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Original Article

Predicting venous thromboembolism in non-surgical hospitalized patients with type 2 diabetes mellitus: development and validation of a nomogram

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Abstract: Background: Due to confounders like hyperglycemia, patients with type 2 diabetes mellitus (T2DM) have an increased susceptibility to venous thromboembolism (VTE). However, formal risk assessment models, such as using the Padua score, do not include all T2DM-associated risk factors for VTE. Therefore, this study aims to develop and validate a predictive nomogram for VTE in non-surgical inpatients with T2DM. Methods: We retrospectively analyzed the clinical and biochemical data of 420 non-surgical inpatients with T2DM between 2017 and 2021 from three centers (the PLA 474th hospital, the Second Affiliated Hospital of Xinjiang Medical University and the Fifth Affiliated Hospital of Xinjiang Medical University). A multivariate analysis based on logistic regression model was performed to identify independent risk factors and construct a nomogram. The predictive values were compared by calculating the integrated discrimination improvement (IDI) and net reclassification improvement (NRI), and by decision curve analysis (DCA). Results: Old age, BMI, D-dimer, hypoproteinemia, acute infection, acute myocardial infarction, cerebral ischemic stroke, reduced mobility, and heart/respiratory failure were independent risk factors for VTE in non-surgical inpatients with T2DM, as indicated by the multivariate analysis. The nomogram demonstrated superior discriminative ability compared to the Padua score (area under the curve: 0.923 vs. 0.849). NRI and IDI were also observed, and the DCA identified the greater net benefit and clinical utilization of the new nomogram. Conclusions: A predictive nomogram for VTE in non-surgical inpatients with T2DM was developed and validated in this study. The nomogram is highly predictive and easy to operate, but external data verification is required before it can be further used.

Keywords: Type 2 diabetes mellitus, venous thromboembolism, nomogram, predicting factor

Introduction

Venous thromboembolism (VTE), a condition comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a prevalent and grievous complication in hospitalized patients, contributing to significantly increased disability and mortality. In addition, VTE is often misdiagnosed due to nonspecific clinical presentations, resulting in adverse effects on patient safety. The awareness of this disease should be enhanced so that patients with risk factors can be more vigilant and be assessed for clinical possibilities [1]. VTE is a disease that can be prevented through early intervention and management, which significantly reduced the morbidity and mortality [2]. In China, the prevention and control of VTE in inpatients still shows room for improvement.

As a multifactorial process, VTE has a connection with risk factors such as advanced age, history of thrombophilia, prior VTE attacks, family history of VTE, acute myocardial infarction (AMI), congestive heart failure (HF) or respiratory failure (RF), stroke, cancer, recent trauma, surgery, reduced mobility, acute infection, central venous catheters, obesity, hormone thera-

py, tobacco use, and type 2 diabetes mellitus (T2DM) [3, 4]. Multiple VTE risk assessment models, such as the Wells scoring system, Padua score, revised Geneva score, and Caprini risk model, have been utilized in clinical settings [5, 6]. However, the most optimal one for acutely ill medical patients has not yet been defined [7]. Furthermore, these VTE risk assessment models are critical to reducing the incidence of DVT and PE, as they enable early identification of patients eligible for pharmaceutical or mechanical thromboprophylaxis [8].

Among all hospital-associated VTE events, half to three fourths occur in non-surgical patients. The latest updated guidelines recommend the Padua score as a risk assessment index for VTE in hospitalized medical patients [9]. T2DM, which has a rapidly increasing prevalence in China, is one of the most common conditions in hospitalized medical patients and a known risk factor for VTE [10]. Meanwhile, T2DM is often associated with obesity, hyperglycemia, dyslipidemia, hyperuricemia, cardiovascular disease, acute infection, stroke and cancer, all of which are risk factors for VTE [11]. Thus, identifying high-risk groups for VTE among T2DM patients and initiating effective prophylaxis can reduce the burden of VTE and its consequences and enhance patients' quality of life [12]. The Padua score includes 11 risk factors [13] rather than all the VTE risk factors associated with T2DM patients. Irrespective of the development and clinical application of some formal risk assessment models for DVT, there is currently no such risk model for the diabetic population. Given the limitations of the Padua score, it is necessary to build a comprehensive risk assessment model for T2DM non-surgical inpatients.

Accordingly, this study aimed at developing a nomogram to assess VTE risk in T2DM non-surgical inpatients using their clinical and laboratory parameters, and assessing its predictive performance, discriminative ability and clinical utilization through a comparative analysis with the Padua score.

Methods

Study subjects

We retrospectively studied 216 non-surgical inpatients with T2DM and VTE from three centers (the PLA 474th hospital, the Second Affiliated Hospital of Xinjiang Medical University and the Fifth Affiliated Hospital of Xinjiang Medical University). The included patients were admitted from June 2017 to June 2021. Of these patients, 6 were excluded due to missing important clinical characteristic data, and the rest 210 patients were assigned to a VTE+ group. During the same period, 210 T2DM patients without VTE were included in a control group (VTE- group). In total, 420 patients were enrolled. This study was approved by the Ethics Committee of the PLA 474th Hospital.

The inclusion criteria: 1) inpatients who were diagnosed with T2DM and DVT according to the Prevention and Management of Type 2 Diabetes Mellitus in China (2017 edition) [14], Chinese Expert Consensus on the Diagnosis and Management of Acute Pulmonary Embolism (2015) [15], and Guidelines for the Diagnosis and Treatment of Deep Venous Thrombosis (3rd edition) [16]; 2) inpatients who were not on anticoagulation or thrombolytic therapy before or after hospitalization; 3) patients with complete clinical and inspection data. The exclusion criteria: 1) patients aged under 18 years; 2) patients who were pregnant or lactating; 3) patients with recent trauma (≤1 month); 4) patients who had any surgical procedure during admission; 5) patients who were directly admitted to an intensive care unit.

Clinical evaluation

Patients' clinical and biochemical features were collected for analyses. The collected parameters included age, prior VTE, history of hypertension, dyslipidemia or hyperuricemia, body mass index (BMI), waist circumference (WC), diabetic duration, AMI, cerebral ischemic stroke (CIS), congestive HF or RF, cancer, hormone replacement therapy (HRT), acute infection (pneumonia, urinary tract infection, infectious diarrhea, sepsis, pyodermitis, etc.), immobility for 3 days or longer due to disease, and treatment or medical indications.

BMI was classified based on the Chinese criteria: normal <24 kg/m^2; abnormal ≥24 kg/m^2. The duration of T2DM was the time elapsed since diagnosis. Glycated hemoglobin (HbA1C) represents the level of blood glucose. Dyslipidemia, hyperuricemia, hypertension and hypoproteinemia were defined, respectively, as follows: total cholesterol levels ≥5.7 mmol/L,

triglycerides ≥1.7 mmol/L, or use of lipid-lowering treatment; serum uric acid ≥420 μmol/L, or use of uric acid-lowering drugs; systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive agents; serum albumin level <35 g/L. DVT and PE diagnoses were made by venous compression ultrasound and pulmonary angio-CT.

Laboratory tests

The platelet count and levels of serum albumin, total cholesterol, triglycerides, blood uric acid, HbA1C and plasma D-dimer (DD) were assessed in all patients.

Statistical analyses

Baseline categorical variables and continuous variables were expressed as number of cases (percentage) and median (IQR), respectively, and analyzed using the χ^2 test and Mann-Whitney U-test, respectively. The potential risk factors from the dataset were identified using the univariate logistic regression analysis, and those with a *P*-value <0.05 were further assessed using the multivariate analysis. Moreover, the odds ratio (OR) and corresponding 95% confidence interval (CI) were evaluated for each risk factor. Subsequently, a nomogram was built based on the multivariate logistic regression results, and its discriminative ability was evaluated via the area under the ROC curve (AUC). The calibration was performed using bootstrapping with 1,000 resamples. This was followed by a comparison of the actual outcome and the predicted probability using the calibration curve. The prediction accuracy of the new model versus the Padua score was estimated by calculating the NRI and IDI. Finally, the clinical utility and net benefits of the nomogram were identified using the decision curve analysis (DCA).

All statistical analyses were performed with the use of the R software (v3.6.2; http://www.r-project.org/). A two-tailed P<0.05 was considered significant.

Results

Patient characteristics

This study enrolled 420 patients and assigned them into a VTE+ group and a VTE- group. Patient baseline characteristics and clinical data can be found in **Table 1**. Out of 210 cases in the VTE+ group, 99 (47.14%) were female, and 111 (52.86%) were male. In the VTE- group, 105 (50%) were female and 105 (50%) were male (P = 0.6254). Platelet count, HbA1C, diabetic duration, history of dyslipidemia and history of hypertension were similar in VTE+ and VTE- groups (P = 0.4873, 1, 0.5361, 0.1735 and 0.1047, respectively). However, the two groups were significantly different in age, BMI, WC, DD, history of hyperuricemia, history of hypoproteinemia, prior VTE, AMI or CIS, HF/RF, cancer, acute infection, HRT and reduced mobility (all P<0.001).

Risk factors for VTE in non-surgical inpatients with T2DM and development of the nomogram

The univariate analysis identified a significant correlation of the following covariates with VTE: age, BMI, WC, DD, hyperuricemia, hypoproteinemia, acute infection, AMI or CIS, cancer, prior VTE, reduced mobility, HF/RF, and HRT (**Table 2**; all P<0.001). While no statistically significant correlation was observed between VTE and sex, platelet count, HbA1C, diabetic duration, dyslipidemia and hypertension. Multivariable analyses revealed that old age, BMI, DD, hypoproteinemia, acute infection, AMI or CIS, reduced mobility and HF/RF were significant independent factors for VTE in non-surgical inpatients with T2DM. Finally, the 8 independent predictors with strong connection with VTE were identified from the dataset by univariate and multivariate analyses, namely, age (≥75) at diagnosis (OR = 7.29, 95% CI: 3.04-18.51, P<0.001); BMI (kg/m^2) ≥24 (OR = 4.26, 95% CI: 1.90-9.90, P<0.001); DD ≥0.5 mg/L (OR = 4.26, 95% CI: 2.18-8.50, P<0.001); hypoproteinemia (OR = 4.37, 95% CI: 1.87-10.73, P<0.001); AMI or CIS (OR = 2.74, 95% CI: 1.13-6.91, P = 0.028); HF/RF (OR = 5.82, 95% CI: 2.90-12.14, P<0.001); acute infection (OR = 4.43, 95% CI: 2.25-8.97, P<0.001); reduced mobility (OR = 3.10, 95% CI: 1.20-8.68, P = 0.024) (**Table 2**).

A nomogram used to predict the probability of VTE in non-surgical inpatients with T2DM was then built based on the 8 predictors above (**Figure 1**). Each predictor corresponds to a particular point by plotting a line straight upward to the Points axis. After summing the scores to

Table 1. Baseline characteristics of study groups

Category	Total No. (%)	VTE+ No. (%)	VTE- No. (%)	*P*-value
Age				<0.0001
41-60 y	137 (32.62)	37 (17.62)	100 (47.62)	
61-74 y	174 (41.43)	89 (42.38)	85 (40.48)	
≥75 y	109 (25.95)	84 (40)	25 (11.9)	
Sex				0.6254
Male	216 (51.43)	111 (52.86)	105 (50)	
Female	204 (48.57)	99 (47.14)	105 (50)	
BMI				<0.0001
<24 kg/m^2	183 (43.57)	68 (32.38)	115 (54.76)	
≥24 kg/m^2	237 (56.43)	142 (67.62)	95 (45.24)	
WC				<0.0001
<85 (M) or 80 (F)	171 (40.71)	63 (30)	108 (51.43)	
≥ 85 (M) or 80 (F)	249 (59.29)	147 (70)	102 (48.57)	
Platelet count (× 10^9/L)	210.5 (169.75, 250.5)	211 (162, 248)	210 (178, 252.75)	0.4873
HbAIC				1
<6.5%	105 (25)	52 (24.76)	53 (25.24)	
≥6.5%	315 (75)	158 (75.24)	157 (74.76)	
Diabetic duration (y)	5 (1, 10)	5 (1, 10)	6 (1, 10)	0.5361
D-dimer				<0.0001
<0.5 mg/L	221 (52.62)	60 (28.57)	161 (76.67)	
≥0.5 mg/L	199 (47.38)	150 (71.43)	49 (23.33)	
Dyslipidemia				0.1735
no	317 (75.48)	152 (72.38)	165 (78.57)	
yes	103 (24.52)	58 (27.62)	45 (21.43)	
Hyperuricamia				<0.0001
no	378 (90.00)	176 (83.81)	202 (96.19)	
yes	42 (10.00)	34 (16.19)	8 (3.81)	
Hypertension				0.1047
no	153 (36.43)	68 (32.38)	85 (40.48)	
yes	267 (63.57)	142 (67.62)	125 (59.52)	
Hypoproteinemia				<0.0001
no	330 (78.57)	133 (63.33)	197 (93.81)	
yes	90 (21.43)	77 (36.67)	13 (6.19)	
Prior VTE				0.0004
no	385 (91.67)	182 (86.67)	203 (96.67)	
yes	35 (8.33)	28 (13.33)	7 (3.33)	
AMI or CIS				<0.0001
no	339 (80.71)	144 (68.57)	195 (92.86)	
yes	81 (19.29)	66 (31.43)	15 (7.14)	
Heart/respiratory failure				<0.0001
no	299 (71.19)	114 (54.29)	185 (88.1)	
yes	121 (28.81)	96 (45.71)	25 (11.9)	
Cancer				<0.0001
no	364 (86.67)	164 (78.1)	200 (95.24)	
yes	56 (13.33)	46 (21.9)	10 (4.76)	
Acute infection				<0.0001
no	258 (61.43)	78 (37.14)	180 (85.71)	
yes	162 (38.57)	132 (62.86)	30 (14.29)	
Hormone replacement therapy				0.0005
no	375 (89.29)	176 (83.81)	199 (94.76)	
yes	45 (10.71)	34 (16.19)	11 (5.24)	
Reduced mobility				<0.0001
no	334 (79.52)	134 (63.81)	200 (95.24)	
yes	86 (20.48)	76 (36.19)	10 (4.76)	

Notes: VTE, Venous Thromboembolism; BMI, Body Mass Index; WC, Waist Circumference; AMI, Acute Myocardial Infarction; CIS, Cerebral Ischemic Stroke.

Table 2. Risk factors for VTE in non-surgical inpatients with T2DM according to logistic regression model

Category	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age				
41-60 y	1		1	
61-74 y	2.83 [1.76, 4.61]	<0.001	3.34 [1.69, 6.80]	<0.001
≥75 y	9.08 [5.13, 16.56]	<0.001	7.29 [3.04, 18.51]	<0.001
Sex				
Male	1			
Female	0.89 [0.61, 1.31]	0.558		
BMI				
<24 kg/m^2	1		1	
≥24 kg/m^2	2.53 [1.70, 3.77]	<0.001	4.26 [1.90, 9.90]	<0.001
WC				
<85 (M) or 80 (F)	1		1	
≥85 (M) or 80 (F)	2.47 [1.66, 3.70]	<0.001	1.41 [0.64, 3.12]	0.391
Platelet count (× 10^9/L)	1.00 [1.00, 1.00]	0.386		
HbAIC				
<6.5%	1			
≥6.5%	1.03 [0.66, 1.60]	0.910		
Diabetic duration(y)	1.00 [0.97, 1.03]	0.971		
D-dimer				
<0.5 mg/L	1		1	
≥0.5 mg/L	8.21 [5.34, 12.84]	<0.001	4.26 [2.18, 8.50]	<0.001
Dyslipidemia				
no	1			
yes	1.40 [0.90, 2.20]	0.141		
Hyperuricamia				
no	1		1	
yes	4.88 [2.31, 11.58]	<0.001	2.06 [0.70, 6.66]	0.203
Hypertension				
no	1			
yes	1.42 [0.95, 2.12]	0.085		
Hypoproteinemia				
no	1		1	
yes	8.77 [4.84, 17.12]	<0.001	4.37 [1.87, 10.73]	<0.001
Prior VTE				
no	1		1	
yes	4.46 [2.01, 11.32]	<0.001	2.15 [0.62, 8.19]	0.242
AMI or CIS				
no	1		1	
yes	5.96 [3.35, 11.23]	<0.001	2.74 [1.13, 6.91]	0.028
Heart/respiratory failure				
no	1		1	
yes	6.23 [3.84, 10.43]	<0.001	5.82 [2.90, 12.14]	<0.001
Cancer				
no	1		1	
yes	5.61 [2.86, 12.09]	<0.001	1.33 [0.49, 3.78]	0.579

Acute infection				
no	1		1	
yes	10.15 [6.38, 16.59]	<0.001	4.43 [2.25, 8.97]	<0.001
Hormone replacement therapy				
no	1		1	
yes	3.49 [1.77, 7.42]	<0.001	2.42 [0.85, 7.19]	0.104
Reduced mobility				
no	1		1	
yes	11.34 [5.92, 24.07]	<0.001	3.10 [1.20, 8.68]	0.024

Notes: VTE, Venous Thromboembolism; BMI, Body Mass Index; WC, Waist Circumference; AMI, Acute Myocardial Infarction; CIS, Cerebral Ischemic Stroke.

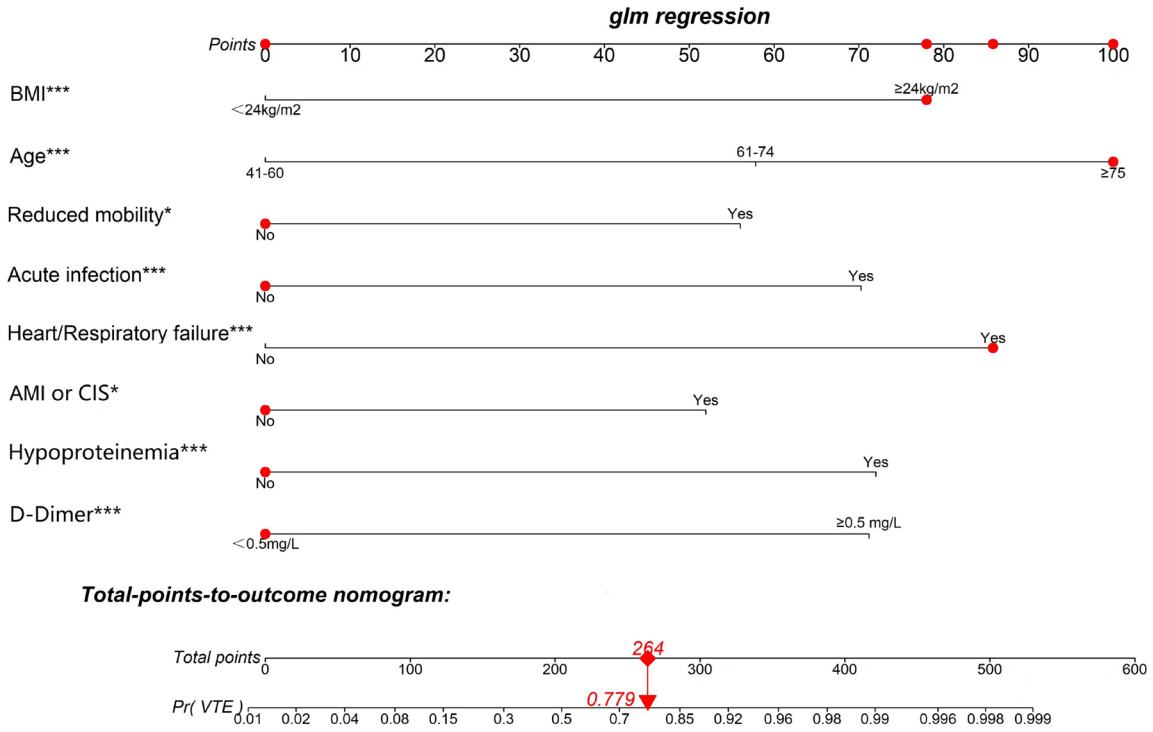

Figure 1. A nomogram predicting the probability of VTE in non-surgical inpatients with type 2 diabetes. Each clinical factor corresponds to a specific point by drawing a line straight upward to the Points axis. After summing the points to obtain the total score located on the Total Points axis, a vertical line was drawn straight down to determine the diagnostic probability of VTE. BMI, Body Mass Index; AMI, Acute Myocardial Infarction; CIS, Cerebral Ischemic Stroke; VTE, Venous Thromboembolism.

obtain the total score on the Total Points axis, a vertical line was drawn down from the total score to determine the probability of VTE. For example, the total point of a 75-year old T2DM patient (100 points), with BMI of 24 kg/m^2 (78 points), DD <0.5 mg/L (0 points), no hypoproteinemia (0 points), no AMI or CIS (0 points), combined HF (86 points), no acute infection (0 points), and no reduced mobility (0 points) would get 264 points, which indicates that the probability of VTE risk is about 77.9%.

Accuracy and validation of the nomogram

A better discriminative ability of the nomogram we constructed was identified compared to that of the Padua score (AUC: 0.923 vs. 0.849, **Figure 2A**). Besides, the actual observations were in good agreement with the predicted outcomes, as demonstrated by the calibration plots (**Figure 2B**). Accuracy analysis demonstrated a NRI of 0.205 (95% CI: 0.118-0.292) and an IDI of 0.209 (95% CI: 0.167-0.250).

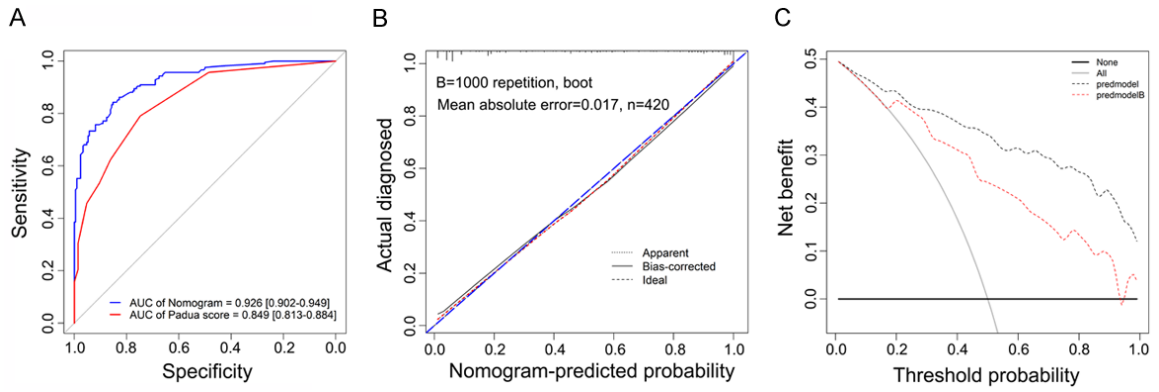

Figure 2. Accuracy and validation of the nomogram. A. Receiver operating characteristic curve analysis. B. A calibration plot for the nomogram. The dotted line indicates the location of the ideal nomogram, in which the predicted and actual probabilities are identical. The broken line indicates the actual nomogram performance. The expected performance on future data is represented by the solid line. C. A decision curve analysis of the logistic model. It demonstrates the net benefit associated with the use of the nomogram with (full model) or without (base model) the inclusion of the risk score as covariate.

These results showed the superior predictive performance of the new nomogram compared to that of the Padua score. The comparison of the clinical usability and benefits between our nomogram and the Padua score by the DCA curves revealed that our nomogram showed a greater net benefit across the VTE risk range (**Figure 2C**).

Discussion

Diabetic patients have a greater probability to develop cardiovascular disease and VTE [12]. Diabetes-associated thrombosis is a major cause of morbidity and mortality in DM patients. Confounders, rather than the intrinsic effect of DM on venous thrombotic risk, are the main reason for elevated risk of DM-associated VTE [17]. Besides, patients with hyperglycemia are at an elevated risk of thrombosis, as high blood sugar can lead to elevated coagulation factors and impaired fibrinolysis [18]. Furthermore, the risk of VTE in DM patients can be increased by comorbidities such as obesity, dyslipidemia, hyperuricemia, acute infectious diseases, diabetic nephropathy, chronic lung disease, ischemic heart disease, CIS and cancers. Identifying non-surgical inpatients with T2DM at increased risk of VTE using an individualized approach is therefore of increasing importance.

To develop a nomogram for predicting VTE, we retrospectively analyzed the clinical and laboratory parameters of non-surgical inpatients with T2DM from three centers between June 2017 and June 2021. Strong associations were found between VTE and old age, BMI, hypoproteinemia, acute infection, AMI or CIS, reduced mobility, HF/RF and elevated DD levels, which were identified as independent risk factors for VTE in non-surgical inpatients with T2DM. Old age, acute infection, AMI or CIS, reduced mobility, HF/RF and elevated DD levels as risk factors are consistent with prior reports. Elevated level of DD, an independent predictor at diagnosis, has a connection with elevated risk of fatal PE and long-term recurrent VTE [19-21].

In the multivariate regression analysis, both overweight and hypoproteinemia seem to be linked to VTE progression in non-surgical inpatients with T2DM. The hazards listed in the ACCP's VTE-risk assessment include obesity (BMI ≥30 kg/m^2). Our results showed that overweight patients (BMI ≥24 kg/m^2) might be at increased risk of VTE.

This research suggested a connection between VTE risk and hypoproteinemia (serum albumin level <35 g/L) in T2DM patients. Previous evidence [22] proposed lower serum albumin as an effective independent predictor for VTE in diabetic kidney disease (DKD), one of the most severe chronic microvascular complications in diabetic patients. DKD is characterized by proteinuria and low serum albumin levels (hypoproteinemia). Patients with DKD may present with endothelial dysfunction, enhanced platelet activation and aggregation, coagulation system activation, and reduced endogenous anti-

coagulants [23]. Urinary loss of anticoagulant factors (antithrombin III, protein S, and plasminogen) and enhanced synthesis of procoagulant factors (factor V and VII, von Willebrand factor, fibrinogen, and alpha-2 macroglobulin) play a role in the underlying mechanism [24]. As the patient's albumin level decreases, the probability of developing VTE increases.

We did not find significant correlation of hyperglycemia, hypertension, hyperuricemia, dyslipidemia with the onset of VTE. However, since none of the three centers had oncology departments, only a small number of cancer patients were enrolled in this study, which may lead to the risk being underestimated.

We compared our nomogram to the Padua score, a VTE risk assessment tool in medical inpatients recommended by the Chinese Expert Consensus. Previously, several prospective studies have used the Padua score to identify high-risk groups for VTE among admitted medical patients [25, 26]. The discriminative ability of our nomogram was found to be superior to that of the Padua score (AUC: 0.923 vs. 0.849). Predictor indices were compared with each other using novel metrics including NRI, IDI and DCA. IDI is commonly used to compare two risk prediction models. It summarizes the extent of increased risk in events and decreased risk in non-events. NRI is a popular measure for evaluating the improvement of prediction performance gained by adding a marker to a set of baseline predictors. DCA was developed to determine whether the use of a prediction model in clinic to inform decision-making would do more good than harm. Our new nomogram exhibited superior predictive performance than the Padua score did, as indicated by the results of NRI (0.205) and IDI (0.209). The subsequent comparison of the clinical usability and benefits between the two tools by the DCA curves revealed that our nomogram showed greater net benefits across a range of VTE risks. The main difference between the current nomogram and the Padua score may be the study cohort. The Padua score was derived from patients admitted to an internal medicine service in Italy, while the current nomogram was constructed based on relevant parameters of non-surgical hospitalized patients with T2DM. Diabetes-associated overweight and hypoproteinemia were determined to be independent predictors for VTE in the current nomogram. Elevated DD levels were also included, as opposed to the Padua score. Hence the current nomogram allows for broad application among diabetes patients.

This study still shows room for improvement. First, retrospective collection of patient data may present a potential risk of bias, warranting further validation of the predictive ability of this nomogram in prospective research. Second, the nomogram was validated internally, and the sample size should be expanded in multiple centers. Nevertheless, our findings need to be interpreted with caution and confirmation. Therefore, a prospective study using participants from multiple centers is warranted to further confirm the accuracy and validity of this nomogram.

Conclusion

In conclusion, this research argues that among non-surgical inpatients with T2DM, VTE risk can be reliably predicted using a nomogram built on 8 clinical and laboratory parameters. To our knowledge, a risk assessment model for VTE in T2DM patients has not yet been established. This nomogram is highly predictive and easy to be carried out, providing a useful clinical instrument for stratifying VTE risk and identifying those who may gain benefits from thromboprophylaxis. In the T2DM population, identifying high-risk patients for VTE followed by initiation of effective prophylaxis contributes to reduced morbidity and mortality, as well as improved quality of life and rational use of health care resources.

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Disclosure of conflict of interest

None.

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