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Predictive value of dynamic assessment of thrombose-related factors in diabetic nephropathy patients for thrombotic risk

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Abstract: Objective To explore the value of dynamic evaluation of thrombus-related factors for predicting thrombotic risk in diabetic nephropathy (DN) patients. **Methods** A retrospective study was conducted to select 98 patients with DN who were treated in Cangzhou Hospital of Integrated TCM-WM from January 2020 to September 2022. Follow-up was conducted after treatment, with the occurrence of deep vein thrombosis as the observation endpoint. Finally, 96 patients obtained follow-up and were divided into thrombosis group (n=21) and a non-thrombosis group (n=75) based on the presence or absence of thrombosis. The clinical data of patients were collected, and the influencing factors of prognosis of DN patients were analyzed by univariate and multivariate logistic analysis. Receiver operating characteristic (ROC) curve was used to evaluate the predictive value of thrombus-related factors [thrombin antithrombin complex (TAT), plasmin-α-2-plasmin inhibitor complex (PIC), tissue plasminogen activator/plasminogen activator inhibitor-1 complex (t-PAIC) and soluble thrombomodulin(sTM)] for thrombotic risk in DN patients. **Results** There were no significant differences in general information, duration of diabetes, glucose metabolism, lipid metabolism and renal function between the two groups (P>0.05). The differences in prothrombin time (PT), activated partial thromboplastin time (APTT) and D-dimer (D-D) between the two groups were statistically significant(P<0.05). In the thrombosis group, the levels of TAT, PIC, t-PAIC and sTM before and after treatment, the difference between pro-treatment and post-treatment, and the variation coefficient between pro-treatment and post-treatment were all increased compared to the non- thrombosis group (P< 0.01). Multivariate logistic regression analysis showed that the increased variation coefficients of PAT, PIC, t-PAIC and sTM (OR=3.367, P=0.010; OR=19.106, P=0.042; OR=4.313, P=0.005; OR=9.389, P=0.003) were the independent risk factors affecting the thrombotic risk in DN patients. The ROC curve results showed that the AUCs of the variation coefficients of TAT, PIC, T-PAIC and sTM in predicting the thrombotic risk in DN patients were 0.818, 0.806, 0.873 and 0.825, respectively. **Conclusion** Elevated levels of thrombus-related factors are the independent risk factors for thrombosis in DN patients, and TAT, TM, PIC, and t-PAIC can be used as important indicators to predict their thrombotic risk.

Keywords: Diabetic nephropathy; Thrombus; Thrombin-antithrombin complex; Plasmin-α-2-plasminase inhibitor complex; Tissue type plasminogen activator/plasminogen activator inhibitor-1 complex; Soluble thrombomodulin
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Diabetic nephropathy (DN) refers to the specific pathological structure and function of the kidney caused by the changes of the kidney and the impact of diabetes on the kidney in diabetic patients (including type 1 and type 2), and it is also one of the main causes of end-stage renal disease (ESKD) [1]. Evidence suggests that DN patients manifest premature atherosclerosis and more extensive vascular diseases, making them more prone to plaque rupture and thrombosis [2]. In addition, DN patients exhibit a higher tendency for thrombosis due to high platelet reactivity, increased activation of thrombogenic factors, and reduced fibrinolysis [3]. However, there are currently no accurate, effective, and highly sensitive indicators to evaluate changes in coagulation function in early DN. Recent studies have confirmed that thrombin antithrombin complex (TAT), plasmin-α2-plasmin inhibitor complex (PIC), tissue plasminogen activator/plasminogen activator inhibitor-1 complex (t-PAIC), and soluble thrombomodulin (sTM) are novel indicators of early changes in the vascular endothelium, coagulation, and fibrinolysis. These indicators can be used for early diagnosis of thromboembolism, risk assessment and efficacy evaluation of thrombosis in high-risk populations, as well as screening for thrombosis risk in healthy individuals [4]. Therefore, the author hypothesizes that these four new coagulation function indicators have already changed in the early stage of DN and can predict the risk of bleeding in DN. This study retrospectively analyzed the changes of these four new indicators in DN patients and discussed their application in predicting the risk of thrombosis in DN.

1 Data and Methods

1.1 Clinical Data

Inclusion criteria: (1) Meeting the diagnostic criteria in the "Expert Consensus on Prevention and Treatment of Diabetic Nephropathy (2014 Edition)" [5]; (2) Age ranging from 18 to 75 years old; (3) Glycosylated hemoglobin (HbA1c) level between 7% and 10%; (4) Microalbuminuria/creatinine ratio (mAlb/Cr) ≥ 30 mg/(g•24 h).

Exclusion criteria: (1) Type 1 diabetic patients; (2) Patients with hypoglycemic coma, diabetic ketoacidosis, hyperosmolar non-ketotic coma, or acute diabetic complications; (3) Fasting blood glucose>13.3 mmol/L; (4) Total bilirubin>2.5 times the normal value; (5) Male patients with serum creatinine>133 μmol/L, female patients>124 μmol/L; (6) Patients with a history of hypertension, drug abuse, alcohol dependence, or drug allergy; (7) Patients who have taken angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or anticoagulants within the past 3 months.

1.2 Research Protocol

1.2.1 General Information

After approval by the hospital ethics committee (2023259) and obtaining informed consent from all patients and their families, 98 patients with DN treated at Cangzhou Hospital of Integrated TCM-WM from January 2020 to January 2022 were selected as the research subjects. Based on the results of ultrasound and CT examinations, patients were divided into thrombosis and non-thrombosis groups according to whether they had thrombotic events (such as cerebral embolism, pulmonary embolism, renal artery-vein thrombosis, limb thrombosis, and mesenteric thrombosis). At the same time, according to previous literature reports and clinical references, baseline-related data of patients were collected to analyze the risk factors for thrombosis in DN patients.

1.2.2 Treatment Protocol

All patients were treated according to the *Expert Consensus on Prevention and Treatment of Diabetic Nephropathy (2014 edition)* [5]. Patients were administered dapagliflozin (AstraZeneca Pharmaceuticals, National Medicine Permission No. HJ20170119), 10 mg/time, *qd.*, and valsartan capsules (Beijing Novartis Pharmaceuticals, National Medicine Permission No. H20040217), 80 mg/time, *qd*. On this basis, patients' blood sugar was reasonably controlled (choosing oral hypoglycemic drugs or insulin therapy based on various factors such as the patient's blood sugar level, to maintain fasting blood glucose < 7 mmol/L), and their blood lipids were controlled (using statin drugs to bring blood lipids to normal range). Meanwhile, health education was provided to cultivate healthy living habits.

1.3 Observation Indicators

All patients were drawn 5 mL of venous blood in the morning, and the blood sample were placed at room temperature for 30 minutes, centrifuged, and the supernatant was taken for testing: (1) Biochemical indicators such as fasting blood glucose (FBG), glycated hemoglobin (HbA1c), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol (TC), blood urea nitrogen (BUN), and serum creatinine (Scr) were detected by Beckman Coulter Chemistry Analyzer; (2) 24-hour urinary microalbumin excretion rate (UAER) was detected using IMMULITE 1000 Immunoassay System (Siemens); (3) Prothrombin time (PT) and activated partial thromboplastin time (APTT) were detected using AutoCimo C6000 automatic coagulation analyzer; (4) D-dimer (D-D) was detected using DG5035A enzyme-linked immunosorbent assay detector; (5) TAT, PIC, t-PAIC, and sTM were detected using Wondfo FC-302.

1.4 Follow-up and Thrombosis Risk Assessment

After treatment, patients were followed up for 1 year. According to the diagnostic criteria for deep venous thrombosis in the *Guidelines for Diagnosis and Treatment of Deep Venous Thrombosis (third edition)* [6], patients with DN were assessed for the occurrence of thrombosis. The observation endpoint was the occurrence of deep venous thrombosis in patients. If no endpoint event occurred during the follow-up period, the final follow-up cut-off event was taken as the observation endpoint. The follow-up method was to review the medical records in the inpatient and outpatient electronic medical record system or by phone, and the follow-up cut-off date was January 1st, 2023.

1.5 Statistical Methods

Epidata was used for data entry, while SPSS 22.0 was use for data analysis. Measurement data were first tested for normality, and data with normal distribution and homogeneity of variance were expressed as $\bar{x} \pm s$. Group *t*-test was used for comparison between groups, and *t'* test was used for unequal variances. Count data were expressed as *n*(%), and chi-square test was used. Multivariate logistic regression analysis was performed on all variables without collinearity, and ROC curves were plotted to evaluate the predictive value of thrombus-related factors on the risk of thrombosis in DN patients. $P<0.05$ was considered statistically significant.

2 Results

2.1 Follow-up Results

By January 1st, 2023, 96 patients were followed up, among which 21 cases (21.88%) developed thrombosis and were classified as the thrombosis group, while 75 cases (78.12%) without thrombosis were classified as the non-thrombosis group.

2.2 Comparison of Clinical Data between the Two Groups

There was no significant difference in general data, FBG, HbA1c, insulin resistance index, serum cystatin C, uric acid, BUN, SCr, TG, TC, HDL-C, LDL-C, 24 h UAER, and eGFR between the two groups ($P>0.05$). However, the APTT and TP levels in the thrombosis

group were lower than those in the non-thrombosis group, while the D-D level was higher, with a significant difference (P<0.05) **[Table 1]**.

Tab.1 Comparison of clinical data between two groups ($\bar{x}$±s)

Clinical data	Thrombosis group (n=21)	Non-thrombosis group (n=75)	t/χ^2 Value	P Value
Age (years)	61.36±5.38	59.10±5.95	1.569	0.120
Gender [n (%)]			0.084	0.120
Male	8 (38.10)	26 (34.67)		
Female	13 (61.90)	49 (65.33)		
BMI (kg/m^2)	25.33±3.42	24.16±3.09	1.498	0.137
Smoking [n (%)]	14 (66.67)	52 (69.33)	0.054	0.816
Course of diabetes (years)	11.53±1.76	10.83±1.52	1.801	0.075
SBP (mmHg)	114.71±3.87	112.98±3.46	1.973	0.051
DBP (mmHg)	63.26±4.54	61.48±3.59	1.891	0.062
FBG (mmol/L)	6.05±1.05	5.91±0.98	0.570	0.570
HbA1c (%)	9.49±2.11	8.36±2.37	1.975	0.051
HOMA-IR	3.79±0.81	3.54±0.77	1.300	0.197
CysC (mg/L)	2.43±0.71	2.11±0.67	1.910	0.059
Uric acid (μmol/L)	323.80±77.51	299.56±63.98	1.464	0.147
BUN (mmol/L)	8.47±2.82	8.16±2.25	0.527	0.599
SCr (μmol/L)	75.36±23.61	72.92±21.65	0.448	0.655
TG (mmol/L)	2.23±0.62	2.10±0.51	0.984	0.328
TC (mmol/L)	4.54±1.21	4.42±1.18	0.410	0.683
HDL-C (mmol/L)	1.43±0.35	1.51±0.48	0.711	0.479
LDL-C (mmol/L)	3.27±0.81	3.15±0.76	0.630	0.530
24hUAER (μg/min)	414.09±102.13	377.13±81.14	1.740	0.085
eGFR[mL/(min·1.73m^2)]	64.61±12.20	69.77±10.57	1.911	0.059
APTT (s)	31.96±5.44	34.72±5.57	2.013	0.047
PT (s)	14.24±2.00	15.67±3.13	2.524	0.015
D-D (ng/mL)	1.09±0.21	0.99±0.20	2.016	0.047

2.3 Comparison of Thrombosis-Related Factors between the Two Groups

The levels of TAT, PIC, t-PAIC, sTM, their differences before and after treatment, and their coefficients of variation (CV) before and after treatment in the thrombosis group were all higher than those in the non-thrombosis group, with a significant difference (P<0.01) **[Table 2]**.

Tab.2 Comparison of thrombus related factors between two groups ($\bar{x}$±s)

Item		Thrombosis group (n=21)	Non-thrombosis group (n=75)	t value	P Value
TAT (mg/L)	Pre-treatment	18.46±4.27	15.28±3.86	3.260	0.002
	Post-treatment	25.07±5.12	20.14±3.39	4.164	<0.001
	D-value	6.79±1.44	5.36±0.94	4.301	<0.001
	CV (%)	35.81±9.04	25.26±4.37	5.181	<0.001
PIC (μg/mL)	Pre-treatment	1.48±0.21	1.11±0.29	5.451	<0.001
	Post-treatment	2.95±0.65	2.04±0.52	7.692	<0.001
	D-value	1.34±0.28	0.93±0.24	6.680	<0.001
	CV (%)	90.54±10.26	74.08±6.67	6.952	<0.001
t-PAIC (ng/mL)	Pre-treatment	7.92±1.14	7.01±1.02	3.521	0.001
	Post-treatment	19.12±1.61	15.94±1.73	7.554	<0.001
	D-value	11.87±1.16	9.92±1.49	5.542	<0.001
	CV (%)	160.93±11.42	139.92±9.45	8.594	<0.001
sTM (TU/mL)	Pre-treatment	7.62±0.57	7.16±0.38	3.488	0.002
	Post-treatment	14.81±1.26	12.92±1.65	4.860	<0.001
	D-value	7.32±0.73	6.59±0.59	4.735	<0.001
	CV (%)	99.36±6.38	84.24±7.34	8.570	<0.001

2.4 Logistic Regression Analysis of Risk Factors Related to Thrombosis Risk in DN Patients

With thrombosis occurrence as the dependent variable (0 for no thrombosis, 1 for thrombosis), and statistically significant variables (actual measured values of continuous variables) in **Tables 1** and **Table 2** as independent variables, univariate and multivariate logistic regression analyses were performed. The results of multivariate logistic regression analysis showed that increased CV of TAT, PIC, t-PAIC, and sTM were independent risk factors for thrombosis in DN patients (P<0.05) **[Table 3, Table 4]**.

Tab. 3 Univariate logistic regression analysis of risk factors of thrombosis in DN patients

Indicators	β	SE	$Wald$	P Value	OR	95%CI
ATPP	-0.093	0.048	3.795	0.051	0.911	0.829-1.001
PT	-0.166	0.087	3.668	0.055	0.847	0.715-1.004
DD	2.532	1.299	3.799	0.051	12.582	0.986-160.553
TAT CV	1.172	0.294	15.847	<0.001	3.229	1.813-5.749
PIC CV	3.604	1.013	12.651	<0.001	36.750	5.043-267.787
t-PAIC CV	1.279	0.305	17.615	<0.001	3.592	1.977-6.527
sTM CV	1.888	0.492	14.721	<0.001	6.605	2.518-17.325

Tab. 4 Multivariate logistic regression analysis of risk factors related to thrombosis in DN patients

Indicators	β	SE	$Wald$	P Value	OR	95%CI
TAT CV	1.214	0.472	6.608	0.010	3.367	1.334-8.498
PIC CV	2.950	1.453	4.120	0.042	19.106	1.107-329.78
t-PAIC CV	1.462	0.517	7.988	0.005	4.313	1.565-11.885
sTM CV	2.240	0.748	8.958	0.003	9.389	2.166-40.695
Constant	-44.093	11.409	14.937	<0.001	0.000	

2.5 ROC Curve Analysis of Thrombosis-Related Factors for Predicting Thrombosis Risk in DN Patients

ROC curve analysis showed that for predicting thrombosis risk in DN patients, the AUC of TAT CV was 0.818 (95%CI: 0.704-0.932, P<0.01), with a critical value of 6.965 mg/L, a sensitivity of 57%, and a specificity of 97%; the AUC of PIC CV was 0.806 (95%CI: 0.698-0.914, P<0.01), with a critical value of 1.322 μg/mL, a sensitivity of 71%, and a specificity of 87%; the AUC of t-PAIC CV was 0.873 (95%CI:

0.778-0.968, *P*<0.01), with a critical value of 11.224 ng/mL, a sensitivity of 86%, and a specificity of 84%; the AUC of sTM CV was 0.825 (95%*CI*: 0.717-0.933, *P*<0.01), with a critical value of 7.088 TU/mL, a sensitivity of 76%, and a specificity of 81% **[Figure 1]**.

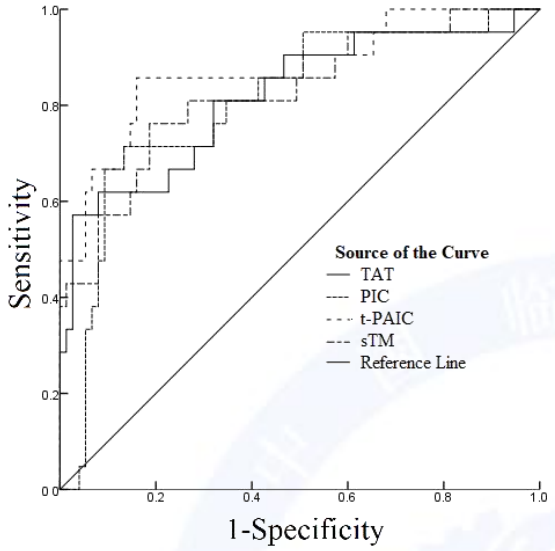

Fig.1 ROC curve of the predictive value of thrombose-related factors on thrombotic risk in DN patients

3 Discussion

Hyperglycemia and insulin resistance are the main metabolic abnormalities in DN, which have been proposed to lead to a pre-thrombotic state in DN through a series of events including endothelial dysfunction, platelet hyperactivity, impaired fibrinolysis, oxidative stress, and low-grade inflammation. Therefore, timely and accurate diagnosis of thrombosis is a persistent challenge for DN patients [7]. Currently, routine laboratory parameters for coagulation testing, such as PT, APTT, thrombin time, fibrinogen, D-D, fibrinogen degradation products (FDP), and coagulation factors, have covered the coagulation and fibrinolytic systems [8]. However, all these parameters are passive tests and late screenings after thrombosis, and they are not sensitive to pre-thrombotic states and disseminated intravascular coagulation. Recent studies have found that TAT, PIC, t-PAIC, and sTM can be used to assess the risk of venous thromboembolism related to human coagulation, plasmin, and endothelial function [9-10]. However, there are relatively few studies on the risk of thrombosis in DN patients, so this study chose to explore the predictive value of thrombus-related factors for thrombosis risk in DN patients, aiming to provide theoretical guidance for clinical practice.

Thromboembolic diseases, including venous thromboembolic diseases (pulmonary thromboembolism syndrome, deep venous thrombosis) and arterial thromboembolic diseases (acute coronary syndrome, atrial fibrillation, stroke, etc.), have become one of the leading causes of death worldwide [11]. With the continuous advancement of medical technology, clinical laboratory tests for thrombosis and hemostasis are gradually increasing. Related studies have found that compared with conventional coagulation tests such as PT and APTT, the four thrombotic indicators can undergo significant changes in the early stage of coagulation and fibrinolytic system activation, which is conducive to early diagnosis and treatment of diseases [12]. At the same time, Hinton *et al.* [13] found that TAT, PIC, t-PAIC, and thrombomodulin (TM) were significantly higher in male thrombotic patients than in male healthy controls. The results of this study were similar, showing that TAT, PIC, t-PAIC, and TM are independent risk factors affecting the risk of thrombosis in DN patients. This may be because thrombin, an activated form of prothrombin, plays a crucial role in the activation of its natural substrates, including fibrinogen, factor V, factor VIII, protein C (PC), etc. The activity of thrombin in plasma is regulated by the rapid interaction with AT to form TAT, and its formation is the best time to judge anticoagulation treatment [14]. In addition, TM is a type I transmembrane glycoprotein that is primarily expressed in vascular endothelial cells and serves as an important cofactor for activating anticoagulant proteins, contributing to hemostatic balance. Specifically, TM regulates the activity of thrombin from a coagulant to an anticoagulant protease. When thrombin binds to TM, activated protein C (APC) selectively inactivates coagulation factors Va and VIIa to prevent excessive coagulation [15]. Simultaneously, TM can enhance the proteolytic activity of thrombin-activated fibrinolysis inhibitor (TAFI), thereby delaying the dissolution of thrombus [16]. Moreover, the fibrinolytic system is activated during thrombus formation in the body. Subsequently, the resulting plasmin combines with specific inhibitors, leading to the formation of PIC, which is an indicator of high fibrinolysis. In a study of 175 patients with liver cirrhosis, TAT and TAT/t-PAIC were identified as potential biomarkers for predicting thrombosis in patients with liver cirrhosis [17]. t-PAIC is a tissue-type plasminogen activator (t-PA) complex, and its type 1 inhibitor (PAI-1) is the most important regulatory factor for the balance between fibrinolysis and coagulation. Elevated plasma PAI-1 levels are closely related to many cardiovascular diseases and have significant value in assessing the risk of myocardial infarction and venous thromboembolism [18]. Therefore, these biomarkers may play an important role in the early diagnosis of thrombosis in patients with DN.

To further clarify the predictive value of thrombus-related factors for the risk of thrombosis in patients with DN, this study plotted an ROC curve and found that the AUC of thrombus-related factors (TAT, sTM, PIC, and t-PAIC) for predicting the risk of thrombosis in patients with DN was 0.911 (95%*CI*: 0.837-0.959), confirming the predictive value of thrombus-related factors. However, it is worth noting that this study has some limitations. Firstly, the sample size of the study is limited, so all the above results should be

interpreted in the context of a small study population. Secondly, t-PAIC peaks around 08:00. and is lowest at night, while this test was conducted based on urgent needs, which may lead to lower diagnostic efficiency of t-PAIC. Larger-scale studies are needed in the future to validate the findings.

In summary, this study confirms that increased levels of thrombus-related factors are independent risk factors for thrombosis in patients with DN, and TAT, sTM, PIC, and t-PAIC can be used as important indicators for predicting the risk of thrombosis in patients with DN.

Conflicts of Interest: None

References

[1] Zhang LL, Han L, Wang XM, et al. Exploring the mechanisms underlying the therapeutic effect of Salvia miltiorrhiza in diabetic nephropathy using network pharmacology and molecular docking[J]. Biosci Rep, 2021, 41(6): BSR20203520.

[2] Zheng C, Huang L, Luo W, et al. Inhibition of STAT3 in tubular epithelial cells prevents kidney fibrosis and nephropathy in STZ-induced diabetic mice[J]. Cell Death Dis, 2019, 10(11): 848.

[3] Huang TS, Wu T, Wu YD, et al. Long-term statins administration exacerbates diabetic nephropathy via ectopic fat deposition in diabetic mice[J]. Nat Commun, 2023, 14(1): 390.

[4] Wang LL, Zhong JM, Xiao D, et al. Thrombomodulin (TM), thrombin-antithrombin complex (TAT), plasmin-α2-plasmininhibitor complex (PIC), and tissue plasminogen activator-inhibitor complex (t-PAIC) assessment of fibrinolytic activity in postpartum hemorrhage: a retrospective comparative cohort study[J]. Ann Transl Med, 2022, 10(23): 1273.

[5] Microvascular Complications Group, Diabetes Society, Chinese Medical Association. Expert consensus on prevention and treatment of diabetic nephropathy (2014 edition) [J]. Chin J Diabetes Mellit, 2014, 6(11): 792-801. **[In Chinese]**

[6] Group of Vascular Surgery, Surgical Society of Chinese Medical Association. Guidelines for diagnosis and treatment of deep venous thrombosis (third edition)[J]. Chin J Gen Surg, 2017, 32(9): 807-812. **[In Chinese]**

[7] Chen ZK, Chen KL, Ying CM, et al. COX proportional hazards regression model analysis for factors affecting prognosis of diabetic kidney disease[J]. Chin Arch Tradit Chin Med, 2024, 42(2): 28-33. **[In Chinese]**

[8] Jolugbo P, Ariëns RAS. Thrombus composition and efficacy of thrombolysis and thrombectomy in acute ischemic stroke[J]. Stroke, 2021, 52(3): 1131-1142.

[9] Lirong T, Minmin X, Manqiu Y, et al . Performance evaluation of thrombus molecular markers thrombomodulin, thrombin-antithrombin complex, plasmin-α2-plasmin inhibitor complex, and tissue plasminogen activator-inhibitor complex by a chemiluminescence analyzer[J]. Hippokratia，2022，26(2):78-82.

[10] Lurie A, Wang J, Hinnegan KJ, et al. Prevalence of left atrial Thrombus in anticoagulated patients with atrial fibrillation[J]. J Am Coll Cardiol, 2021, 77(23): 2875-2886.

[11] Li JZ, Zhou JY, Ren H, et al. Clinical Efficacy of Soluble Thrombomodulin, Tissue Plasminogen Activator Inhibitor complex, Thrombin-Antithrombin complex, α2-Plasmininhibitor-Plasmin complex in Pediatric Sepsis[J]. Clin Appl Thromb Hemost, 2022, 28: 10760296221102929.

[12] Hinton W, Nemeth B, de Lusignan S, et al. Effect of type 1 diabetes and type 2 diabetes on the risk of venous thromboembolism[J]. Diabet Med, 2021, 38(5): e14452.

[13] Kato D, Takahashi M, Yonezawa T, et al. Evaluation of an automated point-of-care test system for measuring thrombin-antithrombin complex in dogs[J]. J Vet Emerg Crit Care, 2020, 30(1): 102-106.

[14] Ye NF, Liu ZZ, Wang XF, et al. Evaluation of analytic and clinical performance of thrombin-antithrombin complex and D-dimer assay in prognosis of acute ischemic stroke[J]. Blood Coagul Fibrinolysis, 2020, 31(5): 303-309.

[15] Nakayama H, Inada H, Inukai T, et al. Recombinant human soluble thrombomodulin suppresses arteritis in a mouse model of Kawasaki disease[J]. J Vasc Res, 2022, 59(3): 176-188.

[16] Awano N, Jo T, Izumo T, et al. Recombinant human soluble thrombomodulin for acute exacerbation of idiopathic pulmonary fibrosis: a nationwide observational study[J]. J Intensive Care, 2022, 10(1): 14.

[17] Ren WH, Zhang J, Chen YY, et al. Evaluation of coagulation, fibrinolysis and endothelial biomarkers in cirrhotic patients with or without portal venous thrombosis[J]. Clin Appl Thromb Hemost, 2020, 26: 1076029620982666.

[18] Zhou K, Zhang J, Zheng ZR, et al. Diagnostic and prognostic value of TAT, PIC, TM, and t-PAIC in malignant tumor patients with venous thrombosis[J]. Clin Appl Thromb Hemost,2020 ,26:1076029620971041.

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·论　著·

糖尿病肾病患者血栓相关因子动态评估对血栓风险的预测价值

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摘要：目的　探讨血栓相关因子动态评估对糖尿病肾病（DN）患者血栓风险的预测价值。**方法**　回顾性选取 2020 年 1 月至 2022 年 9 月于沧州中西医结合医院进行治疗的 98 例 DN 患者为研究对象，治疗后进行随访，以患者出现深静脉血栓为观察终点，最终 96 例获得随访，根据有无血栓形成分为血栓组（$n=21$）和非血栓组（$n=75$）。收集患者的临床资料，通过单因素和多因素 logistic 分析 DN 患者血栓风险的影响因素。采用受试者工作特征（ROC）曲线评价血栓相关因子［凝血酶—抗凝血酶复合物（TAT）、纤溶酶-α-2-纤溶酶抑制剂复合物（PIC）、组织型纤溶酶原激活物/纤溶酶原激活物抑制剂-1 复合物（t-PAIC）和可溶性血栓调节蛋白（sTM）］对 DN 患者血栓风险的预测价值。**结果**　两组患者一般资料、糖尿病病程、糖代谢、脂代谢和肾功能指标比较差异无统计学意义（$P>0.05$）；两组患者的凝血酶原时间（PT）、活化部分凝血活酶时间（APTT）及 D-二聚体（D-D）比较，差异有统计学意义（$P<0.05$）；血栓组患者 TAT、PIC、t-PAIC、sTM 治疗前和后的水平，治疗前后水平的差值，治疗前后的变异系数，均高于非血栓组患者（$P<0.01$）。多因素 logistic 回归分析结果显示，TAT、PIC、t-PAIC、sTM 的变异系数增高（$OR=3.367$，$P=0.010$；$OR=19.106$，$P=0.042$；$OR=4.313$，$P=0.005$；$OR=9.389$，$P=0.003$）为影响 DN 患者血栓风险的独立危险因素。ROC 曲线结果显示，TAT、PIC、t-PAIC 和 sTM 的变异系数预测 DN 患者血栓风险的 AUC 分别为 0.818、0.806、0.873 和 0.825。**结论**　血栓相关因子水平增高是 DN 患者血栓风险的独立危险因素，TAT、sTM、PIC 和 t-PAIC 可作为预测其血栓风险的重要指标。

关键词：糖尿病肾病；血栓；凝血酶—抗凝血酶复合物；纤溶酶-α-2-纤溶酶抑制剂复合物；组织型纤溶酶原激活物/纤溶酶原激活物抑制剂-1 复合物；可溶性血栓调节蛋白
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Predictive value of dynamic assessment of thrombose-related factors in diabetic nephropathy patients for thrombotic risk

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Abstract: Objective　To explore the value of dynamic evaluation of thromose-related factors for predicting thrombotic risk in diabetic nephropathy (DN) patients. **Methods**　A retrospective study was conducted to select 98 patients with DN who were treated in Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine from January 2020 to September 2022. Follow-up was conducted after treatment, with the occurrence of deep vein thrombosis as the observation endpoint. Finally, 96 patients obtained follow-up and were divided into the thrombosis group ($n=21$) and the non-thrombosis group ($n=75$) based on the presence or absence of thrombosis. The clinical data of patients were collected, and the influencing factors of thrombotic risk of DN patients were analyzed by univariate and multivariate logistic analysis. The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of thrombose-related factors [thrombin-antithrombin complex (TAT), plasmin-α-2-plasmin inhibitor complex (PIC), tissue plasminogen activator/plasminogen activator inhibitor-1 complex (t-PAIC) and soluble thrombomodulin(sTM)]

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for thrombotic risk in DN patients. **Results**　There was no significant difference in general information, duration of diabetes, glucose metabolism, lipid metabolism and renal function between the two groups ($P>0.05$). The differences in prothrombin time (PT), activated partial thromboplastin time (APTT) and D-dimer (D-D) between the two groups were statistically significant($P<0.05$). In the thrombosis group, the levels of TAT, PIC, t-PAIC and sTM before and after treatment, the difference between pre-treatment and post-treatment, and the variation coefficient between pre-treatment and post-treatment were all increased compared to the non-thrombosis group($P<0.01$). Multivariate logistic regression analysis showed that the increased variation coefficients of TAT, PIC, t-PAIC and sTM ($OR=3.367$, $P=0.010$; $OR=19.106$, $P=0.042$; $OR=4.313$, $P=0.005$; $OR=9.389$, $P=0.003$) were the independent risk factors affecting the thrombotic risk in DN patients. The ROC curve results showed that the AUCs of the variation coefficients of TAT, PIC, t-PAIC and sTM in predicting the thrombotic risk in DN patients were 0.818, 0.806, 0.873 and 0.825, respectively. **Conclusion**　Elevated levels of thrombose-related factors are the independent risk factors for thrombosis in DN patients, and TAT, sTM, PIC, and t-PAIC can be used as important indicators to predict their thrombotic risk.

Keywords: Diabetic nephropathy; Thrombus; Thrombin-antithrombin complex; Plasmin-α-2-plasmin inhibitor complex; Tissue plasminogen activator/plasminogen activator inhibitor-1 complex; Soluble thrombomodulin

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糖尿病肾病(diabetic nephropathy, DN)是指糖尿病(包括 1 型和 2 型)患者肾脏的改变以及糖尿病对肾脏的影响所导致的特定病理结构和功能,也是终末期肾病(end-stage renal disease, ESKD)的主要病因之一[1]。有证据表明,DN 患者表现为过早的动脉粥样硬化和更广泛的血管疾病,使其更容易发生斑块破裂和血栓形成[2]。另外,DN 患者由于血小板的高反应性和血栓凝血因子的激活增加以及纤维蛋白溶解减少而表现出更高的血栓形成倾向[3]。但目前尚没有准确、有效、高灵敏度的指标来评价 DN 早期凝血功能的变化。最新研究证实凝血酶—抗凝血酶复合物(thrombin-antithrombin complex, TAT)、纤溶酶-α-2-纤溶酶抑制剂复合物(plasmin-α-2-plasmin inhibitor complex, PIC)、组织型纤溶酶原激活物/纤溶酶原激活物抑制剂-1 复合物(tissue plasminogen activator/plasminogen activator inhibitor-1 complex, t-PAIC)和可溶性血栓调节蛋白(soluble thrombomodulin, sTM)是血管内皮、凝血和纤溶早期变化的新指标,可用于血栓形成高危人群的血栓栓塞早期诊断、血栓形成风险评估和疗效评价,以及健康人群血栓形成风险筛查[4]。因此笔者假设在 DN 早期,这 4 项新的凝血功能指标已经发生了变化,可以预测 DN 的出血风险,通过回顾性研究分析这 4 项新指标在 DN 患者中的变化,并讨论其在预测 DN 血栓风险中的应用。

1　资料与方法

1.1　临床资料　纳入标准:(1) 符合《糖尿病肾病防治专家共识(2014 年版)》[5]中的诊断标准;(2) 年龄 18~75 岁;(3) 糖化血红蛋白(HbA1c)水平在 7%~10%;(4) 微量蛋白尿/肌酐(mAlb/Cr)≥30 mg/(g·24 h)。排除标准:(1) 1 型糖尿病患者;(2) 低血糖昏迷、糖尿病酮症酸中毒、高渗非酮症昏迷或糖尿病急性并发症患者;(3) 空腹血糖(FBG)>13.3 mmol/L;(4) 总胆红素值超过正常值的 2.5 倍;(5) 男性患者血清肌酐(SCr)>133 μmol/L,女性患者>124 μmol/L;(6) 有高血压、药物滥用、酒精依赖或药物过敏史者;(7) 在 3 个月内服用血管紧张素转换酶抑制剂、血管紧张素受体阻滞剂或抗凝药物者。

1.2　研究方案

1.2.1　一般资料　本研究经医院伦理委员会批准(2023259),所有患者及家属均签订知情同意书。回顾性选取 2020 年 1 月至 2022 年 1 月于沧州中西医结合医院进行治疗的 98 例 DN 患者为研究对象,根据超声和 CT 检查结果分析患者是否发生(包括脑栓塞、肺栓塞、肾动静脉血栓栓塞、四肢血栓栓塞和肠系膜血栓栓塞等)血栓分为血栓组和非血栓组。同时根据既往文献报道和临床实际参考,收集患者基线相关资料,分析 DN 患者血栓形成风险发生影响因素。

1.2.2　治疗方案　所有患者均根据《糖尿病肾病防治专家共识(2014 年版)》[5]进行治疗,予患者达格列净(阿斯利康制药,国药准字 HJ20170119),10 mg/次,每日 1 次,缬沙坦胶囊(北京诺华制药,国药准字 H20040217),80 mg/次,每日 1 次。在此基础上合理的控制患者血糖(根据患者的血糖水平等各方面情况选择口服降糖药或注射胰岛素治疗,使空腹血糖<7 mmol/L),控制患者血脂(应用他汀类药物治疗,使血脂控制到正常范围),同时予健康教育,培养健康的生活习惯。

1.3　观察指标　所有患者均于清晨抽取静脉血 5 mL，放置于室温下静置 30 min，离心，取上清液进行检测：(1) FBG、HbA1c、高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)、三酰甘油(TG)和总胆固醇(TC)、血尿素氮(BUN)、SCr 等生化指标均应用 Beckmancoulte 全自动生化分析仪进行检测；(2) 24 h 尿微量白蛋白排泄率(24 h UAER)应用 IMMULITE 全自动化学发光免疫分析仪检测；(3) 凝血酶原时间(PT)、活化部分凝血活酶时间(APTT)应用 AutoCimo C6000 全自动凝血分析仪检测；(4) D-二聚体(D-D)应用 DG5035A 酶联免疫检测仪检测；(5) TAT、PIC、t-PAIC 和 sTM 应用 Wondfo FC-302 全自动化学发光免疫分析仪检测。

1.4　随访及血栓形成风险评估　治疗后随访观察 1 年，根据《深静脉血栓形成的诊断和治疗指南(第 3 版)》[6]中深静脉血栓的诊断标准评估 DN 患者是否出现血栓，以患者出现深静脉血栓为观察终点，若随访期间未发生终点事件，则以最终随访截止时间为观察终点。随访方式为查阅住院、门诊电子病历系统病案记录或电话，随访截止时间为 2023 年 1 月 1 日。

1.5　统计学方法　采用 Epidata 软件进行数据录入及 SPSS 22.0 统计软件进行数据分析。计量资料先予以正态性检验，正态分布且方差齐同的资料采用 $\bar{x}\pm s$ 表示，组间比较采用成组 t 检验，方差不齐采用 t' 检验；计数资料用例(%)表示，采用 χ^2 检验；对所有变量进行共线性诊断且对不存在共线性变量行多因素 logistic 回归分析，绘制 ROC 曲线评价血栓相关因子对 DN 患者血栓形成风险的预测价值。$P<0.05$ 为差异有统计学意义。

2　结　果

2.1　随访结果　截止 2023 年 1 月 1 日，最终 96 例获得随访，其中 21 例(21.88%)出现血栓归为血栓组，75 例(78.12%)未发生血栓归为非血栓组。

2.2　两组患者临床资料比较　两组患者一般资料及 FBG、HbA1c、胰岛素抵抗指数、血清胱抑肽 C、尿酸、BUN、SCr、TG、TC、HDL-C、LDL-C、24 hUAER、估算的肾小球滤过率(eGFR)比较差异无统计学意义($P>0.05$)；而血栓组患者的 APTT、PT 水平低于非血栓组，D-D 水平高于非血栓组($P<0.05$)。见表 1。

2.3　两组患者血栓相关因子比较　血栓组患者 TAT、PIC、t-PAIC、sTM 治疗前、后的水平，治疗前后水平的差值，治疗前后的变异系数(CV)，均高于非血栓组，差异有统计学意义($P<0.01$)。见表 2。

2.4　DN 患者血栓风险相关危险因素的 logistic 回归分析　以发生血栓与否为因变量(未发生血栓=0，发生血栓=1)，以表 1、表 2 差异有统计学意义的变量(连续变量实测值)为自变量，进行单因素和多因素 logistic 回归分析。结果多因素回归分析显示，TAT、PIC、t-PAIC、sTM 的 CV 增高为 DN 患者血栓风险的独立危险因素($P<0.05$)。见表 3、表 4。

表 1　两组患者临床资料比较　($\bar{x}\pm s$)

Tab. 1　Comparison of clinical data between the two groups　($\bar{x}\pm s$)

临床资料	血栓组 (n=21)	非血栓组 (n=75)	t/χ^2 值	P 值
年龄(岁)	61.36±5.38	59.10±5.95	1.569	0.120
性别(例,女/男)	8/13	26/49	0.084	0.120
BMI(kg/m^2)	25.33±3.42	24.16±3.09	1.498	0.137
吸烟[例(%)]	14(66.67)	52(69.33)	0.054	0.816
糖尿病病程(年)	11.53±1.76	10.83±1.52	1.801	0.075
SBP(mmHg)	114.71±3.87	112.98±3.46	1.973	0.051
DBP(mmHg)	63.26±4.54	61.48±3.59	1.891	0.062
FBG(mmol/L)	6.05±1.05	5.91±0.98	0.570	0.570
HbA1c(%)	9.49±2.11	8.36±2.37	1.975	0.051
胰岛素抵抗指数	3.79±0.81	3.54±0.77	1.300	0.197
血清胱抑肽 C(mg/L)	2.43±0.71	2.11±0.67	1.910	0.059
尿酸(μmol/L)	323.80±77.51	299.56±63.98	1.464	0.147
BUN(mmol/L)	8.47±2.82	8.16±2.25	0.527	0.599
SCr(μmol/L)	75.36±23.61	72.92±21.65	0.448	0.655
TG(mmol/L)	2.23±0.62	2.10±0.51	0.984	0.328
TC(mmol/L	4.54±1.21	4.42±1.18	0.410	0.683
HDL-C(mmol/L)	1.43±0.35	1.51±0.48	0.711	0.479
LDL-C(mmol/L)	3.27±0.81	3.15±0.76	0.630	0.530
24hUAER(μg/min)	414.09±102.13	377.13±81.14	1.740	0.085
eGFR	64.61±12.20	69.77±10.57	1.911	0.059
APTT(s)	31.96±5.44	34.72±5.57	2.013	0.047
PT(s)	14.24±2.00	15.67±3.13	2.524	0.015
D-D(ng/mL)	1.09±0.21	0.99±0.20	2.016	0.047

注：eGFR 单位为 mL/(min·1.73 m^2)。

表 2　两组患者血栓相关因子比较　($\bar{x}\pm s$)

Tab. 2　Comparison of thrombus related factors between the two groups　($\bar{x}\pm s$)

血栓相关因子		血栓组 (n=21)	非血栓组 (n=75)	t 值	P 值
TAT(mg/L)	治疗前	18.46±4.27	15.28±3.86	3.260	0.002
	治疗后	25.07±5.12	20.14±3.39	4.164	<0.001
	差值	6.79±1.44	5.36±0.94	4.301	<0.001
	CV(%)	35.81±9.04	25.26±4.37	5.181	<0.001
PIC(μg/mL)	治疗前	1.48±0.21	1.11±0.29	5.451	<0.001
	治疗后	2.95±0.65	2.04±0.52	7.692	<0.001
	差值	1.34±0.28	0.93±0.24	6.680	<0.001
	CV(%)	90.54±10.26	74.08±6.67	6.952	<0.001
t-PAIC(ng/mL)	治疗前	7.92±1.14	7.01±1.02	3.521	0.001
	治疗后	19.12±1.61	15.94±1.73	7.554	<0.001
	差值	11.87±1.16	9.92±1.49	5.542	<0.001
	CV(%)	160.93±11.42	139.92±9.45	8.594	<0.001
sTM(TU/mL)	治疗前	7.62±0.57	7.16±0.38	3.488	0.002
	治疗后	14.81±1.26	12.92±1.65	4.860	<0.001
	差值	7.32±0.73	6.59±0.59	4.735	<0.001
	CV(%)	99.36±6.38	84.24±7.34	8.570	<0.001

2.5　血栓相关因子预测 DN 患者血栓风险的 ROC 曲线　ROC 曲线分析显示,对预测 DN 患者血栓风险,TAT CV 的 AUC 为 0.818(95%*CI*: 0.704~0.932),临界值 6.965 mg/L,敏感度 57%,特异度 97%;PIC CV 的 AUC 为 0.806(95%*CI*: 0.698~0.914),临界值 1.322 μg/mL,敏感度 71%,特异度 87%;t-PAIC CV 的 AUC 为 0.873(95%*CI*: 0.778~0.968),临界值 11.224 ng/mL,敏感度 86%,特异度 84%;sTM CV 的 AUC 为 0.825(95%*CI*: 0.717~0.933),临界值 7.088 TU/mL,敏感度 76%,特异度 81%。见图 1。

表 3　DN 患者血栓危险因素的单因素 logistic 回归分析
Tab. 3　Univariate logistic regression analysis of risk factors of thrombosis in DN patients

因素	*β*	标准误	Wald	*P* 值	*OR* 值	95%*CI*
APTT	−0.093	0.048	3.795	0.051	0.911	0.829~1.001
PT	−0.166	0.087	3.668	0.055	0.847	0.715~1.004
D-D	2.532	1.299	3.799	0.051	12.582	0.986~160.553
TAT CV	1.172	0.294	15.847	<0.001	3.229	1.813~5.749
PIC CV	3.604	1.013	12.651	<0.001	36.750	5.043~267.787
t-PAIC CV	1.279	0.305	17.615	<0.001	3.592	1.977~6.527
sTM CV	1.888	0.492	14.721	<0.001	6.605	2.518~17.325

表 4　DN 患者血栓危险因素的多因素 logistic 回归分析
Tab. 4　Multivariate logistic regression analysis of risk factors of thrombosis in DN patients

因素	*β*	标准误	Wald	*P* 值	*OR* 值	95%*CI*
TAT CV	1.214	0.472	6.608	0.010	3.367	1.334~8.498
PIC CV	2.950	1.453	4.120	0.042	19.106	1.107~329.780
t-PAIC CV	1.462	0.517	7.988	0.005	4.313	1.565~11.885
sTM CV	2.240	0.748	8.958	0.003	9.389	2.166~40.695
常量	−44.093	11.409	14.937	<0.001	0.000	

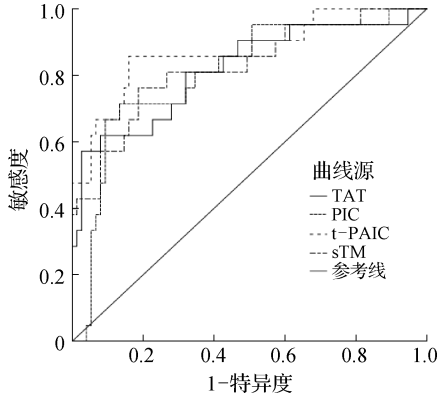

图 1　血栓相关因子对 DN 患者血栓风险预测价值的 ROC 曲线
Fig. 1　ROC curve of the predictive value of thrombose-related factors on thrombotic risk in DN patients

3　讨　论

高血糖和胰岛素抵抗是 DN 的主要代谢异常,已被提出通过一系列事件,包括内皮功能障碍、血小板亢进、纤维蛋白溶解受损、氧化应激和低度炎症,而导致 DN 血栓形成前状态。因此,及时、准确诊断血栓对 DN 患者来说是一个持续的挑战[7]。目前,常规实验室凝血参数,如 PT、APTT、凝血酶时间、纤维蛋白原、D-D、纤维蛋白原降解产物(FDP)、凝血因子等的检测已覆盖凝血和纤溶系统[8-9]。然而,所有这些参数都是被动检测和血栓形成后的晚期筛查,对血栓前状态和弥散性血管内凝血不敏感。最新研究发现 TAT、PIC、t-PAIC、sTM 可用于评估与人凝血、纤溶酶和内皮功能相关的静脉血栓栓塞风险[10]。但对 DN 患者血栓风险的研究相对较少,因此本研究选择探讨血栓相关因子对 DN 患者血栓风险的预测价值。

血栓栓塞性疾病主要包括静脉血栓栓塞性疾病(肺血栓栓塞综合征、深静脉血栓形成)和动脉血栓栓塞性疾病(急性冠状动脉综合征、心房颤动、中风等),已成为世界范围内死亡的主要原因之一[11]。相关研究发现,与常规凝血项目 PT、APTT 相比,血栓四项指标在凝血及纤溶系统激活的早期可发生明显变化,有利于疾病的早期诊断和治疗[12]。与此同时,Hinton 等[13]研究发现男性血栓患者 TAT、PIC、t-PAIC 和血栓调节蛋白(TM)均显著高于男性健康对照组。本研究结果与其相似,显示 TAT、PIC、t-PAIC 和 sTM 是影响 DN 患者血栓风险的独立影响因素。可能由于凝血酶是凝血酶原的一种活化形式,在其天然底物的活化中起着至关重要的作用,包括纤维蛋白原、因子Ⅴ、因子Ⅷ、蛋白 C 等。血浆中凝血酶的活性是通过与抗凝血酶的快速相互作用而形成 TAT 来调节的,它的形成是判断抗凝治疗的最佳时间[14]。另外,TM 是一种Ⅰ型跨膜糖蛋白,主要表达于血管内皮细胞,是激活抗凝蛋白的重要辅助因子,有助于止血平衡。具体来说,TM 调节凝血酶从凝血剂到抗凝血蛋白酶的活性。当凝血酶与 TM 结合时,凝血活性蛋白 C(APC)选择性地使凝血因子Ⅴa 和Ⅷa 失活,以防止过度凝血[15]。同时,TM 还可以增强凝血酶激活的纤溶抑制剂(TAFI)的蛋白水解活性,从而延缓血栓的溶解[16]。此外,在体内形成血栓时纤溶系统被激活。随后,由此产生的纤溶酶与特定抑制剂结合,导致 PIC 的形成,PIC 是高纤溶的一个指标。在一项对 175 名肝硬化患者的研究中,TAT 和 TAT/t-PAIC 被确定为预测肝硬化患者血栓形成的潜在生物标志物[17]。t-PAIC 是一种组织型纤溶酶原激活物(t-PA)复合物,其 1 型抑制剂(PAI-1)是纤溶和凝血系统平衡最重要的调节因子,血浆 PAI-1 水平升高与许多心血管疾病密切相关,在评估心肌梗死和静脉血

栓栓塞的风险方面具有重要价值[18]。因此,这些生物标志物可能在 DN 患者血栓的早期诊断中具有重要作用。

为进一步明确血栓相关因子对 DN 患者血栓风险的预测价值,本研究绘制 ROC 曲线发现血栓相关因子(TAT、sTM、PIC 和 t-PAIC)对 DN 患者血栓形成风险预测的 AUC 为 0.806~0.873,均有较高的预测价值。但值得注意的是,本研究存在一些局限性,首先,研究的样本量有限,所以上述所有结果都应该在小研究人群的背景下解释。其次,t-PAIC 在上午 8 点左右达到峰值,晚上最低,而本试验是根据紧急需要进行的,这可能导致 t-PAIC 的诊断效率较低。未来需要进行更大规模的研究来验证。

综上所述,血栓相关因子水平增高是 DN 患者血栓风险的独立危险因素, TAT、sTM、PIC 和 t-PAIC 可作为预测 DN 患者血栓风险的重要指标。

利益冲突　本文不存在任何利益冲突。

参考文献

[1] Zhang LL, Han L, Wang XM, et al. Exploring the mechanisms underlying the therapeutic effect of *Salvia miltiorrhiza* in diabetic nephropathy using network pharmacology and molecular docking[J]. Biosci Rep, 2021, 41(6): BSR20203520.

[2] Zheng C, Huang L, Luo W, et al. Inhibition of STAT3 in tubular epithelial cells prevents kidney fibrosis and nephropathy in STZ-induced diabetic mice[J]. Cell Death Dis, 2019, 10(11): 848.

[3] Huang TS, Wu T, Wu YD, et al. Long-term statins administration exacerbates diabetic nephropathy via ectopic fat deposition in diabetic mice[J]. Nat Commun, 2023, 14(1): 390.

[4] Wang LL, Zhong JM, Xiao D, et al. Thrombomodulin (TM), thrombin-antithrombin complex (TAT), plasmin-α2-plasmininhibitor complex (PIC), and tissue plasminogen activator-inhibitor complex (t-PAIC) assessment of fibrinolytic activity in postpartum hemorrhage: a retrospective comparative cohort study[J]. Ann Transl Med, 2022, 10(23): 1273.

[5] 中华医学会糖尿病学分会微血管并发症学组.糖尿病肾病防治专家共识(2014 年版)[J].中华糖尿病杂志,2014,6(11):792.
Microvascular Complications Group, Diabetes Society, Chinese Medical Association. Expert consensus on prevention and treatment of diabetic nephropathy (2014 edition)[J]. Chin J Diabetes Mellit, 2014, 6(11): 792.

[6] 中华医学会外科学分会血管外科学组.深静脉血栓形成的诊断和治疗指南(第三版)[J].中华普通外科杂志,2017,32(9):807.
Group of Vascular Surgery, Surgical Society of Chinese Medical Association. Guidelines for diagnosis and treatment of deep venous thrombosis (third edition)[J]. Chin J Gen Surg, 2017, 32(9): 807.

[7] 陈占科,陈凯丽,应春苗,等.糖尿病肾脏疾病预后影响因素的 COX 比例风险回归模型分析[J].中华中医药学刊,2024,42(2):28.
Chen ZK, Chen KL, Ying CM, et al. COX proportional hazards regression model analysis for factors affecting prognosis of diabetic kidney disease[J]. Chin Arch Tradit Chin Med, 2024, 42(2): 28.

[8] Jolugbo P, Ariëns RAS. *Thrombus* composition and efficacy of thrombolysis and thrombectomy in acute ischemic stroke[J]. Stroke, 2021, 52(3): 1131-1142.

[9] 张心钰,田凤胜.纤维蛋白原与糖尿病肾病相关性的研究进展[J].中国医药导报,2023,20(18):61-64.
Zhang XY, Tian FS. Research progress on the correlation between fibrinogen and diabetic nephropathy[J]. China Med Her, 2023, 20(18): 61-64.

[10] Lirong T, Minmin X, Manqiu Y, et al. Performance evaluation of thrombus molecular markers thrombomodulin, thrombin-antithrombin complex, plasmin-α-2-plasmin inhibitor complex, and tissue plasminogen activator-inhibitor complex by a chemiluminescence analyzer[J]. Hippokratia, 2022, 26(2): 78-82.

[11] Lurie A, Wang J, Hinnegan KJ, et al. Prevalence of left atrial *Thrombus* in anticoagulated patients with atrial fibrillation[J]. J Am Coll Cardiol, 2021, 77(23): 2875-2886.

[12] Li JZ, Zhou JY, Ren H, et al. Clinical efficacy of soluble thrombomodulin, tissue plasminogen activator inhibitor complex, thrombin-antithrombin complex, α2-plasmininhibitor-plasmin complex in pediatric sepsis [J]. Clin Appl Thromb Hemost, 2022, 28: 10760296221102929.

[13] Hinton W, Nemeth B, de Lusignan S, et al. Effect of type 1 diabetes and type 2 diabetes on the risk of venous thromboembolism[J]. Diabet Med, 2021, 38(5): e14452.

[14] Kato D, Takahashi M, Yonezawa T, et al. Evaluation of an automated point-of-care test system for measuring thrombin-antithrombin complex in dogs[J]. J Vet Emerg Crit Care, 2020, 30(1): 102.

[15] Nakayama H, Inada H, Inukai T, et al. Recombinant human soluble thrombomodulin suppresses arteritis in a mouse model of Kawasaki disease[J]. J Vasc Res, 2022, 59(3): 176-188.

[16] Awano N, Jo T, Izumo T, et al. Recombinant human soluble thrombomodulin for acute exacerbation of idiopathic pulmonary fibrosis: a nationwide observational study[J]. J Intensive Care, 2022, 10(1): 14.

[17] Ren WH, Zhang J, Chen YY, et al. Evaluation of coagulation, fibrinolysis and endothelial biomarkers in cirrhotic patients with or without portal venous thrombosis[J]. Clin Appl Thromb Hemost, 2020, 26: 1076029620982666.

[18] Zhou K, Zhang J, Zheng ZR, et al. Diagnostic and prognostic value of TAT, PIC, TM, and t-PAIC in malignant tumor patients with venous thrombosis [J]. Clin Appl Thromb Hemost, 2020, 26: 1076029620971041.

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