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Original Article

Establishment and validation of a nomogram that predicts the risk of type 2 diabetes in obese patients with non-alcoholic fatty liver disease: a longitudinal observational study

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Abstract: Objective: This study aimed to establish and validate a nomogram for better assessment of the risk of type 2 diabetes (T2D) in obese patients with non-alcoholic fatty liver disease (NAFLD) based on independent predictors. Methods: Of 1820 eligible participants from the NAGALA cohort enrolled in the study. Multivariate Cox regression was employed to construct the nomogram. The performance was assessed by area under the receiver operating characteristic curve (AUC), C-index, calibration curve, decision curve analysis, and Kaplan-Meier analysis. Results: Five predictors were selected from 17 variables. The AUC values at different time points all indicated that the model constructed with these five predictors had good predictive power. Decision curves indicated that the model could be applied to clinical applications. Conclusions: We established and validated a reasonable, economical nomogram for predicting the risk of T2D in obese NAFLD patients. This simple clinical tool can help with risk stratification and thus contribute to the development of effective prevention programs against T2D in obese patients with NAFLD.

Keywords: Type 2 diabetes, obesity, non-alcoholic fatty liver disease, nomogram, cohort study

Introduction

Type 2 diabetes (T2D) is a disorder caused by relative insulin deficiency and insulin resistance [1, 2]. Due to its debilitating effect, T2D has a significant negative impact on human health [3]. Early identification of individuals at risk for T2D is important because early intervention can slow the progression of T2D and prevent the development of complications [3-5].

Non-alcoholic fatty liver disease (NAFLD) is an important etiology of chronic liver disease [6-8]. In addition to concerns related to liver disease, NAFLD has been highlighted as a manifestation of systemic metabolic diseases [9-11]. Over the past few decades, the global obese population has been increasing [12]. Both obesity and NAFLD are extremely prevalent chronic metabolic disorders and global public health challenges [13]. There is growing evidence that obesity, NAFLD, and T2D are closely related [14]. Several epidemiological studies have also shown that both obesity and NAFLD are independent risk factors for T2D [15, 16]. In the presence of obesity and NAFLD together, individuals are more likely to develop cardiometabolic complications such as insulin resistance and T2D, all of which are strongly associated with inappropriate ectopic lipid deposition [17]. Overall, based on the close association between obesity, NAFLD, and T2D, systematic screening of obese NAFLD patients to accurately estimate the risk of T2D helps to reduce the morbidity through timely intervention in high-risk groups [18].

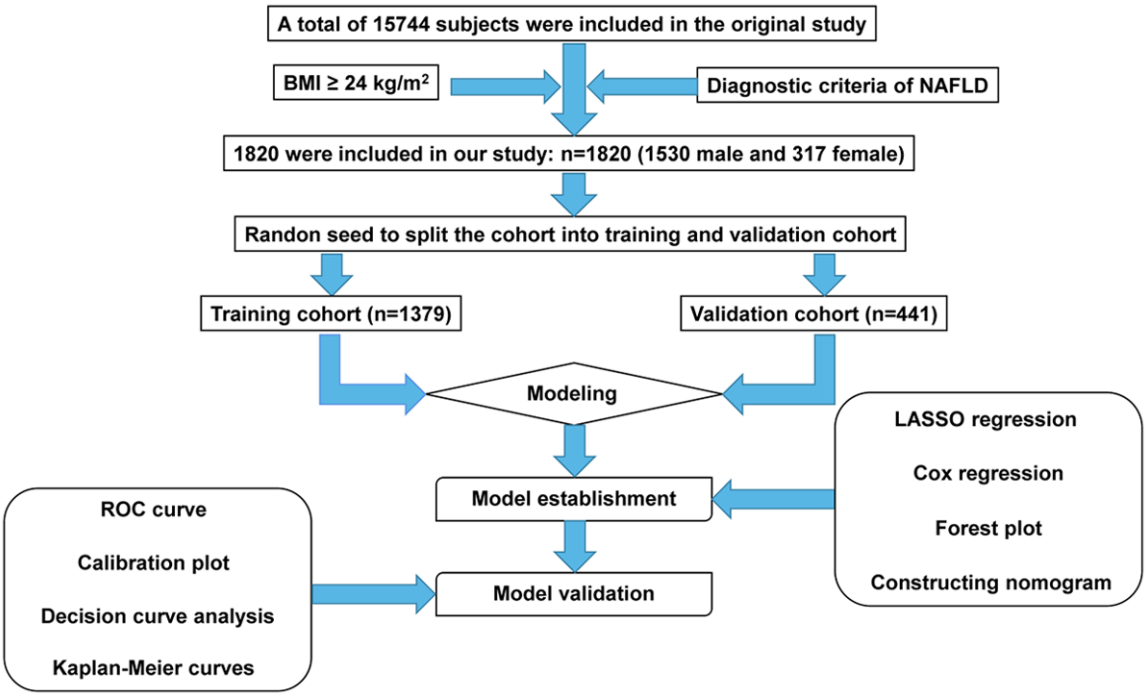

Figure 1. Flow chart.

According to our knowledge, there is no nomogram available to predict the risk of T2D in obese NAFLD patients [19-21]. Therefore, our study tended to establish and validate a nomogram for predicting the risk of T2D in obese patients with NAFLD.

Materials and methods

Data source

Clinical information for this study was derived from the Dryad.

Study design and participants

The NAGALA cohort is a longitudinal population-based observational study conducted at Murakami Memorial Hospital. Okamura et al. [22] recruited 15744 participants without diabetes at baseline from 2004 to 2015. Exclusion criteria for the original research were referenced from previously published papers [22, 23]. Besides the above exclusion criteria, the following more stringent exclusion criteria were established for this research: (i) body mass index (BMI) <24 kg/m^2 and (ii) absence of NAFLD at baseline examination. Ultimately 1820 subjects participated in the study. The flow chart is depicted in **Figure 1**.

Data description

The raw data files included baseline information, follow-up duration, and incident T2D. From the raw data, we derived information about gender, waist circumference (WC), age, BMI, habits of drinking, exercise, smoking, as well as baseline diastolic blood pressure (DBP), systolic blood pressure (SBP), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), high density lipoprotein cholesterol (HDL-c), triglyceride (TG), fasting plasma glucose (FPG), and hemoglobin A1c (HbA1c).

Definitions

Participants' alcohol status was then divided into 4 categories: none or minimal drinkers, light drinkers, moderate drinkers, or heavy drinkers. Similarly, for smoking status, participants were classified into 3 groups: never, past, and current smokers. Furthermore, exercise habits were identified for attendees who did any exercise type once a week. Obesity was defined as a BMI of ≥24 kg/m^2. The ultrasound was conducted by a professional technologist and NAFLD diagnosed by experienced gastroenterologists. T2D was defined as HbA1c

≥48 mmol/mol, FPG ≥126 mg/dl, and/or self-reported diabetes during follow-up.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation or median (IQR), as appropriate. Categorical data were expressed as numbers (percentages). The least absolute shrinkage selection operator (LASSO) method was applied to select best predictors. Then, a multivariate Cox regression was performed on risk variables selected in the LASSO regression. Finally, a nomogram was constructed based on the results of multivariate Cox regression. The discriminative power of the clinical model was estimated based on the C-index and the time-dependent area under the receiver operating characteristic curve (AUC). Calibration curves were plotted against actual and predicted incidence to estimate the calibration of the model. Then, the "surv_cutpoint" function was used to generate cutoff points for risk stratification. Kaplan-Meier analysis was applied to assess the difference in disease-free survival between the low- and high-risk groups. Decision curve analysis was employed to assess clinical outcomes.

All statistical analyses were done using R 3.6.3 with two-sided *P*-values <.05.

Results

Baseline characteristics

The information of the eligible participants is listed in **Table 1**. **Figure 1** illustrates a detailed flowchart. The present study included 1820 eligible participants (82.58% male and 17.42% female). During the 1865 days of the median follow-up duration, there were 167 participants with new-onset T2D. The mean BMI was 27.02±2.59 kg/m^2. The mean WC was 89.26±6.98 cm. The mean SBP and DBP were 126.26±14.70 and 79.80±10.11 mmHg, respectively. The mean FPG and HbA1c were 97.73±6.36 mg/dl and 34.48±3.67 mmol/mol, respectively.

Selection of risk features

All 17 potential characteristics were enrolled in the LASSO regression for 1379 participants in the training cohort. Then, five characteristics with non-zero coefficients were selected when lambda.1se = -4.106. The five features were smoking status, WC, HDL-c, HbA1c, and FPG. The results of the LASSO regression are presented in **Figure 2A**, **2B**, and the detailed parameters are listed in **Table 2**.

Multivariate Cox regression

We identified smoking status [hazard ratio (HR)=1.35], WC (HR=1.06), HDL-c (HR=0.97), HbA1c (HR=1.29), and FPG (HR=1.08) of patients as independent factors correlated with T2D in obese patients with NAFLD. A forest plot was used to portray the effect and contribution of each independent risk factor to HR (**Figure 3**).

Nomogram performance

A nomogram was constructed to predict the risk of T2D in obese patients with NAFLD (**Figure 4**). For different time points in the training cohort, the AUC of the model ranged from 0.873 to 0.899. In the validation cohort, the AUC of the model for different time points ranged from 0.821 to 0.895 (**Figure 5A**, **5B**). In addition, we assessed the ability of the prediction model to discriminate between patients with T2D at different time points. In the training cohort, AUCs were 0.889 at 3 years, 0.889 at 5 years and 0.884 at 8 years. In the validation cohort, AUCs were 0.839 at 3 years, 0.847 at 5 years and 0.888 at 8 years. The C-index was 0.844 for the training cohort and 0.829 for the validation cohort (**Table 3**). The calibration curve demonstrated a good concordance between the predicted and observed results for the nomogram (**Figure 6A**, **6B**). This was supported by the results of the Hosmer-Lemeshow test (P=0.417 and P=0.138 for training and validation cohorts, respectively). According to the risk stratification derived from the nomogram, all attendees were grouped into low-risk and high-risk clusters. Kaplan-Meier curves revealed that the two curves differed significantly in the whole cohort (*P*-value <0.001) (**Figure 7**).

Clinical utility

The decision curve analysis of the nomogram are shown in **Figure 8A**, **8B**. The model predicting the risk of T2D provided more net benefit than the "all treatment" or "no treatment" sce-

Table 1. Characteristics of the population

Variables	Total cohort	Training cohort	Validation cohort	*P*-value
No. of participants	1820	1379	441	
Age (years)	44.38±8.29	44.36±8.24	44.42±8.43	0.934
Body mass index (kg/m^2)	27.02±2.59	27.05±2.62	26.94±2.50	0.458
Waist circumference (cm)	89.26±6.98	89.23±6.99	89.33±6.94	0.797
Alanine aminotransferase (IU/L)	29.00 (21.00-42.00)	29.00 (21.00-42.00)	29.00 (21.00-42.00)	0.178
Aspartate aminotransferase (IU/L)	21.00 (17.00-27.00)	21.00 (17.00-27.00)	21.00 (17.00-28.00)	0.178
γ-glutamyl transpeptidase (IU/L)	24.50 (18.00-36.00)	24.00 (18.00-36.00)	25.00 (18.00-38.00)	0.253
High density lipoprotein cholesterol (mg/dl)	44.75±10.16	44.68±10.32	44.96±9.66	0.618
Total cholesterol (mg/dl)	211.98±33.47	212.34±33.71	210.88±32.73	0.425
Triglyceride (mg/dl)	117.00 (81.00-167.00)	117.00 (82.00-168.00)	116.00 (78.00-164.00)	0.543
Hemoglobin A1c (mmol/mol)	34.48±3.67	34.54±3.65	34.32±3.74	0.282
Fasting plasma glucose (mg/dl)	97.73±6.36	97.64±6.43	98.00±6.13	0.432
Systolic blood pressure (mmHg)	126.26±14.70	126.32±14.64	126.05±14.91	0.734
Diastolic blood pressure (mmHg)	79.80±10.11	79.75±10.05	79.95±10.30	0.727
Gender [n (%)]				0.051
Female	317 (17.42%)	254 (18.42%)	63 (14.29%)	
Male	1503 (82.58%)	1125 (81.58%)	378 (85.71%)	
Habit of exercise [n (%)]				0.558
No	1563 (85.88%)	1188 (86.15%)	375 (85.03%)	
Yes	257 (14.12%)	191 (13.85%)	66 (14.97%)	
Alcohol consumption [n (%)]				0.175
Non	1372 (75.38%)	1056 (76.58%)	316 (71.66%)	
Light	192 (10.55%)	135 (9.79%)	57 (12.93%)	
Moderate	176 (9.67%)	129 (9.35%)	47 (10.66%)	
Heavy	80 (4.40%)	59 (4.28%)	21 (4.76%)	
Smoking status [n (%)]				0.457
Never	798 (43.85%)	603 (43.73%)	195 (44.22%)	
Past	480 (26.37%)	356 (25.82%)	124 (28.12%)	
Current	542 (29.78%)	420 (30.46%)	122 (27.66%)	
Follow-up duration (days)	1865.00 (815.75-3355.50)	1844.00 (815.50-3329.50)	2009.00 (832.00-3398.00)	0.545
Incident type 2 diabetes [n (%)]				0.221
No	1653 (90.82%)	1246 (90.36%)	407 (92.29%)	
Yes	167 (9.18%)	133 (9.64%)	34 (7.71%)	

Data are presented as n (%), mean ± SD, or median (interquartile range).

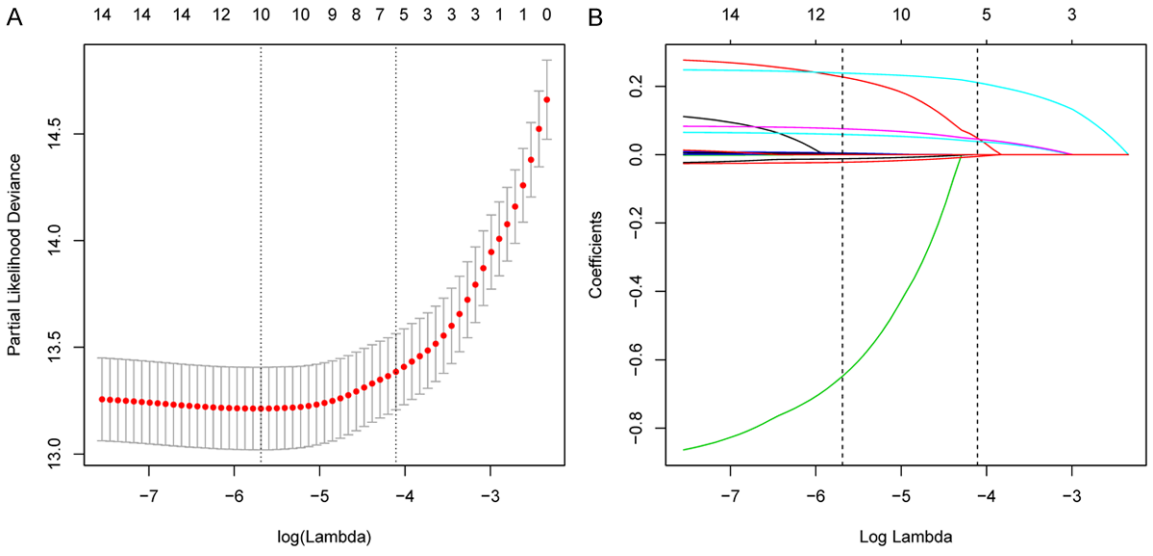

Figure 2. Texture feature selection using the least absolute shrinkage selection operator regression. A. Optimal parameter selection. B. Coefficient profiles.

Table 2. Coefficients and lambda.1se value of the LASSO regression model

Factors	Coefficients	Lambda.1se
Habit of exercise	0	-4.106
Smoking status	0.049	
Alcohol consumption	0	
Gender	0	
Age	0	
Body mass index	0	
Waist circumference	0.038	
Alanine aminotransferase	0	
Aspartate aminotransferase	0	
γ-glutamyl transpeptidase	0	
High density lipoprotein cholesterol	-0.005	
Total cholesterol	0	
Triglyceride	0	
Hemoglobin A1c	0.211	
Fasting plasma glucose	0.045	
Systolic blood pressure	0	
Diastolic blood pressure	0	

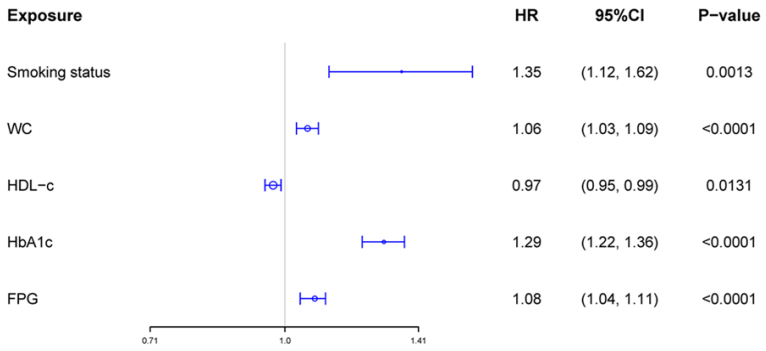

Figure 3. Forest plot.

narios when the threshold probability ranged from 2% to 72%. Therefore, our prediction model is feasible and has high clinical validity and application value.

Discussion

Obesity and NAFLD are known to be independent risk factors for T2D [24]. There is growing evidence that the coexistence of obesity, NAFLD, and T2D is significantly correlated with an elevated risk of cardiovascular disease, stroke, and nontraumatic amputation, thus posing a significant cardiovascular health burden [25, 26]. Evidence from multiple large-scale intervention studies suggests that early prevention and timely interventions targeting populations at high risk for T2D are essential for diabetes control [27, 28]. Therefore, this prompted us to conduct the present study.

Although many diabetes prediction models already exist in different populations, they all have several limitations [29, 30]. First, they mainly target European and American populations, and few T2D risk prediction models are based on Asian populations, especially populations in East Asia. T2D risk prediction models developed in white populations are not applicable to other racial groups. Possible reasons for this are that people of different races have different environmental and genetic characteristics, such as climate, diet, body size, and other lifestyle factors. Critically, these T2D prediction models are limited studies that focus on low-risk individuals. Therefore, there is a need to propose new risk prediction models to screen obese patients with NAFLD at high risk for T2D.

In this research, we established and validated a nomogram to predict the risk of T2D in obese patients with NAFLD. Our model consists of five parameters: smoking status, WC, HDL-c, HbA1c, and FPG. The nomogram has the following advantages: good reproducibility, low cost, graphical display, and practicality. Most of the variables included in our model are similar to those in previous T2D risk prediction models. Many observational investigations have demonstrated that smoking is strongly related to an increased risk of new-onset diabetes [31, 32]. WC is an easy anthropometric parameter for centripetal obesity and is a recognized risk factor for diabetes [33].

Most patients with T2D have varying degrees of dyslipidemia, as evidenced by decreased HDL-c and elevated TG [34]. In addition, changes in

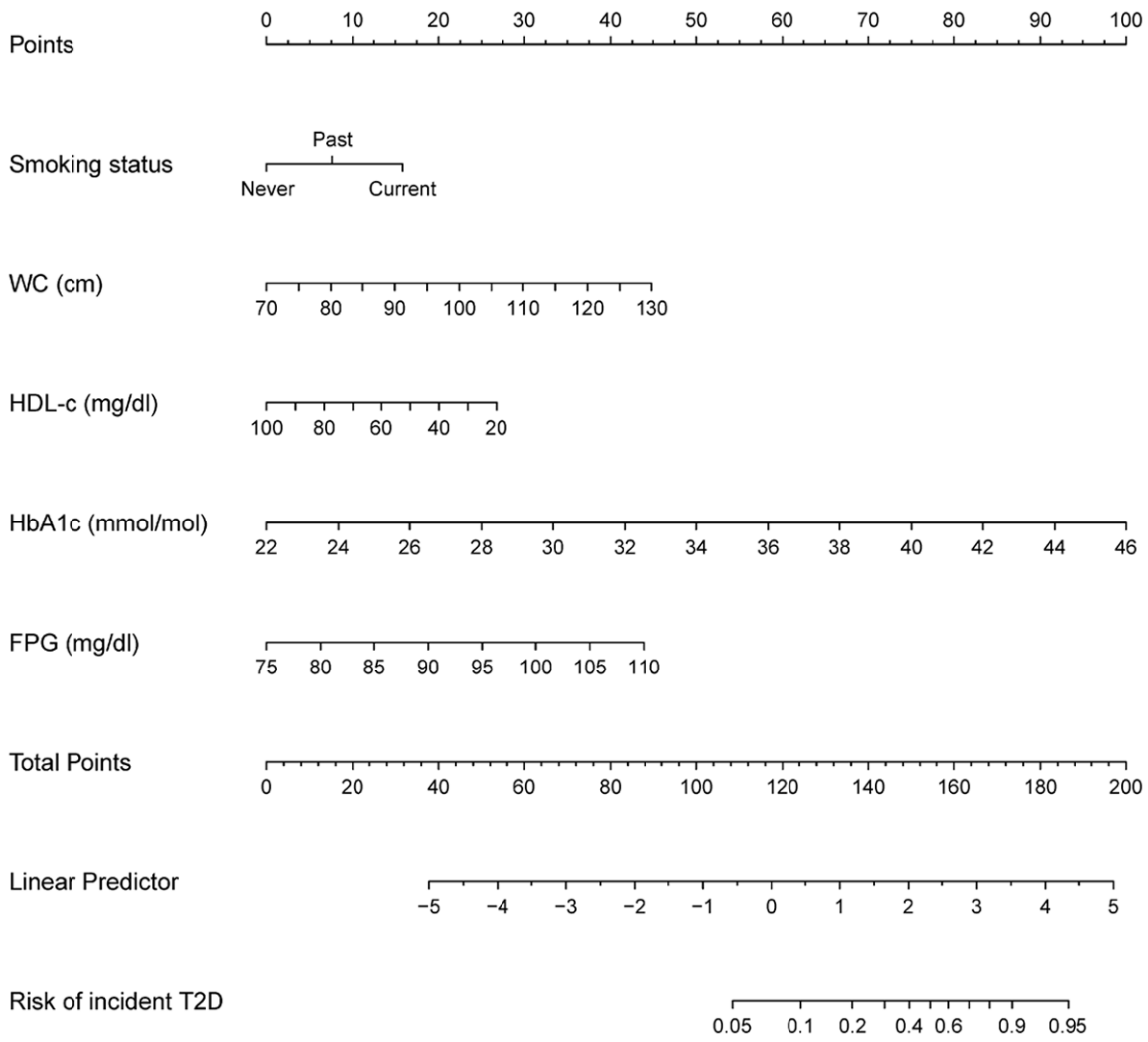

Figure 4. Nomogram to predict risk of type 2 diabetes in obese patients with non-alcoholic fatty liver disease.

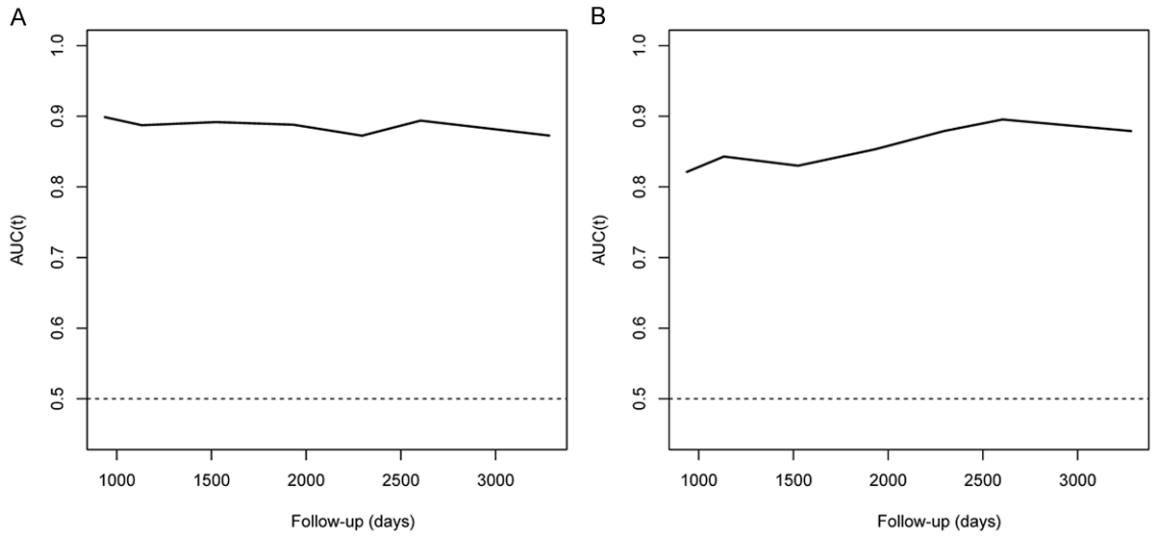

Figure 5. Performance evaluation. A. Training cohort. B. Validation cohort.

Table 3. C-index in the nomogram

	C-Index (95% CI)	Dxy	aDxy	Variance	Z-value	*P*-value	n
Training cohort	0.844 (0.813, 0.876)	0.689	0.689	0.032	21.619	<0.001	1379
Validation cohort	0.829 (0.753, 0.906)	0.659	0.659	0.078	8.473	<0.001	441

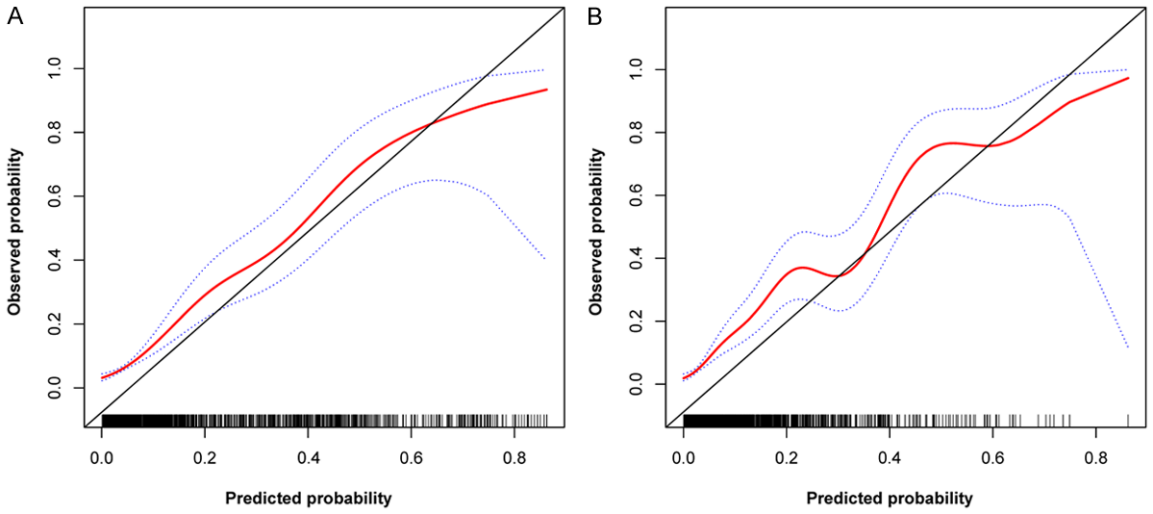

Figure 6. Calibration curves. A. Training cohort. B. Validation cohort.

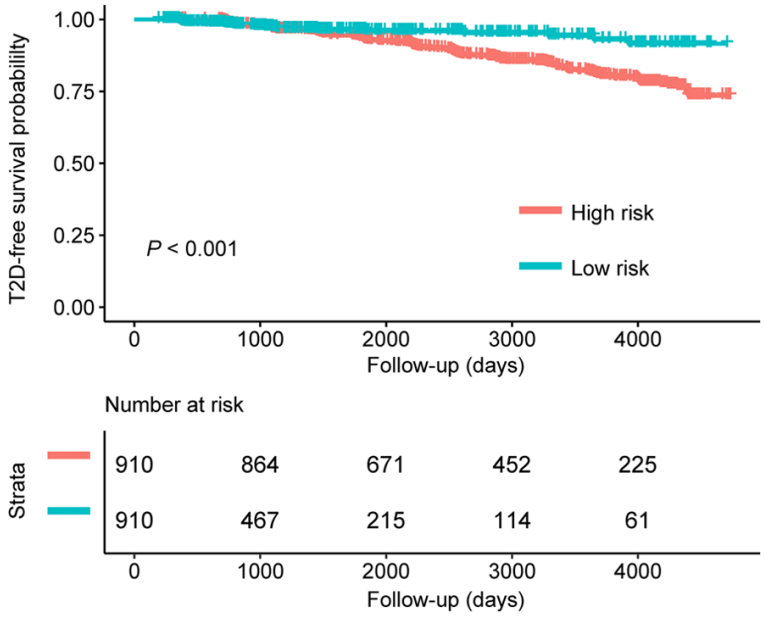

Figure 7. Kaplan-Meier curves.

HDL-c levels, HDL-c particles, and their major apolipoproteins, Apo A-I, have been reported to be present years before the onset of T2D [35]. Related studies suggest that HDL-c levels may be significantly associated with insulin resistance, impaired β-cell function, small LDL particles, and increased estimates of the number of LDL particles that may contribute to the accelerated development of T2D [36]. Indeed, both in vivo and in vitro research have suggested that HDL-c concentrations and their functional status affect pancreatic β-cell function. High HDL-c concentrations have an anti-apoptotic effect on pancreatic β-cells [37]. HDL-c deficiency leads to decreased cholesterol efflux, resulting in cholesterol accumulation in β-cells, causing β-cell dysfunction, inducing β-cell apoptosis, disrupting insulin secretion, and increasing blood glucose [38]. Both FPG and HbA1c levels may reflect the level of basal insulin secretion and function [39].

Although our nomogram performed well, some limitations should be considered for cautious

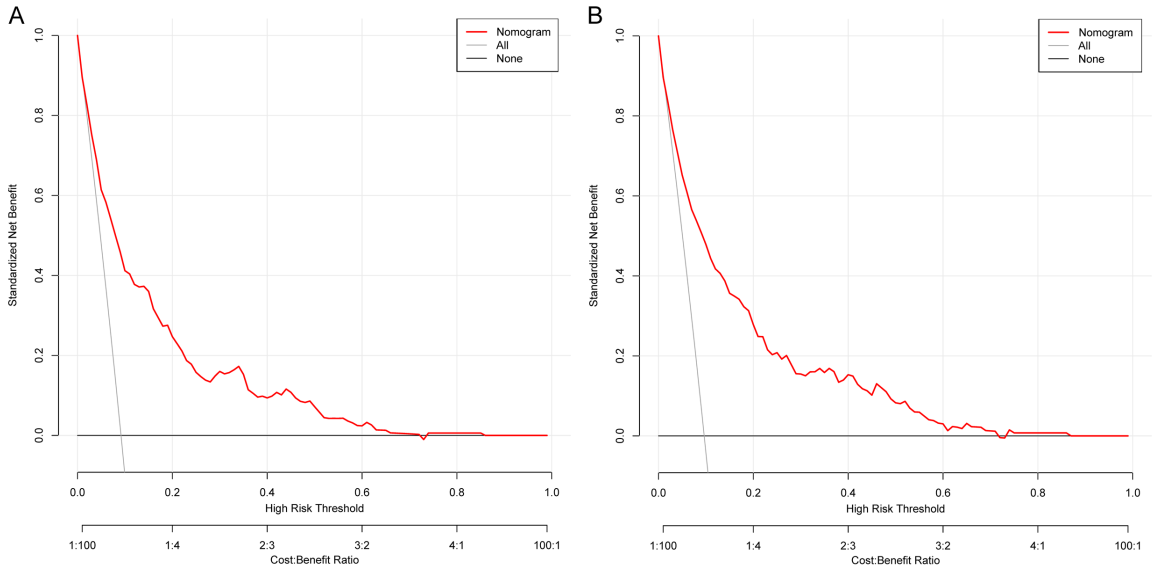

Figure 8. Decision curve analysis. A. Training cohort. B. Validation cohort.

interpretation. First, we rely on FPG and HbA1c, rather than two hours after the glucose load test to define the occurrence of T2D. There is evidence that in Asia, relying on FPG and HbA1c alone to diagnose patients with new-onset T2D may cause it to be underdiagnosed. However, due to the complexity of the procedure, it is not practicable to conduct a 2-hour post-load glucose test in a large cohort study. Secondly, our two cohorts were from the same population, which may indicate overly optimistic results. Therefore, some clinical studies using real data from hospitals are needed to further confirm our observations and conclusions. Thirdly, although adjustments were made for many confounders, there were still some indicators that were not included in this study because data on dietary behavior, family history, and medication were not collected in the database. Finally, ultrasound is commonly used to diagnose NAFLD, but ultrasound does not determine the severity of NAFLD. However, ultrasound is widely utilized for NAFLD-related epidemiologic investigations owing to its affordability and accuracy [40].

Conclusion

Our nomogram consists of five parameters: smoking status, WC, HDL-c, HbA1c, and FPG. This simple clinical tool can help identify risk stratification and thus contribute to the development of effective prevention programs against T2D in obese patients with NAFLD.

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Disclosure of conflict of interest

None.

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