Diagnostic and prognostic value of TAT,PIC,TM, and t-PAIC in malignant tumor patients with venous thrombosis

Running title:Thrombotic markers in patients with malignant tumors

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Abstract

Background: Venous thromboembolism (VTE) is an important complication in patients with malignant tumors.Its exact diagnosis and treatment are still lacking.We used a high-sensitive chemiluminescence method to detect thrombin–antithrombin III complex (TAT),plasmin-α2-plasmininhibitor complex (PIC), thrombomodulin (TM),and tissue plasminogen activator–inhibitor complex(t-PAIC) in combination with D-dimer and fibrin degradation product (FDP) to analyze their diagnostic and prognostic value in patients with malignant tumors.

Methods: In total, 870 patients with confirmed malignant tumors were included, 82 of whom had suspected VTE;200 healthy individuals were classified as the control group. The TAT, PIC,TM, and t-PAIC were detected using Sysmex HISCL5000 automated analyzers, whereas FDP and D-dimer were detected using Sysmex CS5100 coagulation analyzer.Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic efficiency.Survival probabilities were determined using Kaplan–Meier analysis, and multivariate analyses were performed using a Cox regression model.

Results: Compared with healthy controls,patients with malignant tumors showed significantly elevated TAT,PIC,TM,t-PAIC,D-dimer, and FDP. Similarly, compared with patients in the non-thrombosis group, those in the thrombosis group showed significantly elevated levels of the above mentioned markers. Logistic regression analysis showed that TAT, PIC, TM, t-PAIC, D-Dimer, and FDP were all associated with VTE.ROC analysis showed that "TAT+PIC+TM+t-PAIC+D-dimer+FDP"showed the highest sensitivity and specificity.Patients with elevated TAT,PIC,TM, and t-PAIC had a significantly shorter survival.Multivariate Cox survival analysis showed that TM and t-PAIC were significantly associated with poor prognosis.In addition,

the incidence of VTE was significantly lower in patients with malignant tumors who were treated with low-molecular-weight heparin (LMWH), and their survival period was significantly longer than that of patients with malignant tumors who were not treated with LMWH.

Conclusion:TAT, PIC, TM, and t-PAIC combined with D-dimer and FDP were better than the application of a single marker in the diagnosis of VTE in patients with malignant tumors.TAT and PIC can be used as sensitive markers in the diagnosis of VTE but not as prognostic markers. TM and t-PAIC might be independent prognostic indicators in patients with malignant tumors, regardless of the state of thrombus.

Introduction

Venous thromboembolism (VTE) is one of the important complications in patients with malignant tumors, and one of the main causes of death in patients with malignancies[1,2]. VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE)[3,4].A large-scale epidemiological study reported that about 20% of new cases of VTE are related to potential tumors[5]. Compared with patients without cancer, those with cancer have an increased risk of VTE[6,7], and those with metastasis have a 4–13-fold higher risk of VTE[8,9]. In addition, hospitalized patients with tumors who undergo treatment are more likely to have VTE[10-12].Although the formation of VTE has seriously affected the survival rate and mortality rate of patients with cancer[13], VTE is still underdiagnosed and undertreated in these patients[14,15].Currently, the gold standard of VTE diagnosis is still imageology examination;D-dimer and fibrin degradation product (FDP)are passively detected after thrombosis and are not useful for early diagnosis of VTE.

The thrombin–antithrombin III complex (TAT) is recognized as a marker of activation of the coagulation system, plasmin-α2-plasmininhibitor complex (PIC) is an indicator of activation of the fibrinolysis system, thrombomodulin (TM) can monitor the function of endothelial cells, and tissue plasminogen activator–inhibitor complex (t-PAIC) is a fibrinolytic marker. These are important markers in the process of venous thrombosis, which can be significantly elevated before thrombus. This study aimed to use a high-sensitivity chemiluminescence enzyme immunoassay method to detect TAT,PIC,TM, and t-PAIC in combination with D-dimer and FDP to analyze their diagnostic and prognostic value in patients with malignant tumors,and to preliminarily evaluate the preventive

effect of low-molecular-weight heparin(LMWH) in patients with malignant tumors.

Patients and methods

Clinical samples

This was a multicenter, prospective observational study conducted in three research institutes in China. In total, 870 patients (368 male and 502 female) with confirmed malignant tumors were included in the study as the malignant tumor group from January 2017 to December 2019.Patients who had not received coagulant drugs within 1 week of the study and those whose malignant tumors were confirmed by CT, MRI, histopathology, or cytology were included.Among the included patients, 403 had lung cancer, 235 had pancreatic cancer,125 had gastric cancer, and 107 had ovarian cancer.Patients whose deep vein thrombosis(DVT) was confirmed by color Doppler ultrasound or angiography, or those who were diagnosed with pulmonary embolism(PE) by using spiral CT pulmonary arteriography and MRI pulmonary arteriography(n = 82) were regarded as the thrombosis group.In total, 200 healthy individuals (119 female and 81 male, mean age 57.50 ± 9.14 years) who visited the hospital for physical examination during the same period were selected as the healthy control group.These individuals did not have hyperlipidemia, diabetes, or coagulation-related diseases.The study protocol was approved by the Human Ethics Review Committee of each hospital(File no: HLJ-NK-2017-0016) and supported by Heilongjiang Provincial Health and Family Planning Commission (Grant no.2017-566).Written informed consent was obtained from the patients or their relatives before enrolment into the study.All patients were followed up through hospital re-examination, WeChat, and telephone until December 2019.The follow-up was conducted once every 3 months to record the living status and the cause of death of the patients.

Methods

In total, 2.7 mL of fasting venous blood was collected with 0.3 mL of 3.2% sodium citrate and mixed 10 times. Whole blood was centrifuged at $1000{\times}g$ for 10 min and immediately tested on the machine. The TAT, PIC,TM, and t-PAIC were detected using Sysmex HISCL5000 automated analyzers (HISCL-5000i, Sysmex, Japan). FDP and D-dimer were detected using Sysmex CS5100 coagulation analyzer (Sysmex, Japan). All reagents and calibrators were matching reagents obtained from the original factory,and they were used according to the manufacturer's instructions.

Statistical analysis

Non-normal distribution data were represented by median(Q_1,Q_3),and the differences between the groups were compared using the Mann–Whitney U test. χ^2 test was used to compare the enumeration data.The relationships between TAT,PIC,TM,t-PAIC,D-dimer,FDP, and VTE were analyzed using binary logistic regression.Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic efficiency, and the maximum value of the Youden index served as the cut-off value.Survival was estimated using the Kaplan–Meier method, and any differences in survival were evaluated using the log-rank test. Multivariable analyses with the Cox proportional hazards model were used to estimate the simultaneous effects of prognostic factors on survival.$P<0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS 20.0 software.

Results

Comparison of basic information of patients with malignant tumors

Among the 870 patients, 82 were diagnosed with VTE as thrombosis group.There were no significant difference in the levels of triacylglycerol, total cholesterol,low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and blood glucose between the thrombosis and non-thrombosis groups(Table 1).

Table 1. Comparison of basic information of patients with malignant tumors in the thrombosis and non-thrombosis groups

Group	n	Male/Female(n)	Age (year, $\overline{x} \pm s$)	Tumor types (LC/PC/GC/OC, n)	TG(mmol/L, $\overline{x} \pm s$)	TC(mmol/L, $\overline{x} \pm s$)	LDL-C(mmol/L, $\overline{x} \pm s$)	HDL-C(mmol/L, $\overline{x} \pm s$)	Glu(mmol/L, $\overline{x} \pm s$)
Malignant tumor group	870	368/502	61.32±10.76	403/235/125/107	1.22±0.29	4.68±0.53	2.78±0.32	1.12±0.09	5.13±0.22
Thrombosis group	82	35/47	62.07±11.54	44/23/9/6	1.29±0.27	4.51±0.60	2.52±0.47	0.92±0.07	5.19±0.25
Non-thrombosis group	788	333/455	60.61±10.09	359/212/116/101	1.24±0.32	4.62±0.55	2.71±0.42	1.03±0.10	5.08±0.23

LC:lung cancer;PC: pancreatic cancer;GC: gastric cancer;OC: ovarian cancer, TG: triacylglycerol; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Glu: blood glucose

Comparison between control group and malignant tumor group.

The mean plasma levels of TAT,PIC,TM,t-PAIC,D-dimer,and FDP in the 200 healthy individuals were 6.20(3.70–8.50) µg/L,0.11(0.10–0.14) mg/L,8.20(6.40–9.70) kU/L,6.80(6.10–7.60)

μg/L,1.43(1.20–1.65) μg/L,and 1.91(1.42–2.31) mg/L,respectively.The levels of TAT,PIC,TM,t-PAIC,D-dimer,and FDP in the malignant tumor group were significantly higher than the corresponding levels in the healthy control group ($P<$ 0.001;Table 2).

Table 2.Comparison between control group and malignant tumor group($M[Q_1,Q_3]$)

Group	n	TAT(μg/L)	PIC(mg/L)	TM(kU/L)	t-PAIC(μg/L)	D-dimer(μg/L)	FDP(mg/L)
Control group	200	6.20(3.70–8.50)	0.11(0.10–0.14)	8.20(6.40–9.70)	6.80(6.10–7.60)	1.43(1.20–1.65)	1.91(1.42–2.31)
Malignant tumor group	870	11.64(6.10–22.76)	0.86(0.43–1.78)	10.70(8.00–16.23)	8.20(5.50–13.41)	2.04(0.79–5.44)	5.56(2.31–14.26)
Zvalue		−11.606	−25.199	−8.179	−7.018	−5.237	−17.419
P value		<0.001[*]	<0.001[*]	<0.001[*]	<0.001[*]	<0.001[*]	<0.001[*]

TAT,thrombin–antithrombin III complex; PIC, plasmin-α2-plasmininhibitor complex; TM,thrombomodulin; t-PAIC,tissue plasminogen activator–inhibitor complex; FDP, fibrin degradation product

*$P<0.05$ considered statistically significant

Comparison between non-thrombosis and thrombosis group among patients with malignant tumors

The levels of TAT,PIC,TM,t-PAIC,D-dimer, and FDP in the thrombosis group were significantly higher than the corresponding levels in the non-thrombosis group ($P<0.001,P<0.001,P=0.001,P=0.013,P=0.001$, and $P=0.009$,respectively; Table 3).

Table 3.Comparison between non-thrombosis group and thrombosis group among patients with malignant tumors(M [Q_1,Q_3])

Group	n	TAT(μg/L)	PIC(mg/L)	TM(kU/L)	t-PAIC(μg/L)	D-dimer(μg/L)	FDP(mg/L)
Non-thrombosis group	788	9.83(5.70–16.5)	0.792(0.41–1.47)	10(7.8–14.5)	7.6(5.2–12.7)	1.82(0.6–5.24)	4.94(2.31–10.68)
Thrombosis group	82	46.81(20.4–120)	1.944(0.78–8.43)	18(10.1–23.9)	10.6(7.5–16.2)	3.77(1.52–7.72)	7.2(3.06–19.02)
Z value		−13.486	−8.149	−7.952	−4.569	−5.094	−4.982
P-value		<0.001[*]	<0.001[*]	0.001[*]	0.013[*]	0.001[*]	0.009[*]

TAT,thrombin–antithrombin III complex; PIC, plasmin-α2-plasmininhibitor complex; TM,thrombomodulin; t-PAIC,tissue plasminogen activator–inhibitor complex; FDP, fibrin degradation product

*$P<0.05$ considered statistically significant

Binary logistic regression analysis showed that TAT,PIC,TM,t-PAIC,D-dimer, and FDP were closely associated with VTE in patients with malignant tumors ($P<0.001$, $P<0.001$, $P = 0.02$, $P = 0.014$, $P = 0.011$, and $P = 0.026$, respectively; Table 4)

Table4.Binary logistic regression analysis of relationship between each molecular marker and VTE

Variable	B	SE	Wald	P-value	Oddsratio
TAT	0.560	0.007	84.5	<0.001*	2.062
PIC	0.473	0.033	66.697	<0.001*	1.314
TM	0.104	0.017	5.382	0.02*	1.04
t-PAIC	0.062	0.025	6.056	0.014*	0.94
D-dimer	0.279	0.031	6.441	0.011*	1.082
FDP	0.022	0.01	4.966	0.026*	1.022
Constant	−5.091	0.421	146.405	<0.001*	0.006

TAT,thrombin–antithrombin III complex; PIC, plasmin-α2-plasmininhibitor complex; TM,thrombomodulin; t-PAIC,tissue plasminogen activator–inhibitor complex; FDP, fibrin degradation product

*P<0.05 considered statistically significant

Evaluation of value of each molecular marker in the diagnosis of VTE by receiver operating curve(ROC) analysis

The areas under the curve (AUC) of TAT,PIC,TM,t-PAIC,D-dimer, and FDP in diagnosing VTE were 0.875,0.739,0.714,0.623,0.637, and 0.634,respectively.The cut-off values of TAT,PIC,TM,t-PAIC,D-dimer, and FDP were 30.76μg/L,4.84mg/L,17.25kU/L,16.55μg/L, 2.56μg/L,and 5.81mg/L, respectively.TAT showed a good diagnostic value for VTE,with a sensitivity of 85.6% and a specificity of 75.4%.The AUC of t-PAIC was 0.623, and its diagnostic efficiency was the lowest (Table 5,Fig.1).When a combination of the six markers was applied,the AUCs of "TAT+PIC+TM+t-PAIC" and "TAT+PIC+TM+t-PAIC+D-dimer+FDP" were significantly higher than the AUC of "D-dimer+FDP" in the diagnosis of VTE in patients with malignant tumors.The AUC,sensitivity, and specificity of "D-dimer+FDP" were 0.637, 74.5%, and 49.2%, respectively,

whereas the AUC, sensitivity, and specificity of "TAT+PIC+TM+t-PAIC" were 0.923,83.2%, and 81.5%, respectively.The AUC, sensitivity, and specificity of "TAT+PIC+TM+t-PAIC+D-dimer+FDP" were 0.937, 89.8%, and 88.5%, respectively. "TAT+PIC+TM+t-PAIC+D-dimer+FDP" showed the highest sensitivity and specificity(Table 6,Fig. 2).

Table5.Diagnostic efficiency of each molecular marker in VTE in patients with malignant tumors

Variable	AUC	Cut-off value	95% CI	*P*-value	Sensitivity(%)	Specificity(%)	Youden index
TAT	0.875	30.76	0.824–0.901	<0.001*	85.6	75.4	0.614
PIC	0.739	4.84	0.669–0.770	<0.001*	70.45	67.5	0.380
TM	0.714	17.25	0.663–0.765	<0.001*	59.1	83.1	0.421
t-PAIC	0.623	16.55	0.572–0.673	<0.001*	83.3	46.8	0.305
D-dimer	0.637	2.56	0.586–0.688	<0.001*	65	60.2	0.252
FDP	0.634	5.81	0.585–0.683	<0.001*	66.4	55.9	0.223

TAT,thrombin–antithrombin III complex; PIC, plasmin-α2-plasmininhibitor complex; TM,thrombomodulin; t-PAIC,tissue plasminogen activator–inhibitor complex; FDP, fibrin degradation product

*$P<0.05$ considered statistically significant
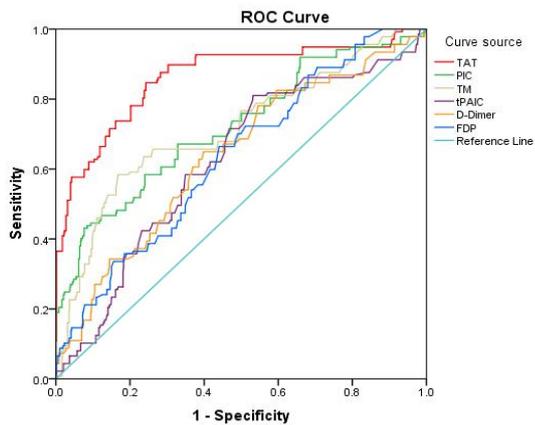
Fig. 1.Receiver operating characteristic (ROC) curve analysis of each marker for VTE

Table6.Combined diagnosis of six markers for VTE by ROC curve

Variable	AUC	95% CI	P-value	Sensitivity(%)	Specificity(%)	Youden index
TAT+PIC+TM+t-PAIC	0.923	0.896–0.949	<0.001*	83.2	81.5	0.717
TAT+PIC+TM+t-PAIC+D-dimer+FDP	0.937	0.910–0.964	<0.001*	89.8	88.5	0.783
D-dimer+FDP	0.637	0.586–0.687	<0.001*	74.5	49.2	0.337

TAT,thrombin–antithrombin III complex; PIC, plasmin-α2-plasmininhibitor complex; TM,thrombomodulin; t-PAIC,tissue

plasminogen activator–inhibitor complex; FDP, fibrin degradation product

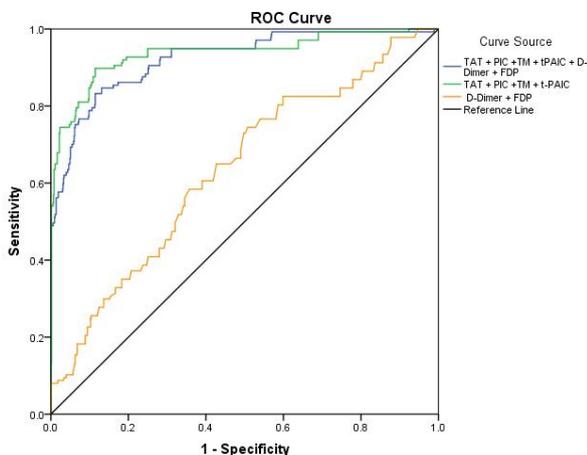*P<0.05 considered statistically significant

Fig. 2.Receiver operating characteristic (ROC)curve analysis of combined six markers in diagnosis of VTE

Evaluation of correlations between TAT, PIC,TM,t-PAIC,D-dimer, FDP, and prognosis using the Kaplan–Meier method

Survival analyses were performed with regard to the expressions of TAT,PIC, TM,t-PAIC,D-dimer, and FDP in patients with malignant tumors.The cut-off values of TAT,PIC,TM,t-PAIC,D-dimer, and FDP were 30.76μg/L,4.84mg/L,17.25 kU/L,16.55μg/L,2.56μg/L,and 5.81mg/L,respectively.Patients in whom the levels of all markers were higher than the cutoff values were classified as the high-level group(TAT>30.76,PIC>4.84,TM>17.25,t-PAIC>16.55,D-dimer>2.56,and FDP>5.81),whereas those in whom the levels were lower than the cutoff value were classified as the low-level group(TAT<30.76,PIC<4.84,TM<17.25,t-PAIC<16.55,D-dimer<2.56,and FDP<5.81).The results indicated that compared with patients with low levels of TAT,PIC,TM, and t-PAIC, those with high levels of the markers had significantly shorter overall survival (OS)(log-rank test $P<0.001$; Fig.3a–3d).However, D-dimer and FDP failed to differentiate between the outcomes of patients with malignant tumors ($P=0.495$ and 0.483, respectively;Fig.3e and 3f).Next, we analyzed the relationship between TAT, PIC, TM,t-PAIC,D-dimer, FDP, and the prognosis of patients with malignant tumors in the thrombosis group.The results showed that TM and t-PAIC can be used as prognostic indicators in patients with malignant tumors, irrespective of whether the thrombus is formed (TM,$P<0.001$; t-PAIC,$P=0.001$) (Fig.4c and 4d),whereas TAT,PIC,D-dimer,and FDP cannot be used as prognostic markers in the thrombosis group($P=0.064,0.246,0.056$, and 0.385, respectively;Fig.4a, 4b, 4e, and 4f).
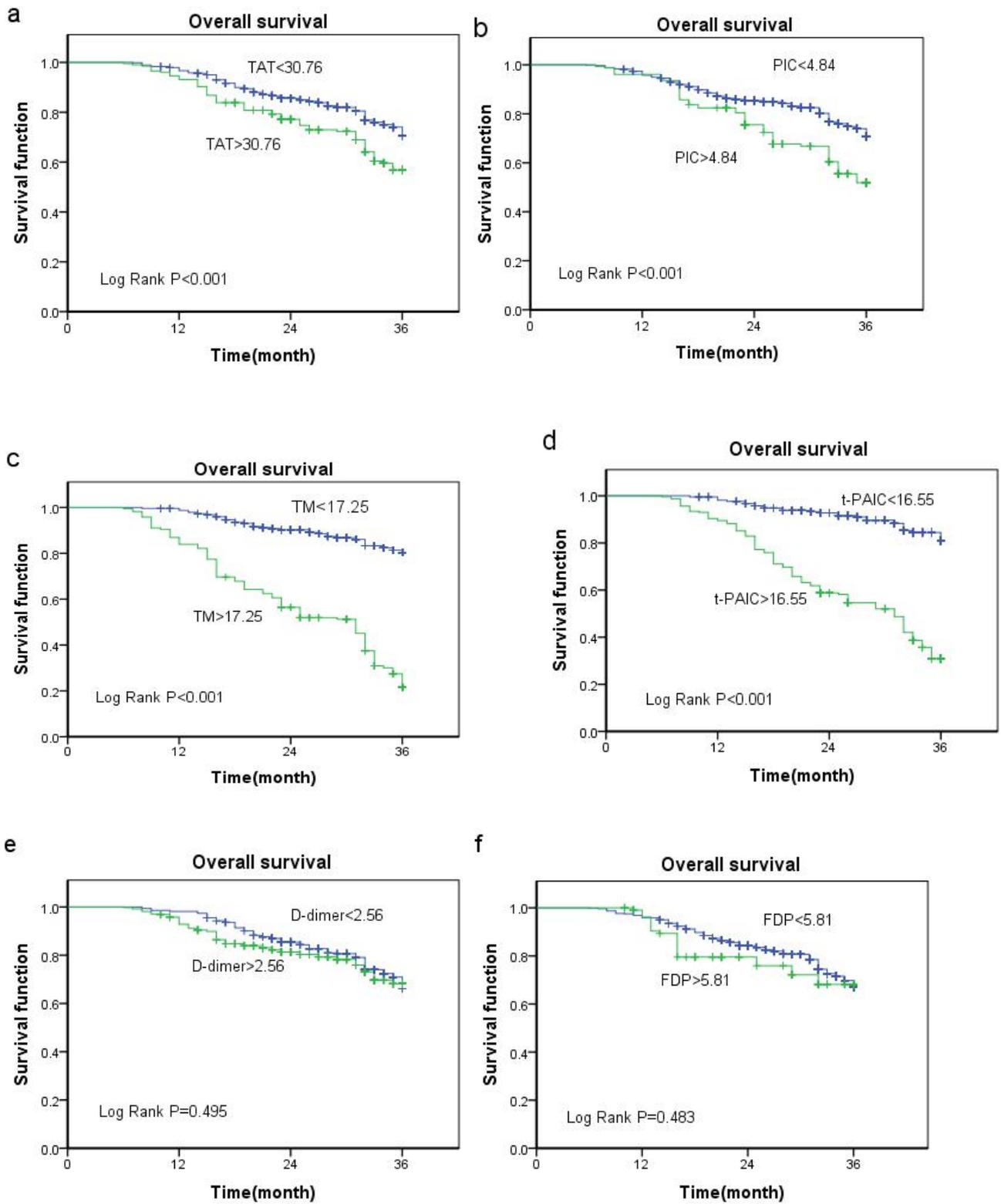
Fig. 3. (a–f)Kaplan–Meier survival curves of TAT, PIC,TM,t-PAIC,D-dimer, FDP, and overall survival in patients
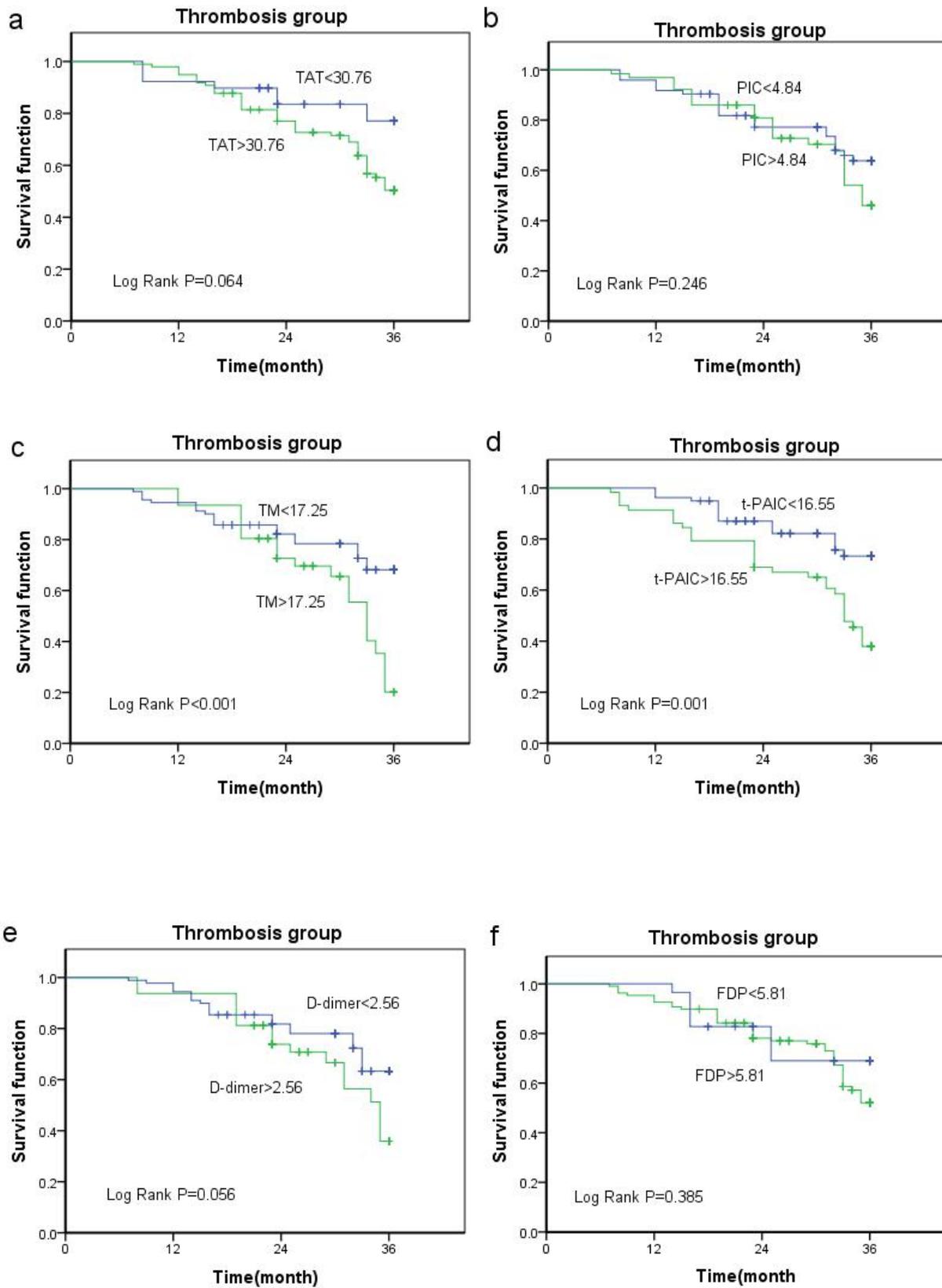
with malignant tumors

Fig. 4. (a–f)Kaplan–Meier survival curve analysis of relationship between TAT, PIC,TM,t-PAIC,D-dimer, FDP,and

survival rate in patients with malignant tumors in the thrombosis group

In addition, multivariate Cox regression analysis was conducted in order to evaluate the possible associations between prognosis and TAT,PIC,TM,t-PAIC,D-dimer,and FDP.Among the parameters, TM (P<0.001) and t-PAIC (P<0.001) were significantly associated with poor prognosis (Table7).TM and t-PAIC were identified as independent prognostic factors.

Table7.Multivariate Cox regression analysis of prognostic markers in patients with malignant tumors

Variable	β	Wald	P-value	Odds ratio	95.0% CI
TAT	0.011	0.668	0.414	0.999	0.997–1.001
PIC	0.019	1.202	0.273	0.983	0.954–1.013
TM	1.270	130.081	<0.001*	1.073	1.057–1.088
t-PAIC	0.885	90.65	<0.001*	1.089	1.077–1.101
D-Dimer	0.028	2.125	0.145	1.028	0.990–1.068
FDP	0.017	4.972	0.066	0.981	0.964–0.998

TAT,thrombin–antithrombin III complex; PIC, plasmin-α2-plasmininhibitor complex; TM,thrombomodulin; t-PAIC,tissue plasminogen activator–inhibitor complex; FDP, fibrin degradation product

*P<0.05 considered statistically significant

Low-molecular-weight heparin(LMWH) for prevention of VTE in patients with malignant tumors

In total, 90 patients with TAT>30.76μg/L or PIC>4.84mg/L were selected from the non-thrombosis group. LMWH was injected into the endothelium 24–36 hours after the elevation of TAT or PIC in 45 patients(experimental group), and this was continued for 6 weeks. The other 45 patients were not treated with LMWH (control group). The two groups were followed up for one year. The incidence of VTE was 2.22%(1/45) in the experimental group and 15.56%(7/45) in the control group.

Significant difference was observed between the two groups,and no bleeding was observed in the experimental group. The survival time of the patients in the experimental group was 10.6±3.1 months and that of the control group was 8.5±2.8 months.The difference between the groups was statistically significant (*P*=0.026;Table8).

Table8.Comparison of incidence of VTE between the experimental and control groups

Group	Experimental group(%)	Control group(%)	χ^2	*P*-value
Venous thrombosis (+)	1(2.22)	7(15.56)		
Venous thrombosis (-)	44(97.78)	38(84.44)	4.939	0.026*

*P<0.05 indicates statistical significance

Discussion

The process of thrombosis is a multifactor continuous complication related to the coagulation system, fibrinolysis system, and endothelial system[16,17]. At present, the routine laboratory parameters fortesting coagulation, such as prothrombin time,activated partial thromboplastin time,thrombin time,fibrinogen,D-dimer,FDP,and coagulation factor have covered the coagulation and fibrinolysis systems;however, all these parameters enable passive detection and involve late screening after thrombosis, and are not sensitive to the pre-thrombotic state and pre-disseminated intravascular coagulation(pre-DIC). Monitoring of thrombolytic therapy failed to provide timely feedback, and early and reliable diagnosis in this regard is still lacking.

TAT is a sensitive marker of thrombin production and an indicator of activation of the coagulation system [18-20]. Its formation is the best time to judge the anticoagulant treatment, and it

can rise in the prethrombotic state.Thus, evaluation of TAT levels is suitable for the early diagnosis of thrombotic diseases and for monitoring thrombolytic therapy. The continuous increase of TAT indicates an increased risk of thrombosis. PIC is the starting pointof the fibrinolysis system,which reflects the activation degree of plasmin[21], monitors the functional status of the fibrinolysis system, and guides the anti-fibrinolysis treatment plan.TM is a marker of the vascular endothelial system, and it can be used to judge the injury or recovery of the vascular endothelium[22]. Damage to the vascular endothelium in patients with malignant tumors can increase the level of TM[23].t-PAIC not only reflects the abnormality of fibrinolysis system but is also related to endothelial damage[24]. TM and t-PAIC are also useful markers for predicting organ failure and clinical prognosis in patients with DIC and thrombotic diseases[25-27,17].

Previous studies have analyzed the diagnostic value of a single marker or the diagnostic and prognostic value of four markers in patients with DIC.In this study, we first combined six markers, namely TAT, PIC, TM, t-PAIC, D-dimer, and FDP to evaluate the diagnostic and prognostic value of VTE in patients with malignant tumors and to investigate the potential use of TAT and PIC as indications for the use of LMWH.

Our results showed that the levels of TAT, PIC, TM, t-PAIC, D-dimer, and FDP in the malignant tumor group were significantly higher than those in the healthy control group, and the levels in the thrombosis group were significantly higher than those in the non-thrombosis group.The results of binary logistic regression analysis showed that TAT, PIC, TM, t-PAIC, D-dimer, and FDP were all related to VTE in patients with malignant tumors.

In addition, the results of ROC analysis showed that the six markers had certain value in the diagnosis of VTE in patients with malignant tumors, of which TAT had the highest diagnostic

value.The best cutoff value of TAT was 30.76 μg/L, the AUC was 0.875, and the sensitivity and specificity were higher than those of D-dimer and FDP.In the diagnosis of VTE, we found that although the application of a single marker has certain clinical significance, a combination of four or six markers can improve the AUC, sensitivity, and specificity. The study by Mei *et al*.[17] reported that TAT, PIC,t-PAIC, and TM had good diagnostic and prognostic value in the diagnosis of DIC in different basic diseases, and that a combination of the four markers showed better efficacy than that shown by a single marker alone.Therefore,TAT, PIC, TM, and t-PAIC combined with D-dimer and FDP can be used as sensitive markers for the diagnosis of VTE in patients with malignant tumors.

Our results indicated that elevated levels of TAT,PIC,TM, and t-PAIC,but not those of D-dimer and FDP,were important prognostic factors for overall survival of patients with malignant tumors. TM and t-PAIC were also significantly associated with the prognosis of patients with malignant tumors of VTE.TM and t-PAIC were independent prognostic indicators in patients with malignant tumors, regardless of the state of thrombus.TAT and PIC can be used as sensitive markers in the diagnosis of VTE but not as prognostic markers.

In addition, monotherapy using LMWH is considered to be the treatment of choice for venous thrombosis[28,29].We found that the incidence of VTE was significantly lower in patients with malignant tumors treated with LMWH, and their survival period was significantly longer than that of the control patients, which indicates that the use of LMWH is effective as apreventive anticoagulation treatment. Patients with high-risk tumors may be treated with prophylactic treatment for thrombosis. The study by Sakon*et al*.[29] entailed the use of enoxaparin to prevent postoperative venous thrombosis in 151 patients who underwent abdominal and pelvic surgeries.The results showed that enoxaparin significantly reduced the incidence rate of VTE and did not increase the risk

of bleeding.In the study by Pelzer*et al.*[9], 312 patients with advanced pancreatic cancer were treated with enoxaparin simultaneously with chemotherapy. The results showed that enoxaparin was safe and effective in the primary prevention of VTE.

In conclusion,TAT, PIC, TM, and t-PAIC can reflect thrombus formation from the coagulation system, fibrinolysis system, and endothelial system, and subsequently predict the prognosis of patients.The detection of TAT, PIC, TM, and t-PAIC combined with D-dimer and FDP is better than the application of a single marker, and is an ideal method for noninvasive detection of VTE at present.The occurrence and formation of thrombus in patients with malignant tumors can be detected in a more sensitive and reliable manner using this method. In addition, this combined detection could help monitor postoperative thrombus and hemorrhage,and evaluate the effect of thrombolysis and endothelial system injury.These markers can also aid early screening of the high-risk groups of VTE among patients with malignant tumors, help patients actively prevent medication, determine the best and optimal time of treatment, improve the prognosis of patients, reduce the incidence and mortality of venous thrombosis, and prolong the survival time of patients.

Authors' contributions

KZ and DW were responsible for the design, writing, and revision of the study. ZZ,XJ,and PL

were responsible for sample collection.YZ and JZ contributed to sample testing and data analysis.BS and LW were responsible for follow-up and recording.All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki. The study was approved by the Ethical Committee of the General Hospital of Heilongjiang Province Land Reclamation Bureau, The 4th Affiliated Hospital of Harbin Medical University, Harbin Medical University Cancer Hospital (Harbin, China), and written informed consent was obtained from all participants before enrolment in the study.

Patient consent for publication

Not applicable

Declaration of Competing Interest

The authors declare that they have no competing interests.

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