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Clinical Efficacy of Soluble Thrombomodulin, Tissue Plasminogen Activator Inhibitor complex, Thrombin-Antithrombin complex,α2-Plasmininhibitor-Plasmin complex in Pediatric Sepsis

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Abstract

Objective: To investigated the clinical efficacy of Soluble thrombomodulin (sTM), tissue plasminogen activator inhibitor complex (t-PAI·C),thrombin-antithrombin complex (TAT),α2-plasmininhibitor-plasmin complex (PIC) in pediatric sepsis and pediatrics sepsis-induced coagulopathy (pSIC).

Methods: We prospectively collected patient data with sepsis diagnosed in the PICU of Shanghai Children's Medical Center from June 2019 to June 2021. sTM,t-PAI·C, TAT,PIC and classical coagulation laboratory tests (CCTs) were evaluated on the day of sepsis diagnosis.

Results: Fifty-nine children were enrolled, There were significant differences in t-PAI·C ($P = 0.001$), Plt ($P < 0.001$), PT ($P < 0.001$), INR ($P < 0.001$), aPTT ($P < 0.001$), and TT ($P = 0.048$) between the pSIC and non-pSIC groups, logistic regression analysis showed that Plt ($P = 0.032$) was an independent risk factor for pSIC. Logistic regression analysis showed that sTM ($P = 0.007$) and Plt ($P = 0.016$) were independent risk factors for the outcome in pediatrics sepsis following discharge. The AUC of sTM combined with Plt on the mortality outcome of children with sepsis at discharge was 0.889 (95%CI: 0.781,0.956). which was better than that for PRISM III (AUC, 0.723), pSOFA (AUC, 0.764), and blood Lac (AUC, 0.717) when sepsis was diagnosed in the PICU.

Conclusions: The t-PAI·C increased in children with pSIC. The prediction of sepsis outcome using sTM combined with Plt was better than with PRISM III, pSOFA, or Lac.Further research is still needed in the future to explore the clinical value of sTM, TAT, PIC, and t-PAI·C in diagnosis and outcome of pediatrics sepsis and pSIC.

Keywords

Sepsis, Sepsis-induced coagulopathy, Novel coagulation markers, Endothelial cell injury, Children

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Introduction

Sepsis is defined as a life-threatening organ dysfunction that is caused by a host immune disorder due to infection,[1] and it is a common and serious disease in pediatric intensive care units (PICUs), with a high morbidity and mortality. Epidemiological surveys over the past 10 years have shown that the incidence rate of sepsis in children is increasing annually.[2] Twenty-six international multicenter studies revealed that the prevalence of pediatric severe sepsis increased to 8.2%, and the mortality rate was as high as 25% in between 2013 and 2014,[3] with sepsis-induced coagulation disorder accounting for 50%–70% of these deaths.[4] Sepsis-induced coagulopathy (SIC) constitutes a series of diseases, from the early activation of the coagulation system to the formation of microthromboses to the massive consumption of coagulation factors and the occurrence of overt disseminated intravascular coagulation (DIC).[5] As up to 70% of patients die of overt DIC in sepsis, SIC remains one of the main causes of death in sepsis.[6]

SIC is a hypercoagulable condition due to inhibition of the anticoagulant system after early endothelial system injury. Since conventional or classical coagulation laboratory tests (CCTs) cannot detect activation of the early rising coagulation system or the inhibition of the fibrinolytic system, coagulation markers that accurately reflect the coagulation status of children with sepsis are sorely needed. Soluble thrombomodulin (sTM), thrombin-antithrombin complex (TAT), α2-plasmininhibitor-plasmin complex (PIC), and tissue plasminogen activator inhibitor complex (t-PAI·C) have been useful in a variety of adult diseases;[7–10] however, there is little research on sTM, TAT, PIC, or t-PAI·C in children. In the present study, we assessed the coagulation status of children with sepsis by determining sTM, TAT, PIC, and t-PAI·C combined with CCTs, and determined their values in the diagnosis of pSIC and the outcome of sepsis in children.

Methods

Study Design

This was a single-center prospective study in which patients were diagnosed as having sepsis or severe sepsis (including septic shock) at the Department of Critical Care Medicine of Shanghai Children's Medical Center, Affiliated with Shanghai Jiaotong University, between June 2019 and June 2021. Sepsis and severe sepsis were diagnosed in accordance with the 2005 International Guidelines for the Diagnosis of Sepsis in Children.[11] This study was approved by the Ethics Committee of Shanghai Children's Medical Center (Shanghai, China, approval number: SCMCIRB-K2021065-1).

Patients

Children who fulfilled the following criteria were included: 1) aged over 28 days and under 18 years; 2) afflicted with acute diseases that required PICU admission; and 3) who received parental consent. The exclusion criteria included 1) patients with congenital coagulation dysfunction; 2) long-term use of anticoagulant drugs (heparin, antithrombin, etc); 3) undergoing blood purification and establishment of in vitro life support, and requiring systemic heparin anticoagulant therapy; and 4) the guardian refusing to sign an informed consent form.

Laboratory Test Methods

The novel coagulation markers sTM, TAT, PIC, and t-PAI·C were determined using matching reagents by a chemiluminescence method on a Sysmex HISCL-5000 chemiluminescence immunoassay analyzer (Sysmex Corporation, Kobe, Hyogo, Japan). CCTs were assessed using a CA-1500 whole-blood coagulation analyzer from the Sysmex Company in Japan (Sysmex Corporation, Kobe, Hyogo, Japan). The timing of coagulation markers measurement was when the child was admitted to PICU to diagnose sepsis or septic shock.

Study Groups

The children were divided into a pSIC group and non-pSIC group according to their sepsis coagulation scores (pSIC score, Table 1).[12] Also, consonant with the outcomes of sepsis patients at discharge, they were divided into survival and non-survival groups.

Observation Indicators

The primary outcome indicators were sTM, TAT, PIC, and t-PAI·C.

The secondary outcome indicators were CCTs that included Plt count (Plt), activated partial thromboplastin time(aPTT), Prothrombin time(PT), Thrombin time(TT), International Normalized Ratio(INR), Fibrinogen(Fib), D-dimers (DD), and Fibrin degradation products(FDP).

Other secondary outcome indicators were inflammation markers, organ-function markers, clinical characteristics, anticoagulant

Table 1. Clinical characteristics in this study

Category	Parameter		0	1	2
	Prothrombin	PT-INR	≤1.2	>1.2, ≤1.4	>1.4
	Coagultaion	Platelet count(10^9/L)	≥150	<150	<100
	pSOFA	pSOFA 4 items	0	1	≥2

Note: pSOFA is the sum of the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA). The score of pSOFA was defined as 2 if pSOFA score exceeded 2.Abbreviations: INR, International Normalization Ratio; pSOFA, pediatric sequential organ failure; PT, prothrombin time

therapy and blood product infusion index, critical-illness scores (PRISM III, pSOFA,P-MODS),[13–15] DIC scores,[16] mechanical ventilation time, vasoactive drug score (VIS),[17] duration in the PICU, total hospital stay, and PICU outcome.

Safety indicators included the presence of active bleeding and thromboses.

Statistical Methods

Measurement data that conformed to a normal or approximately normal distribution are expressed as ($x \pm s$), and we compared two independent samples using the independent-sample *t* test. Measurement data following a non-normal distribution are expressed as median (interquartile interval; P25, P75), and we performed the Mann-Whitney U test to compare two independent samples. Logistic regression analysis was used to analyze the independent risk factors of pSIC and mortality outcome due to sepsis following discharge. We implemented the area under the ROC curve (AU-ROC) method to evaluate the sensitivity and specificity of sTM, TAT, and PIC, and t-PAI·C without or combined with CCTs, to predict the mortality outcome of children with pSIC and sepsis following discharge. Data were analyzed using SPSS 21.0 for Windows (SPSS, Inc.).

Table 2. Clinical characteristics in this study

Variable	pSIC group (n = 46)	Non-pSIC group (n = 13)
Age, months	86.24 ± 68.42	53.38 ± 43.43
Sex, n (%)		
Male	31 (67.4)	8 (61.5)
Female	15 (32.6)	5 (38.5)
DIC score	4.86 ± 1.61	2.69 ± 1.18
pSIC score	6.00 (5.00, 6.00)	3.00 (2.00, 3.00)
PRISM III	20.39 ± 6.56	9.31 ± 5.45
P-MODS	4.15 ± 2.18	2.15 ± 0.99
pSOFA	8.74 ± 3.01	3.46 ± 2.50
VIS	30.00 (0, 61.88)	5.00 (0, 30.00)
LDH, U/L	881 (476.50, 1764.25)	745 (616.00, 803.75)
SF, ng/ml	2180.21 ± 2051.95	1107.60 ± 1673.68
ALT, U/L	35.50 (25.00, 115.25)	37.00 (19.50, 84.50)
TBIL, μmol/L	23.45 (12.55, 54.28)	12.80 (7.90, 17.50)
CRP, μmol/L	39.00 (24.00, 58.00)	27.00 (22.50, 33.00)
BUN, mmol/L,	7.54 ± 5.83	4.95 ± 3.60
Lactate(Lac), mmol/L	2.85 (1.28, 5.43)	1.30 (0.80, 3.40)
WBC, 10^9/L	0.54 (0.08, 4.02)	10.38 (4.20, 25.71)
CRP, mg/L	111.65 ± 77.94	106.94 ± 73.59
PCT, ng/ml	8.04 (2.79, 48.35)	2.03 (0.91, 28.60)
Underlying disease (n,%)		
Leukemia	22 (47.8)	3 (23.1)
Hematological malignancies	8 (17.4)	2 (15.4)
Post liver transplantation	5 (10.9)	0 (0)
Dilated cardiomyopathy	1 (2.2)	0 (0)
Nephrotic syndrome	1 (2.2)	0 (0)
Aplastic anemia	1 (2.2	0 (0)
None	8 (17.4)	8 (61.5)
Pathogen, n (%)		
Gram-positive	37 (80.4)	7 (53.8)
Gram-negative	9 (19.6)	6 (46.2)
Duration of mechanical ventilation, hrs	66 (0, 211.50)	0 (0, 163)
Duration in PICU, days	7 (5, 17.75)	7 (5.5, 10.50)
Duration in hospital, days	33.87 ± 29.34	18.31 ± 11.19
Outcome at discharge, n (%)		()
Survival	32 (69.6)	12 (92.3)
Non-survival	14 (30.4)	1 (7.7)

Results

Clinical Characteristics (Table 2.)

Primary outcomes in the pSIC and non-pSIC groups

There was a significant difference in t-PAI·C between the two groups ($P < 0.05$) (Table 3, Figure 1).

There were significant differences in Plt, PT, INR, aPTT, TT, and DIC scores between the two groups ($P < 0.05$) (Table 4).

Logistic regression analysis of sTM, TAT, and PIC; and t-PAI·C combined with CCTs in predicting pSIC. Multivariate logistic regression analysis showed that Plt ($P = 0.032$) was an independent risk factor for pSIC (Table 5).

Comparison of outcomes due to sepsis at discharge; 44 children survived and 15 died at discharge. There were significant differences in sTM, TAT, Plt, PT, INR, DIC score, pSIC score, PRISM III, and pSOFA between the two groups ($P < 0.05$) (Table 6, Figure 2).

Logistic regression analysis of sTM, t-PAI·C,TAT and PIC combined with CCTs in predicting the mortality outcome of children with sepsis at discharge.

Multivariate logistic regression analysis showed that sTM ($P = 0.007$) and Plt ($P = 0.016$) were independent risk factors for mortality outcome due to sepsis at discharge (Table 7).

AU-ROC was used to evaluate the efficacy of sTM combined with Plt in predicting the mortality outcome with sepsis at discharge.

The area under the ROC curves for sTM combined with Plt in predicting the mortality outcome of children with sepsis at discharge was 0.889 (95%CI: 0.781,0.956), which was higher than that for PRISM III (AUC, 0.723), pSOFA (AUC, 0.764),

Table 3. Primary outcomes of pSIC and non-pSIC groups

Variable	pSIC group (n = 46)	Non-pSIC group (n = 13)	*P*
sTM, TU/mL	11.85 (8.00, 17.15)	10.70 (9.00, 14.95)	0.993
TAT, ng/mL	6.60 (3.20, 16.95)	5.90 (2.85, 11.50)	0.621
PIC, ug/mL	1.09 ± 1.07	1.38 ± 0.93	0.367
t-PAI·C, ng/mL	18.20 ± 17.71	7.35 ± 5.83	0.001

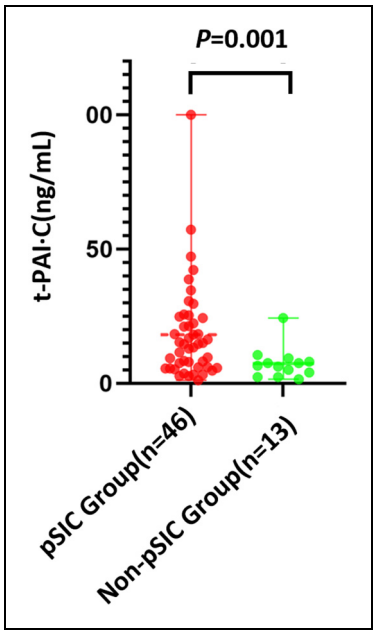

Figure 1. Comparison of t-PAI·C between patients with pSIC and non-pSIC groups Secondary outcomes in the pSIC and non-pSIC groups

Table 4. Secondary outcomes in the pSIC and non-pSIC groups

Variable	pSIC group (n = 46)	Non-pSIC group (n = 13)	*P*
Plt,10^9/L	30.00 (12.75, 76.50)	271 (140.50, 339.50)	< 0.001
PT, s	19.10 (15.25, 26.95)	13.30 (11.60, 14.50)	< 0.001
aPTT, s	50.05 ± 20.02	33.54 ± 5.77	< 0.001
TT, s	16.50 (14.7, 19.20)	15.20 (14.45, 15.50)	0.048
FIB, g/L	2.72 ± 1.80	3.30 ± 1.13	0.274
FDP, ug/ml	8.45 (3.73, 19.28)	15.60 (5.75, 24.60)	0.360
D-dimers, mg/L	0.97 (0.51, 2.79)	2.18 (0.65, 3.60)	0.293
INR	1.75 (1.40, 2.54)	1.23 (1.07, 1.34)	< 0.001
DIC scores	4.86 ± 1.61	2.69 ± 1.18	< 0.001

and blood Lac (AUC, 0.717) when sepsis was diagnosed in the PICU (Table 8, Figures 3).

Discussion

Sepsis leads to endothelial cell damage, activation of the procoagulant system, and inhibition of anticoagulant substances such as antithrombin (AT), protein C (PC), and tissue factor pathway inhibitor (TFPI).[18] Coagulopathy is a disorder of coagulation that includes both bleeding and thrombosis, and the prevalence rates of adult SIC and DIC have been reported to be as high as 50%–70% and 35%, respectively.[19] Early recognition of coagulopathy is therefore critical for clinical diagnosis and treatment. Since the diagnostic criteria for sepsis in children

Table 5. Logistic regression analysis of sTM, TAT, and PIC; and t-PAI·C combined with CCTs in predicting pSIC

Variable	β	S.E.	Wald	*P*	Odds ratio	95% CI Lower	95% CI Upper
Plt,10^9/L	−0.015	0.007	4.606	0.032	0.986	0.973	0.999

Table 6. Primary and secondary outcomes in the survival and non-survival groups

Variable	Survival group (n = 44)	Non-survival group (n = 15)	*P*
sTM, TU/mL	12.30 ± 6.27	21.85 ± 14.01	0.021
TAT, ng/mL	5.15 (2.90, 9.85)	12.30 (3.50, 35.50)	0.012
PIC, ug/mL	1.01 ± 0.80	1.59 ± 1.50	0.170
tPAIC, ng/mL	8.80 (5.05, 20.43)	14.60 (6.30, 24.80)	0.240
Plt,10^9/L	127.36 ± 131.45	33.07 ± 34.38	<0.001
PT, s	15.55 (13.78, 19.55)	29.50 (15.30, 35.10)	0.007
aPTT, s	45.55 ± 19.83	48.95 ± 17.25	0.556
TT, s	15.60 (14.50, 17.20)	16.60 (14.70, 24.10)	0.320
FIB, g/L	2.93 ± 1.44	2.60 ± 2.29	0.523
FDP, ug/ml	10.86 ± 8.26	61.79 ± 94.83	0.057
D-dimers, mg/L	1.44 ± 1.21	8.21 ± 13.02	0.064
INR	1.42 (1.28, 1.80)	2.79 (1.41, 3.24)	0.006
DIC scores	3.93 ± 1.63	5.67 ± 1.50	0.001
pSIC scores	5 (3, 6)	6 (5, 6)	0.009
PRISM III	16.43 ± 7.49	22.40 ± 7.22	0.009
P-MODS	2.93 ± 1.62	6 ± 1.81	<0.001
pSOFA	6.77 ± 3.28	9.93 ± 3.69	0.003

are different from sepsis-3.0 in adults,[1,10] we proposed a pSIC scoring scheme based on pSOFA scores in children and SIC scores in adults.[12] pSIC was then used to evaluate the occurrence of pSIC in the group of children in our study.

As classical coagulation indicators such as PT or aPTT do not reflect the state of overall coagulatory function,[20,21] the ability to diagnose pSIC early remains limited. Among the new coagulation markers, TAT directly reflects the activation of the coagulation system and can be used as a marker of coagulation initiation. When the SIC anticoagulation system is inhibited, the fibrinolytic system also changes. Plasmin is an important component of the fibrinolytic system. The half-life of activated plasmin is very short; and plasmin reacts rapidly with fibrinolytic system α 2 plasmin inhibitor to combine 1:1 and thereby form PIC, which then reflects the early rise in plasmin and measurement of which can be used to evaluate the degree of fibrinolytic activation in vivo. In addition, the fibrinolytic system is principally mediated by plasminogen activator inhibitor-1 (PAI-1) and PIC, and thrombin activator fibrinolysis inhibitor (TAFI) leads to fibrinolytic inhibition. Activated platelets and endothelial cells then promote the rapid increase of PAI-1 in sepsis patients; and PAI-1 forms t-PAI·C by combining with tissue plasminogen activator (t-PA) to inactivate it, thereby inhibiting the dissolution of fibrin.[22] The emergence of t-PAI·C can provide an early

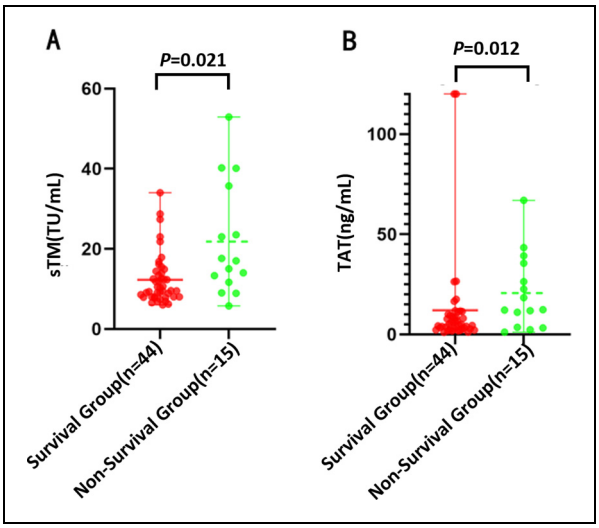

Figure 2. A.Comparison of sTM between patients with Survivla and Non-Survival groups; B. Comparison of TAT between patients with Survivla and Non-Survival groups

Table 7. Logistic regression analysis of sTM, t-PAI·C,TAT and PIC combined with CCTs in predicting the mortality outcome of children with sepsis at discharge.

						95% CI	
Variable	B	S.E.	Wald	*P*	OR	Lower	Upper
sTM, TU/mL	0.304	0.113	7.194	0.007	1.355	1.085	1.692
Plt, 10^9/L	−0.043	0.018	5.834	0.016	0.958	0.925	0.992

indication of the occurrence of fibrinolytic inhibition, and is closely related to endothelial cell injury.[23] Therefore, sTM, TAT, PIC, and t-PAI·C can be utilized to evaluate the changes in coagulation status from the critical environments of many pathophysiological mechanisms that underly SIC—including endothelial cell injury, early-coagulation activation, and fibrinolytic-system inhibition. Asakura[18] recommended that TAR, PIC, and t-PAI·C be detected in sepsis-related DIC to evaluate the status of coagulation disorders.

In this study, the new coagulation marker t-PAI·C was significantly increased in the pSIC and non-pSIC groups ($P = 0.001$). Semeraro et al[24] reported in 280 adult patients with sepsis that the changes in fibrinolytic state in sepsis was mainly due to the increase in PAI-1 and the activation of TAFI. In an animal model of endotoxemia, PAI-1 expression was primarily localized to vascular endothelial cells, suggesting that plasma PAI-1 originated from endothelial cells;[25] and this coincided with the theory of endothelial-cell injury in sepsis. Madoiwa et al[26] reported that increased PAI-1 in sepsis was also associated with organ dysfunction and a poor prognosis

Table 8. AU-ROC of sTM combined with Plt,P-MODS,PRISM III, pSOFA, Lac in predicting the mortality outcome due to sepsis at discharge.

Variable	AUC	SE	95% CI	*P*
sTM combined with Plt	0.889	0.048	0.781,0.956	<0.001
P-MODS	0.899	0.052	0.788,0.990	<0.001
PRISMIII	0.723	0.075	(0.576, 0.870)	0.010
pSOFA	0.764	0.075	(0.616, 0.911)	0.002
Lac	0.717	0.078	(0.656, 0.869)	0.013

in sepsis. The results of our study are thus very similar to those reported in the literature.

Combined with the results from CCTs, Plt was shown to be a risk factor for pSIC in children with sepsis. Mei et al[27] demonstrated that TAT, t-PAI·C, and sTM increased in patients with DIC in adult sepsis, revealing endothelial injury, coagulation activation, and fibrinolytic inhibition in patients with sepsis. The reasons for not obtaining the same research conclusions in the present study may include the following: 1) The diagnostic criteria for sepsis in adults and children were not completely congruent. The diagnosis of sepsis in adults depends upon SOFA score, while sepsis-2.0 is still used for children,[10] and pSOFA is not involved in the diagnosis of sepsis in children. 2) There were many children with hematological malignancies included in our study, and the underlying status of their coagulatory function was different from that of the study by Mei et al and other patients. There may also be damage to hematopoietic function, especially with respect to the impact of platelet count on coagulatory function. Therefore, we herein concluded that platelet count was a risk factor for pSIC. 3) Coagulatory function in children is greatly affected by age-related factors,[28,29] and use of the pSIC score has not yet been proposed by the International Society for Thrombosis and Hemostasis (ISTH). Additional clinical studies are therefore needed to confirm the methods for the early diagnosis of pSIC and to provide timely treatment of sepsis in children.

In the current study, we demonstrated that Plt and sTM were independent risk factors for mortality outcome following discharge after sepsis. We showed that sTM in the non-survival group was significantly higher than in the survival group, and studies have revealed that decreased platelet count and prolonged PT were associated with increased mortality due to sepsis.[30] sTM can also be used as an early predictor of pediatric sepsis death, and the level of sTM in non-survival groups has been significantly increased.[31] Khattab et al[32] depicted a higher level of sTM in pediatric sepsis relative to their control group, and the mortality of children with increased sTM was higher than that for surviving patients ($P = 0.005$). Our AU-ROC for sTM in predicting the outcome of sepsis death in children was 0.711, which was higher than the AU-ROCs for PRISM III and PIM scores (0.918 and 0.960, respectively). The results of this study were also consistent with the conclusions drawn by Khattab et al Thrombomodulin is a transmembrane glycoprotein mainly produced by vascular endothelial

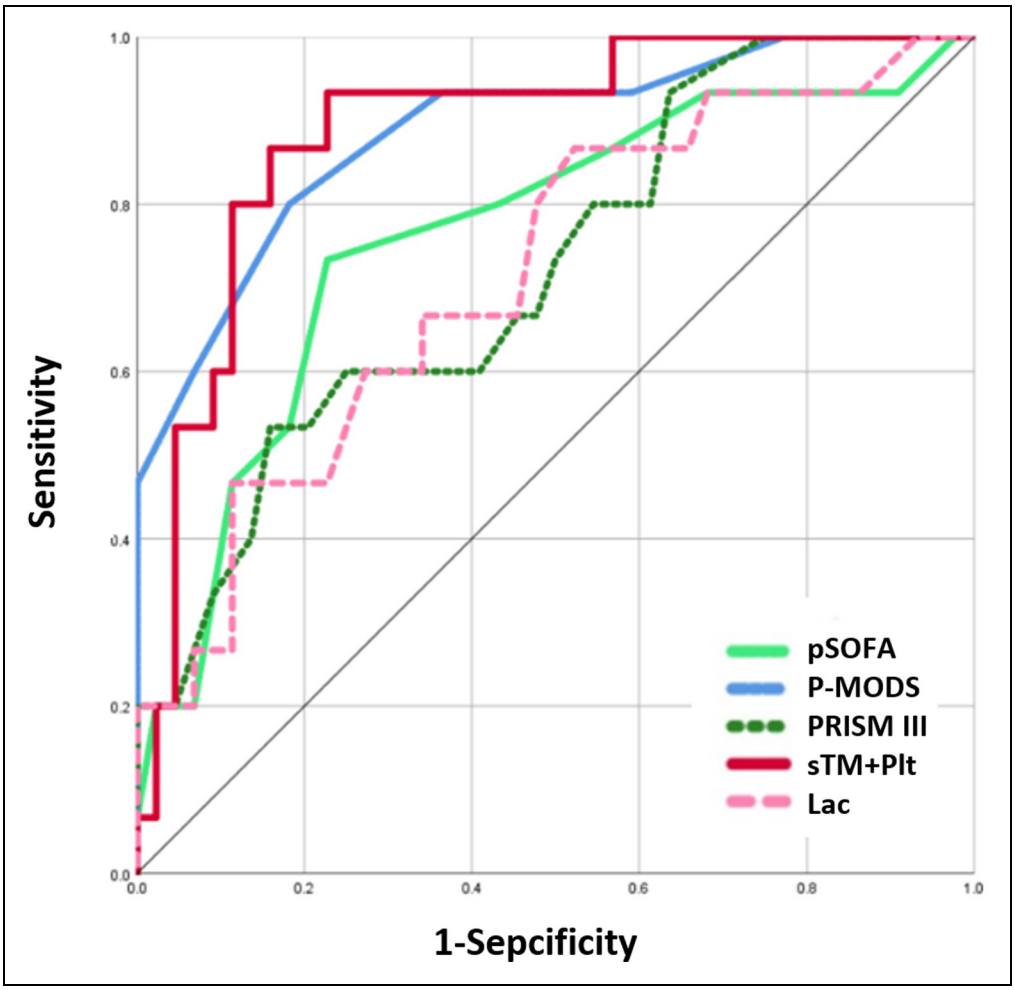

Figure 3. AU-ROC of sTM combined with Plt,P-MODS,PRISM III, pSOFA, Lac in predicting the mortality outcome due to sepsis at discharge.

cells, and indicates injury to vascular endothelial cells. Vascular endothelium is the principal target of sepsis, and one of the characteristics of SIC is endothelial dysfunction.[33] Therefore, the augmented increase in sTM that we observed was consistent with the pathophysiological mechanism underlying endothelial cell injury caused by sepsis. The results of our study thus show that sTM is a reliable biomarker of endothelial cell injury.

pSOFA,PRISM III and P-MODS are commonly used scoring methods for organ-function evaluation and early-warning prognosis in children with sepsis. For example, studies have shown that pSOFA score, PRISM III, and hyperlactatemia are reliable indicators for predicting sepsis death in children.[34,35] In the present study, sTM, TAT, PIC, and t-PAI·C combined with CCTs possessed the strongest predictive capability for mortality outcomes of children with sepsis following discharge (AU-ROC 0.892), followed by pSOFA (AU-ROC 0.764); CCTs (AU-ROC 0.740); sTM, TAT, PIC, and t-PAI·C (AU-ROC 0.738); PRISM III (AU-ROC 0.723); and blood Lac (AU-ROC 0.717). This shows that the prediction of sTM, TAT, PIC, and t-PAI·C combined with CCTs on the prognosis of sepsis patients at discharge is superior to pSOFA, PRISM III, and Lac. The results of our study are thus consistent with the conclusions of Khattab et al.[32] The clinical significance of this study is that after endothelial cell injury caused by sepsis, starting from the initiating links of endothelial cell injury, coagulation factors activation and fibrinolysis function inhibition, through new coagulation markers and combined with CCTs, it can play an early warning role in the prognosis of sepsis and pSIC in children, We recommend further multicenter clinical research to explore the early warning efficacy of the cut-off values of sTM,t-PAI·C,TAT and PIC combined with CCTs on the diagnosis of sepsis and pSIC in children.

It should be noted that the pathophysiology of coagulation disorder in sepsis is the formation of microthrombosis, in which fibrinolytic inhibition constitutes the primary cause of sepsis-related organ dysfunction.[36] After the activation of the coagulation system in sepsis, a large number of immunothromboses are formed in microcirculatory vessels, blocking oxygen delivery and resulting in organ dysfunction and increasing the mortality from sepsis. The physiological coagulation status in children is more likely to encompass a mild hypercoagulable state than in adults,[37] and children's thrombotic

diseases are more often ignored than those of adults.[38] Studies have shown that FDPs and D-dimers are significantly increased during immunothrombosis,[39] but the increase observed in CCTs lacks specificity as these indices are also increased in trauma, tumor, infection, and other diseases;[40] thus, they cannot fully reflect the changes caused by abnormal fibrinolysis in sepsis. The accuracy of FDPs and D-dimers in evaluating the damage to the fibrinolytic system in sepsis has therefore been questioned. sTM, TAT, PIC, and t-PAI·C reflect the initial changes in endothelial cell injury, coagulation-system activation, and fibrinolytic system changes from different aspects. Combined with FDPs and D-dimers, these markers are more conducive to the evaluation of the prethrombotic state. The evaluation of the fibrinolytic state of pSIC should therefore be further investigated in the future to guide more accurate treatment.

We had been paying attention to the influence of developmental hemostasis theory on bleeding and coagulation function in children of different ages.[28,29] This mainly affects the coagulation function in infants. In this study, 12 infants aged less than 1 year were included. because of its relationship to sample size, age stratification was also not delineated. Therefore, we hope to expand the included sample size, reduce the influence of confounding factors, including age, on pediatric sepsis and pSIC as much as possible, and obtain clinical research results that can be used to guide clinical decision-making.

There were several limitations to the present study: 1) this study was a single-center study, and the number of child cases was small; 2) there were many children with hematologic malignancies that were not discussed with respect to disease stratification; 3) changes in sTM, TAT, and t-PAI·C were not continuously monitored so as to reflect their dynamic changes in pediatric sepsis;4) there were many confounding factors in clinical research on sepsis, such as underlying diseases, clinical interventions, enrollment time, age, and gender. Therefore, In the process of logistic regression, we assumed linearity but may not hold true in real world data. We should increase the included sample size in order to control confounding factors; 5) In this study, the ROC curve was based on a training sample. Due to the small sample size, there will be the problem of overfitting. However, the clinical research data of sTM, PIC, t-PAIC, and TAT tests in pediatric sepsis are very limited, especially for the special patient population of pediatric sepsis. In future research, we will further increase the included sample size and carry out multi-center clinical research to obtain more detailed clinical research data.

Conclusions

We herein demonstrated that the novel coagulation marker t-PAI·C increased in children with pSIC. The prognostic prediction for sepsis patients using sTM, TAT, PIC, and t-PAI·C—combined with CCTs—was superior to that for PRISM III, pSOFA, or Lac, particularly with respect to biomarkers of endothelial cell injury. sTM was also related to the mortality outcome with respect to sepsis at discharge. Further research is, however, still needed to explore the clinical value of sTM, TAT, PIC, and t-PAI·C in the diagnosis and prognosis of sepsis and pSIC in children.

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Authors' contributions

JL, JZ, YW, and LX took responsibility of literature search, study design, writing and critical revision. HR, TT and BL mainly participated in data collection, data analysis and data interpretation. All authors contributed to the article and approved the submitted version.

Ethics approval

This study was approved by the Ethics Committee of Shanghai Children's Medical Center (Shanghai, China, approval number: SCMCIRB-K2021065-1).

Consent to participate

Written informed consent was obtained from the parents.

Consent for publication

Not applicable.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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