Article

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Construction of a Nomogram Model to Identify Atherosclerotic Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus

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Background: Approximately 50.0% of patients with type 2 diabetes mellitus (T2DM) experience macrovascular diseases, and nearly 80.0% of them succumb to macrovascular complications. Atherosclerotic cardiovascular disease (ASCVD) ranks among the most prevalent macrovascular complications in T2DM. In this study, we aim to develop a nomogram model for the early detection of ASCVD in T2DM patients, enabling us to provide valuable recommendations for the clinical prevention and management of macrovascular complications in this patient population.

Methods: This retrospective analysis encompassed 2620 T2DM patients admitted between June 2015 and June 2021. The cohort comprised 1270 T2DM patients with coexisting ASCVD (referred to as the "ASCVD group") and 1350 individuals who did not experience ASCVD (the "non-ASCVD group"). We conducted a comparative assessment of their baseline characteristics and clinical data. A nomogram model for the identification of ASCVD in T2DM patients was constructed utilizing Logistic regression analysis and the R package. The model's performance was evaluated through receiver operating characteristic (ROC) curve analysis and calibration curves.

Results: We developed a nomogram model for the identification of ASCVD in T2DM patients, incorporating ten variables: sex, age, hypertension, smoking history, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio, alanine transaminase (ALT), adenosine deaminase (ADA), postprandial 2-hour C-peptide, monocyte count (MONO), and eosinophil count (EOS). ROC curves demonstrated that the area under the curve (AUC) of the nomogram model for identifying ASCVD in T2DM patients was 0.673 for the training dataset (with a cut-off value of 0.473, specificity of 0.629, and sensitivity of 0.637) and 0.655 for the validation dataset (with a cut-off value of 0.460, specificity of 0.605, and sensitivity of 0.675). The calibration curve indicated a substantial agreement between the predicted and observed cases of ASCVD in the training dataset and an acceptable level of agreement in the validation dataset.

Conclusions: The nomogram model effectively identifies ASCVD in T2DM patients, which can be instrumental in pinpointing the high-risk population for ASCVD among T2DM patients and facilitating timely clinical management.

Keywords: type 2 diabetes mellitus; atherosclerotic cardiovascular disease; risk factors; nomogram

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is on the rise, driven by rapid economic development and changes in dietary habits and lifestyle. Diabetes mellitus and its complications are responsible for 11.3% of all-cause deaths [1]. Approximately 50.0% of T2DM patients suffer from macrovascular diseases, and nearly 80.0% of them succumb to macrovascular complications related to diabetes [2]. Currently, the precise molecular mechanisms underlying T2DM-induced atherosclerosis remain incompletely understood. It is generally accepted that atherosclerosis is closely associated with factors such as the response to injury, endothelial cell damage, oxidative stress, L-arginine, and shear stress [3,4]. However, atherosclerotic cardiovascular disease (ASCVD) can affect T2DM patients who have well-controlled blood sugar, blood pressure, and blood lipids [5]. The risk factors for ASCVD in T2DM pa-

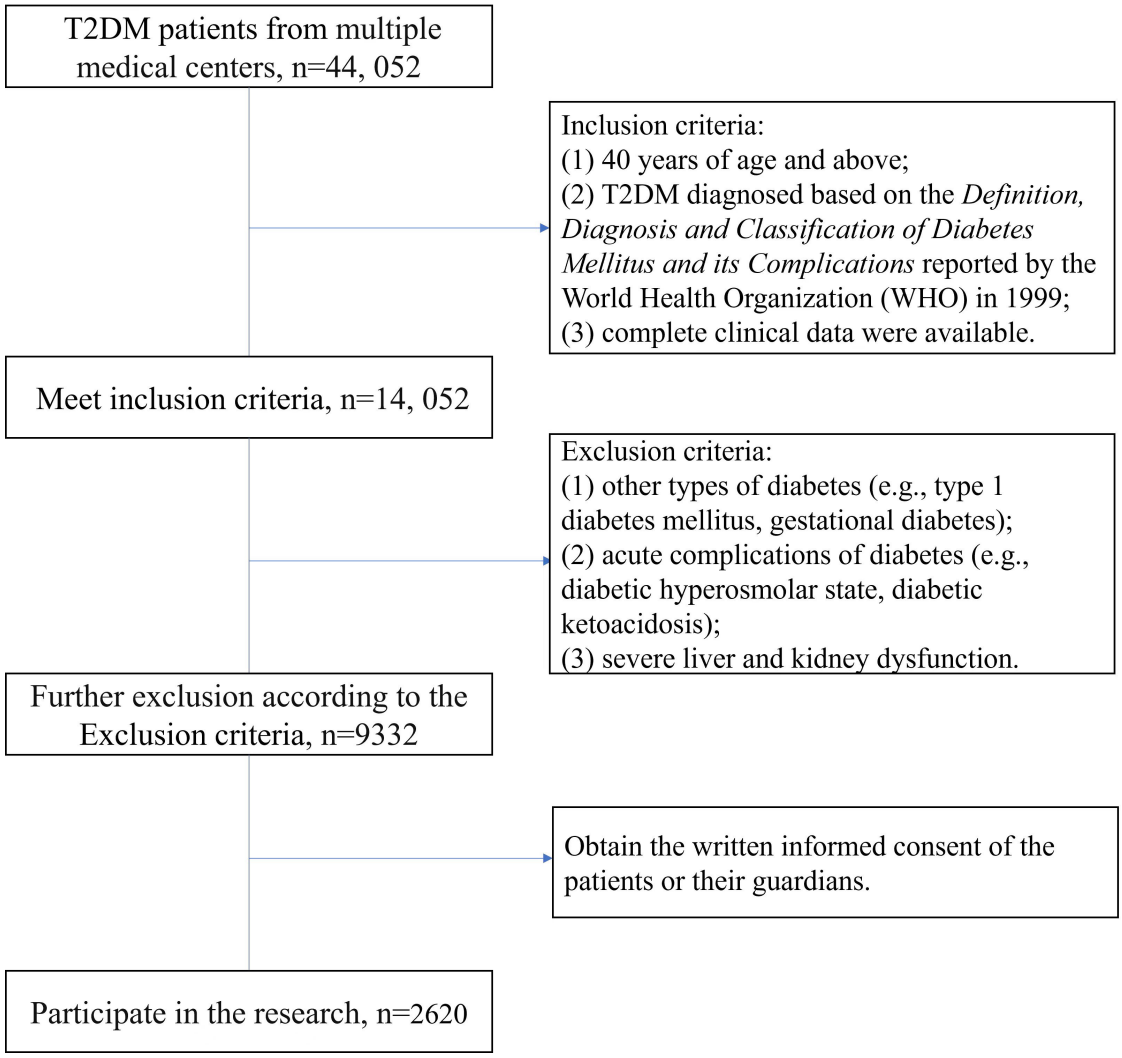

Fig. 1. Flowchart for study population screening. T2DM, type 2 diabetes mellitus.

tients are diverse, and there is an urgent need for an accurate diagnostic model to identify the high-risk population, enabling the prevention and management of macrovascular complications related to diabetes.

Materials and Methods

Subjects

A total of 2620 T2DM patients admitted to Nanjing Pukou People's Hospital, Nanjing Drum Tower Hospital, and the First Affiliated Hospital of Nanjing Medical University between June 2015 and June 2021 were retrospectively included in the study. These patients were categorized into two groups: the ASCVD group (n = 1270) and the non-ASCVD group (n = 1350). The study was approved by the Ethics Committee of Nanjing Pukou People's Hospital (NO. 2023-SR-025), and all the participants signed a written informed consent. We claim the human material or data collection procedures are conducted in accordance with the Declaration of Helsinki.

Inclusion criteria for the study were as follows: (1) Individuals aged 40 years and older; (2) A diagnosis of T2DM in accordance with the *Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications* provided by the World Health Organization (WHO) in 1999 [6]; (3) The availability of complete clinical data. Exclusion criteria were: (1) Other types of diabetes, such as type 1 diabetes mellitus or gestational diabetes; (2) Acute complications of diabetes, including diabetic hyperosmolar state or diabetic ketoacidosis; (3) Severe liver and kidney dysfunction. In the end, a total of 2620 eligible T2DM patients were enrolled in the study, comprising 1579 males and 1041 females, with a mean age of 60.49 $\pm$ 10.80 years (ranging from 40 to 95 years). The screening process is illustrated in Fig. 1 (The figure was original and generated using Microsoft Office PowerPoint).

Definition of ASCVD

We defined ASCVD as a pathological condition encompassing coronary heart disease, atherothrombotic

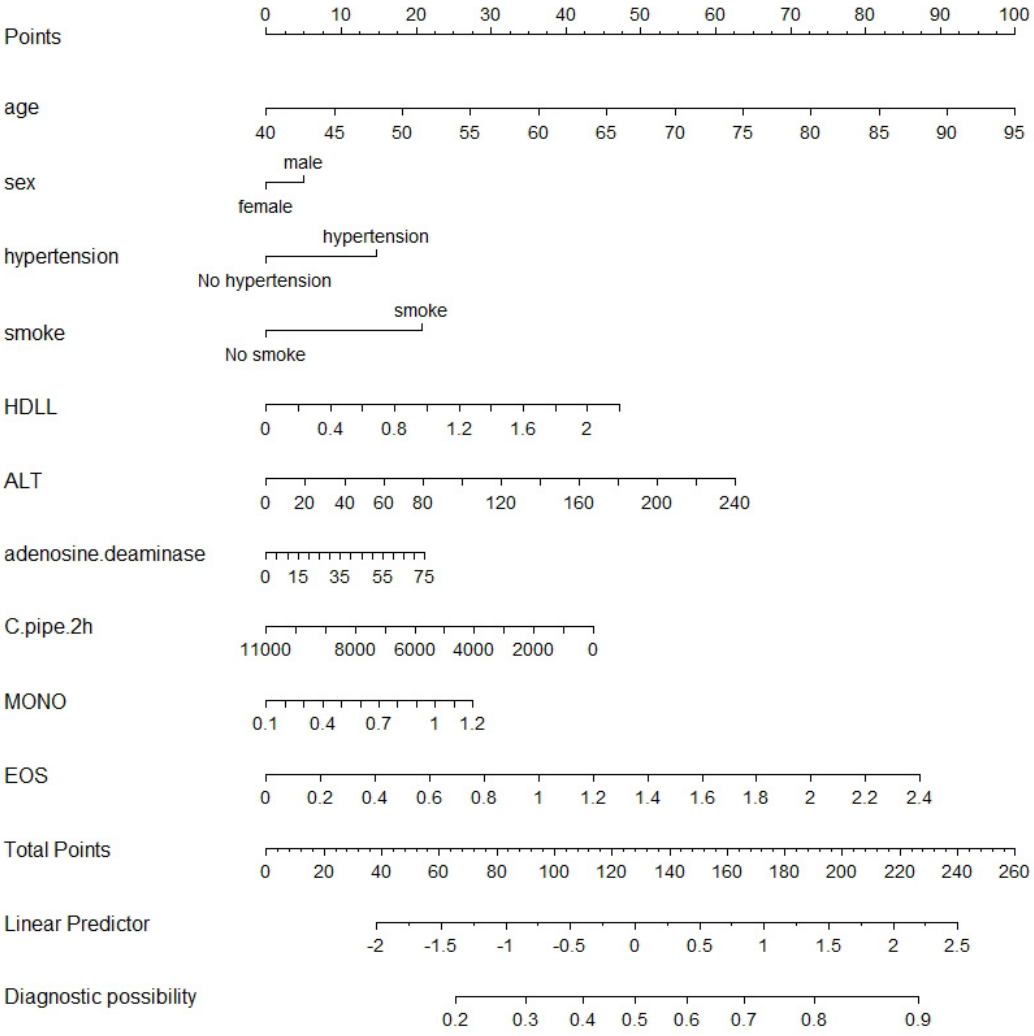

Fig. 2. Nomogram model for identifying type 2 diabetes complicating ASCVD. Note: After obtaining the points from the values of each index, the risk rate could be evaluated by the total points. HDLL, high-density lipoprotein cholesterol/low-density lipoprotein cholesterol; ALT, alanine transaminase; MONO, monocyte count; EOS, eosinophil count.

stroke or transient ischemic attack, and atherosclerotic peripheral arterial disease, as per the guidelines outlined in the *Expert Consensus on Grassroots Management of Adult Atherosclerotic Cardiovascular Disease in China* [7]. The diagnosis of coronary heart disease and atherosclerotic peripheral arterial disease was based on the criteria outlined in the *Internal Medicine, 8th Edition* [8], while atherothrombotic stroke or transient ischemic attack was diagnosed following the criteria detailed in the *Neurology, 7th Edition* [9]. Both sets of criteria were published by the People's Medical Publishing House. Subjects without vascular lesions identified through ultrasound, computed tomography (CT), or coronary computed tomography angiography (CTA) scans, and who lacked symptoms and medical history associated with ASCVD, were classified as the non-ASCVD population.

Data Collection

Baseline characteristics, laboratory testing data and imaging data were collected as follows.

(1) Baseline characteristics, encompassing age, sex, height, weight, body mass index (BMI - calculated as body weight (kg) / body height $(cm)^2$), systolic blood pressure (SBP), diastolic blood pressure (DBP), history of smoking and alcohol consumption, family medical history, as well as individual medical history, which includes information such as the duration of T2DM, hypertension, coronary heart disease, cerebrovascular disease, fatty liver, hyperlipidemia, hyperuricemia, and chronic obstructive pulmonary disease, among other parameters.

(2) Glucose metabolism indices, which consist of fasting blood glucose (FBG), fasting insulin, fasting C-peptide, postprandial 2-hour blood glucose, postprandial 2-hour insulin, postprandial 2-hour C-peptide, and glycated hemoglobin (HbA1C), among others.

Table 1. Basic data comparison between the patients in the training dataset and validation dataset.

Basic data	Training dataset (n = 1747)	Validation dataset (n = 873)	t/Z/χ^2	*p*
Age (year)	60.62 ± 10.87	60.20 ± 10.65	0.933	0.351
Male (n%)	1047 (59.93%)	532 (60.94%)	0.247	0.619
Height	165.5 ± 8.2	165.8 ± 8.3	0.879	0.379
Weight	69.1 ± 12.1	68.9 ± 11.5	0.405	0.685
BMI	25.0 ± 3.3	24.9 ± 3.1	0.746	0.456
Systolic pressure (mmHg)	124.6 ± 16.7	124.3 ± 16.5	0.435	0.663
Diastolic pressure (mmHg)	74.4 ± 11.5	74.2 ± 11.4	0.421	0.674
Hypertension (n%)	1035 (59.24%)	500 (57.27%)	0.932	0.334
Smoke (n%)	428 (24.50%)	243 (27.84%)	3.400	0.065
Drink	326 (18.7%)	173 (19.8%)	0.505	0.477

Note: BMI, body mass index.

(3) Lipid metabolism indices, which encompass total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), the LDL-C/HDL-C ratio, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and the ApoB/ApoA1 ratio, among others.

(4) Liver and kidney function indices, which include alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), leucine aminopeptidase (LAP), lactate dehydrogenase (LDH), cholinesterase (ChE), total serum bile acids (TSBA), adenosine deaminase (ADA), total bilirubin (TBil), direct bilirubin (DBil), serum creatinine (sCr), blood urea nitrogen (BUN), estimated glomerular filtration rate measured by the modification of diet in renal disease (eGFR-MDRD), blood uric acid (UA), and more. Patients meeting any of the following criteria were classified as having severe liver and kidney insufficiency: (i) A history of liver or kidney failure, (ii) Serum creatinine (SCr) levels $\geq$3 times the upper limit of normal, or (iii) Total bilirubin levels $\geq$3 times the upper limit of normal.

(5) Nutritional indices and thyroid hormones, comprising hemoglobin (Hb), albumin (Alb), total protein (TP), globulin, the albumin/globulin (A/G) ratio, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), and other related parameters.

(6) Inflammatory indices and the complete blood count, encompassing C-reactive protein (CRP), white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), monocyte count (MONO), eosinophil count (EOS), basophil count (BASO), red blood cell count (RBC), hematocrit (HCT), mean corpuscular volume (MCV), platelet count (PLT), and so on.

(7) Electrocardiographic findings, which include sinus bradycardia, conduction block, abnormal Q waves, and cardiac ultrasound findings such as atrial volume, ventricular volume, exercise capacity, and left ventricular diastolic function.

(8) Imaging data, including the neck ultrasonography, CT and coronary CTA.

Statistical Analysis

Statistical analysis was carried out using SPSS 22.0 (IBM SPSS Statistics for Windows, version 22.0, IBM Corp., Armonk, NY, USA). Continuous variables underwent an initial assessment for normal distribution and homogeneity of variances. Normally distributed continuous variables were presented as mean ± standard deviation, and group differences were evaluated using the independent samples *t*-test. Non-normally distributed continuous variables were expressed as the median and interquartile range (IQR), with group differences assessed through the Mann-Whitney U test. Categorical variables were represented as constituent ratios or percentages, and group differences were analyzed using the Chi-square test. Ranked data comparisons between groups were conducted using the rank-sum test. A significance level of $p < 0.05$ was considered statistically significant.

The 2620 subjects were randomly divided into a training dataset (n = 1747) and a validation dataset (n = 873). Logistic regression analysis was conducted in the training dataset, and variables demonstrating significance ($p < 0.10$) were subsequently subjected to multivariable logistic regression. The R packages rms, foreign, pROC, regplot, PredictABEL, and nricens were employed to construct the nomogram. The R project used in this study was R 3.5.1 (University of Auckland, Auckland, New Zealand). The performance of the model was evaluated through receiver operating characteristic (ROC) curve analysis and calibration curves.

Results

The Basic Data between the Training Dataset and Validation Dataset

As indicated in Table 1, there were no significant differences in basic demographic characteristics, including age, sex, height, weight, BMI, etc., between the training dataset and validation dataset ($p > 0.05$).

Table 2. Univariable logistic regression analysis of influencing factors for ASCVD in T2DM patients.

	B	S.E.	Wald	Sig.	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Age	0.044	0.005	86.062	0.000	1.045	1.035	1.054
Sex	–0.170	0.098	3.016	0.082	0.844	0.696	1.022
BMI	–0.028	0.015	3.562	0.059	0.972	0.945	1.001
SBP	0.009	0.003	10.561	0.001	1.009	1.004	1.015
DBP	–0.007	0.004	3.188	0.074	0.993	0.985	1.001
Smoking	0.394	0.112	12.386	0.000	1.482	1.191	1.846
Hypertension	0.532	0.099	29.098	0.000	1.702	1.403	2.065
Postprandial 2-hr blood glucose	0.026	0.012	4.654	0.031	1.026	1.002	1.050
Postprandial 2-hr C-peptide	0.000	0.000	2.886	0.089	1.000	1.000	1.000
TC	–0.090	0.040	4.979	0.026	0.914	0.844	0.989
TG	–0.196	0.045	18.831	0.000	0.822	0.752	0.898
HDL-C	–0.203	0.055	13.805	0.000	0.816	0.733	0.908
LDL-C/HDL-C	0.711	0.204	12.171	0.000	2.036	1.366	3.036
ApoB	–0.594	0.209	8.092	0.004	0.552	0.367	0.831
ApoB/ApoA1	0.242	0.090	7.177	0.007	1.273	1.067	1.520
ALT	0.009	0.003	9.931	0.002	1.009	1.004	1.015
GGT	–0.004	0.001	6.591	0.010	0.996	0.994	0.999
LAP	0.014	0.004	10.297	0.001	1.015	0.977	1.094
ADA	0.030	0.008	12.721	0.000	1.030	1.014	1.048
eGFR-MDRD	–0.006	0.002	15.798	0.000	0.994	0.990	0.997
BUN	0.044	0.026	2.829	0.093	1.045	0.993	1.099
FT3	–0.144	0.063	5.136	0.023	0.866	0.765	0.981
MONO	1.353	0.359	14.218	0.000	3.867	1.915	7.812
EOS	1.327	0.423	9.840	0.002	3.770	1.645	8.638
BASO	5.655	3.029	3.485	0.062	285.834	0.754	108,293.395
Left ventricular dysfunction	0.543	0.236	5.310	0.021	1.721	1.084	2.731

Note: T2DM, type 2 diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoB, apolipoprotein B; ApoA1, apolipoprotein A1; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; LAP, leucine aminopeptidase; ADA, adenosine deaminase; eGFR-MDRD, estimated glomerular filtration rate measured by the modification of diet in renal disease; BUN, blood urea nitrogen; FT3, free triiodothyronine; MONO, monocyte count; EOS, eosinophil count; BASO, basophil count.

Table 3. The goodness-of-fit and the identifying potential of three multivariable logistic regression models.

	Log-likelihood	Cox&Snell R^2	Nagelkerke R^2	Percentage correct	*p*
Model 1	2215.083	0.090	0.120	61.6	0.605
Model 2	2234.617	0.080	0.107	52.0	0.452
Model 3	2219.183	0.088	0.118	62.8	0.678

Screen the Variables for Constructing the Model Using Univariate Logistics Regression Methods

Univariable logistic regression analysis was conducted to identify potential factors that could affect ASCVD in T2DM patients within the training dataset (n = 1747). As presented in Table 2, a total of 26 influencing factors with *p*-values less than 0.10 were identified. Additional data and comparisons between the non-ASCVD group and the ASCVD group for these parameters can be found in **Supplementary Tables 1–8**, which include data from a total of 2620 individuals, encompassing both the training dataset and the validation dataset.

Screen the Best Models through Multi-Variate Logistics Regression Analysis Methods

We then conducted multivariable logistic regression analysis using three different methods: Enter (model 1), Forward (model 2), and Backward (model 3). Specifically, model 1 included 19 factors such as age, sex, BMI, smoking history, hypertension, postprandial 2-hour blood glucose, postprandial 2-hour C-peptide, LDL-C/HDL-C ra-

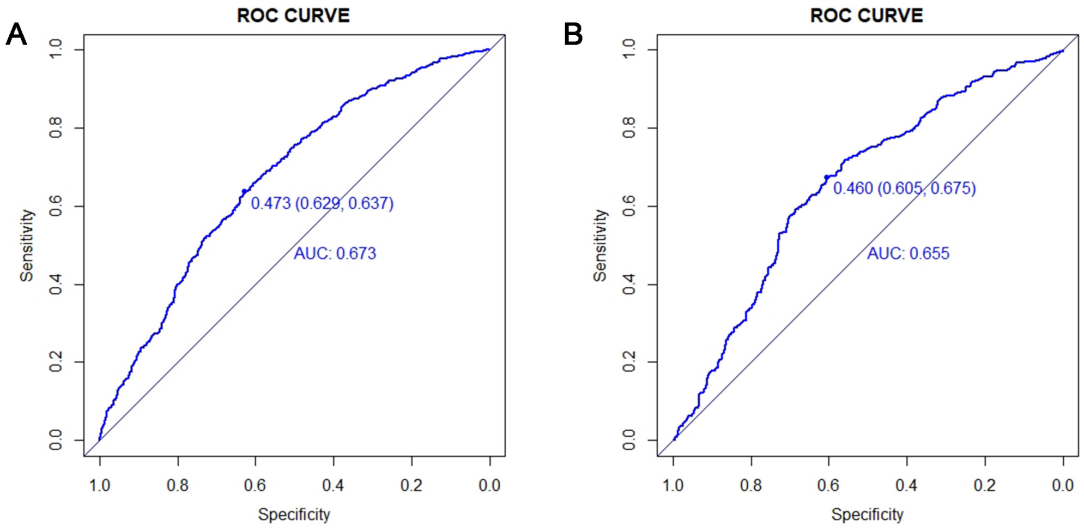

Fig. 3. Receiver operating characteristic (ROC) curves of the nomogram in identifying ASCVD in T2DM patients. (A) The training dataset. (B) The validation dataset. AUC, area under the curve.

tio, ApoB, ALT, GGT, ADA, eGFR-MDRD, FT3, MONO, EOS, BASO, and conduction delay with abnormal Q wave (**Supplementary Table 9**). Model 2 incorporated five factors: age, smoking history, hypertension, postprandial 2-hour C-peptide, and EOS (**Supplementary Table 10**). In model 3, there were 10 factors, including age, sex, smoking history, hypertension, postprandial 2-hour C-peptide, LDL-C/HDL-C ratio, ALT, ADA, MONO, and EOS (**Supplementary Table 11**). It was observed that the goodness-of-fit and the predictive ability of model 2 were suboptimal, while models 1 and 3 demonstrated acceptable and similar performance. Therefore, we ultimately opted for model 3 due to its inclusion of fewer variables (Table 3).

Construction of the Nomogram

A nomogram, incorporating 10 variables, was then constructed using the R software (Fig. 2). The results indicate that the risk of ASCVD in T2DM patients increases with age, with the risk score rising by 7.5 points for every 10-year increment. A higher LDL-C/HDL-C ratio corresponds to a risk score increase of 10 points for every 1-unit increase. Elevated ALT levels are associated with a risk score increase of 7.5 points for every 100 U/L increase, while higher MONO counts lead to a risk score increase of 12.0 points for every 1.0 $\times$ 10^9/L increase. Likewise, higher EOS counts result in a risk score increase of 18.0 points for every 1.0 $\times$ 10^9/L increase. Being male contributes 5.0 points to the risk score, while a history of hypertension and smoking history adds 8.0 and 10.0 points, respectively. Conversely, the risk of ASCVD in T2DM patients decreases with an increase in postprandial 2-hour C-peptide levels, with the risk score decreasing by 8.0 points for every 300 mmol/L decrease. A lower level of ADA results in a risk score decrease of 8.0 points for every 15 U/L decrease.

Performance Validation of the Nomogram

The performance of the constructed nomogram was evaluated in both the training and validation datasets using ROC curve analysis and calibration curves. ROC curves demonstrated that the area under the curve (AUC) of the nomogram for identifying ASCVD in T2DM patients was 0.673 in the training dataset (Fig. 3A) and 0.655 in the validation dataset (Fig. 3B). The associated cut-off values, specificity, and sensitivity were 0.473, 0.629, and 0.637 for the training dataset, and 0.460, 0.605; and 0.675 for the validation dataset, respectively. Additionally, the calibration curve indicated a substantial agreement between the predicted and observed cases of ASCVD in the training dataset (Fig. 4A) and an acceptable level of agreement in the validation dataset (Fig. 4B).

Discussion

The conventional preventive methods for ASCVD in T2DM patients primarily involve the management of blood sugar, blood pressure, and blood lipids, based on clinical experience, along with interventions targeting well-known risk factors [10,11]. T2DM patients are considered a high-risk population for macrovascular diseases, particularly ASCVD. However, there is a notable scarcity of high-quality predictive models for ASCVD in T2DM patients. In alignment with previous data, our cohort of T2DM patients exhibited a high incidence of ASCVD, reaching 48.5% [12,13]. There is an urgent need to establish effective models for identifying and predicting ASCVD in T2DM patients, which would support personalized clinical management and enhance their quality of life [14].

At present, there is a notable global scarcity of mature and validated models for identifying or predicting ASCVD in T2DM patients. Type 2 diabetes mellitus is a com-

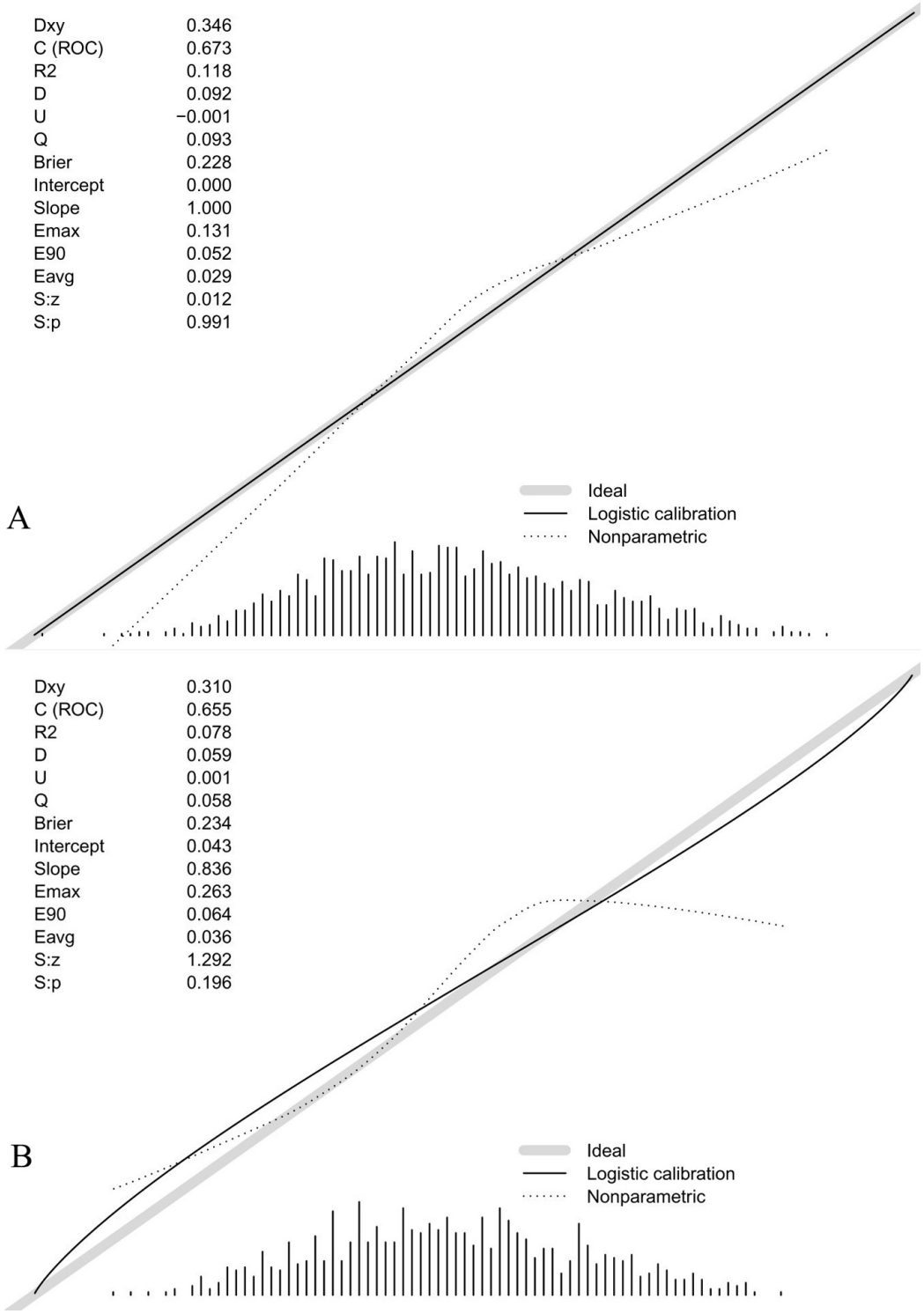

Fig. 4. Calibration curves of the nomogram in identifying ASCVD in T2DM patients. NOTE: (A) The training dataset. (B) The validation dataset.

plex metabolic disease that affects multiple systems in the body, resulting in a wealth of clinical data gathered during diagnosis and treatment. There are two primary reasons for constructing a model to identify ASCVD in T2DM patients. First, these patients have a significantly higher likelihood of developing macrovascular complications compared to the general population, making the development of such a model a critical target for prevention and control. Second, the extensive array of clinical tests and examination protocols for this population overcomes the limitations associated with incomplete data in some physical examinations of the general population. Various models for com-

mon diseases include logistic regression models, classification tree models, backpropagation (BP) neural networks, and nomograms [15–18]. In this study, we opted to create a nomogram for identifying ASCVD in T2DM patients due to its advantages in risk factor screening, consideration of interaction terms, and risk assessment [19]. Our nomogram holds significant importance in identifying the high-risk population for ASCVD in T2DM patients and facilitating early preventive interventions.

Based on the results of the logistic regression analysis, we developed a nomogram that utilizes 10 variables to identify ASCVD in T2DM patients. Notably, these 10 variables encompass various aspects, including baseline characteristics, glucose and lipid metabolism, liver and kidney function, inflammatory indexes, and a complete blood count. Previous evidence has indicated that T2DM patients, even with well-controlled blood sugar and lipid levels, can still be at risk for ASCVD [20,21]. This suggests that factors beyond metabolic factors play a role in the pathogenesis of ASCVD in T2DM patients. One notable inclusion in the nomogram is postprandial 2-hour C-peptide, a marker for the reserve function of pancreatic islet beta cells. It outperforms fasting C-peptide, fasting insulin, and postprandial 2-hour insulin in identifying ASCVD, possibly due to its greater serum stability [22,23]. Fasting insulin and postprandial 2-hour insulin levels can fluctuate significantly and are affected by exogenous insulin supplementation, which can limit their diagnostic potential. The inclusion of the LDL-C/HDL-C ratio in the nomogram is noteworthy. This ratio reflects the balance between atherogenic and anti-atherosclerotic factors and may offer a more comprehensive view than individual LDL-C or HDL-C measurements. Liver function tests play a crucial role in the routine monitoring of T2DM patients. Two liver function indices, ALT and ADA, were incorporated into our nomogram. Elevated ALT levels have been associated with the development of atherosclerosis in patients with or without fatty liver. ADA activity has been found to correlate with atherosclerotic changes in human aortas.

Conclusions

In summary, we have developed a nomogram for identifying ASCVD in T2DM patients and have validated its performance. It is important to note that our findings should undergo further validation in large-scale, high-quality prospective studies to ensure the robustness and generalizability of the model.

Availability of Data and Materials

We claim all the data used in this study are available from the first authors.

Author Contributions

HWS, WZ and YYZ designed the research study. CM, HD, CW, RYL and YLS performed the research. HWS and CM wrote the first version of manuscript. HWS, HY and MYW analyzed the data. YYZ and WZ supervised the project. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. HWS and CM contributed equally to this work. YYZ and WZ are the corresponding authors.

Ethics Approval and Consent to Participate

Approval was obtained from the ethics committee of Nanjing Pukou People's Hospital (NO. 2023-SR-025), and all the participants signed a written informed consent.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202335179.108.

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