble thrombomodulin and tissue plasminogen activator-inhibitor complex as biomarkers for prognosis and early evaluation of septic shock and sepsis-induced disseminated intravascular coagulation

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Background: Endothelium injury and coagulation dysfunction play an important role in the pathogenesis of sepsis. Soluble thrombomodulin (sTM), tissue plasminogen activator-inhibitor complex (t-PAIC), thrombin-antithrombin complex (TAT) and α2-plasmin inhibitor-plasmin complex (PIC) are biomarkers of endothelium injury and coagulation dysfunction. This study aimed to explore the prognostic values and diagnostic performance for septic shock and sepsis-induced disseminated intravascular coagulation (DIC) of endothelial biomarkers.

Methods: We conducted an observational study on patients with sepsis admitted to intensive care unit (ICU) at a teaching hospital from January 2016 to December 2018. Levels of sTM, t-PAIC, TAT and PIC were measured at admission day and day 5–7 after admission and detected by qualitative chemiluminescence enzyme immunoassay performed on HISCL automated analyzers.

Results: A total of 179 septic patients and 125 non-septic ICU controls were enrolled. The level of sTM was higher in septic patients compared to ICU controls (OR =1.093, 95% CI: 1.045–1.151, P<0.001). Moreover, higher levels of sTM and t-PAIC were independent predictors of poor 60-day prognosis for septic patients (HR =1.012, 95% CI: 1.003–1.022, P=0.012; HR =1.014, P=0.009). Level of sTM was also higher in patients with septic shock as revealed by multivariate analysis (OR =1.049, 95% CI: 1.020–1.078, P=0.001), as well as in patients with sepsis-induced DIC (OR =1.109, 95% CI: 1.065–1.158, P<0.001). sTM was considered as a sensitive biomarker for the early prediction of septic shock and sepsis-induced DIC, with AUC up to 0.765 (0.687–0.842) and 0.864 (0.794–0.935) of receiver operating characteristic curve.

Conclusions: Most patients developed coagulopathy which was closely linked to endothelial injury in initial phase of sepsis, which was demonstrated by abnormalities in endothelial biomarkers and their strong association with poor 60-day prognosis and development of septic shock and sepsis-induced DIC.

Keywords: Soluble thrombomodulin (sTM); tissue plasminogen activator-inhibitor complex (t-PAIC); endothelial dysfunction; sepsis; septic shock; sepsis-induced disseminated intravascular coagulation (DIC)

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Introduction

Sepsis is a syndrome of physiological, pathological, and biochemical abnormalities induced by infection which has become a major public health concern (1). Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolic abnormalities are profound enough to influence prognosis. Sepsis and septic shock have an increasing incidence and are considered as leading causes of mortality (2,3), likely reflecting aging populations with more comorbidities and increased recognition due to advanced techniques and awareness of health providers (4-8). The pathogenesis of sepsis is not precisely understood, and mounting evidence suggests that an exaggerated and uncontrolled systemic host inflammatory and coagulation response to infectious pathogens leads to inflammatory injury, microvascular thrombosis, multiple organ dysfunction syndrome (MODS) and even death.

Proinflammatory cytokines secretion initiated by the host response stimulates the expression of tissue factors and activated coagulation system, which in turn modulates inflammatory activity through specific receptors such as protease-activated receptors. Considering the excessive crosstalk between inflammation and coagulation is ongoing from the onset of sepsis, severe coagulopathy may develop in early phase of sepsis, which involves dysfunction of coagulation cascade process, anticoagulant and fibrinolytic systems, as well as relevant endothelial injury and abnormality of blood cells and vascular wall function (9-11). The severity of sepsis-associated coagulopathy is variable, ranging from subclinical abnormalities that are detectable by a mild decrease in platelet count and prolongation of clotting times to severe forms of coagulopathy such as disseminated intravascular coagulation (DIC) (10,12).

The function of endothelium in the pathogenesis of sepsis is regulated by pathways that control vascular permeability, coagulation, and systemic inflammation (13-15). Severe sepsis causes the upregulation of several proinflammatory adhesion molecules and the release of proinflammatory mediators, including cytokines and lipid products, and is accompanied by the dysfunction of coagulation factors, all of which disrupt the barrier of endothelial cells (15,16). Although acknowledged markers such as PT, APTT, D-dimers and platelets have been widely used to identify the development of DIC, those markers have low sensitivity in early diagnosis. Endothelium injury and an abnormal coagulation system play an important role in the development of septic shock and sepsis-induced DIC. Thus, markers that reflect endothelial injury could potentially predict the early stage of septic shock and DIC (17-19). Soluble thrombomodulin (sTM), tissue plasminogen activator-inhibitor complex (t-PAIC), thrombin-antithrombin complex (TAT), and α2-plasmin inhibitor-plasmin complex (PIC) are considered to be sensitive markers of endothelial cell injury and coagulation disorders. Recent studies have found that sTM, t-PAIC, TAT and PIC are related to acute kidney injury, acute respiratory distress syndrome (ARDS) and DIC (20-22). However, it is not clear whether these markers can predict the early occurrence of septic shock or sepsis-related DIC. Therefore, this study intended to investigate these biomarkers as predictors for 60-day mortality in patients with sepsis and evaluate the predictive value of endothelial markers for early prediction of septic shock and sepsis-induced DIC.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2222).

Methods

Patients and study design

A retrospective study was carried out in the emergency ICU of Zhongshan Hospital, Fudan University, Shanghai, China. Patients diagnosed with sepsis on admission from January 2016 to December 2018 were enrolled in this study. The diagnosis of sepsis referred to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), namely suspected infection with Sequential Organ Failure Assessment (SOFA) score ≥2 (23). DIC was diagnosed according to JAAM criteria (score ≥4) (24). All patients were screened for prognosis at day 60 after admission and development of shock and DIC. Septic patients were classified into septic shock and non-septic shock groups, DIC and non-DIC groups according

to developing septic shock or DIC during the first 7 days of ICU stay or not.

Non-septic patients in critical condition admitted to the emergency ICU were recruited as ICU controls, whose diagnoses included (I) acute heart failure (n=29), (II) asthma (n=19), (III) acute exacerbation of chronic obstructive pulmonary disease (n=18), (IV) pneumothorax (n=13), (V) hypertensive emergencies (n=16), (VI) arrhythmia (n=16), (VII) acute stroke (n=8) and (VIII) intoxication (n=6), which were not associated with acute coagulation dysfunction and endothelium injury. The exclusion criteria for both septic patients and ICU controls were as follows: (I) age <18 years; (II) immune system disease; (III) malignancy; (IV) hematological disease; (V) thrombotic disease; (VI) chronic liver disease (Child-Pugh C); (VII) chronic renal failure requiring hemodialysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Research Ethics Committee of Zhongshan Hospital, Fudan University (No: 2006-23). Informed consent for the use of biological samples were acquired from patients or their authorized agents on admission as this study is part of an on-going project regarding pathogenesis of sepsis since 2006, in spite of the retrospective nature of this study. Sepsis treatment was according to Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016 (25).

Data collection

Baseline characteristics including age, gender, site of infection, acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores, requirement for mechanical ventilation and the 60-day prognosis of patients were collected from the Electronic Medical Record System (EMRS) and our sepsis database, which we founded in 2006 to routinely collect the sample and information of patients with sepsis. Underlying medical history was also obtained including ischemic heart disease, chronic heart failure, chronic obstructive pulmonary disease, cerebrovascular accident and diabetes mellitus. The levels of prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT), fibrinogen (FIB), D-dimer, platelet count (PLT) and lactate were collected. Indexes of blood coagulation including PT, TT, APTT and FIB were assayed using the CS-2100i automatic coagulation analyzer (Sysmex, Japan).

Biomarker measurement

2–3 mL venous blood was drawn from patients and preserved in a sample tube (BD Vacutainer with sodium citrate anticoagulant, UK). Processing of samples was carried out according to standardized protocol for the measurement of coagulation indexes of central laboratory of Zhongshan Hospital, Fudan University, which has been approved by ISO15189. The samples were centrifuged at 1,500 g at 4 ℃ for 10 min, and then 500 μL supernatant was collected and stored at –80 ℃. The frozen plasma samples were thawed just before use, by immersion in a water bath at 37 ℃ for 5 min. The levels of sTM, t-PAIC, TAT and PIC were measured via qualitative chemiluminescence enzyme immunoassay performed on HISCL automated analyzers (Sysmex, Japan), which has been commercialized and approved by Pharmaceuticals and medical devices agency of Japan, National Medical Products Administration of China and acquired CE permission in European Union to be used for aided diagnosis and disease monitoring. The examination methods were detailed in the product instructions (HISCL sTM, t-PAIC, TAT and PIC Assay Kit, Japan).

Statistical analysis

Normally distributed continuous variables were expressed as the means ± standard deviations, and non-normally distributed continuous variables were expressed as medians (25th and 75th quartiles). Student's t test or one-way analysis of variance was used to compare normally distributed continuous variables. Kruskal-Wallis one-way analysis or Mann-Whitney U test was utilized to compare nonnormally distributed continuous variables. Categorical data were expressed as numbers (percentages) and compared by Pearson's chi-square test or Fisher's exact test when appropriate. Multivariate logistic regression model based on a forward stepwise method was used to identify the independent factors. Cox proportional hazards regression analyses based on a forward stepwise method was used to estimate the hazard ratios with 95% CIs to discover prognostic markers. Receiver operating characteristic (ROC) curves were constructed and the areas under the ROC curves (AUCs) were determined. The optimal cutoff values with highest Youden index were calculated to maximize the sum of the sensitivity and specificity. Kaplan-Meier estimates were used to illustrate trends in 60-day

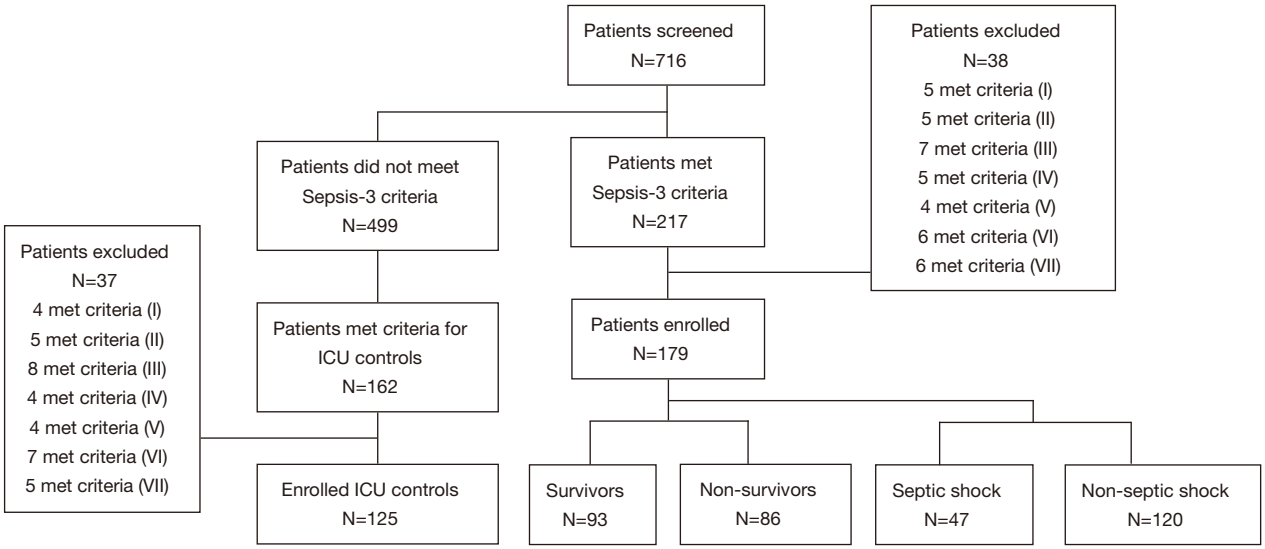

Figure 1 Flow chart of included patients and ICU controls.

mortality, and Log-rank tests were performed to compare survival curves. All statistical analyses were two-tailed, and the significance level was set to P<0.05. Power analysis was conducted on http://powerandsamplesize.com based on a significance level α=0.05 and results have been shown in Table S1. Statistical analyses were performed using SPSS (version 22.0, SPSS, Chicago, IL, USA).

Results

Levels of endothelial injury and hemostatic biomarkers in septic patients and ICU controls

A total of 179 septic patients and 125 non-septic ICU controls were enrolled (*Figure 1*). The baseline characteristics of study population were shown in *Table 1*. Septic patients had longer ICU and hospital stays and higher mortality rates, APACHE II and SOFA scores. For the hemostatic parameters, the levels of PLT, PT, TT, APTT, FIB, and D-dimer all showed statistical difference between septic patients and controls. Moreover, sTM (19.9 *vs.* 11.1 TU/mL, P<0.001), t-PAIC (18.1 *vs.* 7.2 ng/mL, P<0.001) and TAT (19.4 *vs.* 8.7 ng/mL, P<0.0001) levels were higher in septic patients. Then, we performed multivariate analysis and found that difference in levels of APACHE II score (OR =1.112, 95% CI: 1.051–1.176, P_{adj}<0.001), D-dimer (OR =1.097, 95% CI: 1.045–1.151, P_{adj}<0.001) and sTM (OR =1.093, 95% CI: 1.049–1.139, P_{adj}<0.001) between two groups remained statistically significant. These results suggested the endothelial cell injury and coagulation dysfunction during the acute early phase of sepsis.

sTM and t-PAIC as predictors for 60-day mortality in patients with sepsis

According to 60-day mortality, septic patients were divided into survival (n=93) and non-survival groups (n=86). In univariate analyses, age, APACHE II and SOFA scores, the levels of PT, TT, D-dimer, sTM, TAT, t-PAIC and lactate of non-survivors were higher than those of survivors (*Table 2*). As revealed by Cox regression analysis, APACHE II score (HR =1.052, 95% CI: 1.029–1.075, P_{adj}<0.001), age (HR =1.027, 95% CI: 1.013–1.041, P_{adj}<0.001), sTM (HR =1.012, 95% CI: 1.003–1.022, P_{adj}=0.012) and t-PAIC (HR =1.014, 95% CI: 1.004–1.025, P_{adj}=0.009) were independent predictors for 60-day mortality of septic patients.

Analyzing the performance of age, sTM, t-PAIC and APACHE II score for predicting 60-day mortality, the values of the AUC were 0.681 (0.602–0.760), 0.697 (0.620–0.775), 0.716 (0.642–0.790) and 0.747 (0.675–0.818), respectively. Combining the APACHE II score with age, sTM and t-PAIC, the AUC raised up to 0.809 (0.747–0.872, P<0.001) (*Figure 2A*). The median values of sTM and t-PAIC of septic patients of non-survivors were 19.0 TU/mL and 18.3 ng/mL, respectively. According to the median values, we plotted the Kaplan-Meier curves. Septic patients with sTM, t-PAIC concentrations higher

Table 1 Baseline characteristic, endothelial cell injury and coagulation markers of septic and ICU-control patients

Variables	Septic patients	ICU-controls	P value
Number	179	125	
Male, n (%)	105 (58.7)	83 (66.4)	0.260
Age (years)	61 [47–72]	61 [47–74]	0.640
Complications, n (%)			
Diabetes	17 (9.5)	15 (12.0)	0.480
Chronic liver disease	5 (2.8)	4 (3.2)	0.840
Chronic renal failure	18 (10.1)	14 (11.2)	0.750
Congestive heart failure	20 (11.2)	16 (12.8)	0.670
Chronic pulmonary disease	16 (8.9)	14 (11.2)	0.520
Outcomes			
ICU stay (d)	14 [6–21]	8 [4–12]	0.003
Hospital stay (d)	19 [8–26]	13 [6–18]	0.004
Mortality, n (%)	86 (48.0)	24 (19.2)	<0.001
Clinical indexes			
APACHE II score	12 [8–19]	5 [3–10]	<0.001
SOFA score	5 [3–9]	2 [1–4]	<0.001
Lactate (mmol/L)	2.3 (1.5–3.3)	1.8 (1.3–2.3)	<0.001
Coagulation markers			
PLT ($\times 10^9$/L)	138.0 (73.0–214.0)	196.0 (133.0–267.0)	<0.001
PT (s)	13.6 (12.3–15.9)	13.0 (12.3–13.9)	0.002
TT (s)	17.2 (16.0–19.0)	16.8 (16.1–17.6)	0.026
APTT (s)	32.9 (28.6–42.9)	29.3 (27.6–31.9)	<0.001
Fibrinogen (mg/dL)	345.0 (233.0–471.0)	431.0 (320.0–568.0)	<0.001
D-Dimer (mg/L)	7.5 (2.8–15.2)	2.0 (0.8–4.0)	<0.001
Endothelium injury markers			
sTM (TU/mL)	19.9 (15.0–32.1)	11.1 (8.9–15.0)	<0.001
TAT (ng/mL)	19.4 (9.7–49.4)	8.7 (3.6–18.8)	<0.001
PIC (μg/mL)	1.4 (0.8–2.6)	1.5 (1.9–2.2)	0.504
t-PAIC (ng/mL)	18.1 (9.7–32.1)	7.2 (4.6–11.2)	<0.001
Sites of infection, n (%)			
Lung	120 (67.0)		
Abdomen	35 (19.6)		
Bloodstream	6 (3.4)		
Urinary tract infection	8 (4.5)		
Others	10 (5.6)		

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Septic patients	ICU-controls	P value
Microbiology positive, n (%)	70 (39.1)		
Gram-positive	27 (38.6)		
Gram-negative	31 (44.3)		
Fungi	4 (5.7)		
Mixed	8 (11.4)		
Microbiology unknown	109 (60.9)		

APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; PIC, α2-plasmin inhibitor-plasmin complex; PLT, platelet; PT, prothrombin time; SOFA, Sequential Organ Failure Assessment; sTM, soluble thrombomodulin; TAT, thrombin-antithrombin complex; t-PAIC, tissue plasminogen activator-inhibitor complex; TT, thrombin time.

than the median thresholds had a lower probability of 60-day survival (*Figure 2B,2C*).

Then, we detected dynamic changes in the biomarkers within 5–7 days after ICU admission. The SOFA score (3 *vs.* 4, P<0.001), levels of sTM (14.1 *vs.* 18.6 ng/mL, P=0.003), t-PAIC (8.8 *vs.* 18.2 ng/mL, P<0.001) and lactate (1.5 *vs.* 2 mmol/L, P=0.004) in survivors within 5–7 days were significantly lower than those on the first day of ICU admission (*Figure 2D*). However, in the non-survival group, the SOFA score and the level of sTM and t-PAIC within 5–7 days was not found to be significantly different from those on the day of admission (*Table 3*).

Early prediction role of sTM and lactate for septic shock

Septic patients were divided into shock (n=47) and non-shock group (n=120). Patients diagnosed with septic shock on admission were excluded. The mortality rate, APACHE II and SOFA scores were significantly higher in patients developing septic shock (*Table 4*). Univariate analysis revealed that the difference in levels of PLT, PT, APTT, FIB, D-dimer, sTM, t-PAIC and lactate were statistically significant between two groups (*Table 4*). The levels of sTM (OR =1.049, 95% CI: 1.020–1.078, P_{adj}=0.001), lactate (OR =1.307, 95% CI: 1.039–1.644, P_{adj}=0.022) and APACHE II score (OR =1.076, 95% CI: 1.019–1.137, P_{adj}=0.009) remained significantly different in multivariate analysis. The evaluation of predictive value for septic shock of several markers was carried out via receiver operating curve analysis (*Figure 2E*). Among three markers, the AUC was 0.765 (0.687–0.842) for sTM which was higher than 0.691 (0.593–0.790) for lactate and 0.755 (0.674–0.837) for APACHE II score. The AUC for the combination of markers was 0.811 (0.738–0.884).

Early prediction role of sTM, PLT and D-dimer for sepsis-induced DIC

Patients with sepsis-induced DIC (n=28) had higher severity of diseases with higher APACHE II and SOFA scores on admission (n=144). Patients diagnosed with DIC on ICU admission were excluded. The difference in levels of PLT, PT, APTT, FIB and D-dimer on admission were statistically significant between two groups. Additionally, the levels of sTM (42.05 *vs.* 18.4 TU/mL, P<0.001) and t-PAIC (32.25 *vs.* 15.1 ng/mL, P<0.001) in DIC patients were significantly higher than those in non-DIC patients (*Table 5*). In multivariate analysis, PLT (OR =0.970, 95% CI: 0.956–0.984, P_{adj}<0.001), sTM (OR =1.109, 95% CI: 1.063–1.158, P_{adj}<0.001) and D-dimer (OR =1.071, 95% CI: 1.015–1.129, P_{adj}<0.001) are closely related to sepsis-induced DIC. Analyzing the performance of the markers for predicting DIC, the values of AUC were 0.865 (0.807–0.922), 0.864 (0.794–0.935) and 0.775 (0.695–0.856) for PLT, sTM, and D-dimer, respectively. Combining the PLT with sTM and D-dimer, the AUC increased to 0.950 (0.916–0.983) (*Figure 2F*).

Discussion

The current study indicated that high levels of sTM and t-PAIC were independent predictive factors for the poor outcome of septic patients. Combining the APACHE II score with age, sTM and tPAIC, the predictive value raised even higher. In addition, the levels of sTM has early predictive values of septic shock and sepsis-induced DIC.

Table 2 Baseline characteristic and univariate analysis of the endothelial injury and coagulation markers between survival and non-survival groups

Variables	Non-survivor	Survivor	P value
Number	86	93	
Male, n (%)	54 (62.8)	52 (55.9)	0.350
Age (years)	68 [58–75]	55 [41–66]	<0.001
Complications, n (%)			
Diabetes	10 (11.6)	7 (7.4)	0.350
Chronic liver disease	3 (3.5)	2 (2.1)	0.590
Chronic renal failure	12 (14.0)	6 (6.4)	0.100
Congestive heart failure	10 (11.6)	10 (10.6)	0.850
Chronic pulmonary disease	11 (12.8)	5 (5.3)	0.080
Outcomes			
ICU stay (d)	12 [4–20]	15 [9–26]	0.210
Hospital stay (d)	18 [7–28]	21 [9–29]	0.090
Clinical indexes			
APACHE II score	15.5 (11–23.25)	9 [6–14]	<0.001
SOFA score	8 [4–12]	4 [3–7]	<0.001
Lactate (mmol/L)	2.5 (1.7–3.8)	2.2 (1.4–2.8)	0.021
Coagulation markers			
PLT ($\times 10^9$/L)	135.0 (55.3–215.8)	138.5 (90.0–214.0)	0.510
PT (s)	14.5 (12.6–18.1)	13.2 (12.1–14.7)	0.002
TT (s)	17.5 (16.1–19.4)	16.80 (16.0–18.7)	0.049
APTT (s)	34.8 (28.9–46.8)	31.6 (28.4–39.9)	0.088
Fibrinogen (mg/dL)	325.0 (217.3–466.3)	358.5 (265.5–490.8)	0.102
D-dimer (mg/L)	9.4 (4.5–19.2)	4.9 (2.2–12.3)	0.001
Endothelium injury markers			
sTM (TU/mL)	26.5 (18.3–41.8)	16.8 (13.5–24.6)	<0.001
TAT (ng/mL)	27.5 (13.6–57.1)	15.6 (7.1–45.1)	0.003
PIC (μg/mL)	1.4 (0.8–2.7)	1.5 (0.9–2.5)	0.382
t-PAIC (ng/mL)	24.0 (14.2–41.6)	13.2 (6.6–22.8)	<0.001
Sites of infection, n (%)			
Lung	58 (67.4)	62 (66.6)	0.910
Abdomen	18 (20.9)	17 (18.3)	0.660
Bloodstream	2 (2.3)	4 (4.3)	0.460
Urinary tract infection	3 (3.5)	5 (5.4)	0.540
Others	5 (5.8)	5 (5.4)	0.900
Microbiology positive, n (%)	34 (39.5)	36 (38.7)	0.910
Gram-positive	12 (35.3)	15 (41.7)	0.580
Gram-negative	17 (50.0)	14 (38.9)	0.350
Fungi	2 (5.9)	2 (5.6)	0.950
Mixed	3 (8.8)	5 (13.9)	0.510
Microbiology unknown	52 (60.5)	57 (61.3)	0.910

APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; PIC, α2-plasmin inhibitor-plasmin complex; PLT, platelet; PT, prothrombin time, SOFA Sequential Organ Failure Assessment; sTM, soluble thrombomodulin; TAT, thrombin-antithrombin complex; t-PAIC, tissue plasminogen activator-inhibitor complex; TT, thrombin time.

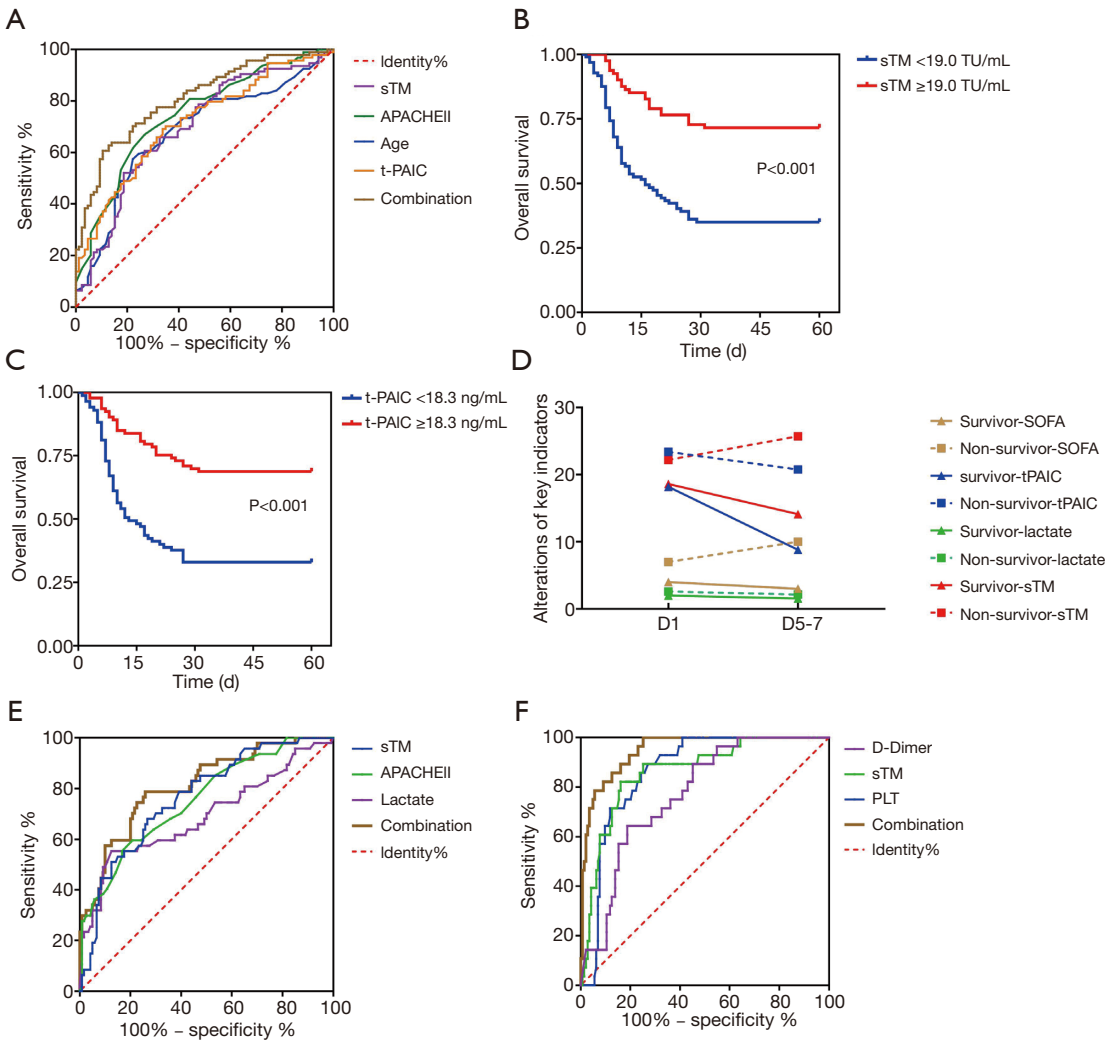

Figure 2 Soluble thrombomodulin, t-PAIC and hemostatic parameters as biomarkers for the prediction of prognosis and early evaluation of septic shock and sepsis-induced DIC. (A) ROC curves for the prediction of 60-day mortality; (B) comparison of Kaplan-Meier survival curves between patients with high and low sTM levels; (C) comparison of Kaplan-Meier survival curves between patients with high and low t-PAIC levels; (D) dynamic changes of SOFA score, levels of sTM (TU/mL), t-PAIC (ng/mL) and lactate (mmol/L) in survivors and non-survivors; (E) ROC curves for the prediction of septic shock; (F) ROC curves for the prediction of sepsis-induced DIC. APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; PLT, platelet, PT, prothrombin time; SOFA, Sequential Organ Failure Assessment; sTM, soluble thrombomodulin; t-PAIC, tissue plasminogen activator-inhibitor complex; DIC, disseminated intravascular coagulation.

These findings emphasized the importance of endothelial injury among patients with sepsis, especially in the early recognition and management of septic shock and sepsis-induced DIC.

Inflammation and coagulation constitute two host defense systems with complementary roles against infection, which means that an overwhelming systemic inflammatory reaction in sepsis is accompanied by coagulopathy, and both may contribute to tissue damage in the early phase of sepsis (26-37). In a mouse model of endotoxemia, the administration of LPS resulted in a reduction in total tissue TM antigen in the lung and brain (35). Under *in vitro* conditions, the addition of LPS and/or cytokines to endothelial cells has been shown to decrease the synthesis of TM, tissue-type plasminogen activator and heparan, increase the expression of tissue factor (TF) and

Table 3 APACHE II score and levels of sTM, t-PAIC in survival and non-survival patients on day 1, day 5-7 after ICU admission

Variables	Survival Group		Non-survival Group		P_1 value	P_2 value	P_3 value
	D1	D5–7	D1	D5–7			
Clinical indexes							
APACHE II score	10 [7–15]	7 [4–11]	15 (10–20.75)	19 (12–28.25)	0.004	0.221	<0.001
SOFA score	4 (3.5–8)	3 [2–5]	7 [4–12]	10 [6–13]	<0.001	0.085	<0.001
Lactate (mmol/L)	2.0 (1.5–3.1)	1.5 (1.3–2.1)	2.6 (1.9–3.8)	2.2 (1.8–4.3)	0.004	0.893	<0.001
Coagulation markers							
PLT ($\times 10^9$/L)	123.0 (89.0–199.0)	187.0 (112.5–270.0)	135.0 (83.3–169.5)	116.5 (60.8–193.8)	0.007	0.366	0.003
PT (s)	13.2 (12.1–14.5)	12.8 (12.2–14.2)	14.2 (12.5–19.5)	14.7 (13.2–19.5)	0.630	0.355	<0.001
TT (s)	17.2 (16.2–18.8)	16.4 (15.6–17.7)	17.7 (16.1–21.1)	17.7 (16.2–20.8)	0.019	0.954	0.006
APTT (s)	31.8 (27.9–41.5)	31.0 (28.0–34.4)	34.8 (26.9–45.0)	35.0 (30.2–45.2)	0.300	0.447	0.005
Fibrinogen (mg/dL)	354.0 (283.5–450.5)	336.0 (253.0–456.5)	285.5 (233.5–496.8)	275.5 (133.3–382.5)	0.575	0.085	0.024
D-dimer (mg/L)	5.5 (2.1–13.8)	5.8 (2.5–9.0)	8.9 (4.4–16.5)	9.0 (5.3–21.7)	0.644	0.317	0.001
Endothelium injury markers							
sTM (TU/mL)	18.6 (14.3–25.0)	14.1 (10.2–30.0)	22.2 (14.8–40.0)	25.7 (18.3–43.9)	0.003	0.275	<0.001
TAT (ng/mL)	18.4 (9.6–46.0)	8.3 (4.7–13.0)	26.7 (13.6–44.1)	26.9 (11.3–93.2)	<0.001	0.627	<0.001
PIC (μg/mL)	1.8 (1.1–3.1)	1.6 (1.0–2.4)	1.3 (0.8–2.2)	1.6 (0.7–7.2)	0.162	0.218	0.809
t-PAIC (ng/mL)	18.2 (10.7–32.3)	8.8 (6.1–13.1)	23.4 (13.5–37.1)	20.8 (14.5–31.8)	<0.001	0.580	<0.001

P_1 value, survival group D1 *vs.* D5–7; P_2 value, non-survival group D1 *vs.* D5-7; P_3 value, non-survival group D5–7 *vs.* survival group D5–7. APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; PIC, α2-plasmin inhibitor-plasmin complex; PLT, Platelet; PT, Prothrombin Time; SOFA, Sequential Organ Failure Assessment; sTM, soluble thrombomodulin; TAT, thrombin-antithrombin complex; t-PAIC, tissue plasminogen activator-inhibitor complex; TT, Thrombin time.

Table 4 Baseline characteristic and univariate analysis of the endothelial cell injury and coagulation markers between shock and non-shock groups

Variables	Shock	Non-shock	P value
Number	47	120	
Male, n (%)	25 (53.2)	70 (58.3)	0.420
Age (years)	63 [44–72]	60 [47–72]	0.750
Complications, n (%)			
Diabetes	5 (10.6)	10 (8.3)	0.760
Chronic liver disease	2 (4.2)	3 (2.5)	0.620
Chronic renal failure	7 (14.9)	10 (8.3)	0.260
Congestive heart failure	6 (12.8)	13 (10.8)	0.790
Chronic pulmonary disease	8 (17.0)	7 (5.8)	0.034
Outcomes			
ICU stay (d)	12 [5–20]	15 [6–22]	0.110
Hospital stay (d)	17 [6–24]	20 [7–28]	0.210
Mortality, n (%)	30 (63.8)	49 (38.3)	0.010
Clinical indexes			
APACHE II score	18 [11–28]	10 (7–15.75)	<0.001
SOFA score	11 [7–14]	4 [3–7]	<0.001
Lactate (mmol/L)	3.3 (1.8–4.8)	2.1 (1.4–2.7)	<0.001
Coagulation markers			
PLT ($\times 10^9$/L)	76.0 (38.0–132.0)	163.0 (107.3–224.5)	<0.001
PT (s)	16.8 (13.7–22.1)	13.2 (12.2–14.6)	<0.001
TT (s)	16.8 (16.0–19.1)	17.2 (16.1–18.7)	0.944
APTT (s)	43.9 (29.9–43.9)	31.4 (27.9–37.5)	<0.001
Fibrinogen (mg/dL)	333.0 (176.0–431.0)	361.5 (251.3–482.0)	0.033
D-dimer (mg/L)	9.0 (2.8–19.3)	7.3 (2.6–13.3)	0.046
Endothelium injury markers			
sTM (TU/mL)	32.3 (20.1–48.6)	18.6 (13.7–28.0)	<0.001
TAT (ng/mL)	21.3 (14.2–59.8)	20.0 (9.6–46.2)	0.204
PIC (μg/mL)	1.4 (0.7–3.4)	1.50 (1.0–2.4)	0.835
t-PAIC (ng/mL)	23.6 (12.7–38.0)	15.7 (8.7–40.0)	0.009
Sites of infection, n (%)			
Lung	31 (65.9)	82 (68.3)	0.710
Abdomen	9 (19.1)	23 (19.2)	1.000
Bloodstream	2 (4.2)	4 (3.3)	1.000
Urinary tract infection	2 (4.2)	6 (5.0)	1.000
Others	3 (6.4)	5 (4.2)	0.690

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Shock	Non-shock	P value
Microbiology positive, n (%)	18 (38.3)	48 (40.0)	0.860
Gram-positive	6 (33.3)	19 (39.6)	0.780
Gram-negative	8 (44.4)	22 (45.8)	1.000
Fungi	2 (11.1)	1 (2.1)	0.180
Mixed	2 (11.1)	6 (12.5)	1.000
Microbiology unknown	29 (61.7)	72 (60.0)	0.860

APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; PIC, α2-plasmin inhibitor-plasmin complex; PLT, Platelet; PT, Prothrombin Time; SOFA, Sequential Organ Failure Assessment; sTM, soluble thrombomodulin; TAT, thrombin-antithrombin complex; t-PAIC, tissue plasminogen activator-inhibitor complex, TT Thrombin time.

Table 5 Baseline characteristic and univariate analysis of the endothelial cell injury and coagulation markers between DIC and non-DIC groups

Variables	DIC	Non-DIC	P value
Number	28	144	
Male, n (%)	16 (57.1)	81 (56.3)	0.93
Age (years)	60 [51–69]	61 [47–73]	0.85
Complications, n (%)			
Diabetes	2 (7.1)	13 (9.0)	1.00
Chronic liver disease	2 (7.1)	3 (2.1)	0.19
Chronic renal failure	3 (10.7)	14 (9.7)	1.00
Congestive heart failure	3 (10.7)	16 (11.1)	1.00
Chronic pulmonary disease	2 (7.1)	14 (9.7)	0.75
Outcomes			
ICU stay (d)	13 [2–20]	16 [5–27]	0.19
Hospital stay (d)	15 [2–25]	19 [7–28]	0.09
Mortality, n (%)	15 (53.6)	62 (43.1)	0.41
Clinical indexes			
APACHE II score	18 [11–23]	11 [7–16]	0.022
SOFA score	10.5 [7–14]	4 [3–7]	<0.001
Lactate (mmol/L)	3.2 (2.4–6.9)	2.1 (1.4–2.8)	<0.001
Coagulation markers			
PLT ($\times 10^9$/L)	69.5 (58.0–110.3)	165.0 (118.0–225.8)	<0.001
PT (s)	16.5 (14.4–24.0)	13.3 (12.2–14.7)	<0.001
TT (s)	18.5 (16.0–22.3)	17.0 (16.0–18.6)	0.059
APTT (s)	47.2 (36.6–56.9)	31.4 (27.9–37.2)	<0.001
Fibrinogen (mg/dL)	218.0 (119.3–343.0)	371.0 (271.3–488.0)	<0.001
D-Dimer (mg/L)	16.0 (8.5–20.5)	5.5 (2.4–12.5)	<0.001

Table 5 (*continued*)

Table 5 (*continued*)

Variables	DIC	Non-DIC	P value
Endothelium injury markers			
sTM (TU/mL)	42.1 (30.6–51.3)	18.4 (13.6–25.5)	<0.001
TAT (ng/mL)	26.1 (15.8–72.2)	17.8 (8.9–46.3)	0.044
PIC (μg/mL)	1.4 (0.8–3.5)	1.5 (0.9–2.4)	0.751
t-PAIC (ng/mL)	32.3 (18.3–54.6)	15.1 (8.2–28.9)	<0.001
Sites of infection, n (%)			
Lung	17 (60.7)	98 (68.1)	0.51
Abdomen	6 (21.4)	27 (18.8)	0.79
Bloodstream	1 (3.6)	5 (3.5)	1.00
Urinary tract infection	2 (7.1)	6 (4.2)	0.62
Others	2 (7.1)	8 (5.6)	1.00
Microbiology positive, n (%)	12 (42.9)	56 (38.9)	0.83
Gram-positive	4 (33.3)	22 (39.3)	0.76
Gram-negative	5 (41.7)	25 (44.6)	1.00
Fungi	1 (8.3)	3 (5.4)	1.00
Mixed	2 (16.7)	6 (10.7)	0.62
Microbiology unknown	17 (60.7)	88 (61.1)	1.00

APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; PIC, α2-plasmin inhibitor-plasmin complex; PLT, platelet; PT, prothrombin time; SOFA, Sequential Organ Failure Assessment; sTM, soluble thrombomodulin; TAT, thrombin-antithrombin complex; t-PAIC, tissue plasminogen activator-inhibitor complex; TT, thrombin time.

plasminogen activator inhibitor-1 (PAI-1), and generate procoagulant microparticles (31-34). Endothelial cells are at the interface between inflammation and coagulation in sepsis (30). The excessive inflammatory response during sepsis leads to endothelial cell injury, which starts coagulation and causes the formation of microthrombi (38). At the same time, vascular endothelial cell injury causes peripheral vascular tension abnormalities, which leads to microcirculatory disorder. Our results showed that sTM and t-PAIC were independent factors for septic shock and DIC suggesting that endothelial injury which occurs as a result of inflammation initiation could in turn result in dysfunction of coagulation and even DIC. The prognostic value of endothelial markers was also studied by many studies (21), And this has been confirmed by our study that higher levels of sTM and t-PAIC are associated with increased 60-day mortality of sepsis.

Thrombomodulin (TM), a transmembrane glycoprotein, is abundant on all endothelial surfaces (39). As an essential component of the protein C system, endothelial-bound TM plays important roles in anti-coagulation (40). Soluble TM is the product of proteolytic degradation of endothelial-bound TM. Under physiological conditions, sTM levels are in a stable range (41). When the endothelium is damaged, endothelial-bound TM is released from the endothelial surface, resulting in a significant increase in sTM concentration (42). As a sensitive marker of endothelial damage, sTM was found to be elevated in sepsis, DIC, vasculitis, venous thrombosis, trauma and ARDS patients (43). t-PAIC is a complex of t-PA and PAI-1. t-PA and PAI-1 are mainly synthesized by endothelial cells. PAI-1 can occur in various molecular forms in blood, including PAI-1 complexed with its target proteases (urokinase-type plasminogen activator and tissue-type plasminogen activator, t-PAIC). The increased concentration of t-PAIC suggests the occurrence of fibrin thrombosis and the sustained damage of endothelial cells, which can be used as a marker to determine the repair degree of the vascular endothelial system.

Increasing evidence has indicated that higher sTM and

t-PAIC levels are indicative of endothelial injury, which showed potential values for the management of relevant diseases. A multicenter, prospective, observational study conducted by Mei *et al.* found that elevated plasma levels of sTM, t-PAIC and TAT were useful for the diagnosis of DIC (20). Another multicenter trial suggested that higher plasma sTM levels are associated with increased mortality in ARDS patients (22). Furthermore, Lin *et al.* found that increased serum TM levels are significantly correlated with illness severity and mortality in pediatric sepsis syndromes (44). Elevated plasma sTM levels are also associated with organ dysfunction in children with ARDS (23). However, only a few studies have focused on the relationship between the levels of sTM, t-PAIC, TAT and septic shock, sepsis-induced DIC. Our study indicated that sTM and t-PAIC are associated with a poor outcome of sepsis, and sTM was useful for the early prediction of DIC. The early prediction of septic shock is also crucial. Although many markers such as lactate level have been introduced for prediction of septic shock, those markers showed poor values in early prediction (45,46). We found the increase of sTM can predict septic shock in early stage, which provides a solution to this issue.

TAT is also a sensitive marker of thrombin generation and development of DIC. But we did not confirm the association between increased level of TAT and sepsis-induced DIC. TAT level in patients without sepsis-induced has also increased due to coagulation dysfunction since they were also diagnosed with sepsis, and this narrowed the difference between two groups. Also, platelets might not be totally discarded after one-time centrifugation of blood samples, this could influence the preciseness of testing results of TAT.

The highlight of our study is that we explored the predictive value of endothelial markers for septic shock and sepsis-induced DIC, which added to the results of previous studies. This study provides two references for the clinicians. (I) A clinician should be aware of the development of sepsis if a patient shows elevated levels of endothelial markers. (II) If a patient has already been diagnosed with sepsis, elevated levels of endothelial markers indicate the higher possibility of developing septic shock, sepsis-induced DIC and poor 60-day outcome, which calls for the appropriate treatment strategy by the clinicians.

Our study had several limitations. First, this study was not a randomized controlled trial, and multiple unmeasured variables might account for the outcome difference observed in the study. Second, power analysis indicated that the analyses for TAT and PIC did not have enough statistical power. Thus, further studies with larger sample size are needed. Third, the testing protocols are varied among different institutes and the results are needed to be verified. The improvement of testing techniques is also crucial to the preciseness of the results.

Conclusions

The results of our study provide evidence that most patients developed severe coagulopathy and endothelial cell injury in the initial phase of sepsis, which was demonstrated by abnormalities in endothelial biomarkers and their strong association with 60-day prognosis and the development of septic shock and sepsis-induced DIC. In particular, the endothelial cell injury markers such as sTM and t-PAIC allowed early prediction of severe coagulopathy and poor outcome, leading to early intervention for patients with sepsis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2222

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Research Ethics Committee of Zhongshan

Hospital, Fudan University (No: 2006-23). Informed consent for the use of biological samples were acquired from patients or their authorized agents.

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