



Full Length Article

Evaluation the combined diagnostic value of TAT, PIC, tPAIC, and sTM in disseminated intravascular coagulation: A multi-center prospective observational study

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ABSTRACT

Background: Accurate and early diagnosis is important in the management of disseminated intravascular coagulation (DIC). We employed new automation technology to detect plasma biomarkers, including thrombin-antithrombin complex (TAT), α 2-plasmininhibitor-plasmin complex (PIC), soluble thrombomodulin (sTM), and tissue plasminogen activator-inhibitor complex (tPAIC), and evaluated their diagnostic performance and prognostic value for DIC in Chinese population.

Methods: This prospective observational study included 444 patients with suspected DIC and 137 healthy people. The molecular markers were measured by qualitative chemiluminescence enzyme immunoassay performed on HISCL automated analyzers. All patients with suspected DIC were followed for 7 days to screen for the development of overt-DIC and 28 days for mortality.

Results: According to the International Society of Thrombosis and Haemostasis (ISTH) scoring system, 157 patients were diagnosed as overt-DIC and 36 were diagnosed as pre-DIC. All four biomarkers were significantly higher in DIC patients than in non-overt DIC patients; TAT, tPAIC, and sTM were significantly higher in pre-DIC patients than in non-overt DIC patients. Four molecular markers behaved differently among various underlying diseases. TAT, tPAIC, and sTM were also good predictors of 28-day mortality, high levels were associated with poor outcomes.

Conclusions: TAT, PIC, tPAIC, and sTM demonstrated good diagnostic performance and prognostic value in DIC patients with different underlying diseases. Besides, TAT, tPAIC and sTM have certain implications in pre-DIC stage. Combination of four makers was demonstrated better behavior than single one.

1. Background

Disseminated intravascular coagulation (DIC) is a severe disorder that causes persistent, generalized, marked coagulation activation and widespread deposition of fibrin in the circulation, which can

compromise the blood supply to multiple organs, thus leading to multiple organ failure. Moreover, the exhaustion of platelets and coagulation proteases due to the ongoing coagulation may result in severe bleeding [1–4]. Any disease that induces an increase in prothrombotic factors or a decrease in endogenous anticoagulants, causes endothelial

Abbreviations: DIC, Disseminated intravascular coagulation; TAT, Thrombin-antithrombin complex; PIC, α 2-plasmininhibitor-plasmin complex; tPAIC, Tissue plasminogen activator-inhibitor complex; sTM, soluble thrombomodulin; ISTH, International society on thrombosis and haemostasis; PT, Prothrombin time; APTT, Activated partial thromboplastin time; FDPs, Fibrin(-ogen) degradation products; TT, Thrombin time; ROC, Receiver operating characteristic; AUC, The area under the ROC curve

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dysfunction, or impairs fibrin degradation can trigger DIC. The most common underlying diseases include infections, solid tumors, hematological malignancies, obstetrical calamities, trauma, liver diseases, and organ destruction [2,5].

DIC is reported to be associated with a high rate of mortality [6], and early treatment based on an appropriate diagnosis is essential for improving the prognosis [7]. Thus far, most of the pathogenic factors of DIC have been identified. However, the accurate diagnosis of DIC may still be a challenge, because most assays focus on the consumption of coagulation factors or platelet counts, which may be detectable only in the later stages of DIC; furthermore, more sensitive biomarkers that indicate activation of coagulation or fibrinolysis are often not available in most hospitals [8,9].

Previous studies have confirmed that the plasma levels of thrombin-antithrombin complex (TAT), and α 2-Plasmininhibitor-Plasmin complex (PIC) are significantly increased both before and after the onset of DIC, but are not associated with multiple organ failure or prognosis. However, tissue plasminogen activator-inhibitor complex (tPAIC) and soluble thrombomodulin (sTM) are significantly increased in DIC patients with organ failure or poor outcomes [10–13]. Some of these markers demonstrate different behaviors in the presence of different underlying diseases or different types of DIC [14,15]. Over the past few years, the clinical utility of these markers has been limited because they could be only measured in specialized laboratories and not on a daily basis in routine care. Moreover, the utility of these molecular markers in diagnosing DIC remains poorly understood.

Herein, we employed novel automation technology to detect the plasma levels of TAT, PIC, sTM, and tPAIC and evaluated their diagnostic performance and prognostic value for DIC in Chinese population.

2. Methods

2.1. Study design and setting

This was a multi-center, prospective observational study, that was conducted in 9 institutes located across China. Data for 444 patients (184 females and 260 males) with suspected DIC and 137 healthy people (70 females and 67 males) from October 1, 2016, to July 31, 2017 were included in this study. The study protocol was approved by the Human Ethics Review Committee of Tong-ji Medical College, Huazhong University of Science. Written informed consent was obtained from the patients or the next of kin.

The inclusion criteria were based on the presence of more than one abnormal finding for the following parameters [16,17]: platelet count < 120 G/L, prolongation of prothrombin time (PT) ≥ 3 s, fibrinogen ≤ 1 g/L, fibrin/fibrinogen degradation products (FDP) ≥ 10 mg/L, D-dimer ≥ 5 mg/L. The exclusion criteria were [18]: age < 17 , heparin induced thrombocytopenia, thrombotic thrombocytopenic purpura, antiphospholipid syndrome or liver cirrhosis classified as Child-Pugh grade C and patients with a current treatment that interfered with coagulation (anticoagulants). The treatment of underlying diseases included the administration of antibiotics or surgical drainage in patients with infectious diseases, anticancer drugs or surgery in patients with malignant diseases. Treatment for DIC including heparin, low molecular weight heparin, danaparoid sodium or blood transfusion were carried out under the observation of the individual physicians after blood sampling was obtained at registration.

One hundred thirty-seven healthy individuals (67 male and 70 female) who attended the hospital for a physical examination during the same time period were recruited as controls. The subjects in the control group were included only if they had normal biochemical indices in all routine examinations and no organic diseases.

DIC scores were calculated according to the International Society on Thrombosis and Haemostasis (ISTH) diagnostic criteria [19]. Patients with DIC scores > 5 on the registration day were diagnosed with overt-DIC, and those that DIC scores < 5 on the registration day but

developed overt-DIC within a week after registration were diagnosed with pre-DIC. Patients that didn't develop overt-DIC during their clinical course were diagnosed with non-overt DIC. All the patients were followed to screen for development of overt-DIC for 7 days and mortality for 28 days.

2.2. Biomarker measurements

Blood samples (2.7 mL, BD Vacutainer with sodium citrate anticoagulant, UK) obtained from patients with suspected DIC at registration and healthy people were collected. PT, levels of fibrinogen, FDP, and D-dimer were measured immediately after centrifugation of the blood samples at $1000 \times g$ for 15 min in each of the institute. The rest of the plasma samples were immediately stored at -80°C . The frozen plasma samples were thawed just before use, by immersion in a water bath at 37°C for 5 min. TAT, PIC, tPAIC and sTM were measured via qualitative chemiluminescence enzyme immunoassay performed on HISCL automated analyzers (HISCL-2000i, Sysmex, Japan). The examination methods are detailed in the product instructions (HISCL TM Assay Kit, Japan; HISCL t-PAIC Assay Kit, Japan; HISCL TAT Assay Kit, Japan; HISCL PIC Assay Kit, Japan).

2.3. Statistical analysis

The data are expressed as the median (25–75th percentile), unless otherwise indicated. The differences between the groups were examined for statistical significance using the Mann-Whitney *U* test. The Spearman's rank correlation analysis was used to analyze the association between the plasma levels of those markers and DIC scores. Receiver operating characteristic (ROC) curves were generated to calculate the area under the receiver operating characteristic curve (AUC) of each studied variable at baseline for the development of overt-DIC and all-cause death. The best cutoff values were calculated to maximize the sum of the sensitivity and specificity. Positive predictive values and negative predictive values were also calculated. Cox proportional hazards regression analyses was used to estimate the hazard ratios with 95% CIs to show molecular makers on all-cause mortality. Kaplan-Meier estimates were used to illustrate trends in 28-day mortality and the log rank test was performed. A *p*-value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using the IBM SPSS 21.0.

3. Results

The plasma levels of TAT, PIC, and sTM in 137 healthy people enrolled were 1.10 (0.70–1.60), 0.44 (0.37–0.56), and 8.60 (7.30–9.90), respectively. The tPAIC level among the healthy females was 5.90 (4.30–8.00), which was significantly lower than that observed in the males, 8.40 (6.90–10.20), ($p < 0.05$). The levels were within the normal range.

Among the 444 patients with suspected DIC, 157 were diagnosed with overt-DIC, 36 were diagnosed with pre-DIC and 251 were diagnosed with non-overt DIC. There were no significant differences in terms of age or sex among the patients with DIC, pre-DIC, and non-overt DIC. The most common underlying disease was hematological malignancy, followed by severe infection, solid tumor, and trauma/surgery (Table 1).

The value of hemostatic parameters, such as the platelet count, prolongation of PT, thrombin time (TT), D-dimer, TAT, PIC, tPAIC, and sTM were significantly different between patients with DIC and those without DIC (Table 2). There was significant difference in the values for platelet count, prolongation of PT and fibrinogen between DIC group and pre-DIC group ($p < 0.05$). These parameters were also different between pre-DIC group and non-overt DIC group. The values for D-dimer were also significantly higher ($p < 0.01$) in the patients with DIC than in those with pre-DIC, but there was no significant difference

Table 1
Clinical conditions of the patients.

Clinical condition	N (%)	Age (years)	Sex (F:M)	Pre-DIC/DIC rate (%)	Mortality (%)
Hematological malignancy	104(23.4)	51 (34–59.75)	40:64	55.8	19.2
Solid tumor	76 (17.1)	58 (48–63)	33:43	17.1	15.8
Sepsis	74 (16.7)	53 (42.5–63.25)	38:36	43.2	36.5
Trauma/surgery	72 (16.2)	46 (38–54.75)	18:54	25.0	13.9
Acute promyelocytic leukemia	47 (10.6)	33 (26–44)	20:27	72.3	8.5
Other	31(7.0)	49 (36–62)	10:21	64.5	38.7
Severe pancreatitis	23 (5.2)	58 (44–64)	10:13	39.1	43.5
Autoimmune diseases	10(2.3)	36 (25.25–56.25)	8:2	70.0	10.0
Obstetric calamities	7 (1.6)	31 (26–35)	7:0	28.6	0.0

between the patients with pre-DIC and those without DIC. The values for TT, TAT, tPAIC, and sTM were significantly higher ($p < 0.05$) in the patients with pre-DIC than those in without DIC, but there was no significant difference in the values for TT, TAT, PIC, tPAIC, and sTM between the patients with overt-DIC and those with pre-DIC (see Table 3).

The evaluation of each molecular marker and global coagulation to diagnose DIC was carried out via a receiver operating curve analysis (Fig. 1). The cutoff value was decided according to the point of intersection between the sensitivity curve and the “1-specificity” curve. Among four molecular markers (Table 4), the lowest area under the curve (AUC) was 0.650 for tPAIC and the highest AUC was 0.731 for sTM. When a combination of the four markers was applied, the AUC increased to 0.807 and the sensitivity to 74.1%. “tPAIC” and “TAT + PIC + tPAIC + sTM” showed the lowest and highest odd ratios, respectively.

The four molecular markers behaved differently in the presence of various underlying diseases (Table 5). There were significant differences in all four biomarkers between patients with DIC and those with non-overt DIC in hematological malignancies and solid tumors. The plasma level of TAT, tPAIC, and sTM were significantly higher in septic DIC patients. tPAIC and sTM showed significant differences in patients with trauma/surgery. Analyzing the performance of the four molecular markers for diagnosing DIC in different underlying diseases, the highest values of AUC were 0.727, 0.769, 0.886 and 0.871 for TAT, tPAIC, sTM and sTM, respectively.

The mortality rate was higher in patients with DIC (35.03%) or pre-DIC (47.22%) than in those without DIC (9.56%). Among the four molecular markers, TAT, tPAIC, and sTM showed significant differences between survivors and non-survivors ($p < 0.001$, respectively). Analyzing the performance of the single molecular marker and ISTH

DIC scores for predicting non-survival at day 28, the values of the AUC were 0.646, 0.755, 0.783 and 0.658 for TAT, tPAIC, sTM and DIC scores ($p < 0.05$), respectively. Combining the ISTH scores with TAT, tPAIC and sTM, the AUC raised up to 0.820 (0.773–0.866, $p < 0.0001$) (Fig. 2). A Cox regression analysis was conducted to evaluate relationship between mortality and age ($p > 0.05$), TAT ($p < 0.05$), PIC ($p > 0.05$), tPAIC ($p < 0.001$), and sTM ($p < 0.001$). The median value of TAT, tPAIC, and sTM were 17.8 ng/mL, 9.75 ng/mL and 14.35 TU/mL, respectively (Fig. 3). High levels of them were associated with poor outcome.

4. Discussion

The development of DIC is extremely complicated. The endothelial cells, the coagulation system, the anticoagulation system and the fibrinolytic system are all involved in the process [9]. Commonly used laboratory indicators including platelet count, PT, APTT, and D-dimer are not suitable for single use to diagnose DIC. Because of the lack of specific markers, it makes sense to diagnose DIC using a scoring system which combines multiple makers that show characteristic changes in DIC [20]. Previous studies have shown that some global coagulation tests such as PT APTT and platelet count, primarily reflect the result of consumption and impaired synthesis rather than ongoing coagulopathy [21,22]. They had limited value for early diagnosis and changed slowly in DIC patients, which is not conducive to treatment monitoring. More sensitive or specific molecular markers need to be explored.

TAT, PIC, tPAIC and sTM could elucidate pathogenesis of DIC from different aspects. TAT is considered to be a sensitive marker of thrombin generation, which plays a crucial role in DIC [23]. PIC is an indicator of plasmin generation, which varies among different underlying diseases [15]. tPAIC is associated with organ failure caused by

Table 2
Comparison between the overt-DIC, pre-DIC, non-overt DIC group.

	Overt-DIC (n = 157)	Pre-DIC (n = 36)	Non-overt DIC (n = 251)
Age (years)	48 (32–58.5)	48.5 (33–61.75)	52 (39–62)
Sex (F:M)	75:82	14:22	95:156
Platelet count	34 (20–57)	133 (77–205)***	82.5 (54.5–120.5)***##
Prolongation of PT (s)	2 (0.9–5.6)	0 (0–1.1)**	1.05 (0–2.65)***#
Thrombin time (s)	20.3 (16.75–23)	19.95 (16.33–22.23) NS*	17 (15.6–18.5)***##
Fibrinogen (g/L)	1.32 (0.9–2.77)	3.65 (2.66–4.97)*	2.38 (1.58–3.48)***##
D-dimer (mg/L)	18.76 (7.17–20)	5.9 (3.57–10.94)**	9.48 (4.66–20)***NS#
APACHE II score	27.3 ± 9.2	28.1 ± 10.0NS*	18.8 ± 6.1***##
SOFA score	10.3 ± 4.9	11.1 ± 5.7 NS*	6.0 ± 2.7***##
Mortality (%)	35.03	47.22	9.56

Data are expressed as median (interquartile range), mean ± SD, or No. (%).

DIC, disseminated intravascular coagulation*; PT, prothrombin time; ISTH, International Society of Thrombosis and Haemostasis; TAT, thrombin-antithrombin complex; PIC, α 2-plasmin inhibitor-plasmin complex; tPAIC, tissue plasminogen activator-inhibitor complex; sTM, soluble thrombomodulin; APACHE, acute physiology and chronic health evaluation; SOFA, Sequential Organ Failure Assessment.

*, $p < 0.05$ in comparison to overt-DIC; **, $p < 0.01$ in comparison to overt-DIC; ***, $p < 0.001$ in comparison to overt-DIC; #, $p < 0.05$ in comparison to pre-DIC; ###, $p < 0.001$ in comparison to pre-DIC; NS* or NS#; not significant in comparison to overt-DIC or pre-DIC.

Table 3
Comparison between overt-DIC group, Pre-DIC group, Non-overt DIC group and Normal group.

	Overt-DIC	Pre-DIC	Non-overt DIC	Normal
Age (year)	48 (32–58.5)	48.5 (33–61.75)	52 (39–62)	43 (32–53)
Sex (F:M)	75:82	14:22	95:156	70:67
TAT (ng/mL)	26.20 12.65–49.05	28.70 NS* 13.30–66.98	15.00***# 7.80–24.50	1.10***##&&& 0.70–1.60
PIC (ug/mL)	4.03 1.35–9.58	1.85 NS* 0.92–7.55	1.60*** NS# 0.87–2.86	0.44***##&&& 0.37–0.56
tPAIC (ng/mL)	12.00 6.40–23.45	20.20 NS* 7.98–35.90	8.30***### 5.20–13.80	7.20***##& 5.10–9.30
sTM (TU/mL)	19.70 12.60–29.00	20.90 NS* 16.55–32.98	11.80***### 9.20–16.30	8.60***##&&& 7.30–9.85
Mortality (%)	35.03	47.22	9.56	/

DIC, disseminated intravascular coagulation*, $p < 0.05$ in comparison to overt-DIC; ***, $p < 0.001$ in comparison to overt-DIC; #, $p < 0.05$ in comparison to pre-DIC; ###, $p < 0.001$ in comparison to pre-DIC; &, $p < 0.05$ in comparison to non-overt DIC; &&&, $p < 0.05$ in comparison to non-overt DIC; NS* or NS#; not significant in comparison to overt-DIC or pre-DIC.

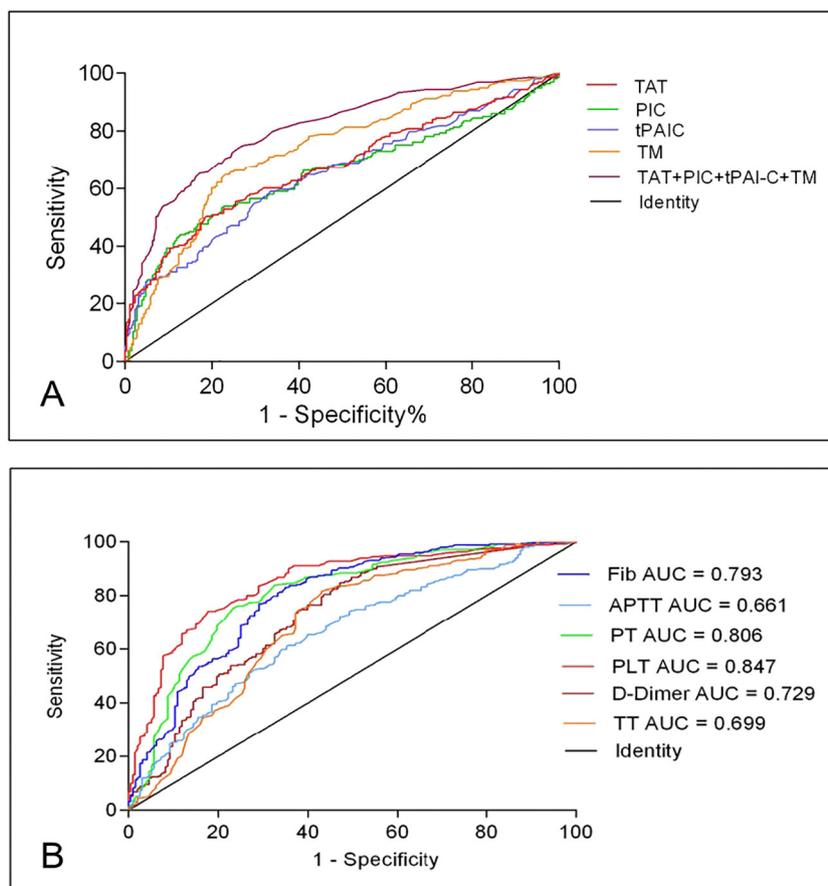


Fig. 1. Receiver operating characteristic analysis for disseminated intravascular coagulation. TAT, thrombin-antithrombin complex; PIC, α 2-plasmin inhibitor-plasmin complex; tPAIC, tissue plasminogen activator-inhibitor complex; sTM, soluble thrombomodulin.

Table 4
Diagnostic efficiency of the molecular markers in patients with DIC with pre-DIC.

	AUC	Cut-off value	Sensitivity	Specificity	PPV	NPV	Odd ratio
TAT (ng/mL)	0.675	27.45	50.3%	81.3%	67.4%	68.0%	4.39
PIC (ug/mL)	0.653	4.64	44.0%	87.3%	72.6%	67.0%	5.39
tPAIC(ng/mL)	0.650	10.95	59.1%	66.5%	57.6%	67.9%	2.87
sTM(TU/mL)	0.731	16.75	64.8%	76.9%	68.3%	73.9%	6.12
TAT + PIC + tPAIC + sTM	0.807		74.1%	74.5%	69.2%	79.2%	8.59

AUC, area under the receiver operating characteristic curves; PPV, positive predictive value; NPV negative predictive value; TAT, thrombin-antithrombin complex; PIC, α 2-plasmin inhibitor-plasmin complex; tPAIC, tissue plasminogen activator-inhibitor complex; sTM, soluble thrombomodulin.

Table 5
Comparison between different underlying diseases (DIC + pre-DIC vs. non-overt DIC).

		TAT	PIC	tPAIC	sTM
Hematological malignancies	DIC (58)	21.10 (7.48–43.43)*	3.51 (1.36–9.40)*	8.60 (5.00–16.88)*	18.80 (11.75–25.20)*
	Non-overt DIC (46)	8.10 (4.50–11.38)	1.11 (0.87–2.29)	5.60 (3.70–8.88)	13.25 (11.15–16.45)
	AUC	0.727	0.712	0.661	0.656
Sepsis	DIC (32)	29.20 (13.02–106.23)*	1.87 (0.82–6.19)	29.35 (15.95–53.98)*	25.80 (19.80–44.35)*
	Non-overt DIC (42)	14.50 (7.65–23.25)	1.60 (1.01–2.06)	12.45 (7.35–22.08)	18.55 (12.35–27.70)
	AUC	0.725	0.563	0.769	0.688
Solid tumor	DIC (13)	40.90 (13.75–61.45)*	3.23 (1.31–8.70)*	21.10 (10.45–36.00)*	24.70 (13.20–37.40)*
	Non-overt DIC (63)	16.60 (10.80–22.80)	1.58 (0.95–3.25)	8.40 (5.20–11.80)	9.60 (8.00–12.80)
	AUC	0.715	0.643	0.798	0.886
Trauma/surgery	DIC (18)	25.50 (13.15–43.40)	0.68 (0.12–1.83)	12.00 (9.35–25.10)*	19.60 (15.08–26.43)*
	Non-overt DIC (54)	22.90 (14.88–34.30)	1.46 (0.50–2.75)	8.45 (5.60–13.5)	10.35 (7.88–12.00)
	AUC	0.523	0.638	0.722	0.871

DIC, disseminated intravascular coagulation; TAT, thrombin-antithrombin complex; PIC, α2-plasmin inhibitor-plasmin complex; tPAIC, tissue plasminogen activator-inhibitor complex; sTM, soluble thrombomodulin.

* $p < 0.05$ between patients with DIC and those without.

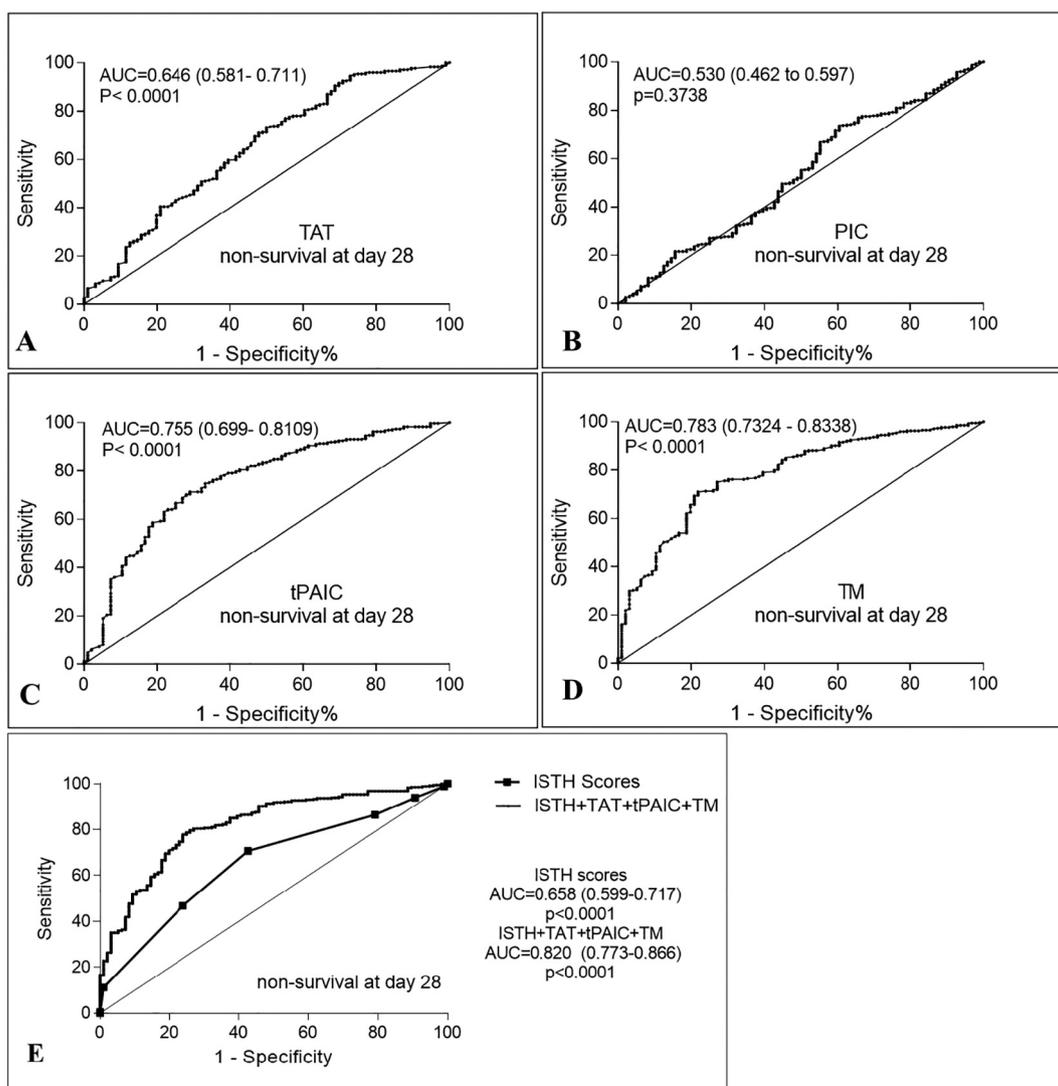


Fig. 2. (A–E) Receiver operating characteristic analysis for predicting non-survival at day 28. TAT, thrombin-antithrombin complex; PIC, α2-plasmin inhibitor-plasmin complex; tPAIC, tissue plasminogen activator-inhibitor complex; sTM, soluble thrombomodulin; ISTH, International Society of Thrombosis and Haemostasis.

microthrombus formation [24], while endothelial cells injury reflected by sTM. These markers may highlight even minimal hemostatic activation and are highly sensitive in diagnosing DIC. DIC is a continuous multifactorial complication associated with coagulation system,

fibrinolytic system and endothelial system. However, previous studies have only evaluated single molecular marker's diagnostic value. This was the first clinical study that combined these four markers to diagnose and predict outcome of DIC among underlying diseases in Chinese

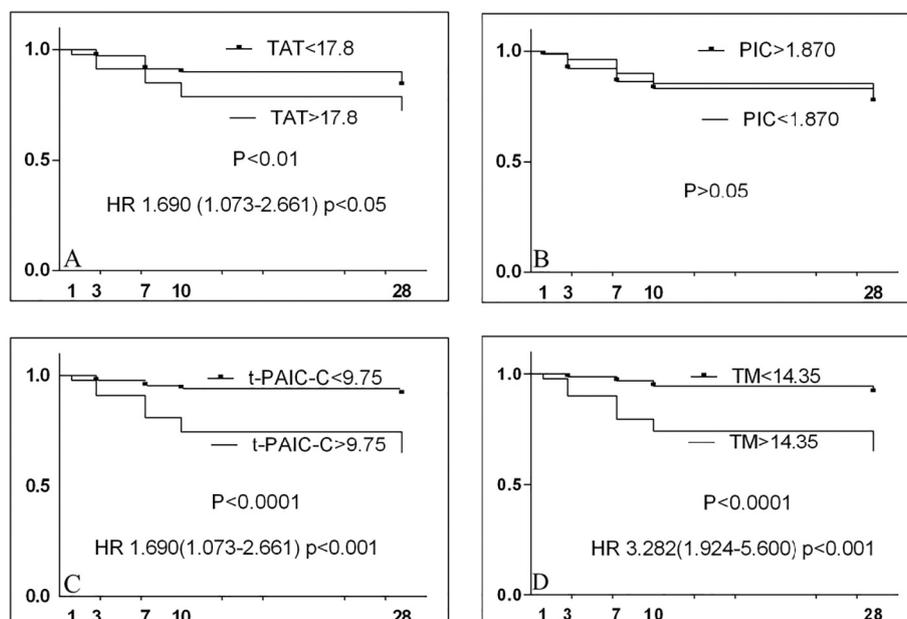


Fig. 3. Kaplan-Meier curves for the association between TAT, tPAIC, and sTM and 28-day all causes mortality.

TAT, thrombin-antithrombin complex; tPAIC, tissue plasminogen activator-inhibitor complex; sTM, soluble thrombomodulin.

population.

As one of the most severe complication of other underlying diseases, DIC is related to poor outcomes, multiple organ failure and high mortality rates. The outcome of DIC was improved with treatment in the early stage, which corresponds to pre-DIC [7,16]. Although diagnosis of pre-DIC is considered to be important for improving prognosis, the diagnostic criteria remains to be established [25–28]. Previously, several reports referred to the state within 1 week before the onset of DIC as pre-DIC [7,29]. We applied this definition to the present study. The results showed that TAT, PIC, tPAIC, and sTM levels significantly differed between the overt-DIC and non-overt DIC group, which was similar to that observed in previous studies [24,30]. Moreover, the plasma levels of TAT, tPAIC and sTM were significantly higher in pre-DIC group than non-overt DIC group. Therefore, these biomarkers can be used to diagnose DIC, especially have certain implication to pre-DIC. In diagnosing DIC, we found that the application of a single marker had limited value. The combination of the four markers demonstrated an increased AUC, sensitivity and odds ratio. Thus, the combination of four markers was superior to a single one.

In this study, the most common underlying diseases were hematological malignancies, sepsis, solid tumor, and trauma/surgery similar to the findings of a previous study [31]. The molecular markers differ among patients with different underlying diseases. Plasma TAT, PIC, tPAIC, and sTM levels were useful for the diagnosis of DIC in patients with hematological malignancies and solid tumors. The tPAIC and sTM can be used to diagnose DIC in patients with trauma/surgery. The activation of coagulation, anticoagulation impairment and insufficient fibrinolysis developed in the process of sepsis [32], which account for its frequent association with vascular endothelial cell injury and multiple organ failure [33]. The elevated plasma levels of TAT, tPAIC and sTM were useful for the diagnosis of DIC in patients with sepsis, while plasma PIC was not significantly increase in septic DIC patients. These biomarkers can be used to explain the pathophysiology of DIC patients due to various diseases.

There have been numerous reports on the prognostic markers of DIC. The plasma level of tPAIC is known to be related with organ failure, and sTM can reflect poor clinical outcomes [11,24]. PIC, however, is not a significant prognostic factor [34]. As for TAT, some reports showed that TAT levels were significantly higher in patients with poor outcomes than those without [35], while another found that there

was no significant difference between the two groups [34]. In this study, we found that TAT, tPAIC, and sTM all showed prognostic values. The varieties and severity of the underlying diseases may be among the factors that contribute to the phenomenon. tPAIC and sTM had better prognostic value than ISTH DIC scores. Combining ISTH DIC scores with TAT, tPAIC and sTM, the prognostic value was evidently improved. In our study, The SOFA score and APACHE score were similarly elevated in DIC patients and pre-DIC patients. The plasma level of tPAIC and sTM was elevated in pre-DIC group and mortality is higher in pre-DIC than overt-DIC. Considering that tPAIC and sTM mainly reflect the endothelial injury and prognosis, the pre-DIC group had relatively more sepsis and less hematological malignancies may account for this. Our study included fewer pre-DIC patients might be another cause.

The molecular markers have both diagnostic and prognostic value in DIC, however, their clinical effects were greatly restricted owing to the inconvenient and inefficient detection methodology. There already have automated analyzer which can provide rapid examination in laboratories with high test volumes and high sensitivity. Moreover, the results are available within 17 min. In this novel test, the minimum volume for a sample is 20 μ L. We firstly employed the analyzer to detect the plasma levels of TAT, PIC, PAIC, and sTM at multiple centers in China. The results can be considered largely representative of China. The ease of conducting tests and the reliability of the results all suggest that these biomarkers are worthy of promotion. Although these markers are not available on 24/7 basis in most laboratories, we could foresee that the rapid clinical routine detection of these markers will be gradually realized driven by the market in the future as many other indicators.

There were some potential limitations to our study. Since there is no gold standard for diagnosis of DIC, we used the ISTH overt DIC criteria as the diagnostic standard. It has a higher specificity for DIC diagnosis and 28th-day mortality but lower sensitivity. The progress in diagnosis of DIC arranged from single coagulation parameter to multiple coagulation parameters to scoring system. Further study is needed to combine scoring system with biomarkers or substitute biomarkers for some global coagulation tests to improve criteria's diagnostic and prognostic performance and reach accurate and early diagnosis of DIC.

5. Conclusions

TAT, PIC, tPAIC, and sTM can be used to diagnose DIC. Besides, TAT, tPAIC and sTM have certain implications in pre-DIC stage. The combination of the four biomarkers provided more reliable results than that when a single marker was applied. Moreover, TAT, tPAIC, and sTM showed prognostic value in predicting poor outcome. The wide application potential of these molecular markers will greatly improve early diagnosis rates and prognosis in China.

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Declarations of interest

None.

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