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ORIGINAL RESEARCH

Glycosylated Hemoglobin A1c Improves the Performance of the Nomogram for Predicting the 5-Year Incidence of Type 2 Diabetes

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Aim: To develop and validate a model, which combines traditional risk factors and glycosylated hemoglobin A1c (HbA1c) for predicting the risk of type 2 diabetes (T2DM).

Materials and Methods: This is a historical cohort study from a collected database, which included 8419 males and 7034 females without diabetes at baseline with a median follow-up of 5.8-years and 5.1-years, respectively. Multivariate cox regression analysis was used to select significant prognostic factors of T2DM. Two nomograms were constructed to predict the 5-year incidence of T2DM based on traditional risk factors (Model 1) and traditional risk factors plus HbA1c (Model 2). C-index, calibration curve, and time-dependent receiver-operating characteristic (ROC) curve were conducted in the training sets and validation sets.

Results: In males, the C-index was 0.824 (95% CI: 0.795–0.853) in Model 1 and 0.867 (95% CI: 0.840–0.894) in Model 2; in females, the C-index was 0.830 (95% CI: 0.770–0.890) in Model 1 and 0.856 (95% CI: 0.795–0.917) in Model 2. The areas under curve (AUC) in Model 2 for prediction of T2DM development were higher than in Model 1 at each time point. The calibration curves showed excellent agreement between the predicted possibility and the actual observation in both models. The results of validation sets were similar to the results of training sets.

Conclusion: The proposed nomogram can be used to accurately predict the risk of T2DM. Compared with the traditional nomogram, HbA1c can improve the performance of nomograms for predicting the 5-year incidence of T2DM.

Keywords: type 2 diabetes, nomogram, risk factor, glycosylated hemoglobin A1c

Introduction

Diabetes mellitus is one of the major public health problems worldwide. According to the International Diabetes Federation statistics, there were approximately 463 million adults (20–79 years) with diabetes in 2019.[1]

Type 2 diabetes (T2DM) is the most common type of diabetes that accounts for approx. 90% of all diabetes cases. The risk factors of T2DM include age, obesity, family history of diabetes, unhealthy lifestyle, and hypertension. Nomogram is a graphic calculating device that can be used to predict the prognosis of diseases. Nomogram integrates clinical risk factors and provides individualized risk predictions for each subject. So far, several nomograms have been developed, which may identify high-risk individuals, thus promoting timely intervention and reducing the incidence of T2DM.[2–4]

The glycosylated hemoglobin A1c (HbA1c) reflects the average level of blood sugar over the past 2 to 3 months. It is an important indicator for evaluating diabetes control.

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Table 1 Characteristics of the Training and Validation Set in Males

Variables		All (n=8419)	Training Set (n=5893)	Validation Set (n=2526)	*P*
Age (yrs)		44.1±9.0	44.1±9.0	44.2±9.1	0.667
Current smoking [n(%)]		3023 (35.9)	2116 (35.9)	907 (35.9)	1.000
Alcohol consumption [n(%)]	Non	5351 (63.6)	3729 (63.3)	1622 (64.2)	0.678
	Light	1365 (16.2)	972 (16.5)	393 (15.6)	
	Moderate	1163 (13.8)	819 (13.9)	344 (13.6)	
	Heavy	540 (6.4)	373 (6.3)	167 (6.6)	
Regular exercise [n(%)]		1597 (19.0)	1126 (19.1)	471 (18.6)	0.621
BMI (kg/m^2)		23.0±3.0	23.0±3.0	23.1±3.0	0.454
Obesity [n(%)]		1893 (22.5)	1314 (22.3)	579 (22.9)	0.530
SBP (mmHg)		118.8±14.1	118.7±14.2	118.9±14.0	0.530
DBP (mmHg)		74.9±10.0	74.8±10.0	74.9±9.8	0.733
Elevated blood pressure [n(%)]		1892 (22.5)	1293(21.9)	599 (23.7)	0.074
TG (mg/dL)		99.1±65.8	99.3±66.5	98.6±64.2	0.628
HDL-c (mg/dL)		50.5±13.4	50.5±13.5	50.6±13.3	0.643
Dyslipidemia [n(%)]		2469 (29.3)	1764 (29.9)	705 (27.9)	0.062
FPG (mg/dL)		95.6±6.7	95.6±6.7	95.7±6.6	0.608
HbA1c (%)		5.2±0.3	5.2±0.3	5.2±0.3	0.845
Follow up duration (yrs)		6.2±3.9	6.2±3.8	6.2±3.9	0.713
Incident T2DM		286 (3.4)	196 (3.3)	90 (3.6)	0.582

Note: Data are expressed as number (%) of subjects or mean ± SD.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; T2DM, type 2 diabetes.

Table 2 Characteristics of the Training and Validation Set in Females

Variables		All (n=7034)	Training Set (n=4914)	Validation Set (n=2120)	*P*
Age (yrs)		43.3±8.8	43.2±8.8	43.5±8.7	0.214
Current smoking [n(%)]		454 (6.5)	323 (6.6)	131 (6.2)	0.537
Alcohol consumption [n(%)]	Non	6451 (91.7)	4508 (91.7)	1943 (91.7)	0.524
	Light	389 (5.5)	265 (5.4)	124 (5.8)	
	Moderate	194 (2.8)	141 (2.9)	53 (2.5)	
Regular exercise [n(%)]		1109 (15.8)	789 (16.1)	320 (15.1)	0.310
BMI (kg/m^2)		21.0±2.9	21.0±2.9	21.0±3.0	0.469
Obesity [n(%)]		628 (8.9)	429 (8.7)	199 (9.4)	0.376
SBP (mmHg)		109.4±14.3	109.4±14.2	109.2±14.5	0.646
DBP (mmHg)		67.6±9.8	67.6±9.7	67.6±9.9	0.927
Elevated blood pressure [n(%)]		633 (9.0)	433 (8.8)	200 (9.4)	0.403
TG (mg/dL)		58.9±36.6	58.7±35.3	59.4±39.5	0.438
HDL-c (mg/dL)		63.8±14.9	63.8±14.9	63.7±14.8	0.824
Dyslipidemia [n(%)]		354 (5.0)	251 (5.1)	103 (4.9)	0.661
FPG (mg/dL)		89.8±7.1	89.8±7.1	89.9±7.1	0.520
HbA1c (%)		5.2±0.3	5.2±0.3	5.2±0.3	0.383
Follow up duration (yrs)		5.9±3.7	5.9±3.7	5.9±3.7	0.758
Incident T2DM		87 (1.2)	60 (1.2)	27 (1.3)	0.855

Note: Data are expressed as number (%) of subjects or mean ± SD.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; T2DM, type 2 diabetes.

HbA1c is a good risk predictor for T2DM.[5] In the present study, we developed and validated a nomogram combined with traditional risk factors and HbA1c to predict the risk of T2DM.

Materials and Methods

Data Source

In the current study, we obtained data from Dryad (http://www.datadryad.org/). The raw data were shared by Okamura et al.[6] The details of the study were described in a previous paper.[7] Briefly, all data were extracted from a population-based longitudinal study, which was performed in the Murakami Memorial Hospital in Japan. The study included 15,464 participants (8430 males and 7034 females) without diabetes at baseline, who were recruited between 2004 and 2015. The median follow-up durations were 5.8-year for males and 5.1-year for females.

Data Description

Variables from the raw data included baseline information, follow up duration, and incident T2DM. The baseline information regarding age, gender, smoking and alcohol habits,

Table 3 Risk Factors of Type 2 Diabetes According to the Cox Proportional Hazards Regression Model in Males

Variables	Univariate Analysis		Multivariate Analysis (Model 1)		Multivariate Analysis (Model 2)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age						
≤40 yrs	Reference		Reference		Reference	
41–50 yrs	1.846 (1.279–2.665)	0.001	1.621 (1.122–2.341)	0.010	1.424 (0.984–2.061)	0.061
≥51 yrs	3.132 (2.146–4.573)	<0.001	2.566 (1.750–3.762)	<0.001	2.106 (1.432–3.096)	<0.001
Current smoking						
No	Reference		Reference		Reference	
Yes	1.570 (1.187–2.078)	0.002	1.838 (1.382–2.445)	<0.001	1.642 (1.232–2.190)	0.001
Alcohol consumption						
No	Reference					
Light	0.778 (0.519–1.164)	0.222				
Moderate	0.780 (0.500–1.216)	0.273				
Heavy	1.190 (0.708–2.002)	0.511				
Regular exercise						
Yes	Reference					
No	1.325 (0.888–1.978)	0.168				
Obesity						
No	Reference		Reference		Reference	
Yes	3.487 (2.635–4.614)	<0.001	2.237 (1.664–3.007)	<0.001	2.152 (1.600–2.893)	<0.001
Elevated blood pressure						
No	Reference		Reference		Reference	
Yes	2.685 (2.018–3.572)	<0.001	1.673 (1.247–2.244)	0.001	1.725 (1.284–2.318)	<0.001
Dyslipidemia						
No	Reference		Reference		Reference	
Yes	2.591 (1.954–3.435)	<0.001	1.619 (1.206–2.172)	0.001	1.512 (1.127–2.029)	0.006
FPG						
<100mg/dl	Reference		Reference		Reference	
≥100mg/dl	7.170 (5.230–9.829)	<0.001	5.403 (3.909–7.467)	<0.001	3.692 (2.643–5.156)	<0.001
HbA1c						
<5.6%	Reference				Reference	
≥5.6%	10.966 (8.258–14.561)	<0.001			5.603 (4.157–7.552)	<0.001

Abbreviations: Model 1, multivariate analysis without HbA1c; Model 2, multivariate analysis with HbA1c; HR, hazard ratio; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c.

physical activity, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c, fasting plasma glucose (FPG), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) were extracted.

Definitions

The appropriate cutoff value for age was determined by X-tile software version 3.6.1. Obesity was defined as a BMI of ≥25 kg/m.[2,7] Elevated blood pressure was defined as SBP≥130mmHg and/or DBP≥85mmHg. Dyslipidemia was defined as TG ≥150 mg/dL and/or HDL ≤40 mg/dL. Elevated FPG was defined as FPG≥100 mg/dL. Elevated HbA1c was defined as HbA1c ≥5.6%.[8] Incident T2DM was defined as HbA1c ≥6.5%, FPG ≥126 mg/dL or self-reported.[7]

Statistical Analyses

The statistical analyses were performed using SPSS 24.0 software (SPSS Inc, Chicago, IL) and R software version 3.6.1 (R Development Core Team; http://www.r-project.org). $P<0.05$ was considered statistically significant.

For nomogram development and validation, 70% of the participants were randomly assigned to the training set and 30% to the validation set. The characteristics of the two

Table 4 Risk Factors of Type 2 Diabetes According to the Cox Proportional Hazards Regression Model in Females

Variables	Univariate Analysis		Multivariate Analysis (Model 1)		Multivariate Analysis (Model 2)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age						
≤40 yrs	Reference		Reference		Reference	
41–54 yrs	2.300 (1.194–4.429)	0.013	1.629 (0.836–3.174)	0.152	1.369 (0.697–2.691)	0.362
≥55 yrs	6.509 (2.911–14.554)	<0.001	3.958 (1.741–8.999)	0.001	2.539 (1.097–5.874)	0.029
Current smoking						
No	Reference		Reference		Reference	
Yes	2.739 (1.299–5.778)	0.008	2.670 (1.263–5.648)	0.010	3.193 (1.502–6.788)	0.003
Alcohol consumption						
No	Reference					
Light	0.595 (0.145–2.439)	0.471				
Moderate	2.045 (0.639–6.543)	0.228				
Regular exercise						
Yes	Reference					
No	1.077 (0.530–2.188)	0.837				
Obesity						
No	Reference		Reference		Reference	
Yes	6.787 (4.014–11.477)	<0.001	3.720 (2.128–6.500)	<0.001	3.091 (1.754–5.446)	<0.001
Elevated blood pressure						
No	Reference					
Yes	3.155 (1.706–5.832)	<0.001				
Dyslipidemia						
No	Reference					
Yes	2.607 (1.183–5.746)	0.017				
FPG						
<100 mg/dl	Reference		Reference		Reference	
≥100 mg/dl	11.148 (6.705–18.535)	<0.001	6.941 (4.019–11.987)	<0.001	4.356 (2.470–7.680)	<0.001
HbA1c						
<5.6%	Reference				Reference	
≥5.6%	12.491 (7.406–21.065)	<0.001			6.242 (3.486–11.175)	<0.001

Abbreviations: Model 1, multivariate analysis without HbA1c; Model 2, multivariate analysis with HbA1c; HR, hazard ratio; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c.

sets were described and compared using the chi-square test or *t*-test. Variables for the development of the nomogram were selected by using multivariate Cox regression analysis. To evaluate the effect of HbA1c on incident T2DM, we developed two models: Model 1 was developed based on traditional risk factors at baseline; while in Model 2, HbA1c was added.

Nomogram validation consisted of two parts, discrimination, and calibration. Discrimination was evaluated using a concordance index (C-index). The time-dependent receiver-operating characteristic (ROC) curve analysis was carried out to assess the predictive performance at different times. Calibration was evaluated using the calibration plot.

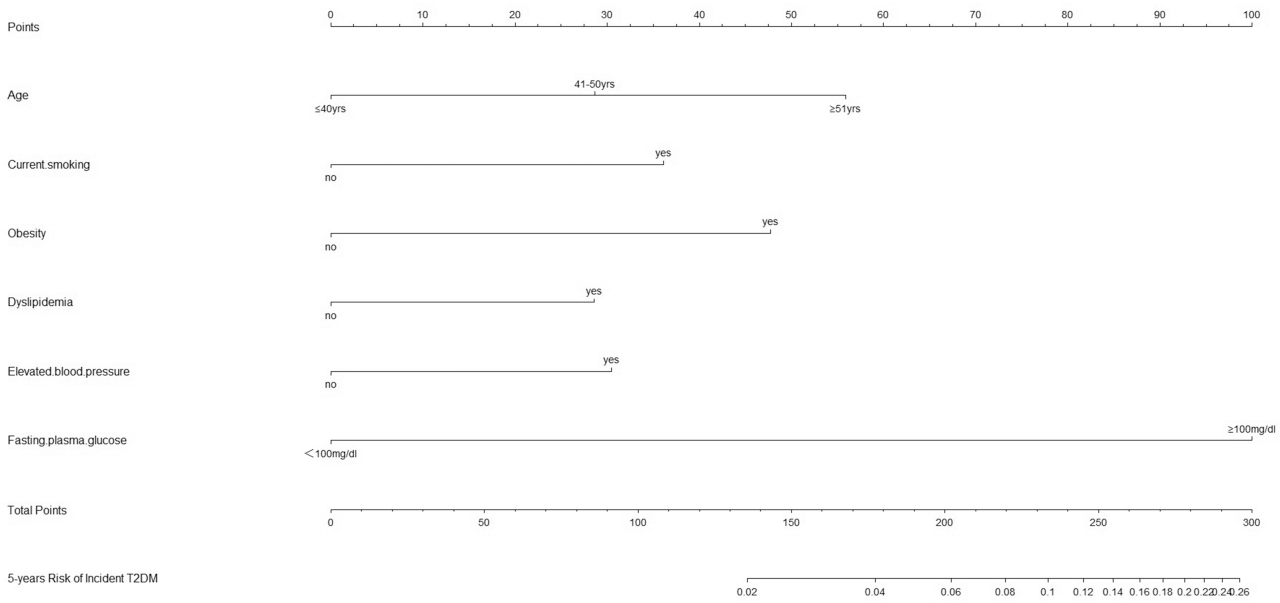

Figure 1 Nomogram for predicting 5-year incidence rate of T2DM in males (Model 1 without HbA1c).

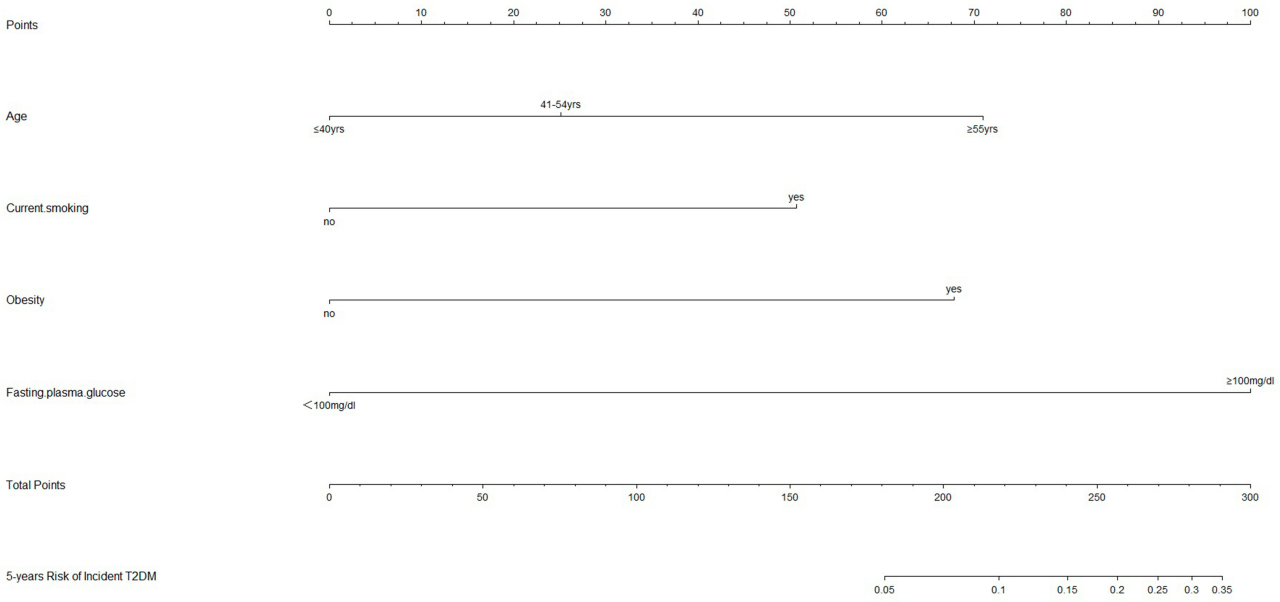

Figure 2 Nomogram for predicting 5-year incidence rate of T2DM in females (Model 1 without HbA1c).

Results

Characteristics of the Development and Validation Sets

In males, 11 participants without HDL-C were excluded, and 8419 males were entered in this study. The participants were divided into males and females because proportional hazards could not be assumed. The participants were randomly divided into training sets and validation sets (males: training set n=5893, validation set n=2526; females: training set n=4914, validation set n=2120). No statistically significant differences in baseline characteristics, follow-up time, and T2DM incidence were observed between the two sets (Tables 1 and 2).

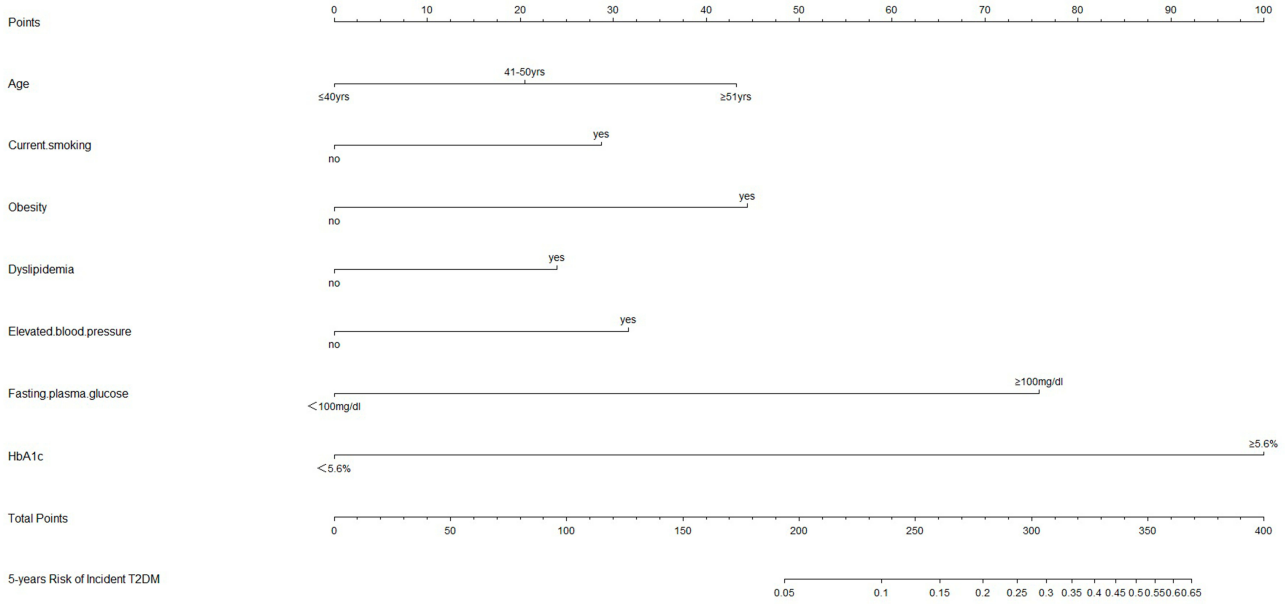

Figure 3 Nomogram for predicting 5-year incidence rate of T2DM in males (Model 2 with HbA1c).

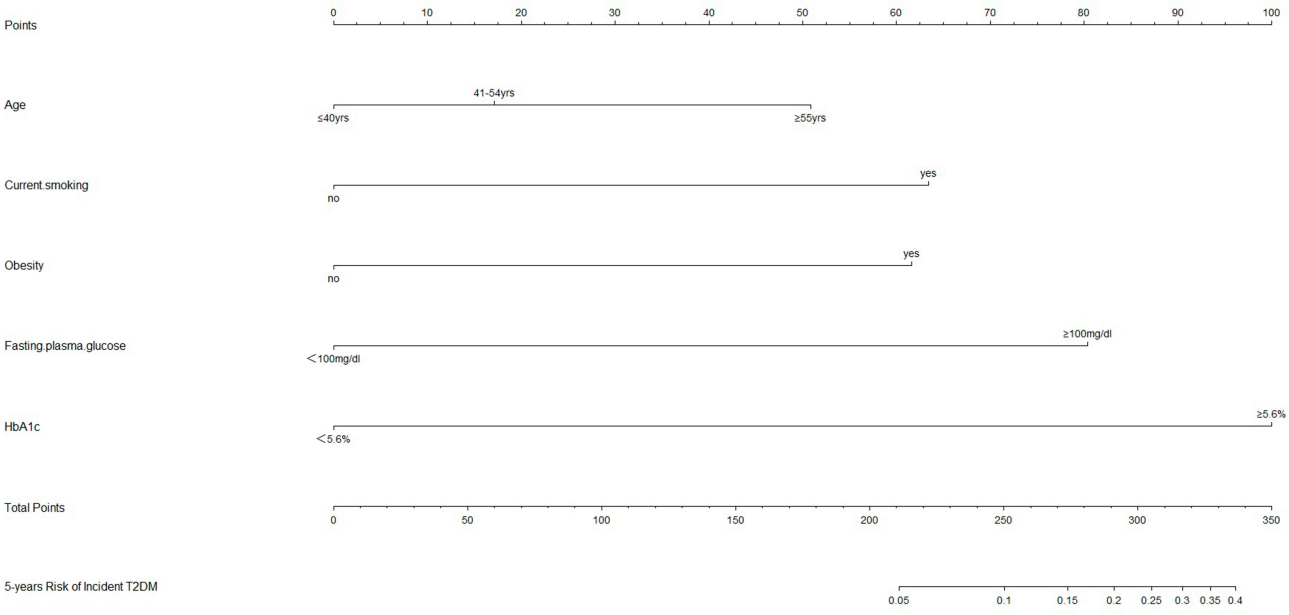

Figure 4 Nomogram for predicting 5-year incidence rate of T2DM in females (Model 2 with HbA1c).

Independent Predictors in the Training Set

The predictors were determined according to two steps. During the first step, the univariate analyses were performed. Multivariate analyses were performed using the significant risk factors determined in the univariate analysis (Tables 3 and 4). Multivariate Cox regression analysis (Model 1) showed that age, current smoking, obesity, elevated blood pressure, dyslipidemia, and elevated FPG were independent risk predictors in males, while age, current smoking, obesity, and elevated FPG were independent risk predictors in females. In Model 2, elevated HbA1c were added both in males and females.

Nomogram Construction and Internal Validation

Based on these results, we developed a nomogram for predicting 5-year incidence risk of T2DM. The nomogram showed that FPG had the largest contribution to prognosis in Model 1 (Figures 1 and 2). In Model 2, HbA1c had the largest contribution to prognosis, followed by FPG (Figures 3 and 4). In males, the C-index was 0.824 (95% CI: 0.795–0.853) in Model 1 and 0.867 (95% CI: 0.840–0.894) in Model 2. In females, the C-index was 0.830 (95% CI: 0.770–0.890) in Model 1 and 0.856 (95% CI: 0.795–0.917) in Model 2. The calibration curves for 5-year T2DM-free probability showed excellent agreement between the predicted possibility and the actual observation in both Model 1 and Model 2 (Figures S1 and S2). The results of time-dependent ROC analyses are shown in Figures 5 and 6. The area under curve (AUC) values of Model 2 to predict T2DM development was higher than those of the Model 1, at every time point, and the differences between two models were significant from 2 years to 5 years follow-up durations in males ($P<0.05$).

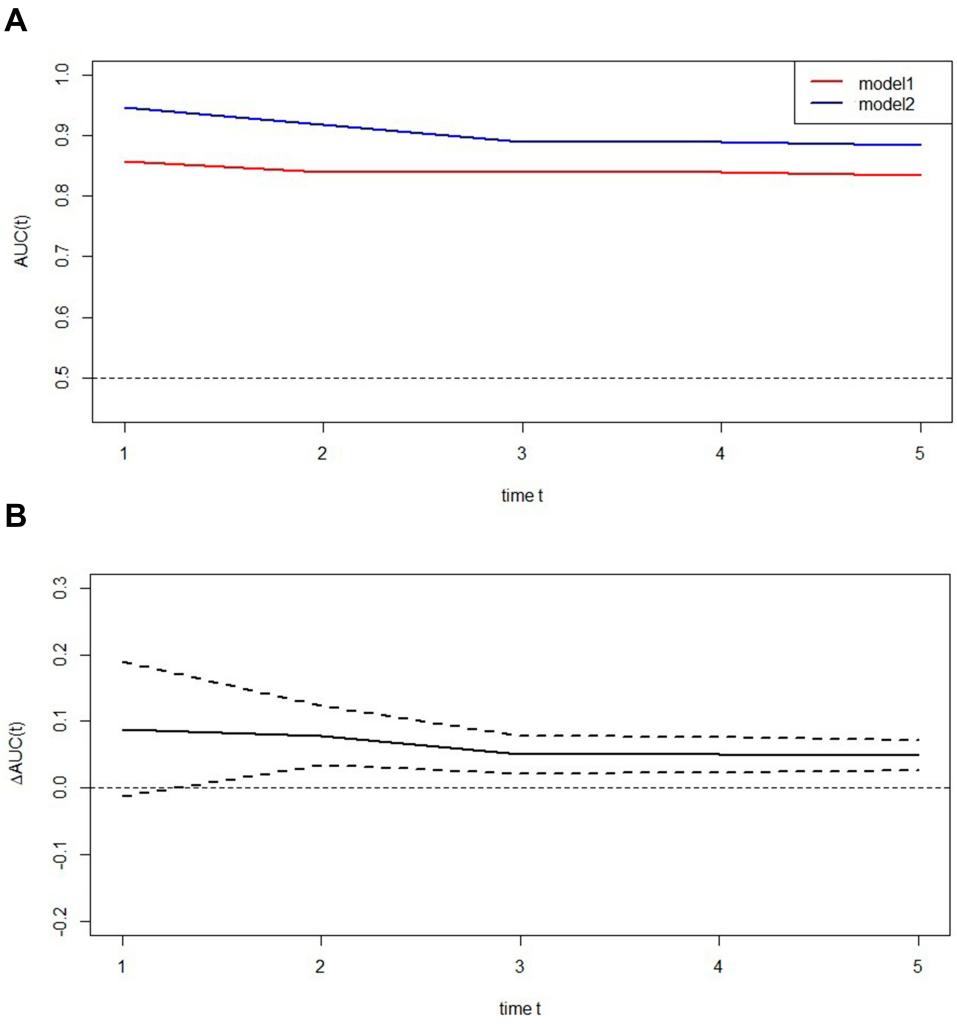

Figure 5 Time-dependent receiver-operating characteristic (ROC) curves of two models in males. (**A**) ROC curves of two models. (**B**) The difference of area under curve (AUC) values between the two models.

In the validation set, the C-index was 0.800 (95% CI: 0.747–0.854) in Model 1 and 0.862 (95% CI: 0.821–0.903) in Model 2 in males. The C-index was 0.838 (95% CI: 0.738–0.938) in Model 1 and 0.874 (95% CI: 0.775–0.972) in Model 2 in females. The results of time-dependent ROC and calibration curves were similar to the results of the training set.

Discussion

Nomogram is a useful tool for screening the risk of developing T2DM. Similar to previous nomograms,[2–4] traditional risk factors can accurately predict the risk of T2DM. In this study, we found that HbA1c can further improve the accuracy of the existing nomogram (which includes traditional risk factors) when assessing the risk of T2DM.

HbA1c can be used as a predictor of T2DM, gestational diabetes, diabetic complication and response to diabetes medication.[9–12] Krabbe et al found that the power of risk scores and HbA1c for predicting the risk of incident T2DM were similar.[5] A more extensive prospective open cohort study conducted in England found that either FPG or HbA1c could elevate the discrimination of a predictive model for 10-year risk of T2DM. However, in the present study, FPG and HbA1c were not used in one model.[13] In a Japanese study, the risk score for predicting the 3-year incidence of T2DM was markedly improved by incorporating FPG and HbA1c.[14] Kowall et al suggested that HbA1c could enhance the prediction of T2DM.[15] Nevertheless, the effects of HbA1c on the prediction model, including FPG, were inconsistent. In Atherosclerosis Risk in Communities study, HbA1c improved the predictive performance of the

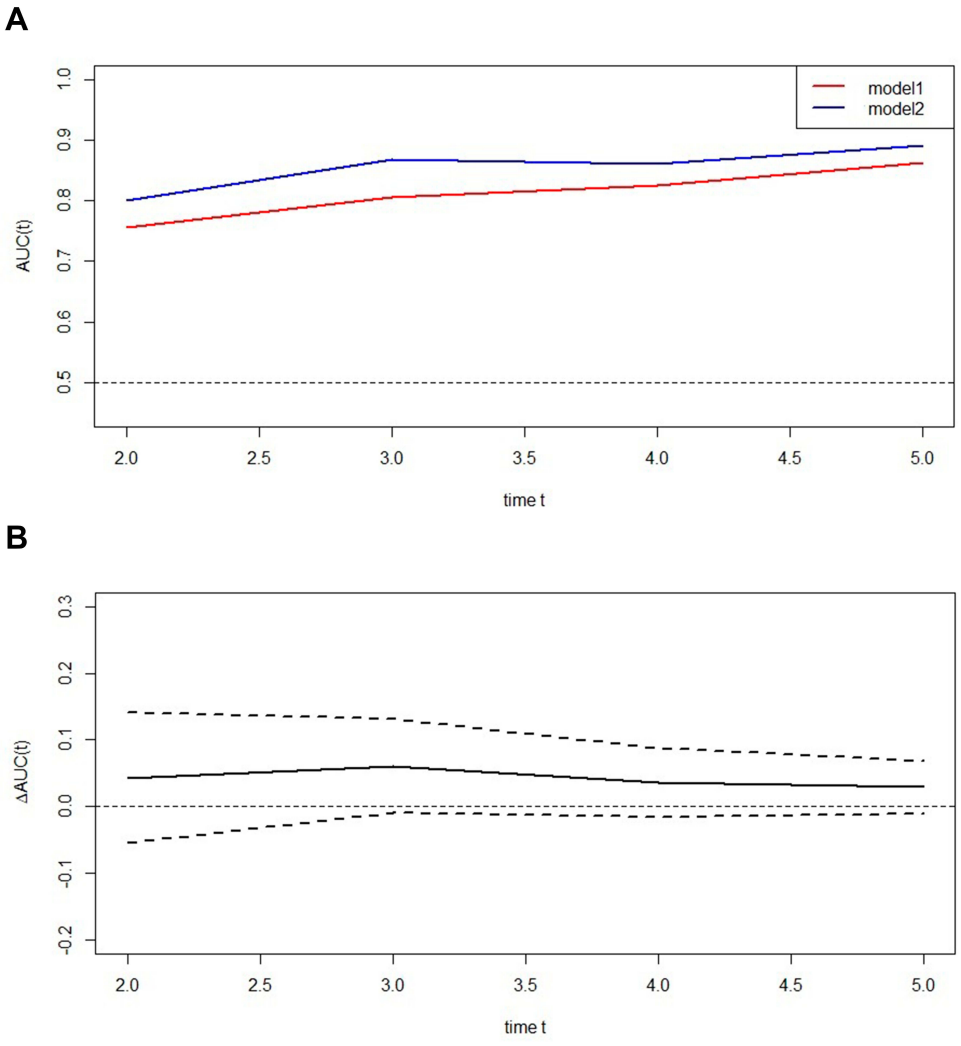

Figure 6 Time-dependent receiver-operating characteristic (ROC) curves of two models in females. (**A**) ROC curves of two models. (**B**) The difference of area under curve (AUC) values between the two models.

model, including FPG. Opposite results were found in the Framingham Heart Study.[9] In our study, we developed a nomogram by combining traditional risk factors, FPG, and HbA1c. Increased C-index and higher AUC values were found in nomogram that included HbA1c. The use of HbA1c has the advantage of not requiring a fasting status and possibility to be performed throughout a routine blood examination.[16]

HbA1c is correlated with both fasting and postprandial hyperglycemia. Postprandial plasma glucose is more strongly related to HbA1c than FPG in well-controlled T2DM patients. In contrast, FPG was the main contributor to the HbA1c in poorly controlled T2DM patients.[17,18] Postprandial plasma glucose accounts for approximately 80% of HbA1c when HbA1c is <6.2%.[18] In our study, the levels of HbA1c were about 5.2%. FPG was related to HbA1c, but FPG only accounted for approximately 10% of HbA1c (see Supplementary Materials). That means HbA1c may more accurately reflect postprandial plasma glucose. Postprandial plasma glucose was a significant prognostic indicator of an increased risk of incident diabetes.[19] That might be why HbA1c can significantly improve the predictive ability of the model, including FPG. Compared with postprandial plasma glucose, HbA1c can be tested with FPG at the same time.

This study has a few limitations. Firstly, some risk factors, such as a family history of T2DM, were not included in the nomogram; however, the validation of the nomogram based on the current risk factors has demonstrated a good performance. Secondly, we performed an internal validation in our study. There were racial differences in the performance of prediction models for incident T2DM,[20] thus, the proposed nomogram should be validated in other populations.

In conclusion, the proposed nomogram can accurately predict the risk of T2DM. Compared with the traditional nomogram, HbA1c can improve the performance of nomograms for predicting the 5-year incidence of T2DM.

Disclosure

The authors report no conflicts of interest in this work.

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