Received: 21 April 2022 | Revised: 19 October 2022 | Accepted: 16 January 2023

DOI: 10.1002/dmrr.3616

WILEY

RESEARCH ARTICLE

Development and validation of a risk prediction model for the recurrence of foot ulcer in type 2 diabetes in China: A longitudinal cohort study based on a systematic review and meta-analysis

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Funding information

National Natural Science Foundation of China, Grant/Award Number: 81973614; The Science & Technology Development Fund of Tianjin Education Commission for Higher Education, Grant/Award Number: 2018KJ047

Abstract

Aims: To develop and validate a risk prediction model for Chinese patients with type 2 diabetes with the recurrence of diabetic foot ulcers (DFUs) based on a systematic review and meta-analysis.

Methods: A prospective analysis was performed with 1333 participants and followed up for 60 months. Three models were analysed using a derived cohort. The risk factors were screened using meta-analysis and logistic regression, and the missing variables were interpolated by multiple imputation. The internal validation was performed using the bootstrap procedure, and the validation cohort was applied to the external validation. The performance of the model was evaluated in the area under the discrimination Receiver Operating Characteristic Curve (ROC). Calibration and discrimination methods were used for the validation cohort. The variables were selected according to their clinical and statistical importance to construct the nomograms.

Results: Three models were developed and validated. Model 1 included seven social and clinical indicators like sex, diabetes mellitus duration, previous DFU, location of ulcer, smoking, history of amputation, and foot deformity. Model 2 included four more indicators besides those in Model 1, which were statin agents used, antiplatelet agents used, systolic blood pressure, and body mass index. Model 3 added further laboratory indicators to Model 2, such as LDL-C, HbA1C, fibrinogen, and blood urea nitrogen. In the derivation cohort, 20.1% (206/1027) participants with DFU recurred as compared to the validation cohort, which was 38.2% (117/306).

Meijun Wang, Dong Chen and Hongmin Fu contributed equally to this study.

Liming Chen and Bai Chang contributed equally to this study.

The areas under the curve in the derivation cohort for Models 1–3 were 0.781 (0.744–0.817), 0.843 (0.813–0.873), and 0.899 (0.876–0.922), respectively. The Youden indexes for Models 1–3 were 0.430, 0.559, and 0.653, respectively. Model 3 showed the highest sensitivity and specificity. All models performed well for both discrimination and calibration.

Conclusions: Models 1–2 were non-invasive, which indicate their role in general screening for patients at a high risk of recurrence of DFU. However, Model 3 offers a more specific screening due to its best performance in predicting the risk of DFU recurrence amongst the three models.

KEYWORDS
clinical prediction model, cohort study, diabetic foot ulcer, meta-analysis, recurrence

The prevalence of global diabetes mellitus (DM) was about 9.3% (463 million people) in 2019, and this figure was predicted to continue to rise to 10.9% (700 million) in 2045.[1] A strong body of articles[2–5] has shown that the recurrence rate of diabetic foot ulcer (DFU) was nearly 60% with a 3-year mortality rate of 33.1%, and the 5-year mortality rate could be as high as 45.8%. DFU has profound impacts on people with diabetes and their healthcare system due to the high prevalence of this complication and high rate of amputation-related hospitalisation.[6] Besides, the long-term costs associated with the wound treatment may become a financial burden to the healthcare system as well. The recurrence of DFU is a multifactorial outcome that could adversely affect the physiological status, mental health, and social function of individuals. Although the recurrence of DFU has attracted more and more attention, some studies[7–9] on the recurrence of DFU can only provide potential risk factors and cannot predict the risk degree through the current state of patients. Moreover, the risk models used in these studies are incomplete and usually lack verification. As we all know, meta-analysis is regarded as high-level evidence of evidence-based medicine.[10] Therefore, we aim to develop and validate the recurrence of DFU risk prediction models based on meta-analysis and a longitudinal cohort study. Comparing the advantages of these models through a multi-dimensional comprehensive evaluation will help to find an earlier intervention opportunity for DFU patients, promote their early and treatment, ultimately reduce the incidence of DFU recurrence, improve the life span and quality of life of diabetic patients, and reduce the medical economic burden.

1 | RESEARCH DESIGN AND METHODS

The inclusion criteria of the derived cohort were based on a meta-analysis. The selection criteria were set according to the meta-analysis; the flow chart of the selection method of meta-analysis research is shown in Figure S1. The characteristics of all these 14 cohorts in the meta-analysis are shown in Table S1. Quality assessment, details of risk factors and publication bias of risk factors are detailed in Tables S2, S3, and S4,[2,3,8,9,11–22] The forest plots of risk factors are shown in Figures S2–S10. This study was approved by the ethics committee of Tianjin Medical University Chu Hsien-I Memorial Hospital (Ethics No.: DXBYYhMEC2021-26), and all participants signed informed consent prior to the participation. Eligible participants were divided into two groups: group 1 (Derivation Cohort) and group 2 (Validation Cohort).

1.1 | Derivation cohort

A total of 2560 patients with DFU who were hospitalised at least twice in Tianjin Medical University Chu Hsien-I Memorial Hospital (baseline from 1 June 2016 to 1 June 2021) were considered for this study. In the derivation cohort, the participants aged between 30 and 90 years were included with full-thickness skin rupture that occurred at least above Wagner stage 1 at baseline,[23] and then had follow ups for more than 12 months. According to the exclusion criteria, patients were excluded due to age ($N = 345$), type 1 diabetes ($N = 135$), incomplete information ($N = 456$), acute and serious diabetic complications ($N = 256$), and follow-ups less than 12 months ($N = 341$). At the end, a total of 1027 eligible participants were included in the derivation cohort. The selection process is listed in Figure 1A.

1.2 | Validation cohort

A validation cohort was established to evaluate the validity of the model in terms of transportability and generalisation. Three hundred and six patients who were treated at Tianjin Medical University Chu Hsien-I Memorial Hospital from June 2016 to June 2017 and had ulcer healing after treatment were selected as research objects (306 of 341 patients completed follow-up). There were 35 patients were ineligible for follow-up according to the eligibility criteria. Telephone follow-ups commenced when the ulcers healed and to collect whether the ulcer recurred and specific relevant data every 1 year. The frequency of follow-ups varied from 1 year to 5 years. The specific flow chart is shown in Figure 1B.

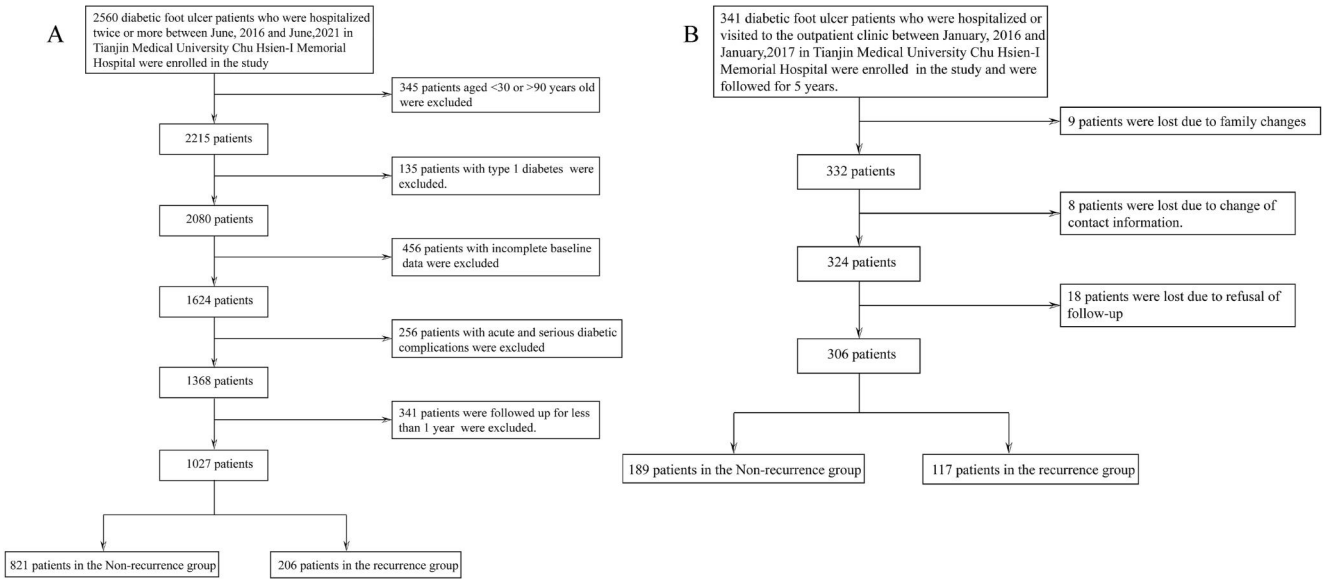

FIGURE 1 (A) Process for the selection of patients in the derivation cohort. (B) Process for the selection of patients in the validation cohort.

1.3 | Predictor variables

In the derivation cohort and validation cohort, a wide range of data was collected from the medical records of inpatient files as demonstrated in Table 1 except the frequency of follow-ups. The degree of ulcers, and the personal history were completed by the medical doctors. Past history was obtained at the first hospitalisation. Pathology parameters were collected at the fasting status according to the specifications. Smokers were defined as smoking more than 100 cigarettes in their lifetime.[24,25] Ulcer healing is defined as epithelial tissue healing for at least 4 weeks. Ulcer recurrence is defined as the occurrence of a new foot ulcer in patients with a previous history of foot ulcer, regardless of whether the site of this ulcer is the same as the previous one and how long the last healed ulcer is separated from this one. We grouped the participants as the following age groups: 30–40, 41–50, 51–61, 61–70, 71–80, 81–90 years old; smoking: smoking and never quitting smoking; duration of diabetes: 0–10, 11–20, 21–30, 31–40, and over 40 years; foot deformity: normal; light (flat foot, foot arch, hallux valgus, and hammer toe); medium (hallux stiffness, prominent metatarsal bone, and/or claw like toe) and; severe (Charcot's foot, front foot amputation, and/or clubfoot).

The missing data were extracted from the analysis as it was vital for the multiple interpolation method and for the modelling of key variables according to guidelines. The JAMA guide[26] suggests to report the loss phenomenon in the results, for example, information withdrawn from clinical trials or unavailability due to loss of follow-ups or in observational studies. The considerations of multiple imputation (MI) were also suggested to interpolate the lost data. At present, this method is known to be the most effective method to reduce bias, and can produce a more applicable and reliable model in clinical practice.[27] Some important variables include body mass index (BMI), systolic blood pressure (SBP), D-dimer, fibrinogen (FIB), 24-h urinary microalbumin, 24-h urinary protein, HbA1c, TG, TC, LDL-C, HDL-C, and Serum creatinine. The missing proportion of these variables is between 1% and 50%. The multivariate normal distribution chain equation was multi-interpolated (MI = 20) to prevent the loss of variables.[26,28] Finally, we repeated the analysis 20 times for each variable, pooled effect sizes using Rubin's rule, and calculated the Monte Carlo Error (MCE). After performing univariate and multivariate regression, the results before and after imputation were compared, that is, sensitivity analysis, and a stable post-imputation dataset was finally obtained.

1.4 | Risk factor selection and modelling

Model 1 was established directly using the risk factors identified from the meta-analysis for modelling, including sex, DM duration, previous DFU, location of ulcer, smoker, history of amputation, and foot deformity. Model 2 was built on the basis of Model 1. The logistic univariate regression analysis was applied to select variables in the complete data set, including those with p value < 0.1 in the logistic multivariate regression, screened those with p value < 0.05 for risk factors, and then eliminated the laboratory indicators. Model 3 was built on the basis of Model 2 and contained laboratory indicators.

1.5 | Model development and validation

Logistic regression was used to screen for risk factors, and the prediction model equation was constructed by multivariate logistic regression. However, the multivariable models were internally validated through a bootstrap procedure (sampling with

TABLE 1 Baseline characteristics of study participants

	Derivation (n = 1027)	Missing values n (%)	Validation (n = 306)	Missing values n (%)	p
Follow-up (months)	29.7 (20.0–40.0)		43.0 (13.0–49.0)		0.15
Socio-demographics					
Males [n (%)]	705 (68.6)		200 (65.4)		0.28
Age (years)	63.1 ± 11.9		63.7 ± 10.3		0.96
DM duration (years)	15.0 (9.0–20.0)		13.0 (7.8–20.0)		0.06
Smoker [n (%)]	507 (49.4)		96 (31.4)		<0.01
Ulcer location [n (%)]					<0.01
Plantar	182 (17.7)		96 (31.4)		
Dorsal	845 (82.3)		210 (68.6)		
Foot deformity [n (%)]					0.015
Absent	865 (84.2)		238 (77.8)		
Mild	123 (12.0)		44 (14.4)		
Moderate	15 (1.5)		9 (2.9)		
Severe	24 (2.3)		15 (4.9)		
History of amputation [n (%)]	552 (53.7)		153 (50.0)		0.25
Previous DFU [n (%)]	475 (46.3)		136 (44.4)		0.58
Clinical parameters					
BMI (kg/m^2)	25.5 ± 4.3	510 (50.0%)	26.0 ± 4.1	104 (34.0)	0.07
SBP (mmHg)	139.6 ± 19.7	7 (0.7%)	141.7 ± 19.0		0.10
DBP (mmHg)	77.9 ± 10.4		78.2 ± 10.4		0.66
BUN (mmol/L)	6.0 (4.6–7.7)		5.7 (4.5–7.1)		0.18
D-Dimer (mg/L)	0.6 (0.4–1.1)	11 (1.1%)	0.7 (0.3–1.2)		0.78
FIB (g/L)	3.8 (2.9–5.0)	11 (1.1%)	3.8 (3.1–5.2)		0.18
24-h urinary microalbumin (mg/24 h)	87.9 (18.3–300)	102 (9.9%)	43.8 (15.5–169.7)		<0.01
24-h urinary protein (g/24 h)	0.3 (0.1–1.7)	102 (9.9%)	0.15 (0.1–0.9)		<0.01
HbA1c (%)	9.1 ± 2.1	9 (1.0%)	8.9 ± 2.0		0.06
Fasting blood glucose (mmol/L)	8.8 ± 3.3		8.1 ± 2.4		<0.01
2-h postprandial glucose (mmol/L)	12.8 ± 4.0		11.4 ± 3.4		<0.01
TG (mmol/L)	1.3 (1.0–1.8)	22 (2.1%)	1.3 (1.0–1.9)		0.13
TC (mmol/L)	4.4 (3.6–5.2)	22 (2.1%)	4.4 (3.6–5.3)		0.48
LDL-C (mmol/L)	3.1 (2.4–3.7)	22 (2.1%)	3.0 (2.5–3.6)		0.67
HDL-C (mmol/L)	1.0 (0.8–1.2)	22 (2.1%)	1.1 (0.9–1.3)		<0.01
SCR (umol/L)	72.3 (59.5–93.9)	17 (1.7%)	74.3 (59.0–89.1)		0.57
Comorbidities					
Diabetic retinopathy [n (%)]	573 (55.8)		164 (53.6)		0.50
Diabetic kidney disease [n (%)]					<0.05
Absent	479 (46.6)		162 (52.9)		
Grade 1	191 (18.6)		23 (7.5)		
Grade 2	57 (5.6)		8 (2.5)		
Grade 3	114 (11.1)		52 (17.0)		
Grade 4	40 (3.9)		22 (7.2)		

TABLE 1 (Continued)

	Derivation (n = 1027)	Missing values n (%)	Validation (n = 306)	Missing values n (%)	p
Grade 5	146 (14.2)		39 (12.7)		
Diabetic peripheral neuropathy [n (%)]	1010 (98.3)		292 (96.2)		<0.01
Peripheral arterial disease	739 (72.0)		232 (75.8)		0.183
Treatment modalities					<0.01
Anti-diabetic therapy [n (%)]					
OAD	339 (33.0)		42 (13.7)		
Insulin	171 (16.7)		24 (7.8)		
OAD with insulin	517 (50.3)		240 (78.4)		
Statin lipid-lowering agents used [n (%)]	431 (42)		131 (43.0)		0.79
Antiplatelet agents used [n (%)]	422 (41.1)		122 (39.9)		0.70

Note: Data are presented as median (interquartile range), mean (SD), number (%).

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; FIB, fibrinogen; HDL-C, high density lipoprotein C; LDL-C, low density lipoprotein C; OAD, Oral Antidiabetic Drug; SBP, systolic blood pressure; SCR, Serum creatinine; TC, total cholesterol; TG, triglyceride.

replacement for 1000 iterations) to assess the bias-corrected estimates of predictability. The area under the curve (AUC) was calculated to evaluate the discrimination-ability of the model. The receiver Operating Characteristic Curve (ROC) was applied to calculate the AUC and its 95% Confidence interval (CI). The closer the AUC value was to 1, the higher the prediction effect of the model. When the AUC was above 0.7, it indicated a positive relationship between discrimination and predictability. Furthermore, the clinical effectiveness or practicability was evaluated through the clinical decision-making curve.

1.6 | Statistical analysis

The mean (± standard deviation [SD]) was used to describe the continuous variables of normal distribution, and the median (25th–75th percentile) to describe the continuous variables of non-normal distribution. The independent sample t-test was used for the continuity variables with normal distribution. In addition, the Mann–Whitney U test was used for the continuity variables with non-normal distribution. Meanwhile, Chi Square test was used for classification variables (2 × C). The discrimination of the prediction model was evaluated by AUC, and the calibration degree was evaluated using the calibration curve. The clinical efficacy was evaluated by decision clinical analysis. The nomograms and scoring tables were used to intuitively show the use of the model. For all risk factors, the odds ratio and 95% CI were calculated. For univariate logistic regression, the significance was set as bilateral $p < 0.1$, and for multivariate logistic regression, the significance was set as bilateral $p < 0.05$. SPSS 25.0 (IBM Corp) and Stata software (Version 15.0, Stata Corp) were used for statistical analysis. We use Stata software to perform multiple interpolation of data and modelling of interpolated data. The relevant installation package is mi estimate.

2 | RESULTS

2.1 | Baseline characteristics of the study population

A total of 1027 participants were included in the derivation cohort, whereas 306 were included in the validation cohort. The average ages for the derivation and validation cohorts were similar (63.1 vs. 63.7 years). The median follow-up time was 29.7 and 41.0 months for the two groups, respectively. The proportion of men was 68.6% and 65.4% respectively. The average values of HbA1c were 9.1% (76 mmol/mol) and 8.9% (74 mmol/mol), respectively, and the median duration of diabetes was 15 and 13 years. We estimated the parametric MCE for the imputation variables. The MCE of the coefficients shown in Table S5 were all close to or less than 10% of the standard errors of the coefficients; from this we can reasonably determine the statistical reproducibility of our results. Among the variables we are interested in, the validation cohort and the derivation cohort are generally similar in terms of sociodemographic characteristics, physical examination indicators and laboratory indicators (detailed in Table 1)

2.2 | Model development

We calculated the risk factors by univariate and multivariate logistic regression (detailed in Table 2), and the final statistically significant risk factors were as follows: Location of ulcer, Foot deformity, BMI, DM duration, SBP, blood urea nitrogen (BUN), FIB, HbA1c, LDL-C, Statin agents used and Antiplatelet agents used. According to the multicollinearity analysis, the variance inflation factor (VIF) for age and DM duration was 5.16 and 5.22, respectively, while all other variables had VIF < 2, so we excluded age as this risk factor. The 3

models we established were as follows, Model 1: the modelling of risk factors from the meta-analysis, including sex, DM duration, previous DFU, location of ulcer, smoker, history of amputation and foot deformity; Model 2 (excluding laboratory indicators): sex, DM duration, previous DFU, location of ulcer, smoker, history of amputation, foot deformity, statin agents used, antiplatelet agents used, SBP, and BMI; Model 3 (including laboratory indicators): sex, DM duration, previous DFU, location of ulcer, smoker, history of amputation, foot deformity, statin agents used, antiplatelet agents used, SBP, BMI, LDL-C, HbA1C, FIB, and BUN.

2.3 | Model discrimination

Table 3 shows the area and performance of each model under the ROC curve of the derivation and validation cohorts. All models showed a fair calibration and discrimination. The ROC curve is shown in Figure 2. The overall performance of Model 3 appeared to be the best, followed by Model 2 and Model 1. In the derivation cohort of Model 1, AUC was 0.781 (0.744–0.817), Youden index was 0.430, and sensitivity and specificity were 75.7% and 67.2%, respectively. The corresponding values of Model 1 in the validation cohort were 0.833 (0.782–0.884), 0.605, 73.5%, and 87.0%. The corresponding values for Model 2 in the derivation cohort were 0.843 (0.813–0.873), 0.559, 82.0%, and 73.8%. The corresponding values of Model 2 in the validation cohort were 0.849 (0.803–0.895), 0.546, 74.3%, and 80.3%. In the derivation cohort of model 3, the corresponding values were 0.899 (0.876–0.922), 0.653, 83.5%, and 81.9%. The corresponding values of Model 3 in the validation cohort were 0.860 (0.815–0.904), 0.473, 76.1%, and 85.5%.

2.4 | Model calibration

In the internal bootstrap verification, as shown in Figure 3A, the nomogram of the curve derived from Model 1 was close to the bias-corrected curve and the ideal curve, with a probability between 0 and 0.40. When the probability was higher than 0.40, Model 1 may slightly overestimate the probability of disease risk. As shown in Figure 3B,C, the derivation cohort of Models 2 and 3 fitted well and showed good calibration. In the external bootstrap verification, as shown in Figure 3D, when the probability is between 0–0.3 and 0.5–0.75, the prediction accuracy of Model 1 may be slightly lower or higher, but the overall 95% confidence interval was basically on the ideal curve. As shown in Figure 3E,F, the validation cohort of Models 2 and 3 fitted well and showed good calibration.

2.5 | Decision curve analysis

In order to compare the clinical practicability of the model, the decision curve analysis was carried out, as shown in Figure 4. The standard net benefit was displayed in the vertical distance from *Y* axis to *X* axis. The *X* axis shows the threshold value of diabetes (the threshold probability). Each line represented the clinical usefulness of each model. In our analysis, Models 1–3 showed better cost-effectiveness than no intervention. In our analysis, Models 1–3 showed better cost-effectiveness than no intervention. In the derivation cohort, these interventions proved useful when the absolute risk thresholds of Models 1 and 2 were about 75% and 85%, respectively, whereas Model 3 showed a higher net benefit. In the validation cohort, the absolute risk thresholds of Models 1–3 performed poorly (ranged: 0–0.18). When the three models were in the range of 0.18–1.00, they had higher clinical benefits.

2.6 | Nomograms

The nomogram provided a quantitative and convenient continuous scoring tool to help patients or doctors judge the risk of disease (Figure 5). The nomogram of Model 1 was sex, DM duration, previous DFU, location of ulcer, smoker, history of amputation and foot deformity to predict the risk of recurrence of DFU. The nomogram of Model 2 included all variables in Model 1 and drug treatment (antiplatelet agents used and statin agents used), SBP, and BMI were added. The nomogram of Model 3 included the variables in Model 2 and BUN, FIB, HbA1c, and LDL-C. In order to obtain the risk of recurrence of DFU, a vertical line was drawn from the values on the point scale to evaluate these points and then compared these points to obtain the value of each variable. The sum included the total score and matches the risk on the bottom axis.

3 | DISCUSSION

This study developed and validated three models to predict the risk of foot ulcer recurrence in Chinese patients with type 2 diabetes. Further validations in the two parts of data and various evaluations were conducted, and the possible deviation caused by missing data is corrected, which proves that the model is stable and has good prediction ability. In the interpolation data set, all three models achieved good discrimination and calibration in the derivation and validation cohort. Our results show that Model 1 based on meta-analysis performed well in clinical net benefit with good clinical application value. In contrast, Model 2 and Model 3 were significantly better than Model 1 in discrimination. It is important to note that Model 3 had the best discrimination amongst all, and the AUC of model 3 was 0.899 (0.876–0.922). Another key finding was the ability to enable a multi-dimensional monitoring and management for patients with DFU and provide an individual risk assessment through lifestyle and demographic characteristics. Thus, the flexible application of the three models can be used for monitoring to avoid or delay the recurrence of DFU.

At present, DFU presents four high characteristics: high recurrence rate, high disability rate, high amputation rate, and high economic burden. It will bring economic, psychological and social

TABLE 2 Logistic regression analysis in the derivation cohort

	Ulcer recurrence HR (95% CI)			
Variable	**Univariable**	***p*-Value**	**Multivariable**	***p*-Value**
Age	1.00 (0.99–1.02)	0.60		
Male	0.71 (0.52–0.98)	0.04	1.07 (0.69–1.66)	0.77
Smoking	1.06 (0.78–1.44)	0.72		
Location of ulcer				
Dorsal	Ref		Ref	
Plantar	1.99 (1.39–2.86)	<0.01	1.58 (0.97–2.60)	0.07
Foot deformity				
Absent	Ref			
Mild	6.31 (4.22–9.44)	<0.01	6.12 (3.58–10.46)	<0.01
Moderate	7.10 (2.53–19.93)	<0.01	8.55 (2.17–33.68)	<0.01
Severe	12.42 (5.20–29.65)	<0.01	14.21 (4.98–40.56)	<0.01
History of amputation	1.50 (1.10–2.05)	0.01	1.48 (0.98–2.23)	0.07
Previous DFU	1.62 (1.19–2.20)	<0.01	1.43 (0.95–2.16)	0.09
BMI	1.11 (1.07–1.15)	<0.01	1.11 (1.06–1.16)	<0.01
DM duration	1.07 (1.05–1.09)	<0.01	1.07 (1.04–1.09)	<0.01
SBP	1.02 (1.02–1.03)	<0.01	1.02 (1.01–1.04)	<0.01
DBP	1.00 (0.98–1.01)	0.70		
BUN	1.04 (1.00–1.07)	0.07	1.06 (1.01–1.12)	<0.05
D-Dimer	0.92 (0.80–1.07)	0.31		
FIB	1.42 (1.29–1.56)	<0.01	1.26 (1.11–1.44)	<0.01
24-h urinary microalbumin	1.00 (1.00–1.00)	0.51		
24-h urinary protein	1.02 (0.98–1.06)	0.37		
HbA1c	1.42 (1.31–1.53)	<0.01	1.42 (1.28–1.58)	<0.01
FBG	1.02 (0.97–1.07)	0.41		
2-h postprandial glucose	1.01 (0.97–1.04)	0.81		
TG	0.99 (0.83–1.18)	0.92		
TC	1.10 (0.97–1.24)	0.14		
LDL-C	1.83 (1.55–2.15)	<0.01	2.22 (1.75–2.81)	<0.01
HDL-C	1.41 (0.91–2.19)	0.13		
SCr	1.00 (1.00–1.00)	0.36		
DR	1.25 (0.92–1.71)	0.16		
DKD				
Absent	Ref			
Grade 1	1.47 (0.98–2.21)	0.06		
Grade 2	0.76 (0.35–1.66)	0.49		
Grade 3	0.99 (0.58–1.69)	0.96		
Grade 4	1.16 (0.52–2.60)	0.72		
Grade 5	1.69 (1.09–2.61)	0.02		

(Continues)

TABLE 2 (Continued)

Variable	Ulcer recurrence HR (95% CI)			
	Univariable	*p*-Value	Multivariable	*p*-Value
DPN	4.08 (0.54–30.90)	0.17		
Peripheral arterial disease	1.23 (0.39–3.64)	0.714		
Statin agents used	0.66 (0.48–0.90)	0.01	0.30 (0.19–0.48)	<0.01
Antiplatelet agents used	2.59 (1.89–3.54)	<0.01	3.10 (2.05–4.70)	<0.01

Note: Data are presented as median (interquartile range), mean (SD), number (%).

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CI, Confidence interval; DBP, diastolic blood pressure; DKD, Diabetic kidney disease; DPN, diabetic peripheral neuropathy; DR, Diabetic retinopathy; FGB, Fasting blood glucose; FIB, fibrinogen; HDL-C, high density lipoprotein C; HR, Hazard ratio; LDL-C, low density lipoprotein C; OAD, Oral Antidiabetic Drug; SBP, systolic blood pressure; SCR, Serum creatinine; TC, total cholesterol; TG, triglyceride.

TABLE 3 Prediction performance of the nomogram for estimating the risk of foot ulcer recurrence in type 2 diabetes

	Model 1		Model 2		Model 3	
	Derivation cohort	Validation cohort	Derivation cohort	Validation cohort	Derivation cohort	Validation cohort
AUC (95% CI)	0.781 (0.744–0.817)	0.833 (0.782–0.884)	0.843 (0.813–0.873)	0.849 (0.803–0.895)	0.899 (0.876–0.922)	0.860 (0.815–0.904)
Youden index	0.430	0.605	0.559	0.546	0.653	0.616
Sensitivity, %	75.7	73.5	82.0	74.3	83.5	76.1
Specificity, %	67.2	87.0	73.8	80.3	81.9	85.5

Note: Youden Index = Sensitivity + Specificity - 1.

Abbreviations: AUC, area under curve, CI, Confidence interval.

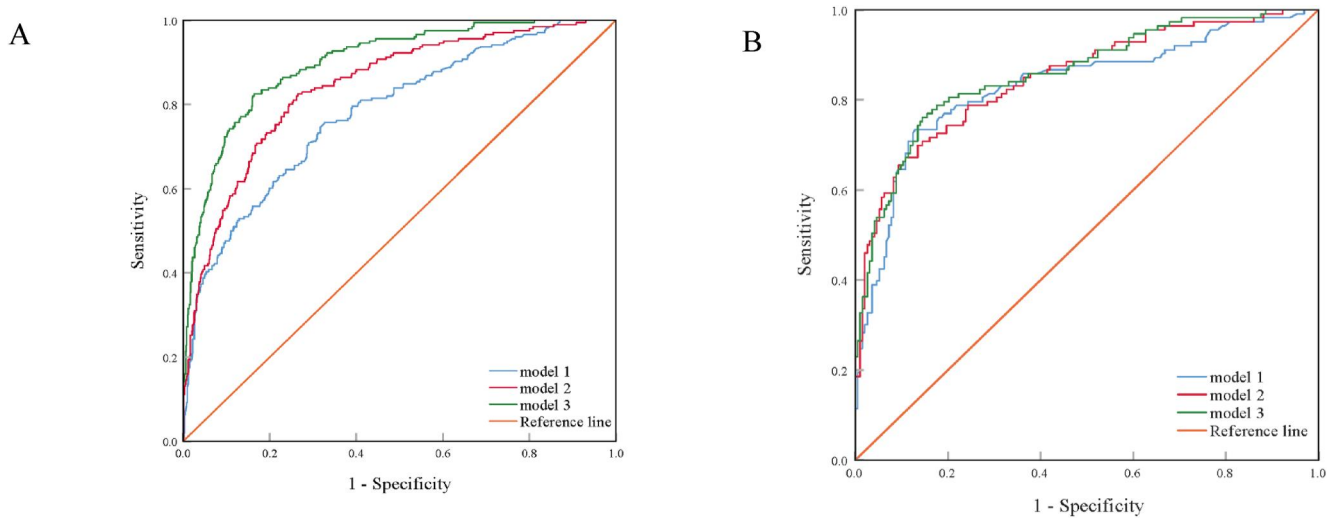

FIGURE 2 ROC curves of the nomogram for the foot ulcer recurrence in T2DM risk in the derivation and validation cohorts. (A) ROC curves of logistic regression models for foot ulcer recurrence in T2DM risk in the derivation cohort. The AUC of model 1 was 0.781 (0.744–0.817), the AUC of model 2 was 0.843 (0.813–0.873) and the AUC of model 3 was 0.899 (0.876–0.922). (B) ROC curves of logistic regression models for foot ulcer recurrence in T2DM risk in the validation cohort. The AUC of model 1 was 0.833 (0.782–0.884), the AUC of model 2 was 0.849 (0.803–0.895), and the AUC of model 3 was 0.860 (0.815–0.904). AUC, area under the curve; ROC, receiver operating characteristic curve.

burdens, and even directly cause the death of patients. The American Diabetes Association (ADA) and the International Diabetes Foot working group (IWGDF) suggest that people with diabetes should be screened more frequently when the risk of ulcers increases.[29,30] However, in the process of risk screening, the severity and the risk of ulcers are quite different, so it is difficult to distinguish between high-risk and low-risk patients. Our prediction model has good discrimination, can provide multi-dimensional monitoring and management

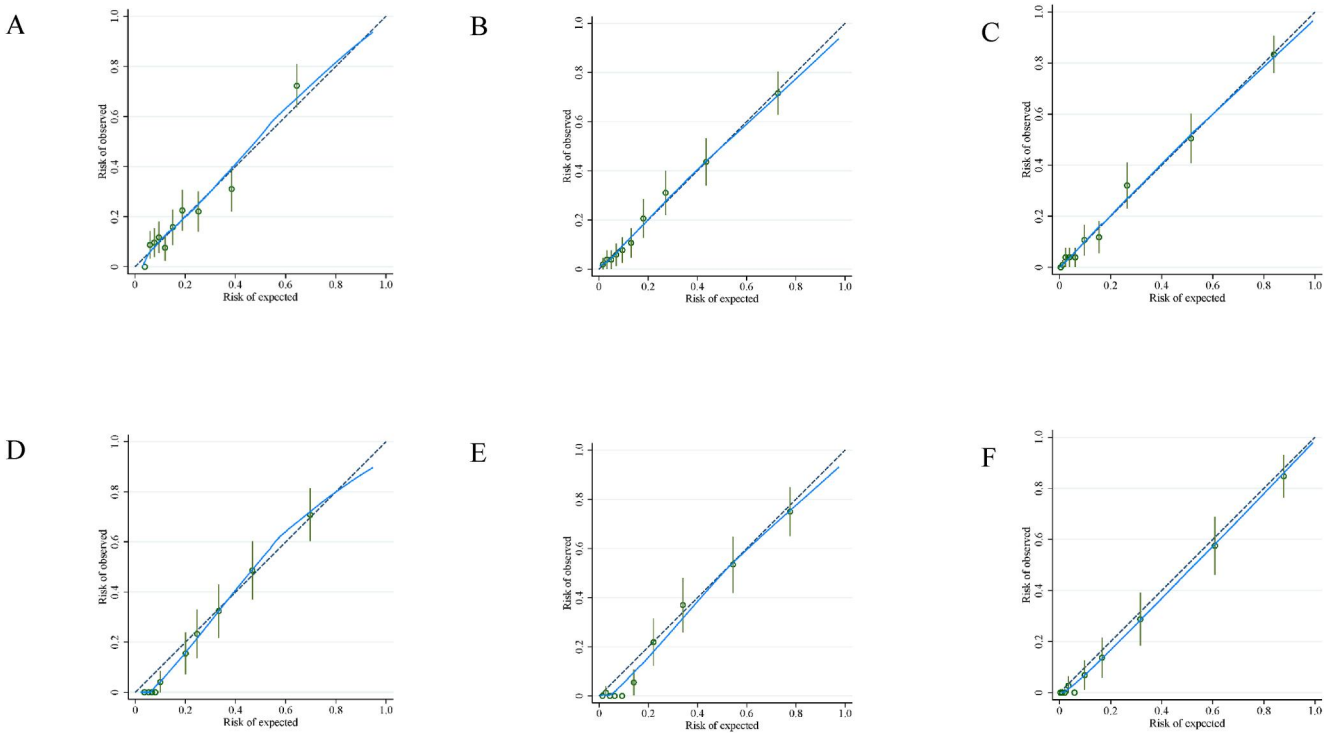

FIGURE 3 Calibration curves for nomograms of logistic regression models using the bootstrap sampling method (B = 1000 repetitions). Calibration curves for the derivation cohort of (A) Model 1, (B) Model 2, and (C) Model 3. Calibration curves for validation cohort of (D) Model 1, (E) Model 2, and (F) Model 3.

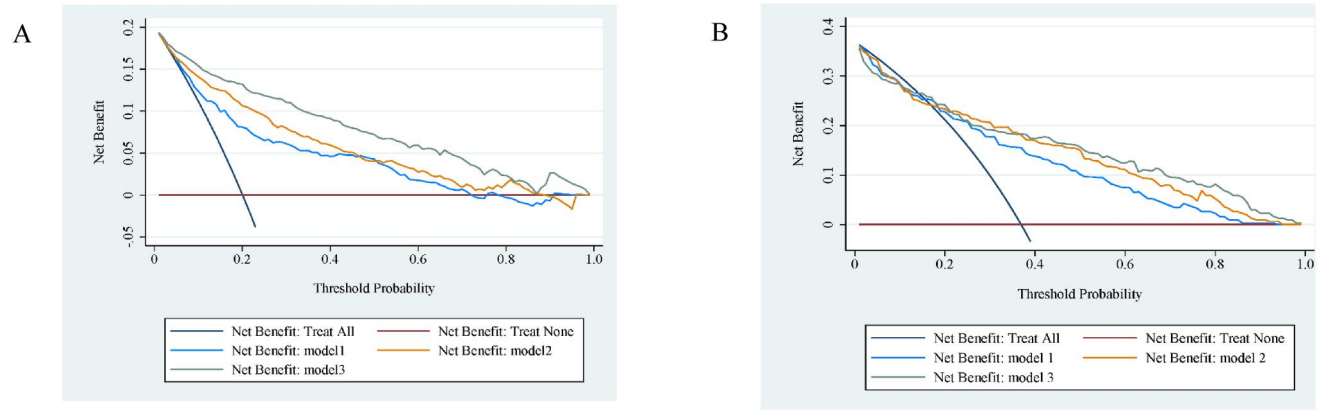

FIGURE 4 Net benefit curves for Models 1, 2, and 3. (A) Net benefit curves for the derivation cohort. (B) Net benefit curves for the validation cohort.

for patients, and can provide comprehensive and individualised risk assessment. Both model 1 and model 2 are based on noninvasive predictors, so patients can complete it alone at home without going to the hospital for examination. After screening the high-risk population through model 1 or model 2, we can help patients improve relevant tests, including clinical indicators such as HbA1c and LDL-c, and further use model 3 to judge more accurately whether they are high-risk groups, and then carry out early intervention to prevent the recurrence of DFU. In our study, Models 1 and 2 can be used at home, and Model 3 increases the prediction efficiency and can be used after physical examination in the hospital. Our data come from patients in the same hospital, so it can be more representative and popularised. In general, doctors and patients can flexibly use these three models to predict the recurrence of DFU.

At present, there are many studies or prediction models on the risk factors of DFU recurrence.[8,9,16,21,31,32] Common risk factors include age, gender, smoking, BMI, and hypertension. Although some had demonstrated good prediction effect, the practicality was poor as well as lacking external verification of the population. In addition, other studies did not include antiplatelet drugs and statins, and their effects were not considered. Some studies[33–35] have shown that statin drugs are preventive factors for protecting blood

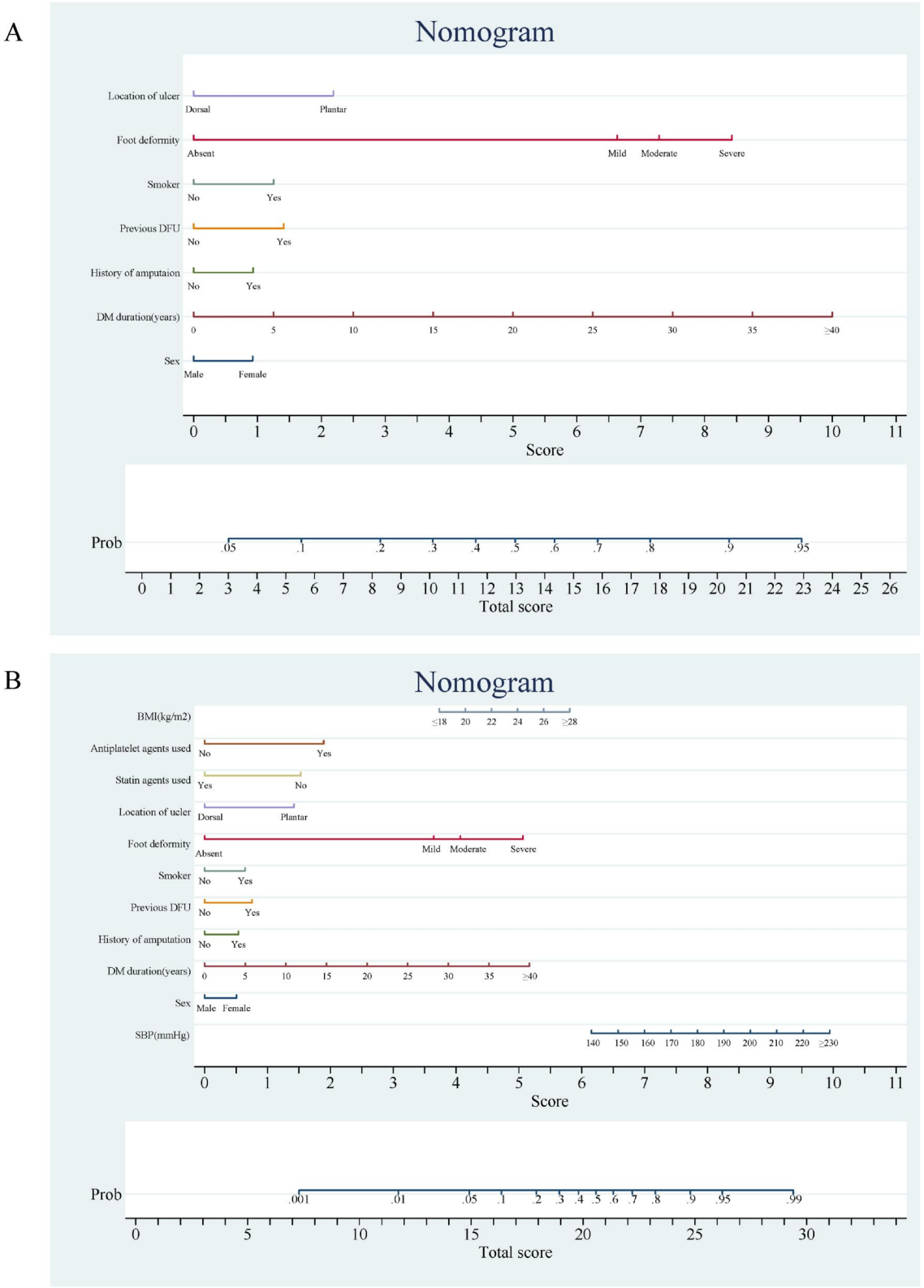

FIGURE 5 Nomogram for (A) Model 1, (B) Model 2, and (C) Model 3.

vessels. Therefore, missing those data could lose the performance of the model. Nonetheless, our study not only considered the effects of these drugs but also stratified and incorporated them into the prediction model to further improve the prediction effectiveness. The models built from the study also achieved good prediction ability while being simple, flexible, and easy-to-use. Indicators that are too expensive or complex should not be included in the model as this will undoubtedly increase the cost of use and

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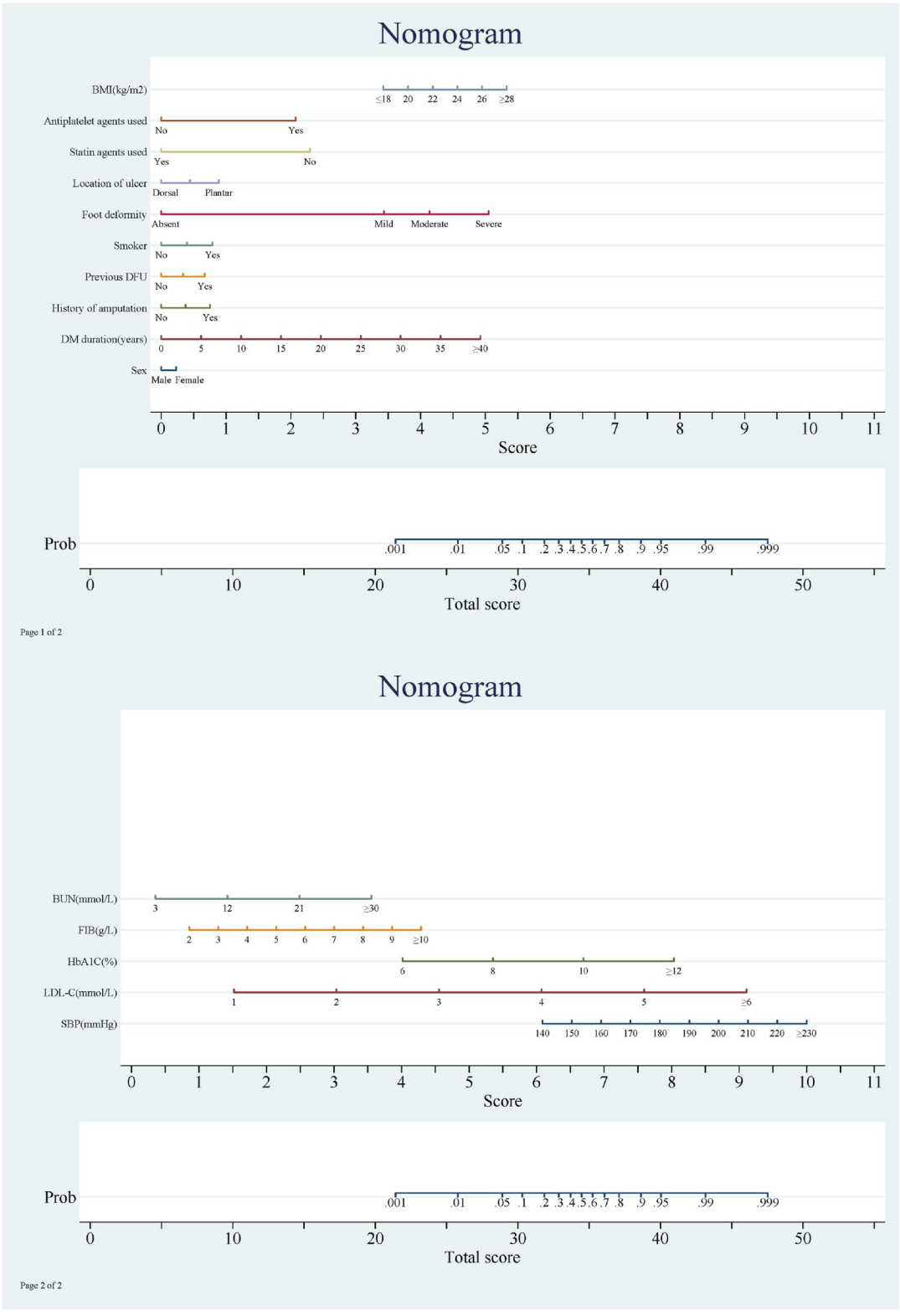

FIGURE 5 (Continued)

models should not be too complex as too many indicators increase the risk of overfitting.[36] In the aspect of model visualisation, we provided a nomogram for convenience. As comparing to the existing models, which only provide web page measurement tools,[9,21] our models are more advantageous in providing clear and detailed methods.

3.1 | Strengths and weaknesses of the study

Firstly, the rigour of methodology has added a great strength to this study. For example, the multiple interpolation method is a highly reliable method with great stability and allows the simulation of data to the greatest extent. The mix methodologies can also effectively reduce bias and generate applicable and reliable models in clinical practice. Secondly, the prediction model has fulfiled the clinical research gaps in clinical practicability and popularisation as it might provide useful early prediction and accurate management of high-risk groups of DFU recurrence. Moreover, both model 1 and model 2 were based on noninvasive predictors, which indicate the feasibility or practicality of the model to be self-administrated by people with diabetes at their own convenience, and model 3 can make a more accurate prediction. In our study, all risk models were internally verified by the bootstrap sampling method and externally validated in the validation cohort. Finally, better prediction results were obtained.

On the other hand, this study also has some limitations. First, the relatively small sample size ($N = 1333$) used in analysis could limit its differentiation in some characteristics in the derived cohort and the validation cohort. Apart from the sample size, the participants might have a similar socioeconomic background as they were recruited from the same region in China. This further compromised the generalisation of the study. The third weakness was derived from the narrow-aged group for the meta-analysis. We only included studies with participants aged 30–90 years. In addition, our models lacked related impact indicators of Albumin/Creatinine Ratio, Estimate glomerular filtration rate, and cardiovascular and cerebrovascular complications on DFU recurrence. Therefore, future research should focus on updating our models to provide a more practical prediction model and better guide the early prevention of DFU recurrence. Another area of improvement can be aimed to increase further external verification by establishing a national multicentre cohort to enhance the prediction ability of the model.

Fast-track pathway for diabetic foot ulceration during COVID-19 crisis: a document from the International Diabetic Foot Care Group and D-Foot International. Meloni M, Bouillet B, Ahluwalia R, Lüdemann C, Sánchez-Ríos JP, Iacopi E, Lazaro-Martinez JL. Diabetes Metab Res Rev. 2021 Mar; 37(3):e3396. doi: 10.1002/dmrr.3396.

3.2 | Implications

The easy-to-use and non-invasive nature of the models indicate their high clinical utility. For example, patients with DFU may screen themselves first. The high-risk groups may undergo further screening, such as drug or behavioural intervention, and then use Model 3 to make a more accurate clinical judgement on the status of their risk.

4 | CONCLUSIONS

Models 1 and 2 can be completed at home, and the patient can decide whether to carry out further laboratory testing. Model 2 contains more details of drug use than model 1, which can be used for self-management and advice when seeking medical treatment. Model 3 shows the best performance and can identify patients who need earlier intervention and intensive follow-up. If these models are used in clinics and intervene against high-risk factors, we can reduce the risk of disease and achieve the purpose of prevention. The clinical application of these models will directly reduce the economic burden associated with DFU patients and better reduce the recurrence rate of DFU patients.

AUTHOR CONTRIBUTIONS

Meijun Wang, Dong Chen, and Hongmin Fu performed the research and statistical analysis and wrote the manuscript. Hongmei Xu and Tiantian Ge collected the data and performed a quality assessment. Shanshan Lin, Qiuyue Ren, Zhenqiang Song, Min Ding, Jun Chang, and Tianci Fan participated in the interpretation of the results and commented on the manuscript. Qiuling Xing, Mingyan Sun, and Xuemei Li contributed to the discussion and reviewed the manuscript. Liming Chen and Bai Chang contributed to the concept and design, and manuscript revision.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge all the patients who participated in this study. This work was supported by the National Natural Science Foundation of China (81973614), and The Science & Technology Development Fund of Tianjin Education Commission for Higher Education (2018KJ047).

CONFLICT OF 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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the ethics committee of Tianjin Medical University Chu Hsien-I Memorial Hospital (Ethics No.: DXBYYh-MEC2021-26), and all participants signed informed consent prior to the participation.

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PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/dmrr.3616.

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How to cite this article: Wang M, Chen D, Fu H, et al. Development and validation of a risk prediction model for the recurrence of foot ulcer in type 2 diabetes in China: a longitudinal cohort study based on a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2023;39(4):e3616. https://doi.org/10.1002/dmrr.3616