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ORIGINAL RESEARCH

A Novel Nomogram for Diabetic Retinopathy Prediction in Young and Middle-Aged Patients with Type 2 Diabetes

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Purpose: The study aims to develop and validate a novel nomogram for predicting diabetic retinopathy (DR) risk specifically in young and middle-aged patients with type 2 diabetes (T2DM).

Methods: This retrospective cohort study analyzed 337 T2DM patients (Age 15–59 years) admitted to Luoyang Central Hospital from July 2022 to January 2024, stratified by fundus examination into DR (n=155) and non-DR (n=182) groups. Demographic characteristics and relevant clinical parameters were systematically collected. A predictive nomogram for DR detection was constructed using significant variables identified through multivariate logistic regression analysis. The calibration, discrimination, and clinical utility of the nomogram were subsequently evaluated using calibration plots, receiver operating characteristic curves, and decision curves.

Results: Multivariate analysis identified four independent predictors of diabetic retinopathy: diabetes duration (OR=1.125, 95% CI: 1.07–1.182, $P<0.001$), brachial-ankle pulse wave velocity (baPWV; OR=1.269, 95% CI: 1.133–1.421, $P<0.001$), blood urea nitrogen (BUN; OR=1.223, 95% CI: 1.052–1.423, $P=0.009$), and age (OR=0.955, 95% CI: 0.922–0.989, $P=0.01$), with the developed nomogram demonstrating excellent discrimination (AUC=0.75, 95% CI: 0.696–0.800), significant improvement over individual predictors (ΔAUC+0.05 to+0.18), strong calibration (Bootstrap C-index=0.749), and clinical utility across 2–85% threshold probabilities by decision curve analysis.

Conclusion: This study presents the first nomogram for DR risk in young and middle-aged patients with T2DM. Integrating four routine clinical parameters (diabetes duration, baPWV, BUN, age), the model demonstrates robust predictive power (AUC=0.75) and clinical utility, enabling early risk stratification and timely intervention.

Keywords: prediction models, line graphs, brachial-ankle pulse wave velocity, diabetic retinopathy

Introduction

Diabetic retinopathy (DR), as one of the most common microvascular complications of type 2 diabetes mellitus (T2DM), has become the leading cause of vision loss and blindness in the working-age population globally.[1] According to recent data from the International Diabetes Federation (IDF) and the Global Burden of Disease (GBD) study, the global population of individuals aged 20 to 79 years with diabetes reached 589 million in 2024 and is projected to surge to 853 million by 2045.[2–4] It is worth noting that the number of DR cases has surpassed 37 million, with the prevalence rising to 50% among patients with a disease duration exceeding 10 years and approaching 100% in those with over 20 years of disease history.[5] These studies reveal that DR constitutes a substantial proportion of diabetes cases, with its incidence significantly increasing as the disease progresses. Research also demonstrated that the primary cause of blindness due to DR is insufficient early screening rates, which lead to most patients being diagnosed at the stage of irreversible vision impairment. This highlights the urgent need to establish scalable and accurate screening systems.[6]

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Although early-stage DR, particularly in its non-proliferative forms, often does not require immediate treatment, implementing targeted screening in young and middle-aged populations remains critically important for several reasons.[7] This demographic offers an extended window for prevention, allowing early detection and timely intervention through glycemic control, blood pressure management, and other modifiable measures that can slow or prevent progression to vision-threatening stages.[8] From a health-economic perspective, early risk stratification in this active population supports more efficient allocation of medical resources, reducing the long-term societal and economic burden of advanced DR management.[9] Additionally, distinct pathophysiological mechanisms may be at play in younger patients, who often exhibit more aggressive metabolic and vascular dysfunction, highlighting the need for prediction tools tailored to their specific risk profile.[10]

Several existing prediction models have been applied to the identification and diagnosis of DR.[11–13] For instance, the study included 1257 patients (28.6% with DR) and found that the panel included disease duration, age at onset, treatment method, total cholesterol, UACR, and urine sugar, demonstrating a relatively good predictive effect (AUC=0.79 in validation).[14] In addition, Wang et al used the Lasso algorithm to select 8 key predictive variables (including disease duration, BMI, FPG, HbA1c, HOMA-IR, TG, TC, and VitD-T3) from 16 independent variables, resulting in a DR prediction model with high discriminative power (C-index = 0848). The decision curve analysis of the nomogram indicates good clinical utility, with a validation score of 0.816.[15] However, most of these models were developed for all-age patient cohorts, which limits their ability to predict DR progression across different age strata and consequently restricts their utility in risk-stratifying individual patients and guiding optimal treatment strategies. Consequently, their ability to stratify individual patients based on risk levels and determine optimal treatment approaches is restricted. In addition, existing biomarkers exhibit limited predictive efficacy. For instance, HbA1c is widely considered the gold standard for diabetes control, and delayed insulin therapy increases the risk of DR and does not serve as a targeted biomarker for its diagnosis.[16] Additionally, conventional renal function indicators such as BUN have often been undervalued, despite serving as independent risk markers for microvascular injury.[17] Additionally, the association between brachial-ankle pulse wave velocity (baPWV) and microvascular complications suggests a potential link with DR.[18,19] In summary, there is still a need to develop more reliable and accurate predictive models of risk factors for DR to reduce clinical risk.

To address these gaps, this study is the first to develop a predictive model for DR that integrates multiple clinical parameters specifically for young and middle-aged patients with T2DM. By systematically screening for unique combinations of predictive factors in this population, we innovatively constructed a visual scoring tool, enabling clinicians to quickly conduct risk assessments based on routine examination data. Our findings reveal that the synergistic effect of baPWV and BUN exposes the central mechanisms of the vascular-metabolic-renal function interaction network in the pathogenesis of DR, offering new insights into microvascular injury mechanisms unique to younger and middle-aged patients.

Data and Methods

Study Population

Patients with T2DM admitted to the Endocrinology Department of Luoyang Central Hospital from July 2022 to January 2024 were included in the study, and their basic information and relevant clinical indicators were recorded. This study was approved by the Ethics Committee of Luoyang Central Hospital (Ethics Approval Number: LWLL-2025-07-09-02). All enrolled patients signed informed consent forms. Inclusion criteria: patients should meet the diagnostic criteria for T2DM according to the 2022 American Diabetes Association guidelines.[20] Exclusion criteria are as follows:

(1) Under 15 years old and over 59 years old;
(2) Other types of diabetes;
(3) Acute diabetic complications;
(4) Diabetic foot;
(5) Chronic liver cirrhosis, renal insufficiency, pregnant or lactating women;

(6) Patients with Graves' ophthalmopathy, glaucoma, or other conditions that prevent cooperation with fundus examination;
(7) Those with mental illness;
(8) Those without baPWV data.

Finally, a total of 337 cases of T2DM were included in this study.

Diagnostic Criteria

DR diagnostic criteria: Meet the DR grading criteria established by the International Ophthalmology Society in 2016 and diagnosed by a professional ophthalmologist.[21]

Research Methods

Data Collection

Data collected from the patients included age, gender, height, weight, waist circumference, hip circumference, subcutaneous fat area, and visceral fat area. BMI was calculated as weight[22] divided by the square of height (m^2).

Biochemical Index Detection

Patients were required to fast for at least 8 hours, after which venous blood was drawn on an empty stomach the following morning. Indicators measured included fasting plasma glucose (FPG), homocysteine (HCY), blood urea nitrogen,[23] triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). HbA1c was measured using high-performance liquid chromatography, while TC, HCY, BUN, TG, HDL-C, LDL-C, and FPG were assessed using an automatic biochemical analyzer.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation and were compared using independent samples t-tests. Categorical variables are expressed as frequencies (n) with corresponding percentages (%) and were analyzed using chi-square tests or Fisher's exact tests, as appropriate. Univariate logistic regression analysis was employed to evaluate the crude association between each independent variable and the outcome, with results expressed as crude odds ratios (ORs) and their 95% confidence intervals (CIs). Subsequently, multivariate logistic regression analysis was conducted to assess independent predictors while adjusting for potential confounders.

Model calibration was visually assessed using a calibration plot, which compares predicted probabilities against observed frequencies. Perfect calibration would align along the 45° reference line. Internal validation was performed using 1000 bootstrap resamples to correct for overoptimism. The discriminative ability of the model was evaluated through receiver operating characteristic curve analysis, with the area under the curve serving as a quantitative measure.[24,25] An AUC between 0.7 and 0.9 indicates good predictive accuracy. Clinical utility was further examined using decision curve analysis (DCA) to assess net benefit across different threshold probabilities.

All statistical analyses were conducted using SPSS version 25 (IBM Corp), GraphPad Prism 9.5.0, and R software. Two-tailed p-values <0.05 were considered statistically significant for all analyses. The study flowchart is shown in Figure 1.

Results

Comparison of General Data and Clinical Indicators Between the Two Groups

The study population was divided into two groups according to the presence or absence of DR. The non-DR group comprised 182 participants (121 males, 66.5%; 61 females, 33.5%), while the DR group included 155 participants (86 males, 55.5%; 69 females, 44.5%). Comparative analysis between the two groups revealed that, relative to the non-DR group, the DR group exhibited significantly longer disease duration ($P < 0.001$) and higher values in baPWV ($P < 0.001$), blood urea nitrogen ($P = 0.01$), and HDL-C ($P = 0.006$). Conversely, the DR group demonstrated significantly lower subcutaneous fat ($P < 0.001$), visceral fat ($P < 0.001$), BMI ($P < 0.001$), waist circumference ($P < 0.001$), hip circumference ($P < 0.001$), waist-to-height ratio ($P = 0.012$), TG ($P = 0.008$), HbA1c/HDL-C ratio ($P = 0.045$), and

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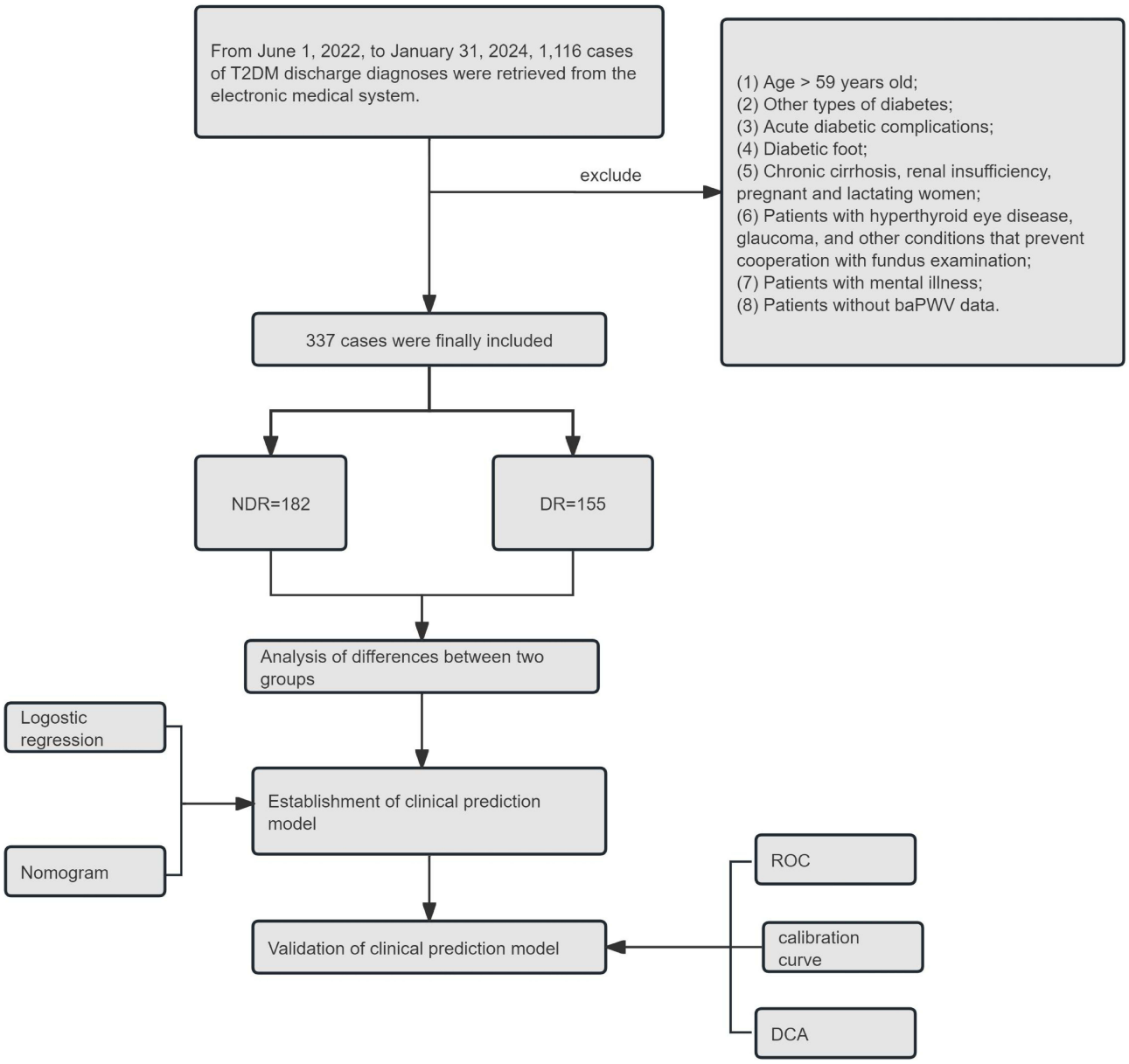

Figure 1 Research Flowchart.

TG/HDL-C ratio (P = 0.004). No statistically significant differences were observed between the groups in alcohol consumption history, waist-to-hip ratio, HbA1c, FBG, HCY, TC, LDL-C, FPG/HDL-C ratio, TC/HDL-C ratio, or LDL-C/HDL-C ratio. Detailed comparative data are presented in Table 1.

Univariate and Multivariate Analysis of the Regression of DR in Patients with Type 2 Diabetes

Using SPSS 25 software, taking DR as the dependent variable, the independent variables were screened in turn, and the candidate variables with P<0.1: diabetes course, baPWV, subcutaneous fat area, visceral fat area, BMI, waist circumference, hip circumference, sex, age, BUN, HbA1c/HDL-C, and HDL-C were subjected to logistic multivariate analysis. The results showed that diabetes course, baPWV, BUN, and age were independent risk factors for DR (Table 2). Using these independent predictors, we created a model and presented it using a nomogram (Figure 2): diabetes course, baPWV, subcutaneous fat area, visceral fat area, BMI, waist circumference, hip circumference, sex, age, BUN, HbA1c/HDL-C,

Table 1 Comparison of General Data and Clinical Indicators Between the Two Groups

Variable	NDR (n=182)	DR (n=155)	Statistics	*p* value
Gender (male/female)	121/61	86/69	−2.064	0.039*
Age (years)	50 (42.3, 54)	53 (46, 56)	−2.332	0.02*
Diabetes course (years)	2 (0.19, 6)	7 (2, 12)	−6.463	*p* <0.001*
Smoking history (Yes/No)	59/123	45/110	−0.67	0.503
Drinking history (Yes/No)	26/156	13/142	−1.685	0.092
baPWV (m/s)	15.1±0.16	16.7±0.24	−5.686	*p* <0.001*
Subcutaneous fat area (cm^2)	208.7±5.08	180±4.82	4.121	*p* <0.001*
Visceral fat area (cm^2)	97.7±2.92	76.9±2.87	5.065	*p* <0.001*
BMI (Kg/m^2)	26.8±0.29	25.1±0.26	4.28	*p* <0.001*
Waist circumference (cm)	94.1±0.76	89.8±0.71	4.064	*p* <0.001*
Hip circumference (cm)	98.5±0.62	95.3±0.61	3.662	*p* <0.001*
Waist-to-height ratio	0.56±0.005	0.54±0.004	2.541	0.012
Waist-to-hip ratio	0.94±0.005	0.95±0.008	0.733	0.464
HbA1c (%)	9.91±0.15	9.87±0.15	0.169	0.866
FPG (mmol/L)	12.1 (8.37, 15.8)	11.8 (8.6, 15.3)	−0.075	0.941
HCY	11.5 (9.5, 14.6)	11.1 (9.3, 14.2)	−1.135	0.256
BUN	5.4 (4.52, 6.33)	5.98 (4.98, 6.97)	−3.335	0.001*
TG (mmol/L)	2.10 (1.42, 3.3)	1.7 (1.17, 2.65)	−2.653	0.008*
TC (mmol/L)	5.11 (4.34, 5.89)	4.98 (4.09, 6.36)	−0.015	0.988
LDL_C (mmol/L)	2.77 (2.08, 3.51)	2.73 (2.18, 3.57)	−0.554	0.579
HDL_C (mmol/L)	0.96 (0.81, 1.11)	1.09 (0.91, 1.2)	−3.795	*p* <0.001*
HbA1c/HDL_C	10.1 (8.39, 12)	9.36 (7.34, 11.4)	−2.705	0.007
FPG/HDL_C	11.7 (8.37, 17.1)	11.1 (7.44, 15.6)	−1.417	0.157
TG/HDL_C	2.23 (1.29, 3.70)	1.62 (1.04, 2.63)	−3.163	0.002*
TC/HDL_C	5.24 (4.34, 6.15)	4.76 (3.72, 5.83)	−2.524	0.012*
LDL_C/HDL_C	2.78 (2.16, 3.44)	2.67 (2.02, 3.31)	−1.508	0.131

Note: *Significant at a *P* value<0.05.

Abbreviations: HbA1c, glycated hemoglobin; FBG, fasting blood glucose; TG, triglyceride; HCY, homocysteine; BUN, blood urea nitrogen; TC, total cholesterol; LDL_C, low-density Lipoprotein Cholesterol; BMI, Body mass index; HDL_C, high-density Lipoprotein Cholesterol.

Table 2 Multivariate Analysis of the Regression of DR in Patients with Type 2 Diabetes

Variable	Univariate Analysis OR (95% CI)	*p* value	Multivariate Analysis OR (95% CI)	*p* value
Gender (male/female)	0.628 (0.404, 0.977)	0.039*	0.844 (0.448, 1.589)	0.599
Age (years)	1.03 (1.00, 1.03)	0.025*	0.955 (0.922, 0.989)	0.01*
Diabetes course (years)	1.128 (1.082, 1.175)	*p* <0.001*	1.125 (1.07, 1.182)	*p* <0.001*
Smoking history (Yes/No)	1.173 (0.736, 1.868)	0.503		
Drinking history (Yes/No)	0.549 (0.272, 1.11)	0.095		
baPWV (m/s)	1.293 (1.176, 1.422)	*p* <0.001*	1.269 (1.133, 1.421)	*p* <0.001*
Subcutaneous fat area (cm^2)	0.993 (0.989, 0.99)	*p* <0.001*	0.997 (0.989, 1.006)	0.558
Bisceral fat area (cm^2)	0.985 (0.979, 0.991)	*p* <0.001*	0.992 (0.981, 1.003)	0.171
BMI (Kg/m^2)	0.878 (0.823, 0.935)	*p* <0.001*	1.008 (0.87, 1.167)	0.92
Waist Circumference (cm)	0.955 (0.932, 0.977)	*p* <0.001*	0.993 (0.937, 1.052)	0.815
Hip circumference (cm)	0.95 (0.923, 0.978)	*p* <0.001*	0.989 (0.941, 1.041)	0.679
HbA1c (%)	0.991 (0.889, 1.104)	0.865		
FPG (mmol/L)	1.004 (0.966, 1.043)	0.842		
HCY	0.975 (0.93, 1.022)	0.287		

(*Continued*)

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Table 2 (Continued).

Variable	Univariate Analysis OR (95% CI)	*p* value	Multivariate Analysis OR (95% CI)	*p* value
BUN	1.251 (1.098, 1.425)	0.001*	1.223 (1.052, 1.423)	0.009*
TG (mmol/L)	0.988 (0.934, 1.045)	0.663		
TC (mmol/L)	1.075 (0.94, 1.229)	0.293		
LDL_C (mmol/L)	1.128 (0.926, 1.376)	0.232		
HDL_C (mmol/L)	3.937 (1.697, 9.13)	0.001*	1.437 (0.345, 5.992)	0.618
HbA1c/HDL_C	0.898 (0.836, 0.965)	0.003*	0.974 (0.865, 1.096)	0.656
FPG/HDL_C	0.974 (0.943, 1.005)	0.104		
TG/HDL_C	0.979 (0.941,1.02)	0.311		
TC/HDL_C	0.944 (0.858, 1.038)	0.235		
LDL_C/HDL_C	0.914 (0.736, 1.135)	0.418		

Note: *Significant at a P value<0.05.

and HDL-C were subjected to logistic multivariate analysis. The results showed that diabetes course, baPWV, BUN, and age were independent risk factors for DR (Table 2). Using these independent predictors, we created a model and presented it using a nomogram (Figure 2).

Validation of Predictive Model Efficacy

The ROC curve analysis results of the predictive model constructed in this study showed that the AUC value for the predictive model group was 0.75 (95% CI: 0.696–0.800), which was significantly better than that of each risk factor. The

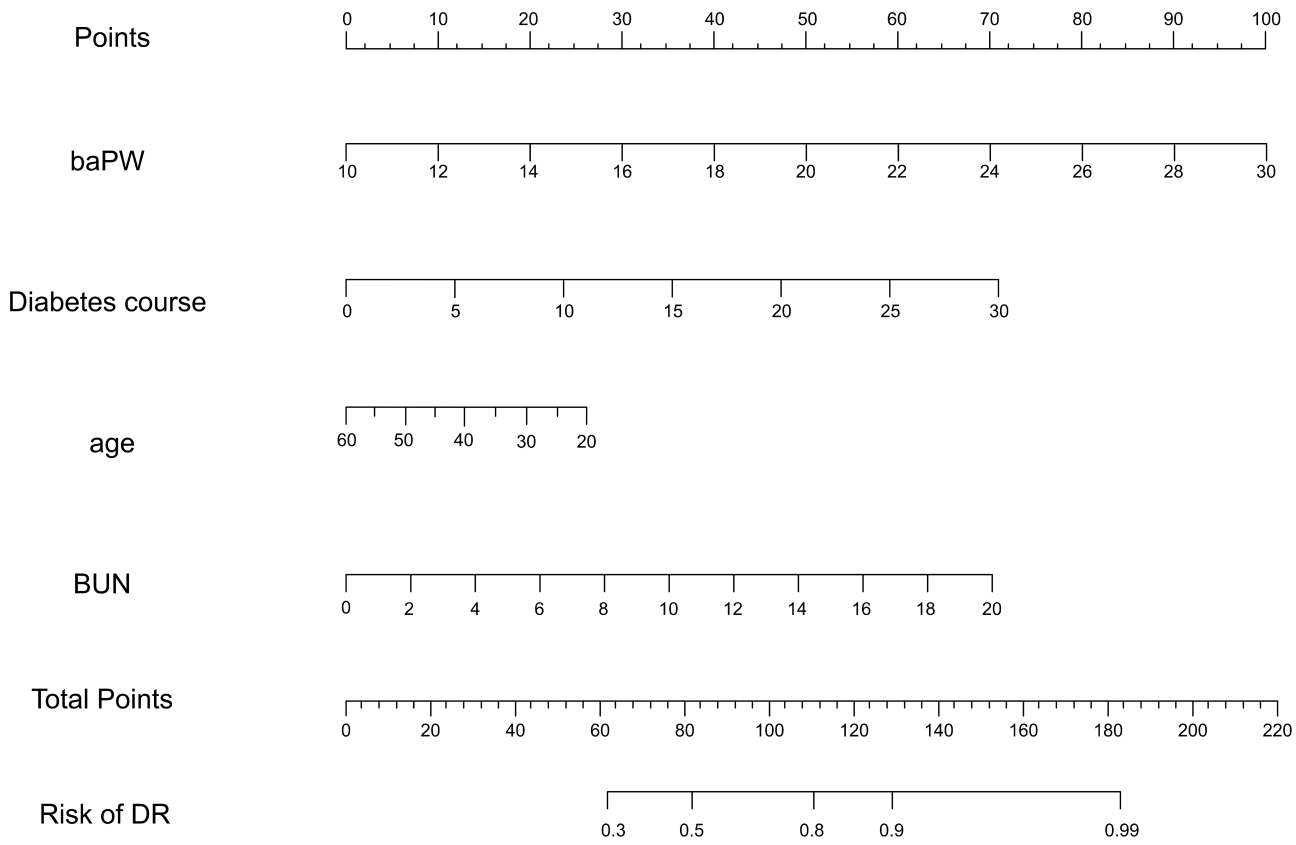

Figure 2 Nomogram for DR risk prediction in young and middle-aged T2DM patients.

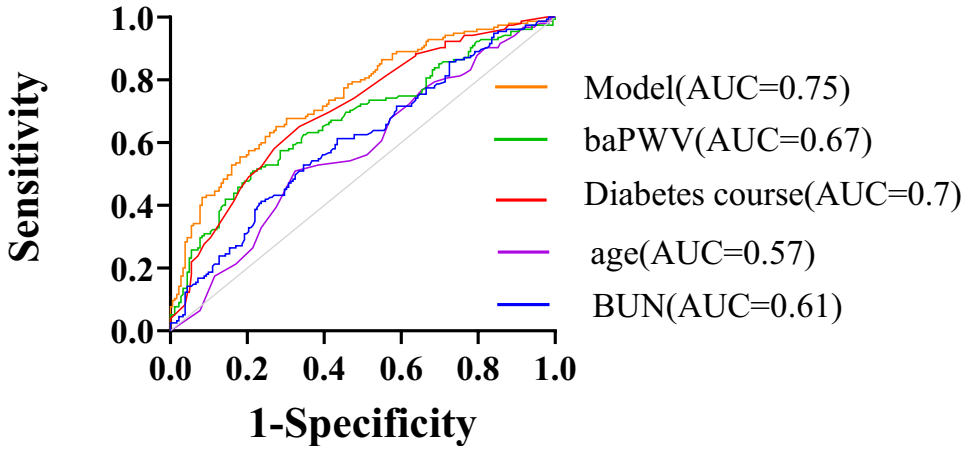

Figure 3 ROC curves comparing the predictive model with individual risk factors.

AUC values for the various risk factors were as follows: baPWV was 0.67 (95% CI: 0.613–0.730), diabetes duration was 0.70 (95% CI: 0.649–0.759), age was 0.57 (95% CI: 0.512–0.635), and BUN was 0.61 (95% CI: 0.545–0.666). This result indicates that, compared to individual risk factors, the comprehensive predictive model established in this study demonstrates superior predictive power for the risk of DR (Figure 3). Further analysis revealed that the C-index for predicting DR occurrence in patients with type 2 diabetes was 0.749 (95% CI: 0.697–0.801), with an internal validation result of 0.999 from Bootstrap, suggesting that the model has good predictive accuracy (Figure 4).

Diagnostic Application

The DR line chart comprises a table of variables used to calculate the probability of specific outcomes. According to the decision curve analysis, if the threshold probabilities for patients and physicians exceed 2% and 80%, respectively, failure to adhere to the line chart will increase the predicted probability of DR occurrence. This study compiled the overlapping data to ensure equivalent net benefits (Figure 5).

Discussion

Diabetic retinopathy (DR), a leading microvascular complication of diabetes, represents the primary cause of vision loss and blindness among the working-age population globally.[26] In China, over 37 million individuals with diabetes are affected by DR, with incidence rates escalating to 50% among those with a disease duration exceeding 10 years and nearly 100% in patients with diabetes for over 20 years.[27,28] This elevated risk arises from prolonged hyperglycemia, which induces microvascular damage through mechanisms such as endothelial dysfunction, oxidative stress, and chronic inflammation, collectively impairing retinal perfusion and promoting pathological neovascularization.[29] The often asymptomatic early stages of DR further complicate timely intervention; most patients remain unaware until advanced stages—such as proliferative DR or diabetic macular edema—when irreversible visual damage has already occurred.[30] Consequently, effective screening methods are essential for preventing disease progression.

To address this need, our study aimed to develop and validate an early risk prediction model for DR in young and middle-aged patients with T2DM. It creates and confirms a risk prediction model for DR using a nomogram through a review of the clinical data of 337 patients (182 in the NDR group and 155 in the DR group). The analysis identified the following independent risk factors for DR: diabetes duration (OR = 1.125, $p < 0.001$), baPWV (OR = 1.269, $p < 0.001$), BUN (OR = 1.223, $p = 0.009$), and younger age (OR = 0.955, $p = 0.01$). The model demonstrates good discriminatory ability (AUC = 0.75, 95% CI: 0.696–0.800) and calibration (Bootstrap validation C-index = 0.749). Decision curve analysis confirms its clinical utility within a threshold probability range of 2–85%, which partially aligns with previously reported risk factors.[31,32] Previous studies indicated that Diabetes duration and age are non-modifiable risk factors for DR, with a more pronounced impact in T2DM.[33] For instance, Gupta et al and Yun et al reported that the presence of DR was significantly associated with extended diabetes duration (>5 years), with no observed differences based on sex,

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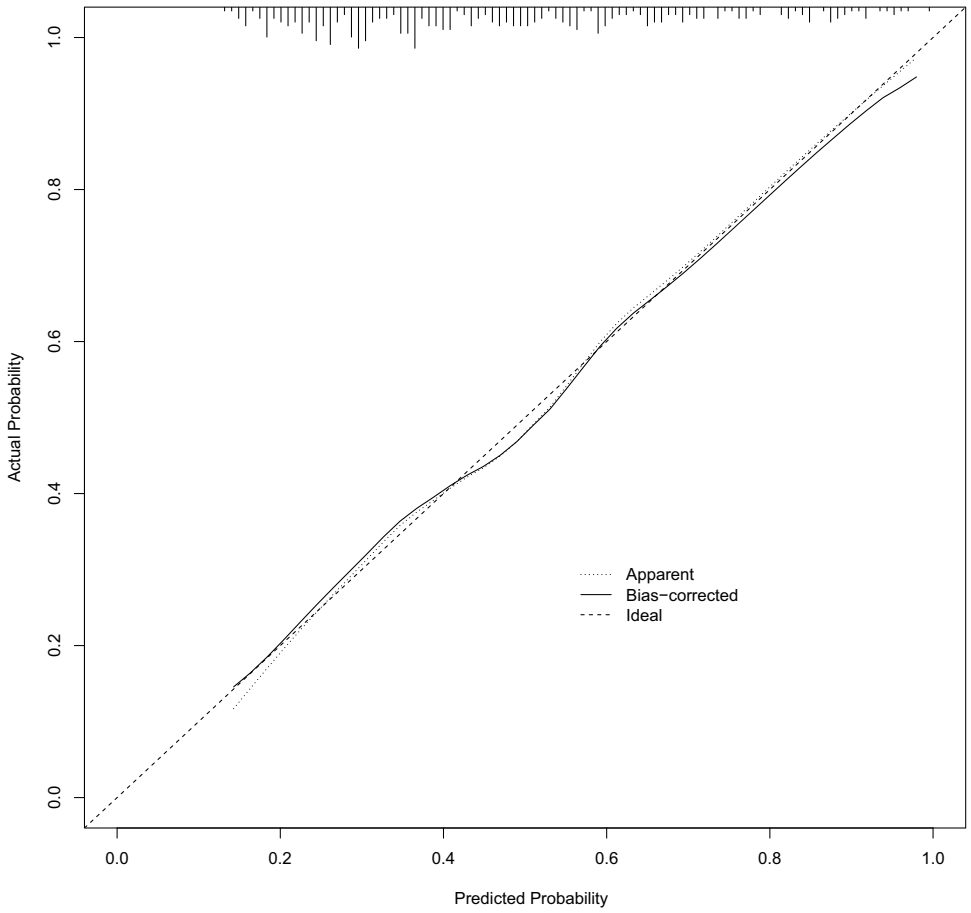

Figure 4 Prediction calibration curve for DR risk assessment.
Note: The X-axis represents the likelihood of DR. The X-axis reflects the probability predicted by the risk assessment. The Y-axis reflects the actual predicted probability.

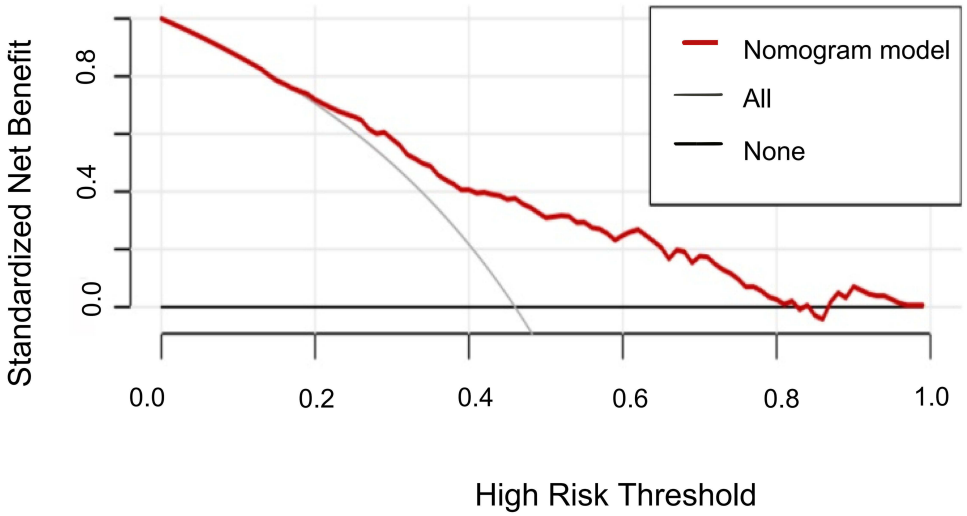

Figure 5 Decision curve analysis of the DR gridline chart.
Note: The X-axis represents the threshold probability. The Y-axis represents the net benefit, with the narrow solid line indicating patients suspected of having DR.

ethnicity, or obesity[34,35] Moreover, younger age at diagnosis has been identified as a risk factor for DR in Chinese patients with T2DM, aligning with our results.[36] This aligns with our model and previous research, and it may be attributed to the fact that younger patients face a higher DR risk due to their longer life expectancy and prolonged exposure to chronic hyperglycaemia and inflammation.

Beyond traditional factors, our model highlights baPWV, a marker of arterial stiffness, as a significant predictor of DR. Recent evidence suggests that baPWV is closely associated with diabetic microvascular complications, including DR.[37] For instance, Pei et al found that baPWV levels are related to diabetic microvascular complications, with the incidence of such complications increasing alongside elevated baPWV levels.[31] In addition, a study of type 2 diabetes patients in China included 2,473 patients and followed 663 of them for 1.44 years, showing that increased baPWV levels might be associated with DR development.[38] The proposed mechanism involves increased arterial stiffness exacerbating retinal microcirculatory ischemia and endothelial dysfunction, thereby accelerating DR progression.[39] Thus, baPWV may serve as a non-invasive and reproducible tool for identifying high-risk individuals, especially those with long-standing diabetes or concomitant hypertension.

Interestingly, BUN—commonly used as an indicator of glomerular filtration rate and renal function,[40] also emerged as an independent risk factor in our model. Elevated BUN levels have been associated with a higher prevalence of DR in diabetic populations. For instance, research by Du et al demonstrated that among diabetic patients with BUN levels exceeding 20 mg/dL, the prevalence of DR significantly increased, suggesting that BUN may serve as a predictor for DR.[41] This relationship may be explained by several interconnected pathways. First, elevated BUN often reflects underlying diabetic kidney disease, which shares common pathogenic pathways with DR, including endothelial dysfunction and chronic inflammation. Second, increased BUN may signal a state of oxidative stress and systemic microcirculatory impairment, potentially worsening retinal ischemia and hypoxia, and facilitating the transition from non-proliferative to proliferative DR.[42] Therefore, BUN may not only be a renal biomarker but also a surrogate marker of systemic microvascular dysregulation pertinent to DR pathogenesis.

In summary, DR remains a major cause of preventable vision impairment in the working-age population. This study developed a clinically applicable risk prediction model for DR in young and middle-aged patients with T2DM, incorporating diabetes duration, baPWV, BUN, and age as key predictors. The model shows good discrimination and clinical utility, providing a practical tool to identify high-risk individuals at an early stage. By enabling proactive and personalized screening and management strategies, this approach may help reduce the incidence and slow the progression of DR in this vulnerable demographic.

Conclusion

In summary, this study developed and validated a visual nomogram for detecting retinopathy in young and middle-aged patients with T2DM. Utilizing a nomogram to assess the risk of DR in this population is a novel concept, and the tool demonstrated robust predictive performance. The nomogram incorporates four common clinical features of T2DM patients: age, BUN, baPWV, and diabetes duration (AUC=0.75, 95% CI: 0.696–0.800). The nomogram enables early identification of high-risk T2DM patients, facilitating targeted interventions such as intensified glycemic control or frequent retinal screening. However, the study has several limitations. The nomogram was validated internally but lacks confirmation with an external dataset. Additionally, the retrospective collection of certain variables, such as diabetes duration, carries a potential for recall bias. Therefore, future prospective multicenter trials are essential to validate the model for broader clinical application.

Data Sharing Statement

The datasets used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval

This study was conducted in strict adherence to the Helsinki Declaration of Principles and received approval from the Ethics Committee of Luoyang Central Hospital Affiliated to Zhengzhou University (LWLL-2025-07-09-02).

Author Contributions

Conceptualization:Leilei Ma,Yanfang Zhang and Ke Huang; Methodology: Surui Shi,Jingfei Wang and Shousen Shi; Software:Yingfeng Zhang, Xi Wang and Shuaibo Shi; Validation:Leilei Ma and Yanfang Zhangand Ke Huang; Formal analysis: Surui Shi,Jingfei Wang and Shousen Shi; Investigation: Yanfang Zhang and Ke Huang; Resources:Yingfeng Zhang,Xi Wang and Shuaibo Shi;Data curation: Surui Shi,Jingfei Wang and Shousen Shi;Writing—original draft preparation: Leilei Ma,Surui Shi,Jingfei Wang,Shousen Shi,Yingfeng Zhang, Xi Wang and Shuaibo Shi; Writing—review and editing:Yanfang Zhang and Ke Huang; Visualization: Yingfeng Zhang, Xi Wang and Shuaibo Shi; Supervision:Yanfang Zhang and Ke Huang; Project administration:Leilei Ma,Yanfang Zhang and Ke Huang.Professor Zhang Yanfang and Dr. Huang Ke are co-corresponding authors, with Professor Zhang Yanfang serving as the primary corresponding author,All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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