ORIGINAL ARTICLE

Development and validation of a model that predicts the risk of diabetic retinopathy in type 2 diabetes mellitus patients

Jing Yang[1] · Sheng Jiang[1]

Abstract

Aims Diabetic retinopathy is the leading cause of blindness in people with type 2 diabetes. To enable primary care physicians to identify high-risk type 2 diabetic patients with diabetic retinopathy at an early stage, we developed a nomogram model to predict the risk of developing diabetic retinopathy in the Xinjiang type 2 diabetic population.

Methods In a retrospective study, we collected data on 834 patients with type 2 diabetes through an electronic medical record system. Stepwise regression was used to filter variables. Logistic regression was applied to build a nomogram prediction model and further validated in the training set. The c-index, forest plot, calibration plot, and clinical decision curve analysis were used to comprehensively validate the model and evaluate its accuracy and clinical validity.

Results Four predictors were selected to establish the final model: hypertension, blood urea nitrogen, duration of diabetes, and diabetic peripheral neuropathy. The model displayed medium predictive power with a C-index of 0.781(95%CI:0.741–0.822) in the training set and 0.865(95%CI:0.807–0.923)in the validation set. The calibration curve of the DR probability shows that the predicted results of the nomogram are in good agreement with the actual results. Decision curve analysis demonstrated that the novel nomogram was clinically valuable.

Conclusions The nomogram of the risk of developing diabetic nephropathy contains 4 characteristics. that can help primary care physicians quickly identify individuals at high risk of developing DR in patients with type 2 diabetes, to intervene as soon as possible.

Keywords Type 2 diabetes mellitus · Diabetic retinopathy · Nomogram · Risk factors · Prediction model

Abbreviations

T2DM	Type 2 diabetes mellitus
DR	Diabetic Retinopathy
DN	Diabetic nephropathy
DPN	Diabetic peripheral neuropathy
ROC	Receiver operating characteristic
DCA	Decision curve analysis
BMI	Body mass index
HbA1c	Glycosylated hemoglobin A1c
Scr	Serum creatinine
BUN	Blood urea nitrogen
LDL-C	Low-density lipoprotein
HDL-C	High-density lipoprotein
TC	Total cholesterol; TG: triglycerides
IGF-1	Insulin-like growth factor-1
IGFBP-3	Insulin-like growth factor binding protein-3
FBG	Fasting blood glucose
OR	Odds ratio
MDRD	Modification of diet in renal disease

✉ Sheng Jiang
  xjjiangsheng@126.com

1 State Key Laboratory of Pathogenesis, Prevention andTreatment of High Incidence Diseases in Central Asia, Department of Endocrinology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi 830017, China

Introduction

Diabetes has become a significant public health concern worldwide. Globally, as of 2021, there were 463 million T2DM patients with a projection of 700 million by 2045, among which China had an estimated 120.9 million cases [1]. Diabetes patients are at elevated risk of developing complications such as diabetic retinopathy, neuropathy,

and kidney disease [2]. Complications of T2DM not only increase medical costs but also affect the quality of life of patients [3]. As the prevalence of diabetes increases, the number of people with diabetic retinopathy is also on the rise [4].

DR, the primary retinal vascular complication of diabetes mellitus, is a leading cause of visual impairment in patients with T2DM [5]. Several studies reported that the prevalence of DR in Chinese diabetic patients ranged from 11.9% to 43.1% [6, 7]. The World Health Organization estimates that the number of DR and vision threatening Dr will increase to 191 million and 56.3 million respectively by 2030 [8]. In the early stages, DR is usually asymptomatic, as the disease progresses DR can affect vision and eventually lead to blindness. The severe impact of DR on vision places a significant burden on individuals, families, communities, and society [9, 10].

DR screening is considered to be an important tool for the early identification of DR [11]. Unfortunately, in China, due to the lack of a convenient tool, DR screening for diabetes is not yet available in most areas.

China is the largest developing country with a mountain of diabetic patients, many of whom suffer from DR, and the current treatment methods have very limited relief of DR. Early detection and diagnosis become particularly important. Hence, in the present study, we aimed to develop a risk nomogram for the prediction of DR.

Materials and methods

Study population

This study retrospectively analyzed T2D patients hospitalized in the First Affiliated Hospital of Xinjiang Medical University from March 2021 to December 2021. The diagnosis of type 2 diabetes was based on the diagnostic criteria for type 2 diabetes issued by the World Health Organization in 1999 [12]. The exclusion criteria were as follows: diabetic ketoacidosis; diabetic foot; Serious chronic diseases including advanced malignancy, liver cirrhosis, liver failure, heart failure, and incomplete information. Finally, 706 patients were included in the study. We divided patients into training and validation sets based on the date of data collection (Fig. 1).

Data collection

The clinicians collected clinical and laboratory data, including age, gender, duration of diabetes, body mass index (BMI), blood pressure, serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3), fasting blood glucose, glycosylated hemoglobin
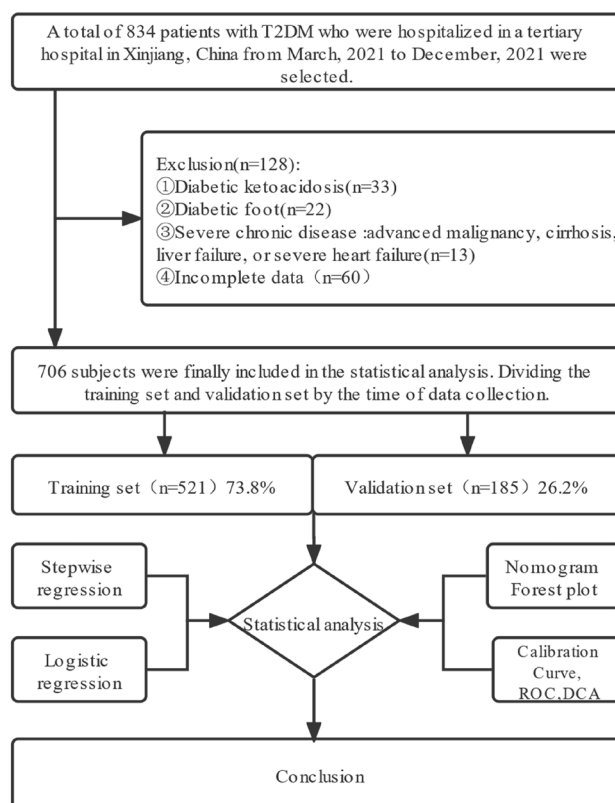

Fig. 1 Flow chart of this study

A1c (HbA1c), total cholesterol (TC), triglycerides (TG), Low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C), BUN, serum creatinine (Scr), as determined by Beckman Coulter Fully Automatic Biochemistry Analyzer.

Serum IGFBP-3 and IGF-1 levels were measured by the chemiluminescence immunometric method (Siemens Healthcare Diagnostics Products Ltd, United Kingdom). Serum creatinine concentration was determined by the Jaffé method. high-density lipoprotein (HDL-C) and Low-density lipoprotein (LDL-C) were measured by the direct method, TG by GPO-POD method, TC by enzymatic method, and fasting blood glucose (FBG) by hexokinase method (Beckman Coulter Fully Automatic Biochemistry Analyzer, Beckman Coulter, Inc, USA). GFR is estimated using the simplified Modification of Diet in Renal Disease (MDRD) formula [13].

Definitions

We used the Optos Daytona Ultra-wide field fundus camera (Scanning Laser Inspection Ophthalmoscope, Optos, Daytona, UK) to image all subjects for assessment of retinopathy. DR was confirmed if the existence of the following retinal lesions: soft exudates, Microaneurysms, hard exudates,

intraretinal hemorrhagic dots, intraretinal microvascular abnormality, venous beading, preretinal hemorrhage, neovascularization, or vitreous hemorrhage [14].

In this study, patients with a previous history of hypertension we defined as hypertensive. Diabetic nephropathy was defined according to Mogensen's (1986) criteria, with both microalbuminuria ($20 \leq UAER \leq 200$ µg/min) and clinical albuminuria ($UAER > 200$ µg/min) indicative of DN [9, 10].

DPN was screened by symptoms and physical examination. In all patients, other causes of neuropathy were excluded. The diagnosis was confirmed by electromyography and/or nerve conduction study.

Statistical analysis

Statistical analysis was performed using the R software (version 4.1.1; https://www.R-project.org). The 706 patients with type 2 diabetes in this study were divided into a training set of 521 participants and a validation set of 185 participants according to the date of data collection for validation, consistent with a theoretical 3:1 ratio [15].

Comparisons of continuous and categorical variables between training and validation sets were performed using the t-test and chi-square test, respectively. Clinical variables were analyzed using univariate logistic regression analysis. According to the research results, the stepwise regression method was used to further screen variables, and select statistically significant indicators to construct a nomogram. The most 'parsimonious' was chosen by Akaike's Information Criterion (AIC) in a stepwise algorithm.

We evaluated the model by three aspects including discriminatory ability, accuracy, and clinical utility. To evaluate the predictive power of the model, we calculated the C-index. To reduce the bias, the calibration was conducted by using 1000 bootstrap samples [3]. AUC is the area under the ROC curve, also known as the C statistic, used to assess the discriminatory power of the model. A value of AUC between 0.7 and 0.9 indicates that the model has moderate predictive power and can be combined with clinical practice for predictive assessment [3]. The decision curve analysis takes into account the clinical benefit of the model unlike traditional diagnostic test metrics and assesses the clinical validity of the model by calculating the net benefit based on different threshold probabilities for patients with T2 DM [3].

Results

Participant characteristics.

A total of 706 patients with T2DM included 268 women and 438 men. The data were divided into training set and validation set according to the date of collection. Baseline characteristics such as demographics, physical examination findings, diabetic complication status, and biochemical indices of patients in both groups are shown in Table 1.

Feature selection

The clinical variables of T2DM patients with proteinuria were included in univariate logistic regression. The related factors of DR included age, diabetes duration, hypertension, DPN, DN, eGFR, Scr, BUN, TC, and LDL-C (Table 2). Based on the results of univariate logistics, the risk factors related to the risk of DR in T2DM patients were further screened by stepwise regression according to the principle of the Akaike Information Criterion.

Construction of the nomogram prediction model

The multivariate logistic regression analysis showed the correlation among DPN, hypertension, Diabetes duration, and BUN independent factors for DR in T2DM patients (Table 3). The results of the multivariate logistic regression analysis establish a nomogram model for predicting the risk of DR (Fig. 2). The binary logistic regression results are shown in the forest plot (Fig. 3).

Performance of the DR risk nomogram

For the 706 T2DM patients in this study, the calibration curves of both the training set (Fig. 4A) and validation set (Fig. 4A) showed good agreement in predicting DR risk. Based on the nomogram prediction model, the AUC value of the training set (Fig. 5A) was 0.781 (95% CI; 0.741–0.822), and the AUC value of the validation set (Fig. 5B) was 0.865 (95% CI; 0.807–0.923).

These results suggest that the nomogram can accurately predict the incidence of DR in T2DM patients.

Clinical use

The decision curve of the DR risk nomogram is shown in Fig. 6. According to decision curve analysis, nomograms are clinically beneficial in predicting the risk of DR incidence between a considerable range of threshold probabilities. One patient was randomly selected from the population based on the characteristic indicators selected by the model. Patient indicators were as follows: DPN = yes, BUN = 6.7 mmol/L, Diabetes duration = 5 years, and hypertension = yes. A dynamic nomogram was created to predict the incidence of DR (Fig. 7).

Table 1 Baseline characteristics of training and validation sets

Characteristic	Training set (n=521)	Validation set (n=185)	P-value
Age [years]	56.84±12.38	54.56±11.13	0.021
Gender (n, %)			0.313
Male	317(60.8)	121(65.4)	
Female	204(39.2)	64(35.6)	
Duration of diabetes [years]	8.76±7.29	8.81±7.30	0.945
BMI [kg/m²]	26.02±4.62	26.06±3.54	0.909
Hypertension (n, %)			0.624
Yes	300(57.6)	102(55.1)	
No	221(42.4)	83(44.9)	
Diabetes complications			
DN (n, %)			0.046
Yes	133(34.3)	62(33.5)	
No	388(65.7)	123(66.5)	
DPN (n, %)			0.223
Yes	298(57.2)	116(62.7)	
No	223(42.8)	69(37.3)	
DR (n, %)			0.778
Yes	313(60.1)	125(67.6)	
No	208(39.9)	60(22.4)	
Lifestyle habits			
Smoking (n, %)			0.141
Never	354(67.9)	114(61.6)	
ever/current	167(32.1)	71(38.4)	
Consuming alcohol (n, %)			0.37
Never	364(69.9)	122(65.9)	
ever/current	157(30.1)	63(34.1)	
Biochemical tests result characteristics			
FBG [mmol/L]	7.93±2.67	7.15±2.13	<0.001
2H-OGTT [mmol/L]	16.69±4.48	16.55±11.06	0.868
HbA1c [%]	8.75±2.21	8.71±1.88	0.833
eGFR [ml/min/1.73 m²]	94.13±21.08	96.08±22.26	0.300
Scr [μ mol/L]	71.74±24.94	70.28±23.97	0.491
BUN [mmol/L]	5.83±2.13	5.74±1.97	0.636
TG [mmol/L]	2.15±1.97	2.10±2.03	0.777
TC [mmol/L]	4.19±1.21	4.2±1.19	0.869
LDL-C [mmol/L]	2.71±0.96	2.77±0.94	0.414
HDL-C [mmol/L]	0.98±0.27	0.99±0.35	0.489
IGF-1 [ng/mL]	152.46±57.08	160.78±43.75	0.042
IGFBP-3 [μ g/mL]	4.03±1.22	4.16±1.16	0.190

Discussion

DR is one of the most common and serious microvascular complications of diabetes and is the ocular manifestation of end-organ damage in diabetes. Data from 35 diabetes-based studies worldwide show that the overall prevalence of DR is approximately 34.6% worldwide. Blindness due to DR accounts for 2.6% of all blindness cases and is increasing at a rate of 8,000 new cases per year[16]. Despite the great

progress in the recognition and treatment of DR, the rising prevalence of diabetes and DR still shows that the task of preventing DR, preventing DR progression, and delaying DR blindness is daunting. Therefore, we developed a diagnostic model based on the risk factors for the occurrence of DR to facilitate early detection of DR.

In the present study, we found that hypertension, BUN, duration of diabetes, and DPN were independently associated with the risk of DR in patients with T2DM. Our

Table 2 Univariable logistic analysis to extract the potential predictors

Variable	OR (95% CI)	P-value
Age [years]	1.03(1.01–1.05)	<0.001
Gender [male vs female]	0.92(0.64–1.32)	0.654
Diabetes duration [years]	1.11(1.08–1.14)	<0.001
BMI [kg/m^2]	0.99(0.96–1.03)	0.691
Hypertension [yes vs no]	2.26(1.58–3.24)	<0.001
DPN [yes vs no]	1.81(1.203–2.76)	<0.001
DN [yes vs no]	2.15(1.40–3.34)	<0.001
Smoking status [Never, Ever/Current]	0.85(0.59–1.24)	0.407
Drinking status [Never, Ever/Current]	1.07(0.73–1.56)	0.743
FBG [mmol/L]	0.99(0.93–1.06)	O.870
2H-OGTT [mmol/L]	0.99(0.96–1.04)	0.976
HbA1c [%]	0.96(0.89–1.04)	0.351
eGFR [ml/min/1.73 m^2]	0.98(0.97–0.99)	<0.001
Scr [μ mol/L]	1.01(1.00–1.02)	0.011
BUN [mmol/L]	1.19(1.09–1.33)	<0.001
TG [mmol/L]	1.06(0.97–1.17)	0.237
TC [mmol/L]	0.86(0.74–0.99)	0.043
LDL-C [mmol/L]	0.77(0.64–0.93)	0.006
HDL-C [mmol/L]	0.53(0.27–1.03)	0.062
IGF-1 [ng/mL]	0.99(0.99–1.00)	0.309
IGFBP-3 [μ g/mL]	0.92(0.79–1.07)	0.281

Table 3 Multivariate logistic regression analysis of step AIC selection to construct a nomogram model

Variable	Multivariate logistic analysis		
	β	OR (95% CI)	P-value
DPN = yes	1.518	4.564(3.058–6.862)	<0.001
Hypertension = yes	0.583	1.792(1.197–2.685)	0.005
Diabetes duration [years]	1.518	1.072(1.039–1.106)	<0.001
BUN [mmol/L]	0.113	1.119(1.004–1.256)	0.048
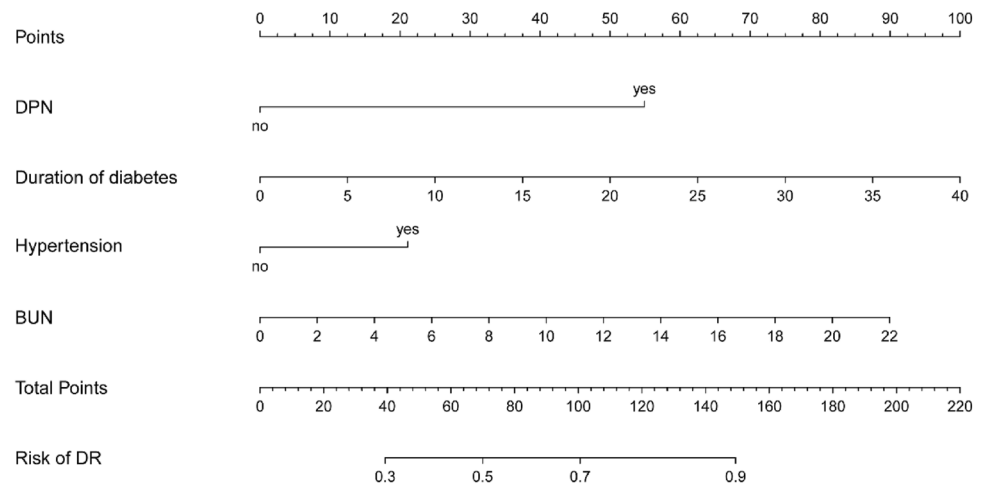
findings are consistent with the risk factors for DR that have been reported in the literature. Longer duration of diabetes, higher systolic blood pressure, and elevated BUN levels were found to be independent risk factors for DR in a multicenter study conducted in eight hospitals in China [16]. In a study of risk factors for DR in community-based diabetic patients, Li et al. found that hypertension, duration of diabetes, and DPN were independent risk factors [16]. We can assume that patients with long-term diabetes, higher BUN, DPN, and hypertension were more susceptible to DR.

The duration of diabetes mellitus is an unmodifiable risk factor for DR in many studies [17–19]. LALES et al. found that the risk of DR would increase by 8% for each additional year of diabetes duration [20]. A cross-sectional study of risk factors for DR conducted at Nanjing Drum Tower Hospital confirmed that the duration of diabetes was strongly associated with the risk of DR [21]. Similarly, in another study on risk factors for DR in southern China, the authors concluded that the duration of diabetes was one of the most important risk factors for DR [22]. Singh et al. showed that in type 2 diabetes, the prevalence of DR was five times higher in patients with a disease duration of > 15 years compared to those with a disease duration of fewer than 5 years [23]. In the present investigation, the duration of diabetes was significantly correlated with the occurrence of DR in the multiple regression model ($P < 0.001$), so we also included the duration of diabetes in the prediction model.

Hypertension was found to be a contributing factor to DR in a Chinese community-based study of risk factor screening for microvascular disease [24]. In the present study, we found that hypertension was closely associated with the progression of DR. In a population-based study, it was found that patients with poorly controlled blood pressure had a higher risk of developing DR compared to diabetic patients with well-controlled blood pressure [25]. Additionally, in a long-term follow-up study conducted in the
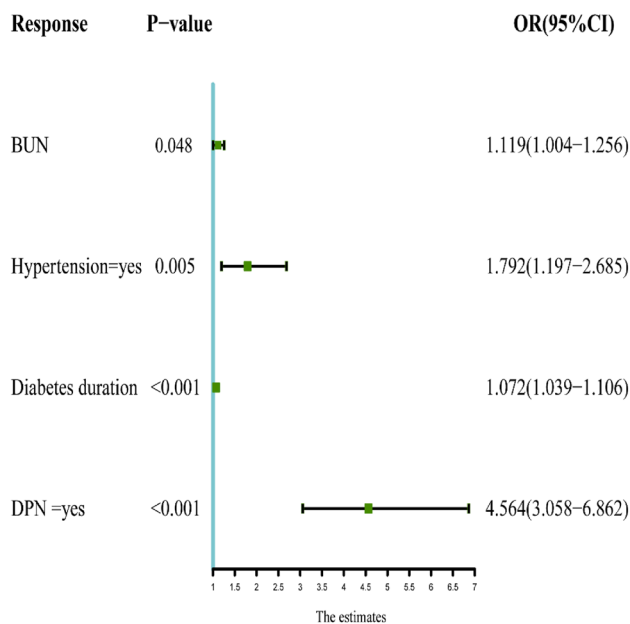

Fig. 2 A nomogram for predicting the incidence of DR in T2DM patients. *Notes* To use the nomogram it is necessary to substitute the variables into the nomogram and draw a vertical line upward for each variable to give the score of each variable, and finally add the scores of the 4 variables to obtain the total score. The probability of DR in type 2 diabetes is obtained by drawing a vertical line down the total score.

Fig. 3 The forest plot of the OR of the selected feature. Use forest plot to visualize logistic regression analysis

United States, it was found that elevated blood pressure can have long-term damage to small retinal arteries, and this damage accumulates gradually. The authors concluded that hypertension may serve as a long-term marker in response to retinal microangiopathy [26]. In this study, we found a positive association between hypertension and the risk of DR, which is consistent with the findings reported above.

Hypertension, BUN, and course of the disease are important risk factors for T2DM patients, among which the course of diabetes is an unmodifiable risk factor. The results showed that the long course of the disease, the higher BUN, and hypertension was closely related to the incidence rate of DR. We should look at them as a whole when we consider the association in it. Here, these risk factors may be about the element of social and era development. With the continuous development of the social economy, People's lifestyle has changed a lot, so that they may spend more time in the office rather than in the gym [27, 28]. In addition, the pursuit of all kinds of delicious food has reached a crazy degree, which to a certain extent increases the risk of hypertension, but also increases the burden on the kidney. Patients with a longer course of the disease have greater psychological and mental stress. These common factors increase the probability of DR.

A retrospective study in Taiwan found that DPN increased the risk of DR onset and progression [29].

Fig. 4 Calibration curves for the nomogram. *Notes* A represents the training set. B represents a validation set. The *x*-axis represents the predicted probability of DR. The *y*-axis represents the actual diagnosed DR. The diagonal dotted line represents a perfect prediction by an ideal model. The solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction.
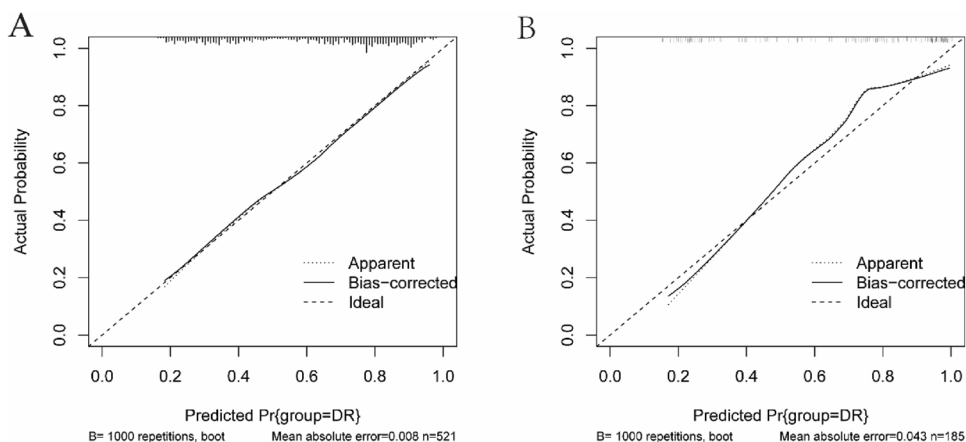

Fig. 5 ROC curves for the nomogram. A represents the training set and B represents the validation set. *Notes* The x-axis represents the false positive rate of the risk prediction, while the y-axis represents the true-positive rate of the risk prediction. The red line displays the performance of the nomogram.
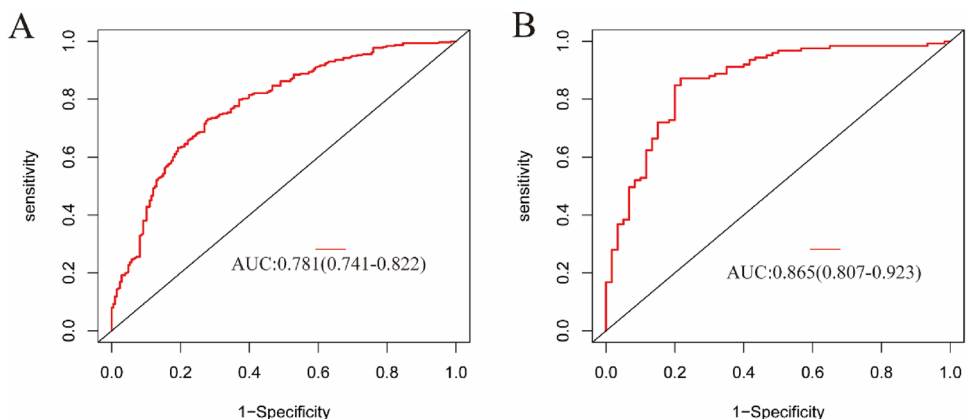
Fig. 6 Decision curve analysis for the DR incidence risk nomogram. A represents the training set and B represents the validation set. *Notes* The y-axis represents the net benefit. The gray slash indicates the hypothesis that all patients have DR, while the black solid line indicates the hypothesis that all patients do not have DR. The blue line represents the risk nomogram.
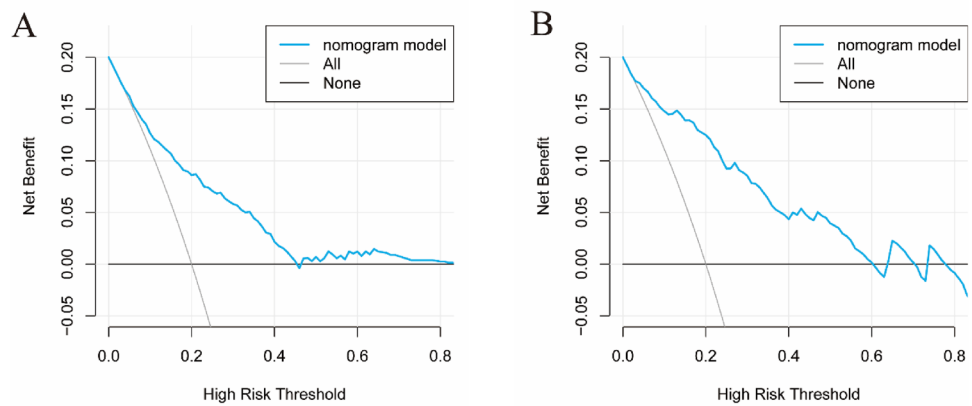
Fig. 7 Dynamic Nomogram. *Notes* To use the nomogram it is necessary to substitute the variables into the nomogram and draw a vertical line upward for each variable to give the score of each variable, and finally add the scores of the 4 variables to obtain the total score. The probability of DR in type 2 diabetes is obtained by drawing a vertical line down the total score. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$
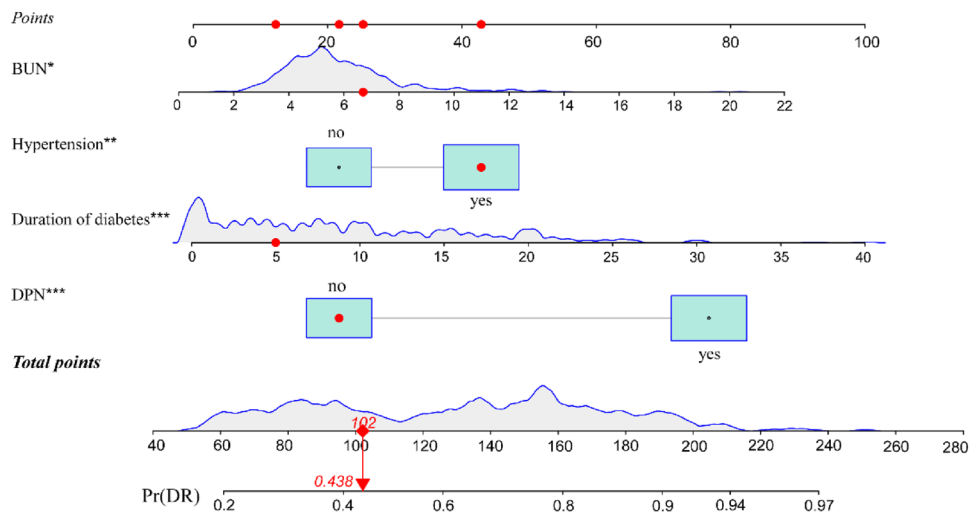
Interestingly, Rasheed et al. found that retinal neurodegenerative changes parallel DPN during diabetes treatment. The authors found a significant association between DR and DPN from a novel perspective assessment [30]. In the present study, we found that DPN was also a risk factor for the development of DR.

It is well known that urea nitrogen is an important component of urea, which is the culprit of chronic kidney disease [31]. Therefore, metabolic indicators of abnormal renal function can also indicate the risk of indirectly related diseases such as eye disease. Elevated levels of circulating urea can directly impair pancreatic beta-cell function, which can lead to disruption of glucose homeostasis and ultimately bring about the development of T2DM and decreased renal function [32]. In addition, Shi et al. noted BUN as a predictor of DR in a columnar line graph study of DR risk, OR: 1.053, 95% CI (1.017–1.091) [33]. Another showed that BUN was a characteristic variable in the presence of DR [16]. Our study showed that high levels of BUN were positively associated with the risk of DR, which is consistent with the results of previous studies.

Our study has many strengths, the parameters used for nomogram construction were derived from clinical practice and could be collected by simple biochemical tests and questionnaires during follow-up. Furthermore, the nomogram does not require the results of an ophthalmic examination, reducing the burden on the patient.

Limitation of this study

This was a cross-sectional study, the patients with DR were observed in the static state, without the monitoring of the dynamic change process. If the patients' indicators were tested dynamically, the accuracy of the prediction model would be improved to a certain extent. In a Cross-Sectional study, we can predict this. However, this is one of the limitations of our article. Secondly, the research design of this study is a cross-sectional study, which cannot accurately determine the causal relationship between exposure and results, and further prospective studies are needed to confirm the results. Thirdly, since all data in this study were derived from fundus color photography, rather than fundus

fluorescein angiography, the DR diagnosis may lack rigor. <u>Furthermore, the patients included in this study are all Chinese, so enlarging the range of the population would be better to increase the representation.</u> Finally, all medical history data and laboratory indicators are obtained from the electronic medical record system, which cannot cover all risk factors for the occurrence of DR, and the accuracy may be biased.

Conclusion

In this study, we developed a nomogram model for patients at high risk of developing DR in type 2 diabetes based on Xinjiang patients with type 2 diabetes. It helps primary care physicians to provide a reference for the screening and early diagnosis of DR.

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