Development and validation of a nomogram based on the hospital information system for quantitative assessment of the risk of cardiocerebrovascular complications of diabetes

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Background: Although the prevention and treatment of the cardiocerebrovascular complications (CCVCs) of diabetes have been clarified, their incidence is still high. This is largely due to the lack of predictive models to objectively assess the risk of CCVC in patients with type 2 diabetes mellitus (T2DM), reducing their treatment adherence. Despite the fact that the risk factors of CCVC in T2DM patients have been identified, no prediction model for identifying T2DM patients with the risk of CCVC is available. Therefore, the aim of this study is to establish a nomogram based on hospital information system data to quantitatively assess the risk of CCVCs in T2DM patients. This model is contributed to individualized therapeutic treatments and motivating T2DM patients to adhere to lifestyle interventions.

Methods: The medical records of 1,556 T2DM patients, comprising 1,145 cases in the training cohort and 411 in the validation cohort were retrospectively analyzed. CCVCs of diabetes, including coronary heart disease, cerebral ischemia, and intracerebral hemorrhage, were extracted from the medical records. Univariate and multivariate logistic regression analyses were performed to screen the independent correlates of CCVCs from the demographic information and laboratory test data, which were utilized to establish a nomogram for predicting the risk of CCVCs in these patients. We used internal and external validation based on the training and validation cohorts to evaluate the model performance.

Results: The incidence of CCVCs in the training cohort (26.99%) was similar to the validation cohort (25.79%). Disease duration, body mass index (BMI), systolic blood pressure (SBP), glycosylated hemoglobin (HbA1c), and uric acid (UA) levels were finally included in the established nomogram. In both the internal and external validation, the nomogram showed good discrimination [area under the curve (AUC) =0.850 and 0.825, respectively] and calibration (P=0.127 and P=0.096, respectively). Decision curve analysis showed that the nomogram produced a net benefit in both the training and validation cohorts.

Conclusions: The nomogram developed for predicting the risk of CCVC in T2DM patients may help improve treatment adherence. Further multi-center prospective investigations are required to predict the timing of CVCC in T2DM patients.

Keywords: Cardiocerebrovascular complications (CCVCs); compliance; hospital information system; nomograms; type 2 diabetes mellitus (T2DM)

Page 2 of 10

Xi et al. Nomogram for CCVCs of diabetes

Introduction

Diabetes mellitus is an independent risk factor for cardiocerebrovascular disease (CCVD): 50–80% of patients with type 2 DM (T2DM) are often complicated with macrovascular disease, and >70% of diabetic patients eventually die of cardiocerebrovascular complications (CCVCs) (1,2). Therefore, the prevention and treatment of CCVCs has generated much interest and researchers have identified risk factors such as obesity, hypertension, dyslipidemia, smoking, and family history (3). The guidelines for diabetes prevention and treatment formulated in China and those formulated by the American Diabetes Association (ADA) both recommend adopting a comprehensive plan to prevent and treat the CCVCs of T2DM based on lifestyle interventions, and comprehensive assessment and management of the multiple risk factors for these CCVCs. Lifestyle interventions for diabetic patients include self-management education, nutritional therapy, exercise therapy, smoking cessation, and psychosocial interventions. Managing the clinical risk factors of T2DM includes managing blood pressure (BP) and blood lipids, antiplatelet therapy, and individualized treatment of cardiovascular disease (CVD) (4,5).

Although preventive and treatment measures for CCVCs of T2DM have been established, these complications still have a high incidence and low control rates (6). Diabetes is a lifelong chronic disease. As patients' physical functions decline due to their increased age, the management of diabetes is challenging (7). In addition, as long-term lifestyle interventions in diabetic patients continue, patients' perception of risk factors can decrease due to a lack of tools to objectively measure these factors, resulting in decreased motivation and compliance (8). These two problems interact synergistically, significantly affecting the management of CCVCs of T2DM.

Therefore, a tool that quantitatively evaluates the risk of the CCVCs of T2DM will dynamically assess changes in the risk of complications to guide clinical treatment, and improve patient compliance through intuitive and visual risk evaluation. Nomograms have been used to predict the risks of developing T2DM and the complications of diabetic nephropathy (9,10). Hochster and Niedzwiecki confirmed that big-data accumulation effectively improves the accuracy of nomograms (11). However, despite the large number of studies analyzing the influencing factors of CCVC of diabetes, only few studies have proposed models to predict CCVD risk in T2DM patients (12,13).
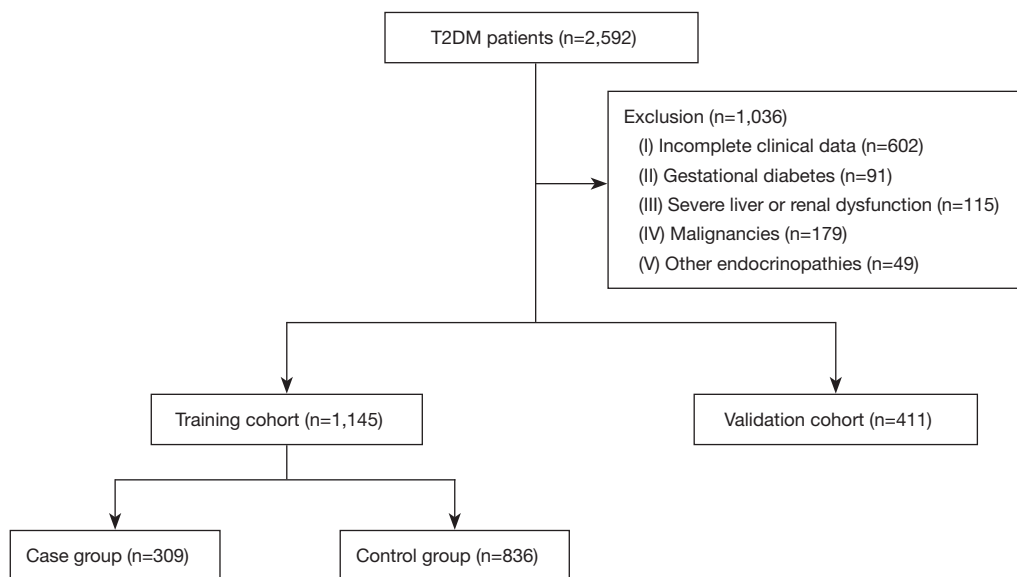
In this study, we conducted a retrospective analysis based on data accumulated in a hospital information system with the aim of constructing a nomogram to quantitatively assess the risk of CCVCs in patients with T2DM. This quantitative prediction model will provide a reference for individualized clinical treatment and mobilize patients with T2DM to adhere to lifestyle interventions. We present the following article in accordance with the TRIPOD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2439/rc).

Methods

Data source

We obtained data for 1,864 inpatients diagnosed with T2DM in Minhang Hospital, Fudan University (Shanghai, China). The data were collected from January 2014 to December 2018 from the hospital's information system database and were used as the training cohort. In addition, we obtained data from the same database for 727 inpatients diagnosed with diabetes at the same hospital, from January 2019 to December 2020, to be used as the validation cohort. Diagnostic criteria for T2DM were in accordance with the Chinese guidelines for the diagnosis of T2DM (4). Structured Query Language was used to exclude data with missing information.

CCVCs of diabetes include coronary heart disease, cerebral ischemia, and intracerebral hemorrhage (14). The CCVCs of the study patients with T2DM were extracted based on medical history and clinical diagnoses in the medical records. Inclusion criteria were patients who: (I) received treatment according to the guideline criteria and (II) were >18 years of age. Exclusion criteria were patients with: (I) information missing from physician's orders, missing clinical data, or unclear medical history in the records; (II) gestational diabetes; (III) severe liver and renal insufficiency; (IV) history of malignancies; and (V) other endocrine disorders. A total of 1,145 patients were included in the training cohort and were further divided into subgroups with and without CCVCs according to their medical records: 309 patients with T2DM plus CCVCs (case group) and 836 as the control group. We included 411 patients in the validation cohort, 106 of whom had CCVCs (*Figure 1*). This retrospective cross-sectional study was approved by the Ethics Committee of Minhang Hospital, Fudan University (No. 2021-14). Informed consent was given by all participants. The study was conducted in

T2DM patients (n=2,592)

Exclusion (n=1,036)
(I) Incomplete clinical data (n=602)
(II) Gestational diabetes (n=91)
(III) Severe liver or renal dysfunction (n=115)
(IV) Malignancies (n=179)
(V) Other endocrinopathies (n=49)

Training cohort (n=1,145)

Validation cohort (n=411)

Case group (n=309)

Control group (n=836)

Figure 1 Flowchart showing the inclusion of patients in this study. T2DM, type 2 diabetes mellitus.

accordance with the Declaration of Helsinki (as revised in 2013).

Research methods

After importing patient data from the hospital information system into the study database, we classified and analyzed demographic information and laboratory test data. The demographic information of the patients included age, sex, duration of T2DM, body mass index (BMI; weight/height^2), BP, heart rate (HR), hypertension history, and smoking history. The other indicators collected from patient's fasting blood test in the morning on admission included glycated hemoglobin A_{1c} (HbA1c), fasting plasma glucose (FPG), 2-h postprandial plasma glucose (2hPG; venous-blood glucose 2 h after oral administration of 75 g glucose), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), blood urea nitrogen (BUN), serum creatinine (sCr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT).

Construction of the nomogram

In the training cohort, we used univariate and multivariate logistic-regression analyses to screen the independent risk factors of CCVCs in patients with T2DM. A nomogram was constructed based on each independent factor to predict the risk of CCVCs, after which we tested the prediction performance of the nomogram in the training and validation cohorts.

Statistical analysis

We used the Kolmogorov-Smirnov test to confirm the normality of the measurement data. The Mann-Whitney U test was utilized to compare differences in non-normally distributed data. Count data were compared using the chi-square (χ^2) test. In the training cohort, univariate and multivariate logistic-regression analyses were used to screen independent risk factors of CCVCs in patients with T2DM and to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). We constructed a nomogram to predict the risk of CCVCs in T2DM patients based on each independent factor that was statistically significant in multivariate Logistic regression. The nomogram was validated internally and externally based on data from the training and validation cohorts. For internal validation, we used bootstrap resampling (×1,000) to evaluate the discrimination of the nomogram by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The calibration of nomogram was evaluated using the calibration curve combined with the Hosmer-Lemeshow (HL) test. Decision curve analysis (DCA) was used to evaluate the clinical applicability of the nomogram.

Page 4 of 10

Xi et al. Nomogram for CCVCs of diabetes

Table 1 Comparison of the clinical characteristics of T2DM patients in the training and validation cohorts

Factor	Training cohort (n=1,145)	Validation cohort (n=411)	P
Age (years)	59.00 (45.00, 76.00)	60.00 (50.00, 69.00)	0.594#
Sex			
Male [n (%)]	378 (33.01)	144 (35.04)	0.456*
Female [n (%)]	767 (66.99)	267 (64.96)	
Disease duration (years)	7.00 (4.00, 11.00)	7.24 (3.37, 10.33)	0.239#
BMI (kg/m²)	25.12 (21.44, 28.86)	24.52 (21.05, 28.02)	0.007#
BP			
Systolic (mmHg)	139.00 (117.00, 158.50)	135.00 (114.00, 153.00)	0.012#
Diastolic (mmHg)	76.93 (66.20, 88.64)	76.23 (67.79, 79.23)	0.435#
Heart rate (beats/min)	74.80 (65.89, 84.91)	73.62 (64.65, 84.48)	0.269#
Hypertension [cases (%)]	450 (39.30)	157 (38.20)	0.672*
Smoking [cases (%)]	299 (26.11)	111 (27.01)	0.724*
HbA1c (%)	7.51 (5.66, 9.45)	7.63 (5.70, 9.37)	0.952#
FBG (mmol)	7.94 (5.97, 9.90)	8.03 (5.85, 10.17)	0.854#
2hPG (mmol)	11.79 (9.81, 13.77)	11.61 (9.48, 13.64)	0.259#
TC (mmol)	5.48 (3.57, 7.75)	5.93 (3.76, 8.04)	0.081#
TG (mmol)	2.13 (1.23, 2.94)	2.06 (1.10, 2.96)	0.194#
HDL-C (mmol)	1.77 (0.98, 2.49)	1.64 (0.92, 2.39)	0.072#
LDL-C (mmol)	3.70 (2.40, 4.90)	3.54 (2.35, 4.89)	0.964#
UA (μmol)	295.55 (224.32, 367.46)	286.10 (214.84, 368.23)	0.132#
BUN (mmol)	5.20 (3.75, 6.70)	5.30 (3.80, 7.00)	0.291#
sCr (mmol)	71.92 (48.78, 93.31)	70.85 (48.61, 92.71)	0.664#
ALT (U/L)	12.98 (10.45, 15.72)	13.10 (10.15, 15.85)	0.583#
AST (U/L)	16.74 (12.31, 21.30)	16.88 (12.51, 21.24)	0.069#
GGT (U/L)	20.06 (13.53, 27.47)	20.25 (12.76, 28.24)	0.901#

Data are shown as mean (range). *, χ^2 test; #, Mann-Whitney U test. 2hPG, 2-h postprandial plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin A$_{1c}$; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; sCr, serum creatinine; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; UA, uric acid.

We performed these analyses using SPSS version 22.0 (IBM Corp., Armonk, NY, USA), MedCalc version 11.0 (MedCalc Software, Ostend, Belgium), and R language version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) software packages. P<0.05 (two-sided) was considered statistically significant.

Results

Clinical data of patients

This study included 309 T2DM patients with CCVCs in the training cohort (26.99%, 309/1,145) and 106 with CCVCs in the validation cohort (25.79%, 106/411). *Table 1*

Table 2 Univariate and multivariate logistic regression analyses of risk factors for CCVCs in patients with T2DM

Factor	Univariate logistic regression			Multivariate logistic regression		
	P	OR	95% CI	P	OR	95% CI
Age	0.080	1.010	1.003–1.017			
Disease duration	0.011	1.043	1.010–1.077	0.005	1.051	1.015–1.088
BMI	<0.001	1.129	1.093–1.166	<0.001	1.129	1.092–1.167
Systolic BP	<0.001	1.015	1.010–1.021	<0.001	1.015	1.009–1.021
HbA1c	0.005	1.091	1.026–1.159	0.002	1.106	1.038–1.179
BUN	<0.001	1.153	1.035–1.137	0.214	1.053	0.971–1.142
UA	<0.001	1.009	1.007–1.010	<0.001	1.003	1.001–1.005

BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CCVC, cardiocerebrovascular complication; CI, confidence interval; HbA1c, glycated hemoglobin A_{1c}; OR, odds ratio; T2DM, type 2 diabetes mellitus.

shows the clinical data, including age, sex, disease duration, HR, BP, hypertension history, smoking history, and biochemical indicators, of the patients in both cohorts. No significant differences in clinical data were found between them (all P>0.05).

Univariate analysis of risk factors for CCVCs in diabetic patients

In the training cohort, patients in the case group had longer disease duration and higher BMI, systolic BP (SBP), HbA1c, UA, and BUN than those in the control group. Univariate logistic-regression analysis showed that disease duration, BMI, SBP, HbA1c, UA, and BUN were the risk factors for CCVCs (all P<0.05). Multivariate logistic-regression analysis further showed that disease duration (OR =1.051), BMI (OR =1.129), SBP (OR =1.015), HbA1c (OR =1.106), and UA (OR =1.003) were independent risk factors of CCVCs in T2DM patients (P<0.05; *Table 2*).

Nomogram for predicting CCVCs in patients with T2DM

Based on the five independent risk factors, we constructed a nomogram to predict the probability of CCVCs in patients with T2DM (*Figure 2*). Each predictor was proportionally assigned a score according to its OR in the multivariate logistic-regression analyses. We used the total score to determine the risk of CCVCs in patients with T2DM.

Validation of the nomogram
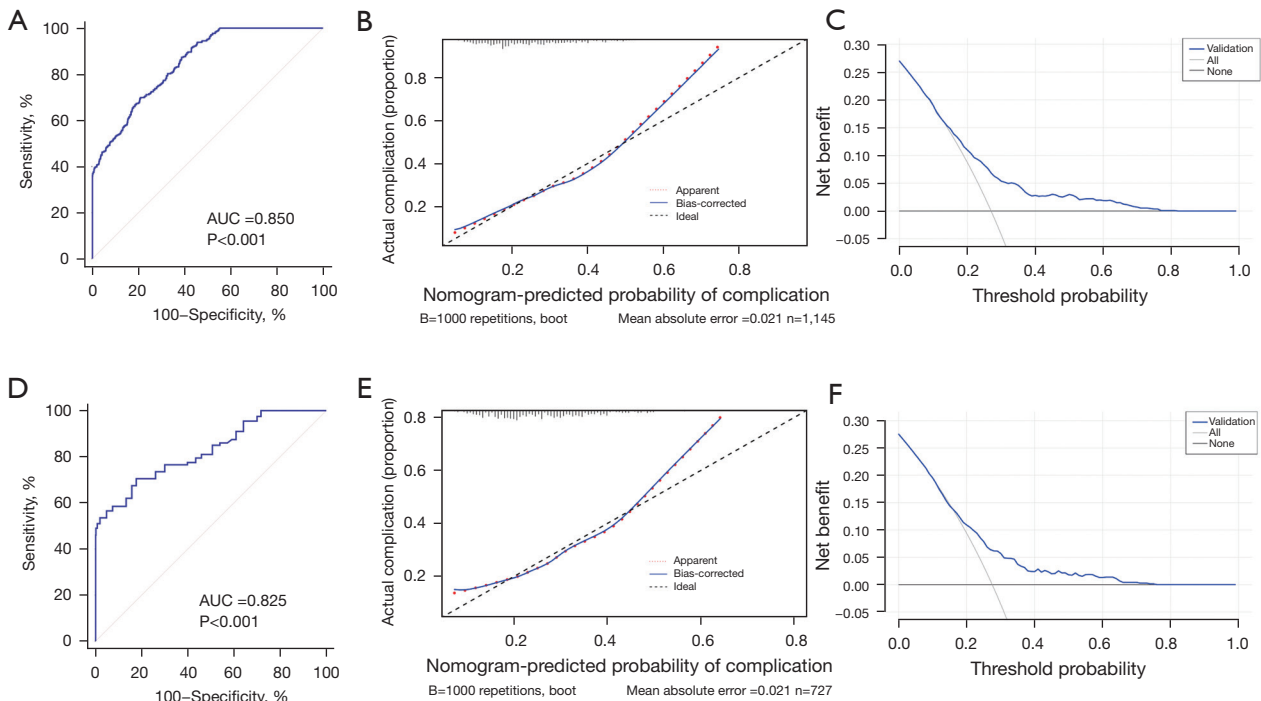
In the internal validation, the nomogram achieved an

AUC of 0.85 (95% CI: 0.828–0.870) after 1,000 bootstrap resampling, indicating good discrimination (AUC >0.75; *Figure 3*). The calibration plot and HL test showed that the probability predicted by the nomogram did not deviate significantly from actual incidence (χ^2=12.596, P=0.127), indicating good calibration (*Figure 3B*). In the external validation using the validation cohort, the nomogram also showed good discrimination (AUC =0.825; 95% CI: 0.795–0.852; *Figure 3D*), and the calibration plot and HL test also showed good agreement (χ^2=4.654, P=0.096; *Figure 3E*). DCA results indicated that the nomogram produced net benefits in both cohorts, indicating good application value in clinical decision making (*Figure 3C,3F*).

Discussion

CCVD is one of the most common complications of diabetes. Several studies have reported the risk factors of CCVCs of diabetes and corresponding preventive and therapeutic measures, but these complications are often not effectively controlled due to factors such as poor patient compliance (15-17). Because changes in objective indicators can effectively improve patients' perception of disease risk, thereby improving compliance, having an objective evaluation of the risk factors for CCVCs of diabetes will boost patients' enthusiasm for participating in long-term treatment (18,19). In this study, we analyzed the relevant data of T2DM patients from a hospital information system and constructed a nomogram for the quantitative assessment of CCVC risk based on the independent risk factors of T2DM patients with CCVCs. By analyzing individual situations and calculating the probability of CCVCs based
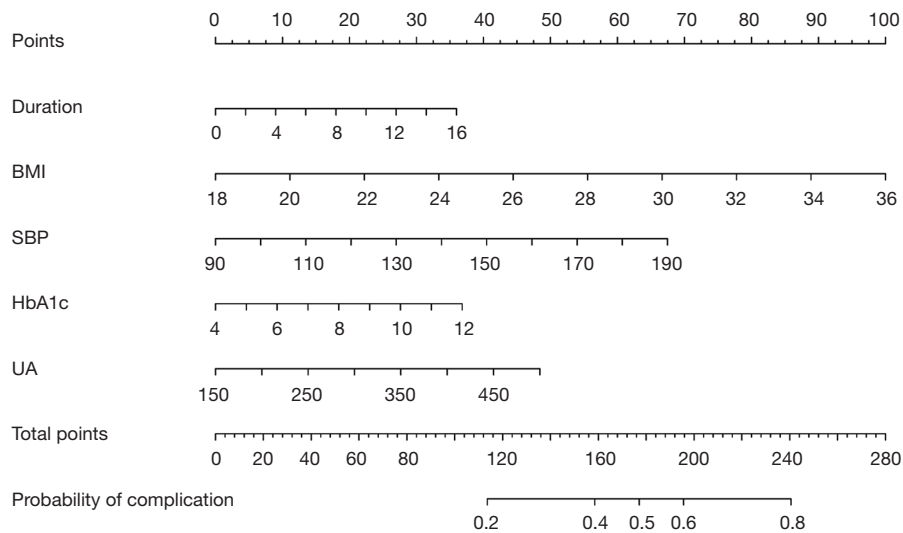
Figure 2 Nomogram predicting the risk of CCVCs in patients with type 2 diabetes mellitus. The score corresponding to each variable was calculated according to the clinical condition of individual patients, and the calculated total score corresponded to their probability of CCVCs. CCVCs, cardiocerebrovascular complications; BMI, body mass index; HbA1c, glycated hemoglobin A$_{1c}$; SBP, systolic blood pressure; UA, uric acid.

Figure 3 Internal and external validation of the nomogram. (A,B) Internal validation based on the training cohort. (D,E) External validation based on the validation cohort. The AUCs of the ROC curves were 0.850 (A) and 0.825 (D) in the training and validation cohorts, indicating good discrimination (>0.75). The calibration plots for both the training (B) and validation (E) cohorts indicated good agreement between the prediction probabilities of the nomogram and the actual results. (C,F) DCA curves of the nomogram, indicating that the nomogram obtained net benefit in both cohorts. AUC, area under the curve; DCA, decision curve analysis; ROC, receiver operating characteristic.

on the nomogram, clinicians can adjust patients' treatment plans according to the indicators and provide them with objective, easy-to-understand consultation indicators to encourage treatment adherence. Our nomogram generated net benefits in both the training and validation cohorts, suggesting it has a role in engaging patients' adherence and motivation.

Diabetes is a chronic disease that requires lifelong treatment. As the disease persists, skeletal muscle mass gradually diminishes, and patients are prone to reduced insulin secretion (20). In addition, muscle mitochondrial function declines with age (21,22), challenging the control of blood glucose and increasing the risk of CCVCs. The basis of treating the CCVCs of diabetes is adherence to lifestyle interventions, so actively encouraging patients to adhere to these interventions is particularly important. Objective and visual risk assessment tools effectively improve patient compliance. Duan *et al.* (23) proposed that health management tools using goal-oriented designs improved self-management compliance in hypertensive patients, so to simply and quantitatively assess the risk of CCVCs in diabetic patients, we developed a nomogram to convert risk factors into quantifiable risk value indicators. Dynamic assessment of their own risk values in diabetic patients with CCVCs will help mobilize these patients' enthusiasm for complying with long-term lifestyle interventions and medical treatment.

The components of the nomogram were the independent risk factors identified from the multivariate logistic-regression analysis. This study identified disease duration, BMI, SBP, HbA1c, and UA as independent risk factors of CCVCs in diabetic patients, and all of them except UA are also common risk factors for CCVD. This result was similar to those of McGurnaghan *et al.* (24), Ilkun *et al.* (25), and Li *et al.* (26). As an independent risk factor for CCVD, UA has been receiving increasing attention. Studies have concluded that hyperuricemia affects lipid metabolism (27,28), and high levels of UA affect the secretory function of vascular endothelial cells (ECs) (29,30). Precipitation of UA salt on the walls of blood vessels causes local changes such as inflammation (31,32), triggering the onset and progression of atherosclerosis, and thereby causing cerebrovascular diseases. Hu *et al.* (33) proposed that elevated plasma UA was associated with an increased risk of insulin resistance. Keerman *et al.* (34) also reported that UA levels were significantly associated with an increased risk of diabetes. We also found that elevated UA was an independent risk factor for CCVCs.

Nomograms integrate multiple risk factors and quantify and visualize them by displaying the risk weight of each in a digital form (35-37). The strength of this study was using a nomogram to convert probabilities of CCVCs in diabetic patients into quantifiable risk factors. The nomogram can predict the risk of CCVCs and help clinicians communicate with patients using easy-to-understand indicators. The nomogram in this study had good discrimination and calibration after internal and external validation. The probability predicted by the nomogram in both the training and validation cohorts generated net benefits, suggesting that it had good application value in predicting CCVCs in diabetic patients. Clinicians can use the nomogram to calculate the probability of CCVCs in diabetic patients; for example, the total score of a patient with T2DM duration of 10 years, BMI of 25, SBP of 150 mmHg, HbA1c of 9%, and UA of 450 µmol would be calculated as 220, suggesting that the probability of CCVCs for this patient would be 70%. A personalized clinical treatment plan could be formulated, and the risk value calculation repeated according to different clinical states to dynamically evaluate improvements in the risk of CCVCs. This would effectively engage the patient to adhere to lifestyle interventions and medical treatments.

This study had several limitations. The retrospective and cross-sectional design of this study limited our access to longitudinal data and outcomes in T2DM patients. As a result, our model was unable to predict when T2DM patients would progress to CVCC. Besides, only patients with complete clinical data and in-hospital treatments were included, resulting in selection bias. Moreover, this study analyzed only common clinical factors, such as medical history and blood biochemical indicators, and did not include many clinical risk factors or the pathogeneses of CCVCs. Therefore, the clinical applicability of the current model should be further verified. Further multi-center prospective investigations are required in the future. We plan to include patients from the community, and to add data on microvascular complications and indicators for monitoring vascular EC functions. These additions should further improve the clinical applicability of our nomogram.

Conclusions

T2DM patients with longer disease duration and higher BMI, SBP, HbA1c, and UA levels had higher probability

Page 8 of 10

Xi et al. Nomogram for CCVCs of diabetes

of developing CCVCs. The nomogram based on these five independent risk factors quantitatively assessed the risk of CCVCs in T2DM patients. Our findings may help clinicians formulate clinical treatment plans and encourage patients to adhere to them.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2439/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2439/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2439/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethical approval for the study was obtained from the Ethics Committee of Minhang Hospital, Fudan University (No. 2021-14). Informed consent was given by all participants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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