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ORIGINAL RESEARCH

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Construction of a nomogram model to predict the development of retinopathy in type 2 diabetes mellitus based on systemic inflammatory indicators

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Abstract

This study examined the association between the incidence of diabetic retinopathy (DR) in male with type 2 diabetes mellitus (T2DM) and the levels of the systemic immunoinflammatory index (SII), platelet/lymphocyte ratio (PLR), and neutrophil/lymphocyte ratio (NLR). A total of 719 T2DM men participated in this study. Patients' basic information, physical examinations, and laboratory examinations were collected. DR in T2DM men was screened for independent influencing variables using both univariate and multivariate logistic regression analysis. A 7:3 ratio of random numbers was used to divide participants into Training cohort (n = 503) and Validation cohort (n = 216). There were 106 (14.74%) DR patients among 719 T2DM men. NLR, PLR and SII levels were significantly higher in DR patients than in non-DR patients in the training cohort ($p < 0.05$). DR occurrence in T2DM men was predicted by the area under curves (AUCs) of NLR, PLR and SII of 0.721, 0.745 and 0.751, respectively. Age, diabetic neuropathy (DN), diabetic kidney disease (DKD), fasting glucose (FPG), glycated albumin (GA), ultrasensitive C-reactive protein (hsCRP), NLR, PLR and SII were the independent risk factors for DR in T2DM men ($p < 0.05$). On the basis of these ten independent risk variables, a nomogram model was constructed for DR prediction. The AUCs for the training and validation cohorts were 0.982 and 0.981, respectively. In both the training and validation cohorts, the Hosmer-Lemeshow test showed a good fit. Also, clinical decision curves supported the model's clinical benefit. DR occurrence in T2DM men is independently influenced by the peripheral blood systemic inflammatory indexes NLR, PLR and SII. With good predictive performance and clinical utility, a nomogram based on inflammatory clinical features can provide a preliminary assessment of DR occurrence in T2DM men.

Keywords

Type 2 diabetes mellitus; Diabetic retinopathy; Systemic inflammatory indexes; Nomogram; Risk factors

1. Introduction

Type 2 diabetes mellitus (T2DM) is a prevalent endocrine-metabolic disease caused by an absolute or relative insulin shortage [1]. Diabetic retinopathy (DR) is T2DM's most serious microvascular complication and the leading cause of blindness [1]. Early detection can delay or prevent DR's onset [1]. Clinically, DR and its risk can be identified by visualizing the retinal vasculature, as well as evaluating blood glucose, lipids, blood pressure, body weight and smoking [2]. In general, male T2DM patients tend to experience multiple complications, including DR, as a result of lifestyle habits, such as smoking and alcohol consumption. Studies on T2DM-related complications have predominantly examined women and the elderly, especially pregnant women, and men have received little attention. The identification of easily accessible biomarkers that can effectively predict DR in men with T2DM is therefore necessary.

Inflammatory responses play a key role in DR development [3]. All components of inflammation, including leukocyte recruitment and/or activation, as well as a range of functional and molecular mediators, are non-specific responses to trauma or stress. Peripheral blood systemic inflammatory markers, such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic immunoinflammatory index (SII), are currently most accessible for clinical testing [4]. A variety of chronic inflammatory diseases, including rheumatoid arthritis, sepsis, DR, cancer and others, have been demonstrated to exhibit high clinical reference values with NLR, PLR and SII in recent years. By defining disease progression accurately and initiating intervention, this lays the foundation for disease management [5, 6]. However, studies on the association

between peripheral blood systemic inflammatory indexes and DR in T2DM patients are limited.

This study examined the correlation between NLR, PLR and SII levels with DR incidence in T2DM men, and assessed their diagnostic efficacy in predicting DR. Moreover, a nomogram model for predicting DR occurrence was constructed based on the influencing factors. This study aimed to identify a reliable and simple prediction method for the early DR prediction in T2DM men.

2. Materials and methods

2.1 Patients

This study included 719 T2DM men at The People's Hospital of Yuhuan between March 2020 to August 2023. Inclusion criteria: (1) age ≥18 years old. (2) T2DM diagnostic criteria were referred to in the Chinese Guidelines for the Prevention and Control of Type 2 Diabetes Mellitus (2020 edition): Typical diabetic symptoms and random blood glucose ≥11.1 mmol/L, or fasting blood glucose (FPG) ≥7.0 mmol/L, or 2-h post-glucose-loaded blood glucose (2hPG) ≥11.1 mmol/L, or glycated hemoglobin (HbA1C) ≥6.5%. Exclusion criteria: (1) Degree of lens clouding affecting fundus examination. (2) History of fundus laser treatment or internal eye surgery. (3) Closed-angle glaucoma is not suitable for dilated pupil examinations. (4) Severe systemic diseases or other diseases affecting ocular circulation (*e.g.*, significant refractive error, glaucoma, retinal vascular occlusion and eye trauma).

2.2 Sample size calculation

Based on an expected effect size of 0.735 and a type I error probability <0.05, the number of events is sufficient to achieve a statistical power of 0.8. The study is based on a binary outcome mode. The sample size meets the minimum size required for a mean absolute precision error (MAPE) <0.05 and an expected uniform shrinkage factor <10%, when a proportion of total variance explained (R^2_{cs}) = 0.1 and a maximum number of 5 potential predictors is considered.

2.3 Data collection

Data was collected regarding patients' demographic and sociological characteristics, lifestyle, behavioral habits, diabetes mellitus duration, family history of diabetes mellitus, disease history, medication history and biochemical indices.

2.4 Fundus examination

The DR diagnosis and staging was carried out systematically by professional ophthalmologists using fundus color photographys. The patient's visual acuity, intraocular pressure, and the basic condition of the anterior segment of the eye were initially evaluated using slit lamp microscopy. A diameter of over 6 mm was achieved for the pupils. A 90D anterior ophthalmoscopy was performed after 1 or 2 eye drops with compound tropicamide, a rapid dilator. Two experienced ophthalmologists performed DR diagnosis and staging according to the uniform criteria recommended by the DR International Society of Ophthalmology in 2002 [7]. This diagnosis is made based on the presence of microaneurysms, hard exudates, intraretinal hemorrhagic dots, soft exudates, venous beading, intraretinal microvascular abnormalities, neovascularization, preretinal hemorrhage or vitreous hemorrhage.

2.5 Statistical analysis

Data analysis was conducted using SPSS 22.0 (IBM Corp., Armonk, NY, USA) and R4.3.2. T2DM men were randomly divided into training and validation cohorts in the ratio of 7:3 according to the Type 2a principle in the TRIPOD statement of the International Code of Predictive Modeling. DR risk was predicted using a nomogram constructed from the training cohort, and internal validation was carried out with the validation cohort. Normally distributed measurements were presented as mean ± standard deviation (SD), independent samples *t*-test was used to compare groups. Non-normally distributed measurements were presented as the median (P25–P75), and group comparisons were made using the Wilcoxon rank sum test. Count data were presented as number of instances and composition ratio, and group comparisons were made by the χ^2 test. For rank information, the Wilcoxon rank sum test was employed. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the diagnostic effectiveness of the pertinent markers for DR. In univariate and multivariate logistic regression analyses, DR in T2DM men was linked with relevant variables. A nomogram prediction model for DR was established based multivariate logistic regression analysis. Internal validation was conducted using Bootstrap self-sampling, and validation was performed externally. Model discrimination was evaluated using C-indexes and ROC curves. Model consistency is evaluated by plotting calibration curves and performing the Hosmer-Lemeshow test. Model clinical validity was assessed by Decision curve analysis (DCA) was used to assess the clinical validity of the model. In all analyses, two-sided tests were conducted, with test level $\alpha = 0.05$.

3. Results

3.1 Basic characteristics

DR patients accounted for 106 (14.74%) of the 719 T2DM men. Among 719 T2DM men, 503 were in the training cohort and 216 were in the validation cohort. In all baseline indices, there was no statistically significant difference between the training and validation cohort ($p < 0.05$, Table 1).

3.2 Comparison of clinical data of DR and non-DR patients in the training cohort

A significant difference was found between the non-DR and DR patients for age, smoking, alcohol consumption, duration of diabetes, diabetic kidney disease (DKD), hyperlipidemia, bimatoprost, FPG, glycated albumin (GA), direct bilirubin (DBIL), indirect bilirubin (IBIL), total bile acids (TBA), estimated glomerular filtration rate (eGFR), urine microalbumin creatinine ratio (UACR), high-sensitivity C-reactive protein (hsCRP), NLR, PLR and SII in the training cohort ($p < 0.05$, Table 2). NLR, PLR and SII levels were significantly higher in

TABLE 1. Comparison of clinical data between training and validation cohort for T2DM men.

	Training cohort (n = 503)	Validation cohort (n = 216)	Statistical value	*p*
Age	64.53 ± 10.28	64.61 ± 10.62	0.093	0.926
BMI	25.41 ± 3.39	25.51 ± 3.33	0.388	0.698
Smoking	275	114	0.218	0.640
Alcohol	104	37	1.205	0.272
Duration of diabetes	11.00 (1–28)	12.00 (1–29)	0.712	0.406
Family history of diabetes	180	77	0.001	0.972
DN	142	57	0.256	0.613
DKD	258	112	0.019	0.891
DF	178	68	1.024	0.311
Hypertension	364	152	0.297	0.586
Hyperlipidemia	285	123	0.005	0.944
Hypoglycemic drugs	383	166	0.042	0.838
Sulfonylureas	225	104	0.711	0.399
Biguanides	270	113	0.113	0.737
Alpha-glucosidase inhibitors	210	87	0.135	0.713
Glargine	203	93	0.454	0.500
Dipeptidyl peptidase IV inhibitors	13	7	0.241	0.624
Insulin Sensitizers	10	3	0.306	0.580
Sodium-glucose cotransporter protein 2 inhibitors	6	5	1.263	0.261
Antihypertensive drugs	168	69	0.145	0.704
Lipotropic drugs	219	98	0.206	0.650
FPG (mmol/L)	10.08 ± 2.44	9.74 ± 1.64		
HbA1c (%)	8.06 ± 1.80	8.16 ± 1.86	0.719	0.472
GA (%)	18.08 ± 7.41	18.16 ± 7.66	0.144	0.885
TBIL (μmol/L)	16.09 ± 9.50	16.08 ± 9.53	0.018	0.986
DBIL (μmol/L)	4.09 ± 2.02	4.32 ± 2.06	1.424	0.155
IBIL (μmol/L)	10.05 ± 5.45	9.79 ± 5.47	0.580	0.562
TBA (μmol/L)	3.76 ± 1.90	3.76 ± 2.00	0.002	0.999
BUN (mmol/L)	5.06 ± 2.07	5.18 ± 2.13	0.696	0.487
Scr (μmol/L)	77.32 ± 40.03	78.96 ± 41.94	0.497	0.619
SUA (μmol/L)	287.58 ± 89.49	290.46 ± 88.29	0.397	0.691
eGFR (mL/min/1.73 m^2/d)	90.21 ± 37.84	92.22 ± 38.73	0.647	0.518
UACR (mg/g)	7.12 ± 6.16	7.34 ± 6.18	0.428	0.669
hsCRP (mg/L)	2.61 ± 2.03	2.50 ± 1.89	0.664	0.507
TC (mmol/L)	5.12 ± 2.67	5.16 ± 2.79	0.157	0.875
TG (mmol/L)	1.69 ± 0.96	1.74 ± 1.00	0.597	0.551
HDL-C (mmol/L)	1.22 ± 0.49	1.20 ± 0.49	0.473	0.636
LDL-C (mmol/L)	2.71 ± 0.89	2.73 ± 0.88	0.273	0.785
LDH (U/L)	156.61 ± 69.49	153.36 ± 67.82	0.578	0.564

TABLE 1. Continued.

	Training cohort (n = 503)	Validation cohort (n = 216)	Statistical value	*p*
α-HBDH (U/L)	130.31 ± 66.18	132.84 ± 63.40	0.477	0.634
AST (U/L)	19.49 ± 8.43	19.29 ± 8.83	0.297	0.767
ALT (U/L)	27.87 ± 18.28	27.42 ± 18.05	0.301	0.763
GGT (U/L)	27.25 ± 17.63	28.07 ± 18.34	0.561	0.575
NLR	1.81 (0.97, 2.77)	1.79 (0.86, 2.81)	0.617	0.537
PLR	93.91 (53.05, 128.13)	89.62 (45.76, 122.81)	0.984	0.326
SII	407.57 (308.77, 506.47)	415.09 (322.14, 499.00)	0.637	0.524
DR	77	29	0.426	0.514

BMI: body mass index; DN: diabetic neuropathy; DKD: diabetic kidney disease; GA: glycated albumin; TBIL: total bilirubin; DBIL: direct bilirubin; IBIL: indirect bilirubin; TBA: total bile acids; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; hsCRP: high-sensitivity C-reactive protein; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LDH: lactate dehydrogenase; α-HBDH: α-hydroxybutyrate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immunoinflammatory index; DR: diabetic retinopathy.

DR patients than in non-DR patients ($p < 0.05$, Table 2). An ROC curve analysis indicated that NLR, PLR and SII could all reliably predict DR occurrence for T2DM men with AUCs of 0.721 (95% CI: 0.664–0.779), 0.745 (95% CI: 0.677–0.814), and 0.751 (95% CI: 0.686–0.815), respectively, according to ROC curve analysis (Fig. 1).

3.3 Multivariate logistic regression analysis

With DR's presence as the dependent variable, multivariate logistic regression analysis was performed. Based on model 1, DR development was independently associated with age, smoking, DN, DKD, FPG, GA, hsCRP, NLR, PLR and SII in T2DM men ($p < 0.05$, Table 3). Further, both models 2 and 3 showed that elevated levels of NLR, PLR and SII contributed to DR ($p < 0.05$, Table 3).

3.4 Construction of the nomogram model

Based on the outcome of the multivariate logistic regression analysis, a nomogram was generated (Fig. 2). The risk factors for each patient were represented by variable axes on the nomogram. Drawing a vertical line upward calculated the score for each risk factor. Chances of developing DR in T2DM men were determined by combining several factors.

3.5 Validation and evaluation of models

Internal validation of the predictive models was conducted using a validation cohort. High degree of discrimination was observed in both training and validation cohorts, with a 0.982 (95% CI: 0.945–0.998) and 0.981 (95% CI: 0.924–0.998) AUC, respectively (Fig. 3). According to calibration correction curves and Hosmer-Lemeshow test, there was no statistically significant difference between the predicted and actual probabilities for either the training cohort ($p = 0.448$) or the validation cohort ($p = 0.243$) ($p > 0.05$, Fig. 4), showing a good fit between the model predictions and the actuals. The clinical decision curve also showed that the model was clinically beneficial (Fig. 5).

4. Discussion

DR is a common complication of diabetes mellitus, caused by damage to retinal microvessels, which seriously affects patients' vision and can even results in blindness. DR incidence also increases as diabetic patients increase year by year. Not only does DR affect patients' vision and quality of life seriously, but it also burdens the family and society economically and psychologically. Compared with those with T2DM alone, patients with T2DM combined with DR have a significantly higher long-term mortality rate, and the mortality risk of patients with DR is about 1.6 times higher than that of patients with T2DM alone in Asian populations [8]. In China, early DR prevention is still emerging. Clinical ophthalmologists who perform fundus examinations must possess high examination techniques and long-term working experience, especially at the grassroots level, where specialized personnel and examination equipment are lacking [3]. Thus, raising awareness of DR and diagnosing it early are of particular importance.

DR development is largely attributed to chronic inflammation [9]. All components of inflammation, including leukocyte recruitment and/or activation, as well as a range of functional and molecular mediators, are non-specific responses to trauma or stress. In the systemic inflammatory response, neutrophils, basophils, eosinophils, lymphocytes, and monocytes play unique biological roles. Neutrophils, for instance, have nonspecific inflammatory responses. Lymphocytes, on the other hand, can be modulated by nutritional status and stress status to inhibit the inflammatory response [10]. With T2DM, hyperglycemia promotes transcription factors expression, leading to neutrophilia and protective lymphocyte reduction [11]. In patients with DR, chronic inflammatory response,

TABLE 2. Comparison of clinical data of DR and non-DR patients in the training cohort.

	non-DR (n = 426)	DR (n = 77)	Statistical value	*p*
Age	63.20 ± 10.05	71.88 ± 8.30	7.150	<0.001
BMI	25.45 ± 3.40	25.15 ± 3.34	0.707	0.480
Smoking	215	60	19.832	<0.001
Alcohol	62	42	63.591	<0.001
Duration of diabetes	6.00 (2, 17)	11.00 (1, 26)	3.936	<0.001
Family history of diabetes	151	29	0.139	0.709
DN	102	40	25.242	<0.001
DKD	195	63	33.911	<0.001
DF	153	25	0.339	0.560
Hypertension	306	58	0.398	0.528
Hyperlipidemia	227	58	12.898	<0.001
Hypoglycemic drugs	325	58	0.034	0.855
Sulfonylureas	187	38	0.785	0.376
Biguanides	220	50	4.634	0.031
Alpha-glucosidase inhibitors	183	27	1.670	0.196
Glargine	178	25	2.352	0.125
Dipeptidyl peptidase IV inhibitors	9	4	2.461	0.117
Insulin Sensitizers	7	3	1.699	0.192
Sodium-glucose cotransporter protein 2 inhibitors	4	2	1.522	0.230
Antihypertensive drugs	289	46	1.924	0.165
Lipotropic drugs	185	34	0.014	0.906
FPG (mmol/L)	9.86 ± 2.48	11.29 ± 1.84	4.825	<0.001
HbA1c (%)	8.00 ± 1.83	8.38 ± 1.63	1.720	0.086
GA (%)	17.27 (12.28, 22.54)	22.05 (18.47, 26.73)	5.392	<0.001
TBIL (μmol/L)	15.07 (8.53, 23.28)	14.26 (9.72, 19.34)	0.772	0.440
DBIL (μmol/L)	4.14 (2.67, 5.62)	3.12 (1.67, 4.74)	3.240	0.001
IBIL (μmol/L)	10.2 (5.99, 14.02)	8.4 (5.02, 12.18)	2.219	0.026
TBA (μmol/L)	3.77 (2.13, 5.08)	4.41 (2.71, 5.60)	2.049	0.041
BUN (mmol/L)	4.91 (3.67, 6.18)	5.33 (3.43, 6.68)	1.058	0.290
Scr (μmol/L)	75.89 (46.67, 102.13)	73.18 (49.44, 120.56)	0.552	0.581
SUA (μmol/L)	288.58 ± 90.85	282.08 ± 81.91	0.568	0.558
eGFR (mL/min/1.73 m^2/d)	82.67 (66.91, 94.73)	91.84 (63.94, 117.86)	2.417	0.016
UACR (mg/g)	5.56 (2.69, 8.72)	11.80 (5.02, 20.62)	6.706	<0.001
hsCRP (mg/L)	2.05 (1.10, 3.27)	3.16 (1.90, 7.00)	4.858	<0.001
TC (mmol/L)	5.20 (2.96, 6.98)	4.84 (4.11, 5.50)	1.017	0.309
TG (mmol/L)	1.59 (0.99, 2.3)	1.64 (1.02, 2.3)	0.622	0.534

TABLE 2. Continued.

	non-DR (n = 426)	DR (n = 77)	Statistical value	*p*
HDL-C (mmol/L)	1.21 (0.83, 1.58)	1.23 (0.97, 1.39)	0.509	0.610
LDL-C (mmol/L)	2.70 ± 0.89	2.77 ± 0.89	0.592	0.554
LDH (U/L)	158.60 (107.30, 201.73)	171.54 (112.81, 229.41)	1.632	0.103
α-HBDH (U/L)	129.02 (82.42, 174.61)	137.25 (91.98, 160.77)	0.136	0.892
AST (U/L)	19.83 (13.55, 25.56)	18.46 (16.54, 21.36)	0.958	0.338
ALT (U/L)	25.82 (12.82, 41.09)	24.59 (12.26, 38.44)	0.916	0.360
GGT (U/L)	25.33 (13.21, 38.84)	25.62 (11.42, 36.41)	0.584	0.559
NLR	1.54 (0.79, 2.51)	2.68 (1.90, 3.27)	6.187	<0.001
PLR	85.25 (51.25, 115.06)	145.87 (90.28, 191.71)	6.858	<0.001
SII	383.12 (279.29, 479.44)	541.29 (427.56, 629.28)	7.007	<0.001

BMI: body mass index; DN: diabetic neuropathy; DKD: diabetic kidney disease; DF: diabetic foot; FPG: fasting blood glucose; HbA1c: glycated hemoglobin; GA: glycated albumin; TBIL: total bilirubin; DBIL: direct bilirubin; IBIL: indirect bilirubin; TBA: total bile acids; BUN: blood urea nitrogen; Scr: serum creatinine; SUA: serum uric acid; eGFR: estimated glomerular filtration rate; UACR: urine microalbumin creatinine ratio; hsCRP: high-sensitivity C-reactive protein; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LDH: lactate dehydrogenase; α-HBDH: α-hydroxybutyrate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immunoinflammatory index; DR: diabetic retinopathy.

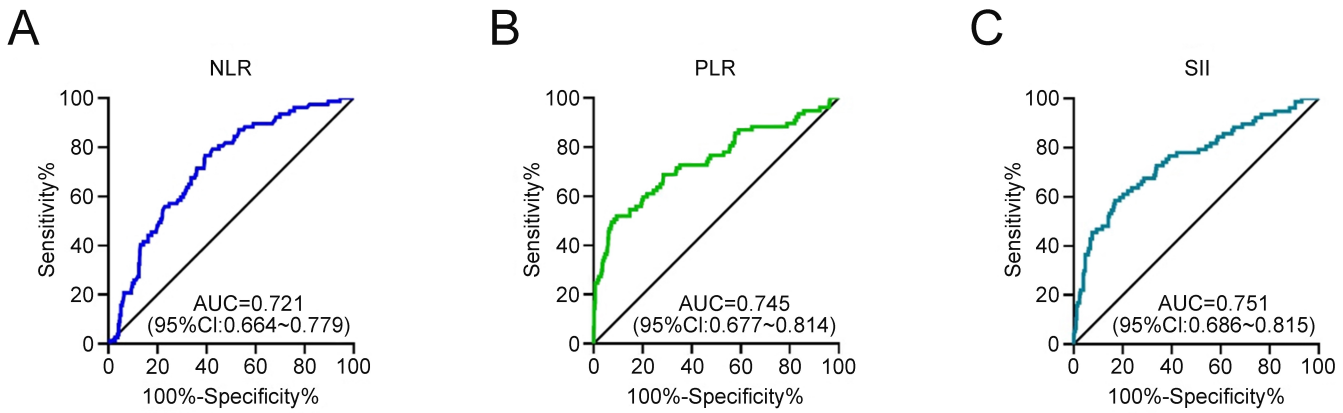

FIGURE 1. ROC curves for predicting DR occurrence in T2DM men. (A) NLR; (B) PLR; (C) SII. NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immunoinflammatory index; AUC: area under the curve; CI: confidence interval.

neuronal degeneration and increased neoangiogenesis form a vicious circle, further promoting disease progression [12]. In this study, NLR, PLR and SII were significantly elevated in DR patients and showed high diagnostic efficacy in predicting DR in T2DM men (AUC >0.7). According to multivariate logistic regression analysis, an increase in NLR, PLR and SII was independently associated with DR in T2DM men. When other influencing factors were corrected, elevated NLR, PLR and SII remained independent influences on DR in T2DM men. Therefore, clinical monitoring of NLR, PLR and SII levels in T2DM men can facilitate early identification of the high-risk group for DR.

DR has a complicated pathogenesis that has not yet been unified in the clinic. This study indicate that aging may be related to the occurrence of DR in diabetic patients due to the obvious decline of a patient's body function. Furthermore, most elderly patients are also suffering from underlying diseases that are less resistant to DR, thereby increasing the risk of DR [13]. The link between unhealthy lifestyles and DR has been the focus of an increasing number of observational epidemiologic. Smoking, alcohol consumption and obesity are three of the most common unhealthy lifestyle habits among Chinese men. DR risk is associated with smoking, alcohol consumption and obesity according to a mendelian randomization study [14]. This study showed differences in these three indicators among men with and without DR, and smoking was an independent risk factor for DR. It has been argued that diabetes mellitus duration is associated with DR, and this may be due to the

TABLE 3. Multivariate logistic regression analysis.

	Model 1			Model 2			Model 3		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.097	1.040–1.157	0.001	-	-	-	-	-	-
Smoking	4.830	1.450–16.088	0.001	-	-	-	-	-	-
DN	3.377	1.262–9.036	0.015	3.280	1.127–9.547	0.029	-	-	-
DKD	3.116	1.251–7.758	0.015	3.936	1.288–12.031	0.016	-	-	-
FPG	1.236	1.039–1.471	0.017	-	-	-	-	-	-
GA	1.103	1.035–1.176	0.003	1.108	1.031–1.191	0.005	-	-	-
hsCRP	1.493	1.221–1.826	<0.001	1.684	1.346–2.107	<0.001	-	-	-
NLR	2.239	1.492–3.360	<0.001	2.410	1.544–3.761	<0.001	1.857	1.443–2.391	<0.001
PLR	1.023	1.014–1.033	<0.001	1.024	1.013–1.035	<0.001	1.019	1.013–1.025	<0.001
SII	1.009	1.005–1.012	<0.001	1.009	1.005–1.013	<0.001	1.006	1.004–1.009	<0.001

Note: Model 1: uncorrected; Model 2: corrected for age and smoking; Model 3: corrected for age, smoking, DN, DKD, FPG, GA, hsCRP.

DN: diabetic neuropathy; DKD: diabetic kidney disease; FPG: fasting blood glucose; GA: glycated albumin; hsCRP: high-sensitivity C-reactive protein; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immunoinflammatory index; DR: diabetic retinopathy; OR: odds ratio; CI: confidence interval.

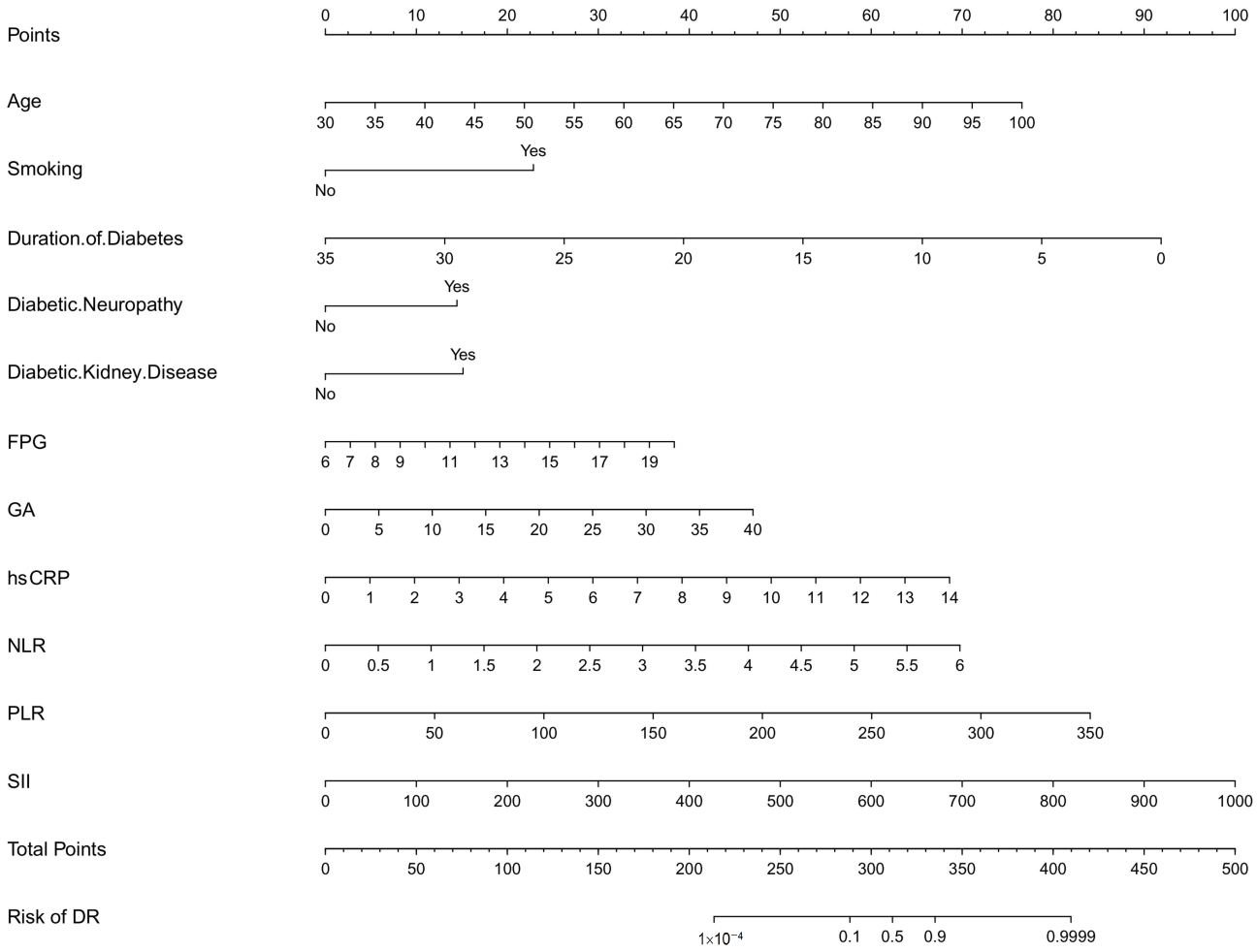

FIGURE 2. A nomogram model for predicting DR occurrence in T2DM men. FPG: fasting blood glucose; GA: glycated albumin; hsCRP: high-sensitivity C-reactive protein; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immunoinflammatory index; DR: diabetic retinopathy.

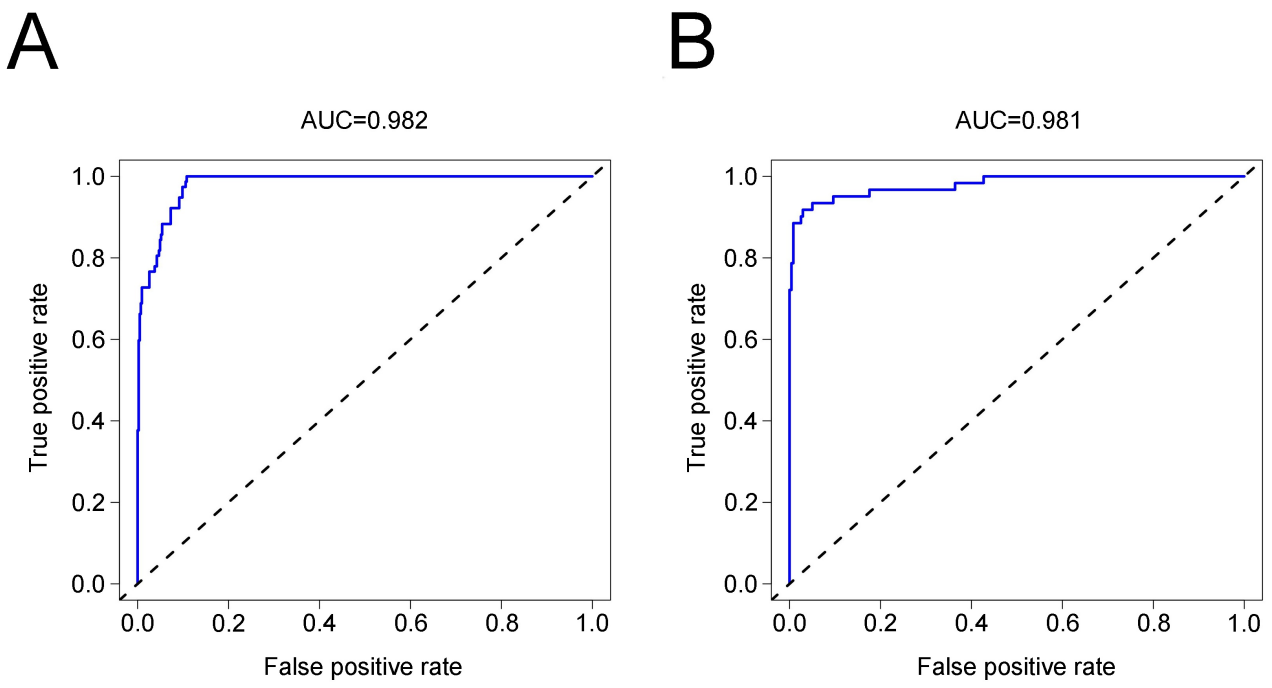

FIGURE 3. ROC curve for nomogram model. (A) The ROC for training cohort; (B) The ROC for validation cohort. AUC: area under the curve.

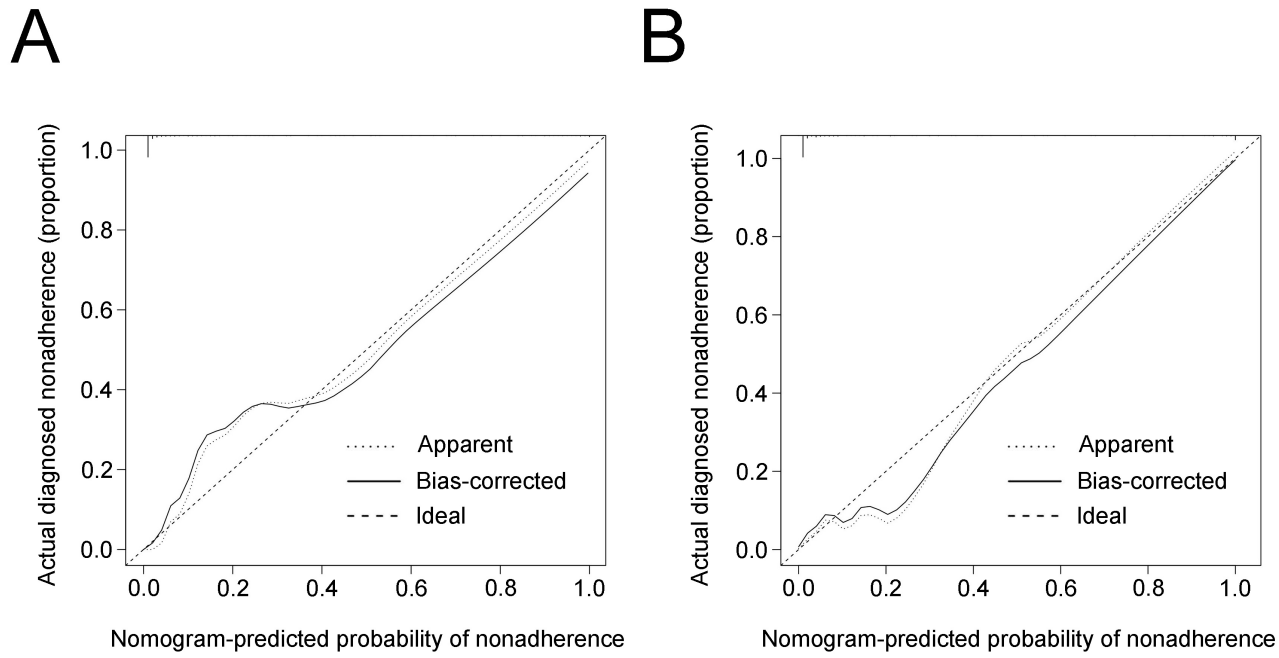

FIGURE 4. Calibration curve for nomogram model. (A) The calibration curve for training cohort; (B) The calibration curve for validation cohort.

fact that patients with diabetes mellitus for a longer period have a greater impact on the structure of the fundus than on its function, which will gradually exacerbate the damage. Blood glucose levels and DR lesions severity were strongly correlated in previous research patients. Diabetes patients with inadequate glycemic control and high HbA1c are more likely to suffer from DR [15]. This is primarily due to slow, long-term and irreversible glycation reactions generating HbA1c. HbA1c levels are influenced by blood glucose concentration and the time blood glucose and hemoglobin come into contact. They may be used as a direct indicator of short-term fluctuations in blood glucose [16]. In comparison with hemoglobin, HbA1c has a higher affinity for oxygen, which may reduce hemoglobin's oxygen content, leading to oxygen not being normally transmitted and diffused in the body, triggering retinal hypoxia and eventually causing morbidity [17]. However, our findings demonstrated that, among the glycemic markers, only the FPG level was an independent risk factor for DR, which

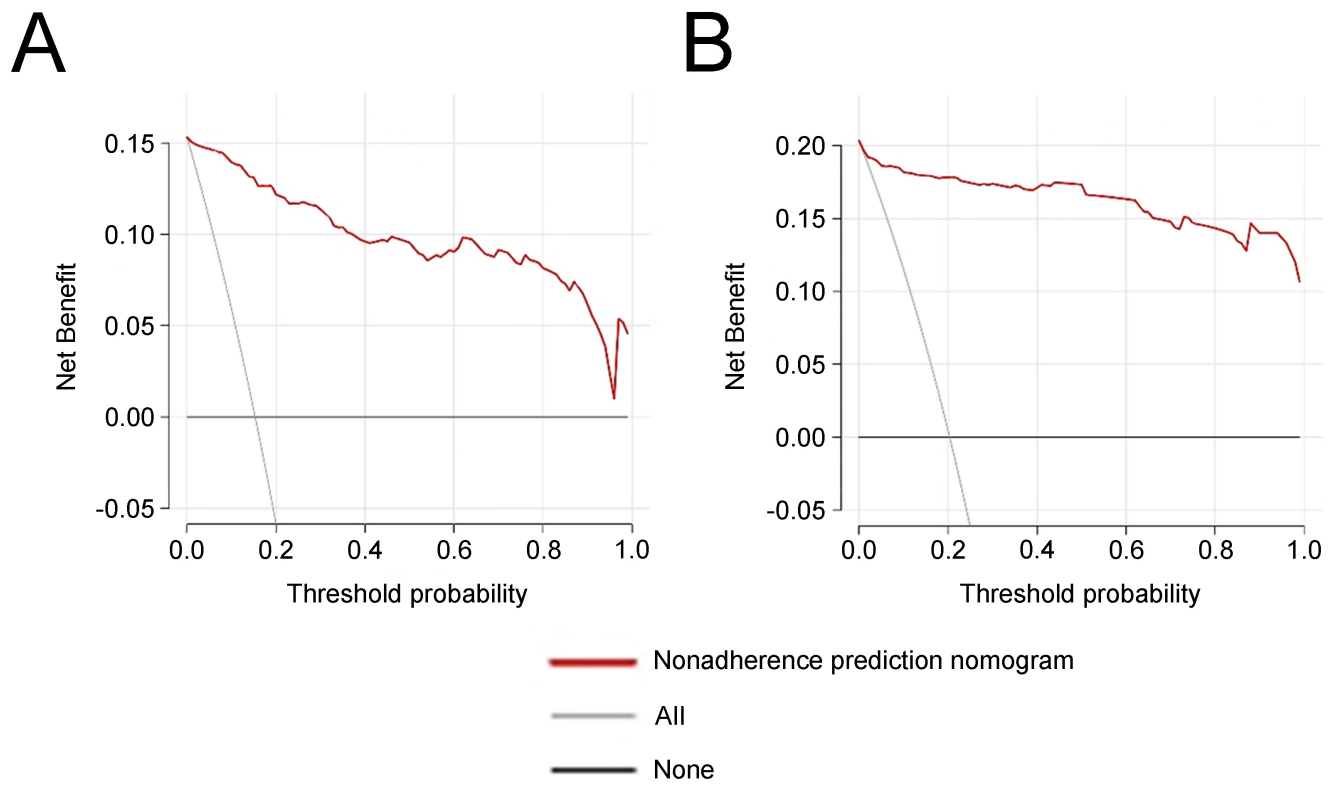

FIGURE 5. Decision curve analysis of nomogram model. (A) The decision curve analysis for training cohort; (B) The decision curve analysis for validation cohort.

may be because blood glucose levels are usually influenced by a variety of factors, including diet, exercise, glucose-lowering treatments, and medication regimens. GA induces apoptosis of retinal peripheral cells, which directly damages retinal nerves. GA also activates microglia and produces pro-inflammatory factors, which contributes to DR [18]. According to Yau *et al.* [19], DN and DKD can raise DR likelihood. Approximately 87% of individuals with proliferative DR also have DKD, and four times more people with DN develop DR than without [20]. DN, DKD and microangiopathy are prevalent microvascular problems associated with diabetes mellitus. Their pathophysiologic processes differ, but all are associated with impaired glucose metabolism, microcirculatory abnormalities, and microangiopathy [21].

The majority of DR prediction models are based on image analysis. However, little research has been conducted on DR prediction based on pertinent indicators. There are numerous diseases where the nomogram is widely used for individualized diagnosis, therapy, and prognosis prediction [22]. In this study, 10 indicators were screened for DR prediction in T2DM men. All of the studies presented in nomogram form by Mo *et al.* [23], Zhu *et al.* [24], Li *et al.* [25], and Yang *et al.* [26] showed the risk of DR was associated with age, diabetes mellitus duration, glycosylated hemoglobin, proteinuria, blood pressure, and serum creatinine value, *etc*. In the present study, systemic inflammation indicators were supplemented with the predictive model, which resulted in an AUC of 0.982. Compared to other studies on DR prediction, this study further developed a nomogram based on the basic clinical information and routine biochemical indicators of the patients, and constructed a prediction model using multifactorial logistic regression analysis, enabling clinicians to quickly and easily assess patients' conditions.

Still, this study has several limitations. This study was a single-center retrospective study with a limited number of cases collected from one hospital. As well, the nomogram of this study demonstrated good differentiation and calibration for internal validation, but was not externally validated. This cross-sectional study provides less evidence than cohort studies; cohort studies are required to validate and improve this model's predictive value. Moreover, this study only examined T2DM men, and comparative studies in women are still needed.

5. Conclusions

In conclusion, DR in T2DM men is independently associated with NLR, PLR and SII, the peripheral blood systemic inflammatory indices. An early evaluation of DR presence in T2DM men can be detected using a nomogram with high prediction efficiency and practical application value.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

HuYC, HoYC—designed the study and carried them out; supervised the data collection, analyzed the data, interpreted the data; prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of the People's Hospital of Yuhuan (Approval no. 2020023). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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