Preventive Medicine Reports 24 (2021) 101618

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

New risk score model for identifying individuals at risk for diabetes in southwest China

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ARTICLE INFO

Keywords:
Diabetes
Prediction
Nomogram
Risk score model
Chinese population

ABSTRACT

The prevalence of diabetes is increasing rapidly and becoming a major public health issue worldwide. We aimed to develop a novel nomogram model for long-term diabetic risk prediction in a Chinese population. A prospective cohort study was performed on 687 nondiabetic individuals who underwent routine physical examination in 1992 and 2007. Using the least absolute shrinkage and selection operator model to optimize feature selection. Multiple Cox regression analysis was performed, and a simple nomogram was constructed. The area under receiver operating characteristic curve (AUC) and calibration plot were conducted to assess the predictive accuracy of the model. The model was subjected to bootstrap internal validation. Of the 687 participants without diabetes at baseline, 74 developed diabetes during the follow-up time. This simple nomogram model was constructed by family history of diabetes, height, waist circumference, triglycerides, fasting plasma glucose and white blood cell count. The AUCs were 0.812 (95% CI: 0.729–0.895) and 0.794 (95% CI: 0.734–0.854) for 10-year and 15-year diabetic risk. The bootstrap corrected c-index was 0.771 (95% CI: 0.721–0.821). The calibration plot also achieved good agreement between observational and actual diabetic incidence. The stratification into different risk groups by optimal cut-off value of 12.8 allowed significant distinction between cumulative diabetic incidence curves in the whole cohort and several subgroups. We established and internally validated a novel nomogram which can provide individual diabetic risk prediction for Chinese population and this practical screening model may help clinicians to identify individuals at high risk of diabetes.

1. Introduction

The prevalence of diabetes is increasing rapidly and becoming a major public health issue worldwide. According to the latest report by the International Diabetes Federation, there were over 400 million individuals suffering from diabetes in 2017 (Cho et al., 2018). In China, the current situation is more serious. The overall prevalence of diabetes in mainland China increased from 10.9% in 2013 to 12.8% in 2017 based on the American Diabetes Association diagnostic criteria (Li et al., 2020; Ma, 2018), representing the largest number of individuals with diabetes than any other countries. Diabetes and its related complications constitute a tremendous disease burden on Chinese healthcare system (Liu et al., 2019). Previous researches have suggested that lifestyle modification could potentially prevent or delay the development of type 2 diabetes (Li et al., 2008). Therefore, there is always interest in investigating certain risk factors or risk models/scores in the prediction of future diabetes, and thus targeted preventive measures could be taken.

Generally speaking, risk models tend to perform better than single variable to predict diabetes. During the past decades, several risk prediction models integrating different major risk factors based on different populations have been proposed (Chien et al., 2009; Hu et al., 2020; Ko et al., 2010; Liu, Pan, & Jin, 2011; Liu et al., 2016; Lu et al., 2019; Wan et al., 2018; Wang et al., 2019; Wong et al., 2016; Xue et al., 2020). Those risk prediction models performed well in their own study cohort but may not suitable for other ethnicities or populations in other regions.

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https://doi.org/10.1016/j.pmedr.2021.101618
Received 22 August 2021; Received in revised form 13 October 2021; Accepted 22 October 2021
Available online 24 October 2021

At present, the established diabetes risk prediction models in China are derived from central or Northern or Northwest or Southern or Southeast part of China (Hu et al., 2020; Hunter, Boeri, Tully, Donnelly, & Kee, 2015; Liu et al., 2011; Liu et al., 2016; Lu et al., 2019; Wang et al., 2019; Xue et al., 2020), as well as Taiwan(Chien et al., 2009) and Hongkong district (Ko et al., 2010; Wan et al., 2018; Wong et al., 2016). There is no available risk prediction model with regards to the population in Southwest China. It is of great clinical significance to develop a risk prediction model for this specific subpopulation since the prevalence of total diabetes in Southwest China was as high as 13.3% and ranked the second place (Li et al., 2020).

The objective of this study is to construct and validate a nomogram model to identify high risk subjects for diabetes by using data of a prospective study cohort with 15-year follow-up in southwest China.

2. Methods

2.1. Study population

In 1992, supported by a project from China's eighth national 5-year research plan (the Chinese multiprovincial cohort study, 1992), medical professionals conducted a survey of cardiovascular disease risk factors according to the Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) protocol in an urban community, located in Chengdu, China. A total of 711 participants were enrolled at that time. In 2007, we conducted a survey for the same group of participants with the same methods. This survey was supported by the megaprojects of science research for China's 11th 5-year plan (trends in the incidence of metabolic syndrome and integrated control in China, 2007). We excluded 24 patients, who already had diabetes at baseline, from the study. Therefore, the present analysis consisted of 687 participants. Other detailed information of these participants has been reported elsewhere (He et al., 2012).

The surveys were approved by the Ministry of Health of China, as well as by the Ethics Committee of West China Hospital of Sichuan University. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All participants provided written informed consent.

2.2. Data collection

The data included demographic characteristics, anthropometric measurements, routine blood tests and biochemical examinations. The information of demographic characteristics was collected by standardized questionnaire. Anthropometric measurements included blood pressure, height, weight, waist circumference (WC) and hip circumference (HC). Routine blood tests included white blood cell count, hematocrit, and so on. Biochemical examinations included fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride. Peripheral blood was drawn from the antecubital vein in the morning after approximately 12 h of overnight fasting.

2.3. Related definitions

Diabetes was defined by self-reported history or FPG $\geq$ 7.0 mmol/L. Hypertension was defined as systolic blood pressure $\geq$ 140 and/or diastolic blood pressure $\geq$ 90 mmHg and/or taking antihypertensive medications. Smoking was defined as average cigarette consumption $\geq$ one/day. Drinking was defined as average intake of alcohol $\geq$ 50 g/day. Physical activity was defined as exercise one or more times per week and at least 20 min for each time.

2.4. Statistical analysis

All participants were divided into 2 groups, subjects with subsequent diabetes and subjects without subsequent diabetes. Characteristics of study population were described as mean (SD) or median (interquartile range) for continuous variables and number (percentage) for categorical variables. Baseline characteristics between groups were compared using the analysis of variance or Kruskal-Wallis tests for continuous variables, and the chi-square or Fisher exact tests for categorical variables.

Least absolute shrinkage and selection operator (LASSO) regression analysis was used for initial variable selection. Multivariable Cox regression analysis was applied to build a predicting model introducing the predictors selected from the LASSO regression analysis. A clinical prediction nomogram to assess the risk of diabetes was created based on the results from the final multivariable Cox regression. Calibration curves were plotted to calibrate the nomogram. Time-dependent receiver operating curve (ROC) was used to identify the best cut-off value. The area under ROC (AUC) was used to evaluate the discriminative ability. Additionally, the nomogram was subjected to 1000 bootstrap resamples for internal validation to assess the predictive

Table 1
Baseline characteristics.

Variable	All	Subsequent non-diabetic subjects (n = 613)	Subsequent diabetic subjects (n = 74)	p value
Age (years)	48.0 (44.0–53.0)	48.0 (44.0–53.0)	51.0 (46.0–54.0)	0.009
Male sex	399 (58.1%)	351 (57.3%)	48 (64.9%)	0.259
Smoking	248 (36.1%)	216 (35.2%)	32 (43.2%)	0.220
Alcohol intake	87 (12.7%)	75 (12.2%)	12 (16.2%)	0.431
Exercise	146 (21.3%)	132 (21.5%)	14 (18.9%)	0.712
Hypertension	104 (15.1%)	88 (14.4%)	16 (21.6%)	0.140
Height (cm)	161 (155–167)	161 (155–167)	160 (154–168)	0.800
Weight (kg)	60.0 (54.0–66.0)	60.0 (54.0–66.0)	65.0 (56.2–72.0)	<0.001
Waist (cm)	76.0 (71.0–82.0)	75.0 (70.0–81.0)	80.5 (76.0–87.0)	<0.001
Hip (cm)	92.0 (88.0–96.0)	92.0 (88.0–95.0)	95.0 (90.2–97.8)	0.001
BMI (kg/m^2)	23.2 (21.4–25.1)	23.1 (21.2–24.9)	24.8 (22.9–27.0)	<0.001
WHR	0.83 (0.78–0.87)	0.82 (0.78–0.87)	0.86 (0.83–0.89)	<0.001
SBP (mmHg)	110 (104–120)	110 (104–120)	120 (107–129)	0.021
DBP (mmHg)	72.0 (70.0–80.0)	72.0 (70.0–80.0)	74.0 (70.0–80.0)	0.095
FPG (mmol/L)	4.22 (3.78–4.72)	4.00 (3.78–4.72)	4.50 (4.00–5.17)	<0.001
TC (mmol/L)	4.44 (3.97–4.99)	4.29 (3.93–4.99)	4.44 (4.27–4.99)	0.023
TG (mmol/L)	1.86 (1.51–2.39)	1.82 (1.51–2.30)	2.39 (1.73–3.09)	<0.001
LDL-C (mmol/L)	2.22 (1.73–2.74)	2.20 (1.73–2.73)	2.41 (1.64–2.87)	0.387
HDL-C (mmol/L)	1.19 (1.06–1.37)	1.24 (1.06–1.37)	1.16 (0.98–1.36)	0.007
WBCC ($\times 10^9$/L)	5.50 (4.90–6.60)	5.50 (4.80–6.50)	5.80 (5.10–6.77)	0.051
Fibrinogen (g/dL)	0.41 (0.34–0.45)	0.41 (0.34–0.45)	0.41 (0.32–0.46)	0.579
Hematocrit (%)	44.0 (40.5–47.0)	44.0 (40.2–47.0)	45.0 (41.1–47.4)	0.068
Plasma viscosity (cP)	2.05 (1.91–2.44)	2.05 (1.91–2.49)	2.04 (1.91–2.27)	0.607
Family history of diabetes	26 (3.78%)	20 (3.26%)	6 (8.11%)	0.051

Data are presented as median with inter-quartile range, or number (percentage). Abbreviations: BMI = body mass index, WHR = waist to hip ratio, SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, TC = total cholesterol, TG = triglyceride, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, WBCC = white blood cell count.

Table 2
Variables included in the final diabetic risk model.

Variable	Beta coefficient	Change	HR (95% CI)	p value
Family history of diabetes	0.969	yes vs. no	2.64 (1.14–6.09)	0.023
Height (cm)	−0.050	per 1-cm increase	0.95 (0.92–0.98)	0.004
WC (cm)	0.106	per 1-cm increase	1.11 (1.08–1.15)	<0.001
TG (mmol/L)	0.189	per 1-mmol/L increase	1.21 (1.04–1.41)	0.016
FPG (mmol/L)	0.633	per 1-mmol/L increase	1.88 (1.40–2.53)	0.000
WBCC ($\times 10^9$/L)	0.357	per 10^9/L increase	1.43 (1.16–1.76)	0.001

HR = hazard ratio; CI = confidence interval
Other abbreviations as in Table 1.

accuracy. The best cut-off value was applied to the whole cohort and different subgroups, including age, sex and FPG, and the corresponding Kaplan-Meier survival curves were delineated.

All analyses were performed with R version 3.6.3 including the "compareGroups", "rms", "nomogramFormula", "DynNom", "survival", "survminer", "tidyverse", "timeROC"and "stats" packages (http://www.R-project.org). All tests were two sided, and p values < 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of participants

During 15 years of follow-up, 74 participants developed diabetes with an incidence rate of 10.8%. (Table 1) shows the demographic data of the whole cohort, stratified according to subjects with or without subsequent diabetes. Age, weight, WC, HC, body mass index (BMI), waist-to-hip ratio (WHR), systolic blood pressure (SBP), FPG, TC,

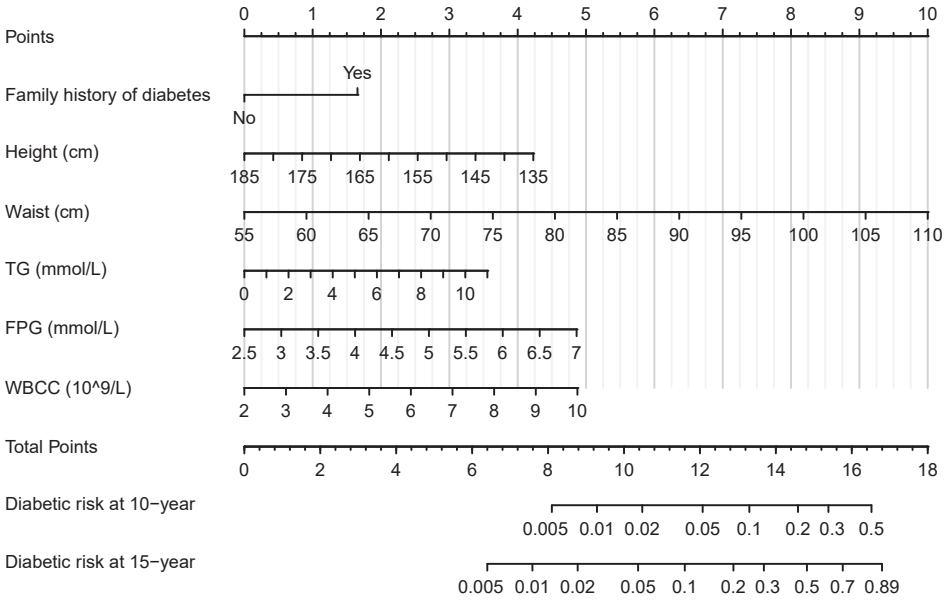

Fig. 1. Nomogram to predict the 10-year and 15-year risk of diabetes for the present study cohort. Abbreviations as in Table 1.

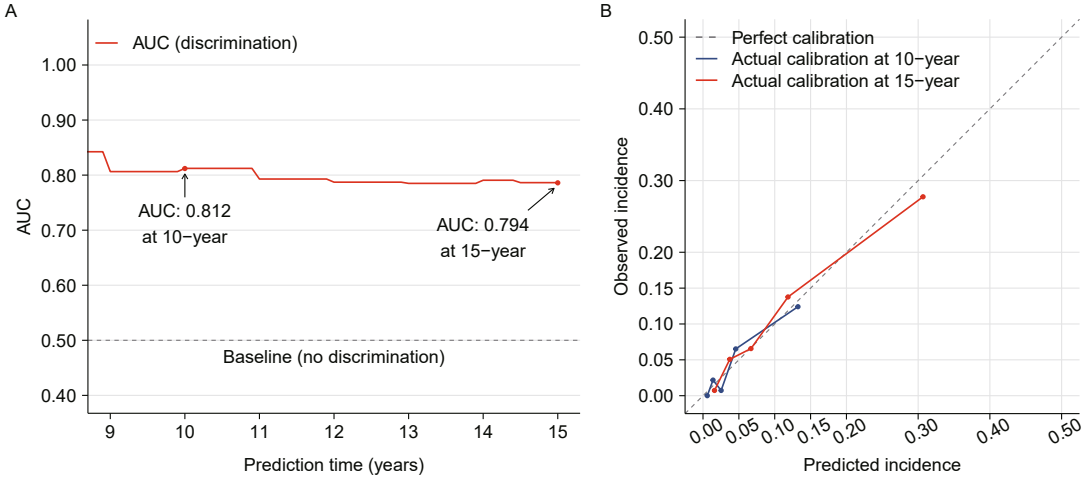

Fig. 2. The time-dependent ROC curves and calibration plots of the nomogram for 10-year and 15-year diabetic risk prediction. A: ROC curve, B: calibration plot. Abbreviations: AUC = area under the receiver operating curve; DM = diabetes mellitus.

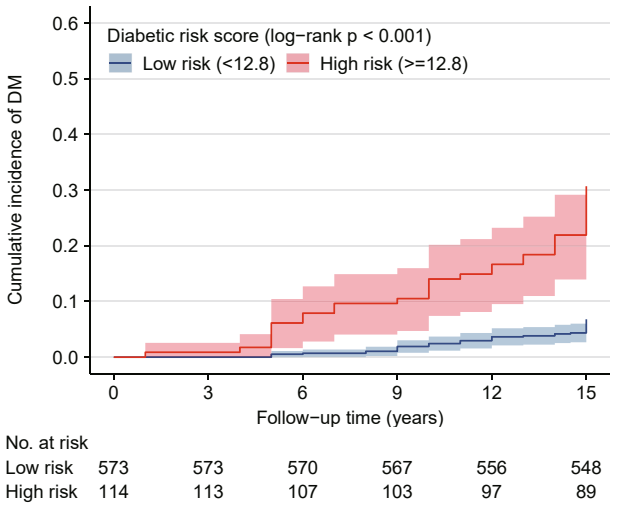

Fig. 3. Risk group stratification for the whole study cohort by optimal cut-off value. DM = diabetes mellitus.

triglycerides were significantly higher in individuals with subsequent diabetes, while HDL-C was significantly lower. No significant difference was observed in other variables between the two groups.

3.2. Selected predictors for model

Thirteen potential predictors were selected from the associated characteristic variables and were with nonzero coefficients in the LASSO regression analysis. These predictors included smoking, family history of diabetes, height, WC, SBP, TC, HDL-C, triglycerides, FPG, white blood cell count (WBCC), age, BMI and WHR. The multivariable Cox regression analysis based on backward stepwise approach revealed that the occurrence of diabetes was significantly associated with six variables, namely family history of diabetes, height, WC, triglycerides, FPG and WBCC (Table 2).

3.3. Predictive nomogram for the risk of diabetes

Based on the final multivariable Cox regression analysis, a nomogram was established which incorporated the aforementioned significant predictors for diabetes (Fig. 1). A total point was generated using family history of diabetes, height, WC, triglycerides, FPG, WBCC. Briefly, each variable was assigned a score on the point scale, By summing up the total score and locating it on the total points scale, we could draw a line straight down to 10-/15-year diabetic risk scale and determine the estimated probability of diabetes at each time point. Since there were only 3 newly developed diabetes at the fifth year of follow-up, we did not construct the 5-year diabetic risk scale in our study.

3.4. Validation of the nomogram

The AUCs were 0.812 (95% CI: 0.729–0.895) and 0.794 (95% CI: 0.734–0.854) for 10-year and 15-year diabetic risk, respectively (Fig. 2A). The internal validation based on bootstrapping yielded a c-index of 0.771 (95% CI: 0.721–0.821), which indicated helpful discrimination. The calibration plots also presented a good consistency between nomogram predictions and actual observations for 10-/15-year diabetic risk (Fig. 2B). To sum up the results from the above validation, the nomogram of the model showed good performance.

3.5. Performance of the nomogram in stratifying risk of subjects

The best cut-off value determined by ROC was 12.8. After applying the cut-off value to group the subjects in our study cohort, Kaplan-Meier analysis showed significantly distinctive cumulative incidence of diabetes between risk groups with log-rank $P < 0.001$ (Fig. 3). When further assessed in several subgroups, including age < 50 or ≥ 50, male or female, FPG < 5.6 mmol/L or ≥ 5.6 mmol/L, the Kaplan-Meier curves continued to present significant distinction, except for FPG ≥ 5.6 mmol/L ($P = 0.210$) (Fig. 4).

3.6. Development of webserver for easy access of our new model

An online version of our nomogram can be accessed at https://happensky.shinyapps.io/Diabetic_Risk_Score_in_Southwest_China/. Researchers and medical practitioners could easily estimate the diabetic probability across time by inputting the information of the related variables and reading output figures and tables generated by the webserver.

4. Discussion

In the present study, we developed a new nomogram model to help diabetic risk stratification for Chinese populations, especially those in southwest China. Risk factors included family history of diabetes, height, WC, triglycerides, FPG and WBCC. This model showed good performance in discrimination and calibration when internally validated. Subjects with a score of ≥ 12.8 were considered to be high-risk subjects and recommended for further diabetes screening, and take appropriate preventive strategies when necessary. To the best of our knowledge, this is the first diabetic risk prediction model designed for populations in southwest China. What's more, the variables in this model could be easily accessed in clinical practice, thus this model might be adopted as decision support for diabetes screening.

Different diabetic risk prediction models have been generated in white populations (Rahman, Simmons, Harding, Wareham, & Griffin, 2008; Wilson et al., 2007) or in other Asian populations, such as Thai (Aekplakorn et al., 2006) and Korean (Hajian-Tilaki, 2018). As we know, Diabetes is a metabolic disorder determined by both genetic and environmental factors(Ha et al., 2018; Murea, Ma, & Freedman, 2012). In this context, the predictive models are not applicable to other ethnic entities, even in individuals of the same ethnic background but living in distinctive cultural settings. In China, of the published models, some were from multiple centers. The New Chinese Diabetes Risk Score (NCDRS), based on data of the China National Diabetes and Metabolic Disorders Study, was developed by Zhou et al in 2013. It included age, sex, WC, BMI, SBP and family history of diabetes (Zhou et al., 2013). In 2018, Li et al generated non-lab and semi-lab nomograms for undiagnosed diabetes screening, the former one included age, sex, BMI, WC, hypertension, ethnicities, vegetable daily consumption and family history of diabetes, and the latter one further included 2 h postprandial glycosuria. The semi-lab nomogram outperformed non-lab nomogram and previous NCDRS in their SENSIBLE study cohort (Li et al., 2018). The two studies mentioned above were restricted by their cross-sectional designs. In a retrospective cohort study, Lin constructed a nomogram for predicting 5-year incidence of type 2 diabetes, which integrated age, sex, BMI, hypertension, dyslipidemia, smoking status and family history (Lin, Guo, Chen, & Zheng, 2020). In a recently published article, Shao et al incorporated not only demographic and anthropometric parameters but also dietary and biochemical data to develop four different large population-based type 2 diabetes predictive models (Shao et al., 2020). However, none of those models have been routinely used in clinical practice so far. The diversity of economic development, living conditions, dietary habits and climate across different areas of China is still a big concern to affect the predictive accuracy.

Given the large diversity and complexities of the Chinese population, some diabetic risk prediction models reflecting regional characteristics were proposed in certain parts of China(Chien et al., 2009; Hu et al., 2020; Ko et al., 2010; Liu et al., 2011; Liu et al., 2016; Lu et al., 2019; Wan et al., 2018; Wang et al., 2019; Wong et al., 2016; Xue et al., 2020)

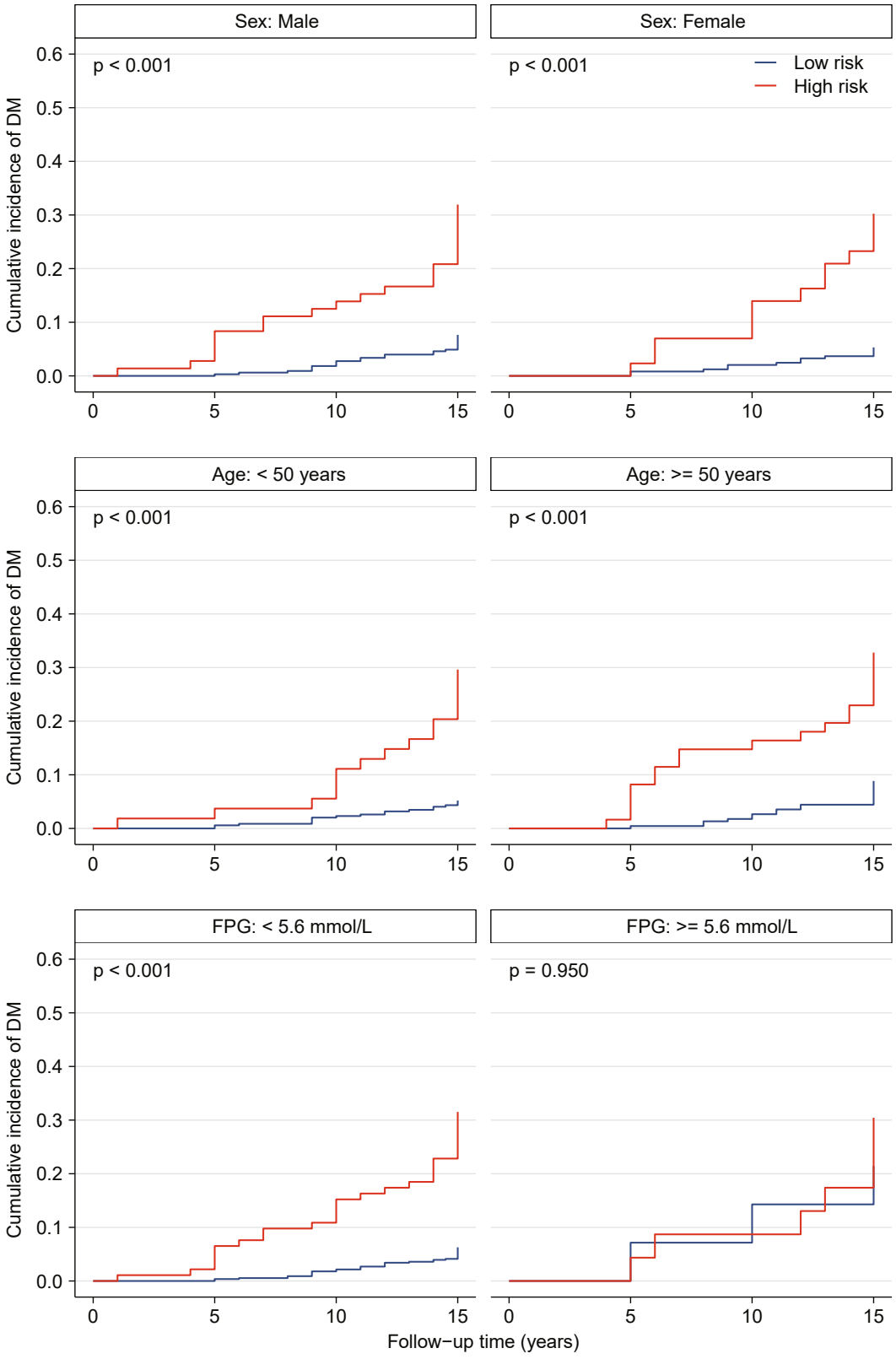

Fig. 4. Risk group stratification for several subgroups by optimal cut-off value. DM = diabetes mellitus.

except the Southwest part. The present study filled this gap and mainly used for the long-term diabetes prediction. Our prediction model provided relatively high AUCs for 10-year (0.812, 95% CI: 0.729–0.895) and 15-year (0.794, 95% CI: 0.734–0.854) diabetic risk. Although the bootstrap corrected c-index slightly decreased (0.771, 95% CI: 0.721–0.821), it still indicated adequate discrimination. The calibration plot also demonstrated good agreement between prediction and actual observation. When the participants were grouped by optimal cut-off value of 12.8, our model managed to stratify individuals who are at high risk to develop diabetes from those who are at low risk. The results remained consistent when explored in different subgroups, except for subjects with prediabetes (FPG $\geq$ 5.6 mmol/L), which could possibly be explained by the limited number of participants in this category.

There are some differences in variables between our diabetes risk prediction model and other previously established models. Our model did not include age, sex, BMI, and hypertension or blood pressure, which were known risk factors for T2D and usually included in other prediction models (Ko et al., 2010; Liu et al., 2011; Liu et al., 2016; Lu et al., 2019; Wan et al., 2018; Wang et al., 2019; Xue et al., 2020). Of note, our prediction model included height and WBCC, which were not common in other prediction models. Nonetheless, it is acceptable for those differences since the variables may vary in terms of intensity or distribution across different derivation cohorts.

This study may be of great public health implications : the components of the risk score are widely available to the public, and the measurement is easy and rapid, and it can be tested even in a community hospital. As an effective and cheap health promotion tool, specially the online version, the risk score can reach a large lay population in a short time period, spreading through short message, WeChat, media, internet and primary care clinics. As a result, the widespread use of the risk score may raise the public awareness of their diabetic risk significantly, as shown by a previous work (Zhang et al., 2012). This may prompt them to adopt early lifestyle interventions, which are associated with the reduction in type 2 diabetes incidence, as shown in the Finnish Diabetes Prevention Study (Tuomilehto et al., 2001), the US Diabetes Prevention Program (Knowler et al., 2002) and the Da Qing Diabetes Prevention Outcome Study (Pan et al., 1997). In addition, further researches in the larger population are needed to determine which subgroups could benefit from the use of the risk score.

The present study is the first diabetes prediction model specifically designed for populations in Southwest China. The performance and internal validation of the model is satisfactory. The study has several limitations. Firstly, dietary habits as a critical determinant for diabetes were not collected in our study since it is difficult to assess precisely. Secondly, self-reported diabetes and FPG but not oral glucose tolerance test (OGTT) or Hemoglobin A1c (HbA1c) were used to define the incidence of diabetes and to exclude individuals without diabetes at baseline. This is likely to result in some biases in the estimation of diabetic risk and hence the performance of our model. However, FPG is more widely used in general health care settings since OGTT and HbA1c are more expensive and time-consuming. In addition, the study had a relatively small sample size. External validation of a large population based on multicenter is required.

In conclusion, we have constructed a novel nomogram model for long-term diabetic risk prediction in a Chinese population. This practical screening tool should enhance individual's awareness, contributing to identify high-risk individuals and improve preventive strategies. Further studies are needed to evaluate the utility and feasibility of this model in larger populations.

Funding

This study was supported by a grant from National Key R&D Program of China (grant number: 2017YFC0910004), the National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Z20192010), the National Natural Science Foundation of China (Grant number: 81600299), a project from China's eighth national 5-year research plan (Grant no: 85-915-01-02), and the megaprojects of science research for China's 11th 5-year plan (Grant no: 2006BAI01A01).

CRediT authorship contribution statement

Liying Li: Data curation, Writing – original draft, Contribution. **Ziqiong Wang:** Data curation, Writing – original draft, Software. **Muxin Zhang:** Manuscript revise. **Haiyan Ruan:** Visualization. **Linxia Zhou:** Investigation. **Xin Wei:** Software, Validation. **Ye Zhu:** Supervision, Validation. **Jiafu Wei:** Writing – review & editing. **Sen He:** Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank all staff members for data collection, data entry and monitoring in this study and all funding sources.

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