A Prediction Model for Worsening Diabetic Retinopathy after Panretinal Photocoagulation

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Research Article

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Abstract

Background

Diabetic retinopathy (DR) as one of the severe complications of diabetes mellitus is the leading cause of blindness in the working age worldwide. While DR still has a high risk of progression after panretinal photocoagulation (PRP) treatment. Hence, this study aims to assess the risk factors and established a model for predicting worsening diabetic retinopathy (DR-worsening) within 5 years after PRP.

Methods

Patients who were diagnosed with severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy and treated with PRP were included and randomly assigned to either a training or validation cohort. The multivariate logistic regression analysis was used to screen potential risk factors in the training cohort. Then the model was developed and validated using discrimination and calibration.

Results

A total of 271 patients were included, and 56.46% of patients had an outcome of DR-worsening. In the training cohort (n = 135), age (odds ratio (OR) = 0.91, 95% confidence interval (CI) 0.85–0.96), baseline best corrected visual acuity (OR = 0.11, 95% CI 0.01–0.87), diabetic nephropathy (OR = 16.83, 95% CI 1.92–147.50) and hyperlipidemia (OR = 5.53, 95% CI 1.25–24.57) were screened out as the independent risk factors, which were incorporated into the predictive model. The area under the receiver operating characteristic curve and the calibration slope in the training and validation cohort were 0.78, 0.99 (95% CI 0.62–1.35), and 0.79, 1.01 (95% CI 0.54–1.49), respectively. Then, two risk groups were developed, and the actual probability in the low-risk and high-risk groups were 37.42% and 85.19%, respectively.

Conclusions

We developed a model to predict the risk of DR-worsening after PRP treatment within 5 years, which can be used as a rapid risk assessment system and remind us to pay attention to the associated risk factors.

Introduction

Diabetic retinopathy (DR), one of the most common microvascular complications of diabetes mellitus, is the leading cause of blindness and visual impairment in the working age (20–65 years) worldwide [1, 2]. It is classified as non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) based on the proliferative status of retinal neovascularization. PDR could be followed by serious complications, such as vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma, a more advanced stage with a risk of poor vision outcome [3–5].

Panretinal photocoagulation (PRP) is currently the standard treatment for PDR and severe NPDR which was recommended in the previous clinical trials [6, 7]. With proper treatment including PRP, PDR patients have a 90% reduced risk of blindness within five years [8]. However, PRP is far from a “one-and-done treatment”, 45% of the eyes required supplemental PRP, intravitreal anti-vascular endothelial growth factor (VEGF) injection, or even vitrectomy, within 2 years after PRP treatment [9, 10]. Those patients usually suffered from very poor visual prognosis, even blindness [11–13]. Therefore, it is necessary to identify risk factors associated with progression after PRP among patients with DR.

Several risk factors have been proposed to be associated with DR-worsening, including age, uncontrolled diabetes, renal dysfunction, lipid metabolic abnormalities, anemia, etc. [14–18]. Although these factors can provide guidance in clinical management, they cannot accurately predict the risk of DR-worsening. Moreover, studies on prediction of the prognosis of PRP are very limited, and without a definitive conclusion. Thus, it is of great clinical significance to further investigate the potential factors associated with post-PRP progression of DR and develop a model of prediction.

Therefore, this retrospective study aimed to develop a model to predict the progression of DR after PRP in order to prevent it better and earlier. We speculated that the model could reflect the relationships between DR-worsening and its potential risk factors and quantify the contribution of these factors by assigning scores and correlation coefficients.

Methods

Study Population

Participants were patients who were diagnosed with PDR or severe NPDR and treated with PRP at Chinese PLA General Hospital between 1 January 2008 and 1 January 2021 (n = 2,519). Treatment of severe NPDR and PDR was performed according to guidelines [19]. According to ETDRS protocol [20], a standard argon-type laser was used in PRP, with the recommended settings including 1200 to1600 spots, approximately 400μm burning in size, 200mW power, and 100ms pulse duration. PRP was administered across four treatment sessions, one session per week. Finally, laser burn spots were scattered evenly across the retina almost to the equator and away from the macula [8, 20].

Patients’ clinical data were extracted and collected from the hospital electronic medical record system. Only one eye of every patient was included in the study, and the eye with more severe DR or lower vision was included if both two eyes met the criteria for inclusion. Participants were excluded if they met any of the following criteria: (1) Missing the outcome of DR within five years; (2) Received anti-VEGF treatment before or after PRP; (3) Having a history of the laser before PRP; (4) Having the history of intraocular surgery other than cataract surgery; (5) Having the history of other retinal diseases, such as age-related macular degeneration, retinal artery/vein occlusion, ischemic optic neuropathy, posterior uveitis, glaucoma, or other eye diseases that affected fundus examination; (6) Missing clinical information. After exclusion, 271 patients were included in this study. (Fig. 1)

The data were collected and recorded by two experienced ophthalmologists to guarantee data quality. When disagreements occurred, they were resolved through discussion. This study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Chinese PLA General Hospital. And patient consent for inclusion was waived because all data were anonymized and the study was retrospective in nature.

Outcome

The positive outcome was DR-worsening within 5 years after PRP treatment. The participant was considered to have a positive outcome if any of the following situations occurred to them within 5 years: vitreous hemorrhage, tractional retinal detachment, neovascular glaucoma, requiring further PRP, intravitreal anti–VEGF injection, or vitrectomy. And the negative outcome was non-DR-worsening, meaning that the above conditions did not occur within 5 years, and the vision remained stable (the decline was not more than two lines). Participants were followed until the occurrence of the outcome, loss to follow-up, or administrative censoring, whichever came first. The last follow-up data was 1 August 2021.

Risk Factors

The study included the following 29 potential risk factors for predicting post-PRP progression of DR: (1) Ocular parameters: stage of diabetic retinopathy (PDR or severe NPDR); baseline best corrected visual acuity (BCVA); (2) Clinical case data: age; sex; type of diabetes (type 1 or type 2); diabetes duration; diabetic nephropathy; diabetes neuropathy; coronary heart disease; prior stroke; hyperlipidemia; grade of high blood pressure (0–3); body mass index; (3) Laboratory parameters: homocysteine; fasting blood glucose; creatinine; urea; uric acid; total cholesterol; triglyceride; high-density lipoprotein; low-density lipoprotein; serum superoxide dismutase; glycosylated serum protein; serum cystatin C; hemoglobin; hematocrit; platelet; neutrophil/lymphocyte ratio.

Ocular parameters were assessed at baseline by recording BCVA, intraocular pressure, slit-lamp examination, retinal examination, and fundus photograph. Baseline BCVA was assessed with the Snellen chart. Detailed fundus examination was performed by the trained ophthalmologist using direct and indirect ophthalmoscope. Fundus fluorescein angiography was performed before laser treatment to identify suspicious but clinically insignificant retinal neovascularization. Macular OCT can determine macular edema or other macular lesions, and B ultrasound can determine retinal detachment and fibrous membrane hyperplasia. Ophthalmic evaluation was conducted by a single retina specialist, stereoscopic fundus photography and fundus fluorescein angiography were conducted by a single examiner.

Diabetic nephropathy was defined as urinary albumin creatinine ratio ≥ 30 mg/g in the absence of other primary causes of kidney damage. Diabetic neuropathy was tested with a 128-Hz tuning fork for vibration sense and a 10-g monofilament test for light touch perception (on four sites per foot) [21]. Hyperlipidemia was defined as total cholesterol ≥ 6.2mmol/L or triglyceride ≥ 2.3mmol/L or low-density lipoprotein ≥ 4.1mmol/L or high-density lipoprotein < 1.0mmol/L [22]. Coronary heart disease and prior stroke were

judged by inquiring about the medical history and referring to their medical records. Venous blood was taken on an empty stomach to detect biochemistry and blood routine.

Statistical Analysis

Model Development

All the included participants were randomly assigned to either the training cohort or validation cohort. Univariate and multivariate logistic regression analysis was respectively used to analyze the potential risk factors of DR-worsening in the training cohort, and the significant risk factors were defined by the result of multivariate analysis finally. The model was established depending on the training cohort subsequently, and significant risk factors were enrolled based on the multiple-stepwise logistic regression analysis (stepwise selection). Then, the model was developed as follows:

$P(Y=1)=e^{(\text{intercept}+ax1+bx2+cx3+dx4)}/(1+e^{(\text{intercept}+ax1+bx2+cx3+dx4)})$. In the model, a, b, c, and d were the estimates of the included significant risk factors and $P(Y=1)$ was the predicted probability of DR-worsening. When the significant risk factors are re-entered into multivariate logistic regression analysis, the estimates are obtained.

Model Evaluation

Discrimination and calibration in both training and validation groups were used to evaluate the performance of the model. The discrimination capability of the model to distinguish patients with and without DR-worsening was mainly assessed by the area under the receiver operating characteristic curve (AUROC) and discrimination slope. And the discrimination slope was defined as the mean difference in the predicted probabilities of developing DR-worsening between patients actually with DR-worsening and without DR-worsening. Besides, the correct classification rate, sensitivity, and specificity were also used to evaluate the formula's discrimination ability. Furthermore, the accuracy between the probability of DR-worsening predicted by the model and the actual observed probability was defined as the calibration capability of the model, which was evaluated based on the calibration curve. Besides, the formula's calibration ability was also evaluated by the Hosmer-Lemeshow goodness-of-fit test, and $P > 0.05$ in the goodness-of-fit statistics indicated a good fit of the model.

Model Classification

Each patient had an actual probability of DR-worsening and a predicted probability, which was calculated using the model. All patients were divided into two risk groups, namely the low-risk group and the high-risk group, depending on the best cut-off value of the predicted probability. Furthermore, we calculated and compared the difference of actual probability and predicted probability of DR-worsening between the two risk groups.

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC) and IBM SPSS 23.0 (IBM Corp, Armonk, NY, USA) for Windows XP. P□0.05 was considered statistically significant

(* P < 0.05, ** P < 0.01, *** P < 0.001).

Results

Patients' Baseline Characteristics

A total of 271 patients were enrolled with a mean age of 50.69 ± 11.24 years and 58.3% of them were men. The majority of comorbidity was hypertension (73.80%), followed by hyperlipidemia (27.68%), diabetic nephropathy (26.57%), coronary heart disease (8.86%), diabetic neuropathy (8.12%), and prior stroke (5.17%). More details about the demographics and laboratory parameters of patients are presented in Table 1. The rate of DR-worsening was 56.46%, and 153 patients were included in the DR-worsening group. Including 112 eyes with vitreous hemorrhage, 26 eyes with vitreous hemorrhage and retinal detachment, 7 eyes with secondary glaucoma and retinal detachment, 4 eyes with vitreous hemorrhage and macular edema, 2 eyes with secondary glaucoma and macular edema, and 2 eyes with secondary glaucoma, within 5 years after PRP treatment.

Compared with the non-DR-worsening group, patients with the DR-worsening outcome were more likely to be younger, have lower baseline BCVA, have more frequency of diabetic nephropathy, diabetic neuropathy, and hyperlipidemia, and the differences in laboratory parameters related to renal function (creatinine, urea, uric acid, serum cystatin C) and anemia (hemoglobin, hematocrit) were also significant (P < 0.05). In addition, the proportion of males and PDR, fasting blood glucose, homocysteine, and neutrophil/lymphocyte ratio were higher in patients with DR-worsening, and regarding blood lipids, total cholesterol, triglycerides, and low-density lipoprotein were also higher in patients with DR-worsening, but the differences were not statistically significant (P 0.05). The detail about the comparison of DR-worsening and non-DR-worsening is in Table 1.

Model Development

The baseline characteristics of patients in the training cohort (n = 135) and validation cohort (n = 136) were shown in **Additional** Table 1. There were no statistically significant differences between the training cohort and the validation cohort in all the 29 risk factors ($P > 0.05$), indicating that patients in the two groups were comparable. In the training cohort, the results of univariate and multivariate logistic regression analysis were shown in Table 2. It indicated that the following factors were all independent risk factors for DR-worsening: age (OR = 0.91, 95% CI 0.85–0.96); baseline BCVA (OR = 0.11, 95% CI 0.01–0.87); diabetic nephropathy (OR = 16.83, 95% CI 1.92–147.50); and hyperlipidemia (OR = 5.53, 95% CI 1.25–24.57). All the above 4 variables were considered and incorporated into the construction of the predictive model of DR-worsening depending on the result of stepwise regression. Finally, a model was developed as presented in **Table 3**. According to the model, lower age, lower baseline BCVA, diabetic nephropathy, and hyperlipidemia were associated with a significantly higher incidence of DR-worsening, which was in line with the result of COX regression analysis (**Additional** Table 2).

A calculator was used to facilitate the utility of the model in clinical practice (**Additional file 2**). The calculation formula was developed as follows:

$P(Y=1)=e^{(1.94-0.03x1-1.68x2+2.19x3+0.83x4)}/(1+e^{(1.94-0.03x1-1.68x2+2.19x3+0.83x4)})$. x1 indicated age; x2 indicated baseline BCVA; x3 indicated diabetic nephropathy; x4 indicated hyperlipidemia. P(Y = 1) indicated the probability of DR-worsening as predicted by the model. An example was shown as follows: If a 52-year-old patient (x1 = 52) with a baseline BCVA of 0.8 (x2 = 0.8) and diabetic nephropathy (x3 = 1) and ortholiposis (x4 = 0), then the predicted probability of this eye of DR-worsening was $P(Y=1)=e^{(1.94-0.03x1-1.68x2+2.19x3+0.83x4)}/(1+e^{(1.94-0.03x1-1.68x2+2.19x3+0.83x4)})=77.31\%.$

Model Validation

The AUROC of the prediction model was 0.78 in the training cohort (Fig. 2A) and 0.79 in the validation cohort (Fig. 2B), the discrimination slope was 0.27 (95%CI: 0.19–0.34) in the training cohort and 0.27 (95%CI: 0.20–0.34) in the validation cohort (Fig. 3), illustrating the good discrimination ability of the prediction model as a clinically useful-to-good tool. Compared with 71.10% in the training cohort, the correct classification rate was 72.80% in the validation cohort. More details about sensitivity and specificity are shown in **Table 4**.

When considering the calibration ability of the model, the calibration slopes in the training and validation cohort were 0.99 (95% CI 0.62–1.35) **(Fig. 4AC**) and 1.01 (95% CI 0.54–1.49) (Fig. 4**BD**) respectively, the X-intercepts and Y-intercepts were all very close to 0, indicating that model had good calibration ability. Moreover, the P values for Hosmer–Lemeshow goodness-of-fit tests were all above 0.05 in the two cohorts, which also indicated good calibration ability. (Table 5)

Risk Stratification

According to the model, each patient could obtain a predicted probability of DR-worsening. According to the best cut-off value of the predicted probability depending on the best sensitivity and specificity, patients were divided into the low-risk group and high-risk group (Table 6). The predicted probability in the two groups was 38% and 84%, respectively. And the corresponding actual probability was 37% (61/163) and 85% (92/108), respectively ($P < 0.0001$). In two groups, the observed actual probabilities were similar to the predicted probabilities of DR-worsening, indicating that the classification was reproducible.

Discussion

This study investigated predictors of DR-worsening after PRP. After adjusting for various confounders, younger age, lower baseline BCVA, and diabetic nephropathy or hyperlipidemia at the start of PRP were found to be independent predictors of a higher probability of DR-worsening after PRP. We then incorporated these four risk factors and developed a new model to predict the risk of DR-worsening following PRP treatment within 5 years.

Age at the onset of diabetes has been proved to be one of the key factors in the development and progression of PDR [23]. Studies have shown that younger patients with PDR had a higher risk of visual loss than older patients, and the onset age of type 2 diabetes under 45 years old was an independent risk factor for the development and progression of PDR [24, 25]. Previous studies have shown that more severe retinal proliferation, greater surgical difficulty, and poorer anatomical success rate due to rapid progression of retinal neovascularization could be found in younger PDR patients undergoing vitrectomy [26, 27]. This study also reached a similar conclusion that younger age was an independent risk factor for DR-worsening after PRP. In addition, younger patients have higher prognostic requirements and higher social burdens associated with visual loss. Therefore, age may be an important but often underappreciated prognostic factor of DR in clinical practice.

This study showed that DR progressed significantly after PRP treatment when the baseline BCVA was low. Because increased visual loss is associated with increased DR severity [23], once DR becomes advanced, active treatment such as PRP or intravitreal anti-vascular endothelial growth factor (VEGF) injection becomes the best way to reduce DR-related blindness [28]. However, in cases where the retinal ischemic is severe, diffusion of oxygen needed by macular may remain insufficient and even lead to macular edema in spite of PRP, which could cause lower vision [15, 29]. This finding is also in line with the study that lower vision is associated with the larger avascular zone area of foveal in DR patients [30]. Therefore, prevention of DR-worsening may be an important strategy to reduce DR-related blindness.

In our study, the association of diabetic nephropathy with DR-worsening after PRP was observed to be statistically significant ($P < 0.05$ in both univariate and multivariate logistic regression analysis), in addition, the laboratory parameters related to renal function including creatinine, urea, and serum cystatin C had a statistically significant association with DR-worsening in the univariate logistic analysis, suggesting that with increasing severity of renal function there will be more likelihood of the DR-worsening. Furthermore, compared with the non-DR-worsening group, the patients in the DR-worsening group had worse kidney function and a greater frequency of diabetic nephropathy. Current studies have confirmed that diabetic nephropathy is closely related to DR, especially PDR or severe NPDR in diabetic patients [31–33]. Similarly, diabetic nephropathy was found to be an independent risk factor of DR-worsening after PRP. The pathophysiology of both DR and diabetic nephropathy is similar. The development of DR and diabetic nephropathy influences and promotes each other, which supports the view that the two diseases share a common etiological basis, and emphasizes that the treatment and care of DR should be combined with a multidisciplinary integrated treatment management model [34].

Our study found that hyperlipidemia is the risk factor for the presence of DR-worsening after PRP treatment. In recent years, hyperlipidemia has been considered one of the strongest risk factors for the occurrence and development of DR [35, 36]. As reported in some studies, lipid-lowing therapy reduces the progression of DR and the need for laser treatment [37, 38], and total cholesterol and low-density lipoprotein are risk factors for the occurrence of any DR [22], in addition, poor control of serum triglycerides is associated with progression of PDR [39], which indicates that intensive lipid control may be associated with better clinical prognosis of DR after PRP treatment.

At present, some studies have suggested that poor blood glucose control, long diabetes duration, hypertension, anemia, and other variables are also independent risk factors for DR-worsening [18, 40, 41]. However, this study did not produce similar results, possibly because of the following limitations: in this study, patients with stable DR tend to lack regular review and even lose follow-up, which results in fewer patients in the non-DR-worsening group than in the DR-worsening group, which may have introduced bias. In addition, this study was a retrospective analysis without diagnostic tests on patients, so there may be differences in the collection of patient's history. While this model is useful for internal validation, external validation is also necessary. Therefore, prospective and multicenter studies are necessary to confirm these findings.

Our Model has 4 risk factors that are easy to obtain in medical records and further explores the interaction between these risk factors and DR-worsening, which have rarely been reported in previous studies and will provide a reference for future studies. Furthermore, the Model can provide patients with an immediate and reliable assessment of DR-worsening within 5 years after PRP treatment. This estimate could guide clinicians to identify ones at high risk of DR-worsening at an early stage and prescribe additional treatment, such as more frequent follow-up, supplemental laser photocoagulation therapy, or intravitreal anti–VEGF injection.

Conclusion

We developed and internally validated a new model to predict the risk of DR-worsening after PRP treatment within 5 years. The model can be used as a rapid risk assessment system for clinical prediction of DR-worsening.

List Of Abbreviations

AUROC	Receiver operating characteristic curve
BCVA	Baseline best corrected visual acuity
BMI	Body mass index
CCR	Correct classification rate
CI	Confidence interval
DR	Diabetic retinopathy
NPDR	Non-proliferative diabetic retinopathy
OR	Odds ratio
PDR	Proliferative diabetic retinopathy
PRP	Panretinal photocoagulation
VEGF	Vascular endothelial growth factor

Declarations

Authors' contributions

Jinglan Li identified and cleaned the data, and wrote the main manuscript text. Xuanlong Li and Mingxing Lei made a statistical analysis of the data. Wanyue Li, Wenqian Chen, Tianju Ma, and Yi Gao collected the data. Zhaohui Li and Zi Ye conceived and designed the study. All authors reviewed the manuscript and approved the final manuscript and all authors agree to be responsible for all aspects of the work.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Chinese PLA General Hospital. And patient consent for inclusion was waived because all data were anonymized and the study was retrospective in nature.

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This submission has not been published anywhere previously and it is not simultaneously being considered for any other publication.

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Tables

Table 1 Patients' Baseline Characteristics

Variables	Total patients (n=271)	DR-worsening （n=153）	non-DR-worsening(n=118)	P value[a]
Age, years	50.69±11.24	49.16±10.90	52.66±11.42	**0.011***
Male, n (%)	158(58.30%)	95（62.1%）	63（53.4%）	0.150
Baseline BCVA	0.52±0.29	0.46±0.29	0.59±0.26	**<0.001****
Diabetes duration, years	12.24±7.37	11.92±7.26	12.64±7.52	0.524
Type 2 diabetes, n (%)	261(96.31%)	145（94.8%）	116（98.3%）	0.127
PDR, n (%)	169(62.36%)	98（64.1%）	71（60.2%）	0.324
Diabetic nephropathy, n (%)	72(26.57%)	65（42.5%）	7（5.9%）	**<0.001****
Diabetic neuropathy, n (%)	22(8.12%)	19（12.4%）	3（2.5%）	**0.003****
Coronary heart disease, n (%)	24(8.86%)	17（11.1%）	9（7.6%）	0.335
Prior Stroke, n (%)	14(5.17%)	8（5.2%）	6（5.1%）	0.958
Hyperlipidemia, n (%)	75(27.68%)	59（38.6%）	16（13.6%）	**<0.001****
Hypertension, n (%)				
0	71(26.20%)	40（26.1%）	31（26.3%）	0.111
1	83(30.63%)	41（26.8%）	42（35.6%）	
2	48(17.71%)	23（15.0%）	25（21.2%）	
3	69(25.46%)	49（32.0%）	20（16.9%）	
BMI, kg/m2	25.52±3.42	25.46±3.67	25.60±3.09	0.732
Homocysteine, umol/L	13.34±7.91	14.14±9.40	12.29±5.27	0.061
Fasting blood glucose, mmol/L	6.96±2.77	7.18±2.81	6.67±2.71	0.085
Urea, umol/L	6.66±3.86	7.58±4.78	5.47±1.47	**<0.001****
Creatinine, mmol/L	94.72±102.35	113.31±131.88	70.61±23.33	**<0.001****
Uric acid, umol/L	327.98±90.23	340.59±89.91	311.64±88.37	**0.009****
Total cholesterol, mmol/L	4.36±1.18	4.49±1.36	4.18±0.89	0.090
Triglyceride, mmol/L	1.55±1.30	1.68±1.52	1.38±0.91	0.139
High-density lipoprotein, mmol/L	1.13±0.34	1.13±0.35	1.12±0.32	0.92

Low-density lipoprotein, mmol/L	2.76±0.97	2.82±1.10	2.67±0.78	0.281
Serum superoxide dismutase, U/ML	146.23±27.01	144.44±30.87	148.56±20.87	0.076
Glycosylated serum protein, umol/L	228.91±75.04	228.53±82.28	229.39±64.80	0.986
Serum cystatin C, mg/L	1.27±1.22	1.47±1.58	1.01±0.25	**0.001****
Hemoglobin, g/L	129.58±18.91	127.04±20.54	132.88±16.07	**0.044***
Hematocrit	0.38±0.05	0.37±0.06	0.39±0.04	**0.026***
Platelet, 10^9/L	215.19±61.32	213.56±64.11	217.31±57.69	0.613
Neutrophil/lymphocyte ratio	2.20±1.21	2.36±1.40	1.98±0.88	**0.017***

[a] For comparison between DR-worsening and non-DR-worsening.

Values are expressed as the mean±SD or number (percentages).

Abbreviations: BCVA best corrected visual acuity; DR diabetic retinopathy; PDR proliferative diabetic retinopathy; BMI body mass index.

***P<0.05, ****P<0.01, *****P<0.001 for T test or chi-square test.

Table 2 Univariate and multivariate analysis of patient's characteristics for predicting DR-worsening.

Variables	Univariate analysis		Multivariate analysis	
	OR 95% CI	P value	OR 95% CI	P value
Age	0.95(0.93,0.98)	**0.003****	0.91(0.85,0.96)	**0.002****
Sex	0.62(0.31,1.24)	0.177	0.63(0.19,2.15)	0.461
Baseline BCVA	0.18(0.05,0.65)	**0.009****	0.11(0.01,0.87)	**0.036***
Diabetes duration	0.99(0.94,1.04)	0.679	1.01(0.93,1.09)	0.876
Type of diabetes	0.23(0.03,2.02)	0.185	1.71(0.06,47.61)	0.753
Stage of DR	1.64(0.80,3.37)	0.180	0.85(0.27,2.65)	0.784
Diabetic nephropathy	11.11(3.17,38.89)	**0.000****	16.83(1.92,147.50)	**0.011***
Diabetic neuropathy	4.09(0.85,19.68)	0.079	2.35(0.18,30.68)	0.515
Coronary heart disease	1.36(0.42,4.39)	0.609	3.78(0.66,21.57)	0.135
Prior Stroke	0.82(0.11,5.99)	0.845	0.36(0.01,8.93)	0.530
Hyperlipidemia	4.40(1.89,10.24)	**0.001****	5.53(1.25,24.57)	**0.025***
Hypertension	1.11(0.82,1.50)	0.512	1.06(0.66,1.70)	0.823
BMI	0.99(0.90,1.08)	0.810	0.98(0.84,1.13)	0.748
Homocysteine	1.02(0.97,1.07)	0.537	0.97(0.89,1.05)	0.420
Fasting blood glucose	1.07(0.94,1.22)	0.318	0.91(0.73,1.13)	0.391
Urea	1.01(1.00,1.02)	**0.049***	1.00(0.98,1.01)	0.798
Creatinine	1.41(1.14,1.74)	**0.002****	1.18(0.84,1.67)	0.343
Uric acid	1.00(1.00,1.01)	0.053	1.00(0.99,1.00)	0.441
Total cholesterol	1.22(0.90,1.65)	0.198	1.10(0.14,8.77)	0.928
Triglyceride	1.18(0.87,1.61)	0.287	0.83(0.24,2.86)	0.764
High-density lipoprotein	1.24(0.48,3.24)	0.657	2.53(0.14,44.59)	0.527
Low-density lipoprotein	1.10(0.77,1.58)	0.591	0.65(0.08,5.21)	0.686
Serum superoxide dismutase	1.00(0.99,1.02)	0.879	1.00(0.98,1.03)	0.728
Glycosylated serum protein	1.00(1.00,1.01)	0.347	1.01(1.00,1.01)	0.237
Serum cystatin C	3.31(1.18,9.31)	**0.023***	1.08(0.15,8.02)	0.941
Hemoglobin	0.99(0.97,1.01)	0.148	0.94(0.82,1.07)	0.359

Hematocrit	0.00(0.00,2.67)	0.095	>10.00(0.001->10.00)	0.262
Platelet	1.00(0.99,1.01)	0.653	0.99(0.98,1.00)	0.215
Neutrophil/lymphocyte ratio	1.21(0.86,1.68)	0.271	1.31(0.87,1.97)	0.202

Abbreviations: BCVA best corrected visual acuity; DR diabetic retinopathy; OR odds ratio; CI confidence interval; BMI body mass index.

***P<0.05; ****P<0.01; *****P<0.001

Table 3 A model to predict DR-worsening.

Parameters	Score Range	Estimates[a]
Intercept		1.94
Age	16-75	-0.03
Baseline BCVA	0.1-1.2	-1.68
Diabetic nephropathy		
Yes	1	2.19
No	0	
Hyperlipidemia		
Yes	1	0.83
No	0	

[a] Indicated the estimates were obtained from the multivariate regression logistic analysis of the four significant factors.

Abbreviations: BCVA best corrected visual acuity; DR diabetic retinopathy

Table 4 Discrimination performances of the model

Cohort	AUROC	Slope	95% CI	P value	CCR	Sensitivity	Specificity
Training cohort	0.78	0.27	0.19-0.34	<0.001	71.10%	52.70%	93.40%
Validation cohort	0.79	0.27	0.20-0.34	<0.001	72.80%	69.60%	77.20%

Abbreviations: AUROC area under the receiver operating characteristic curve; CI confidential interval; CCR correct classification rate.

Table 5 Calibration performances of the model

Cohort	Slope	95% CI	X-intercept	95% CI	Y-intercept	95% CI	R squared	Goodness-of-fit test
Training cohort	0.99	0.62 - 1.35	-0.01	-0.36 - 0.16	0.01	-0.21 - 0.23	0.83	0.32
Validation cohort	1.01	0.54 - 1.49	0.01	-0.53 - 0.22	-0.01	-0.31 - 0.29	0.75	0.94

Abbreviations: CI confident interval; X x-axis; Y y-axis.

Table 6 Classification of low-risk and high-risk groups

Group	Patients (n=271)	Predicted probability[a]	Actual probability[a]	P[b](chi-square)
Low-risk (0-60%)	163	0.38	61/163 (0.37)	<0.001
High-risk (above 60%)	108	0.84	92/108 (0.85)	

[a] indicates the rate of DR-worsening.

[b] indicates an actual rate of DR-worsening between the two risk groups.

Figures

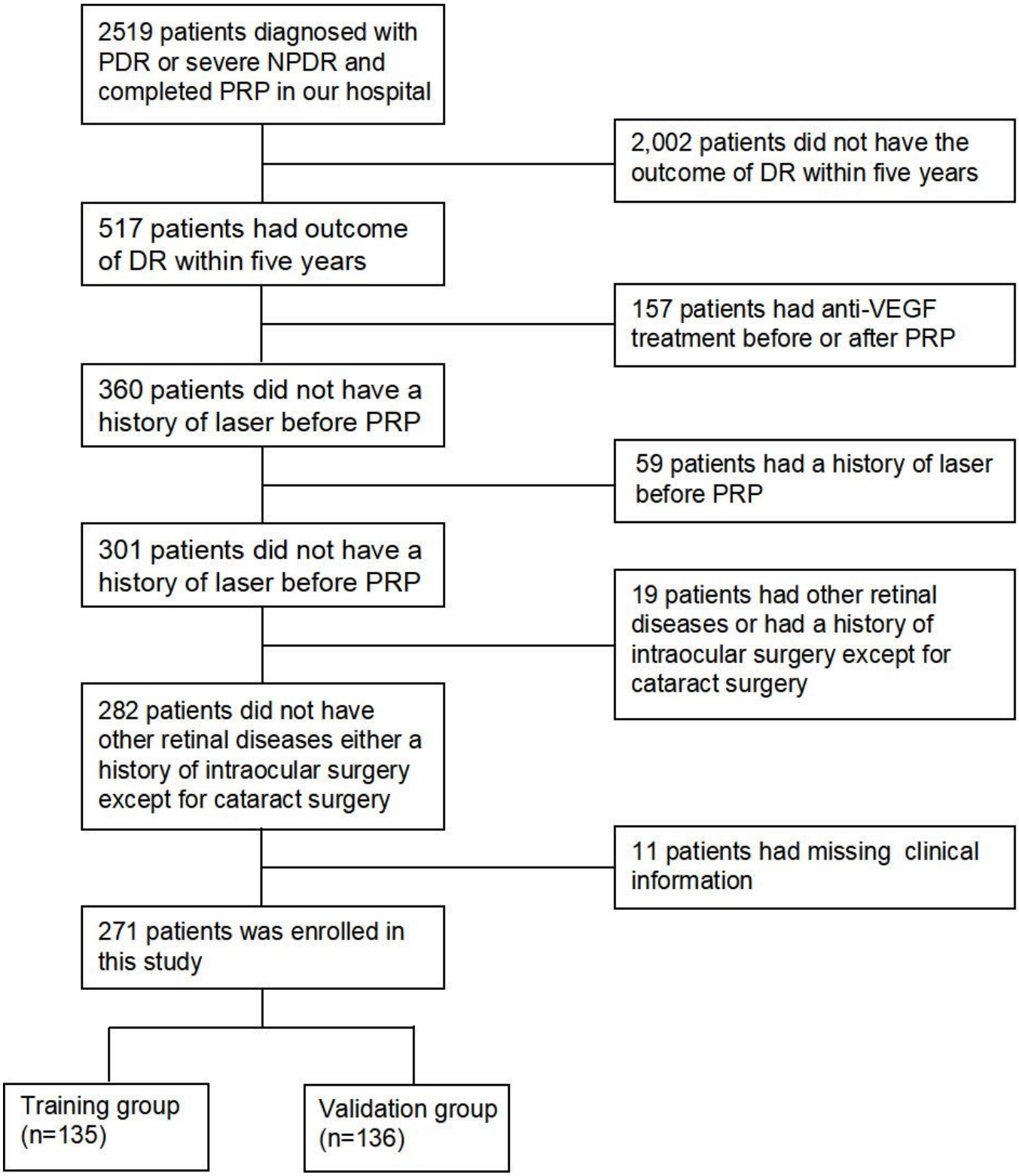

Figure 1

The flow chart

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Figure 2

The area under the receiver operating characteristic (AUROC) curve for the model: (A) the training cohort; (B) the validation cohort.

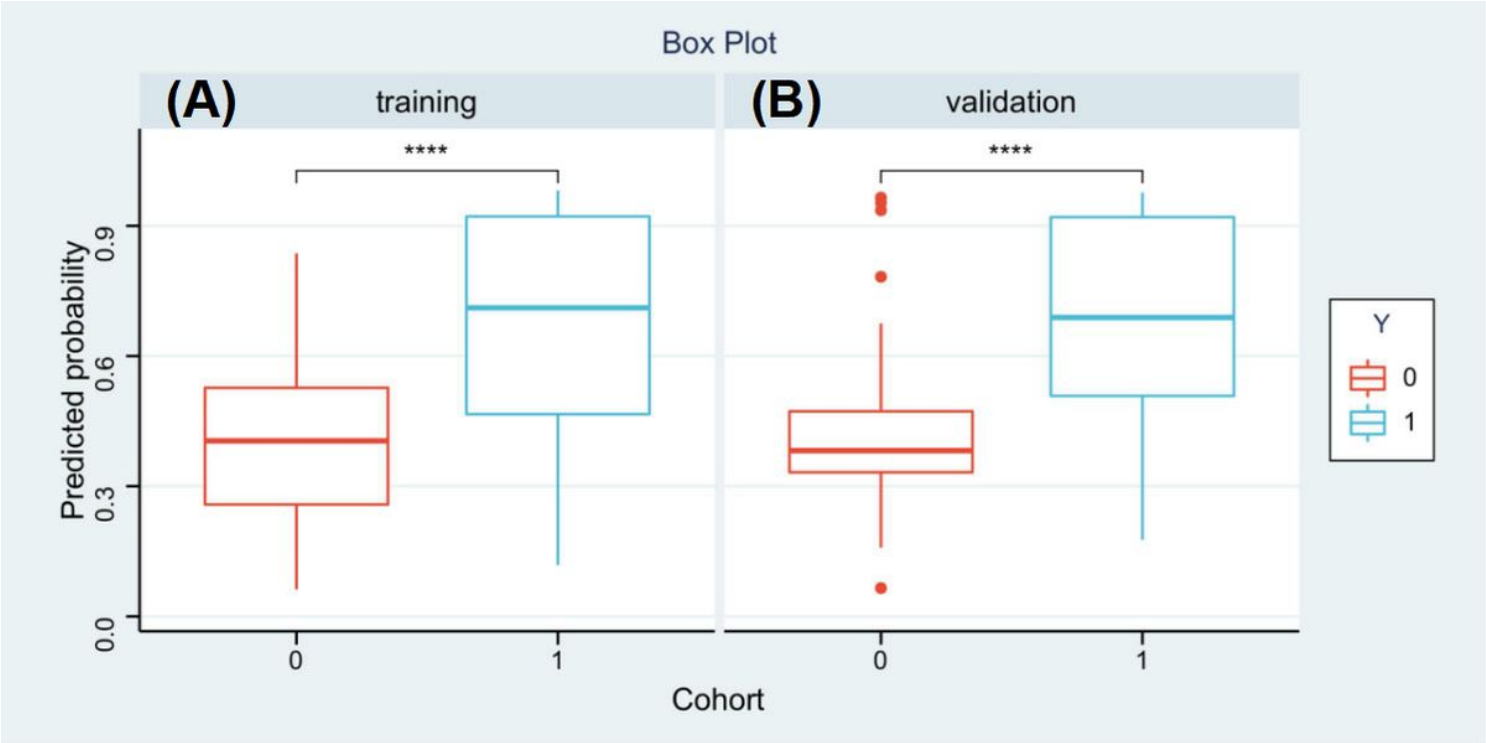

Figure 3

Boxplots of predicted probabilities in the two models: (A) the model with training cohort (Slope = 0.27); (B) the model with validation cohort (Slope = 0.27). The discrimination slope was defined as the difference between the mean predicted probability with DR-worsening (1) and non-DR-worsening (0).

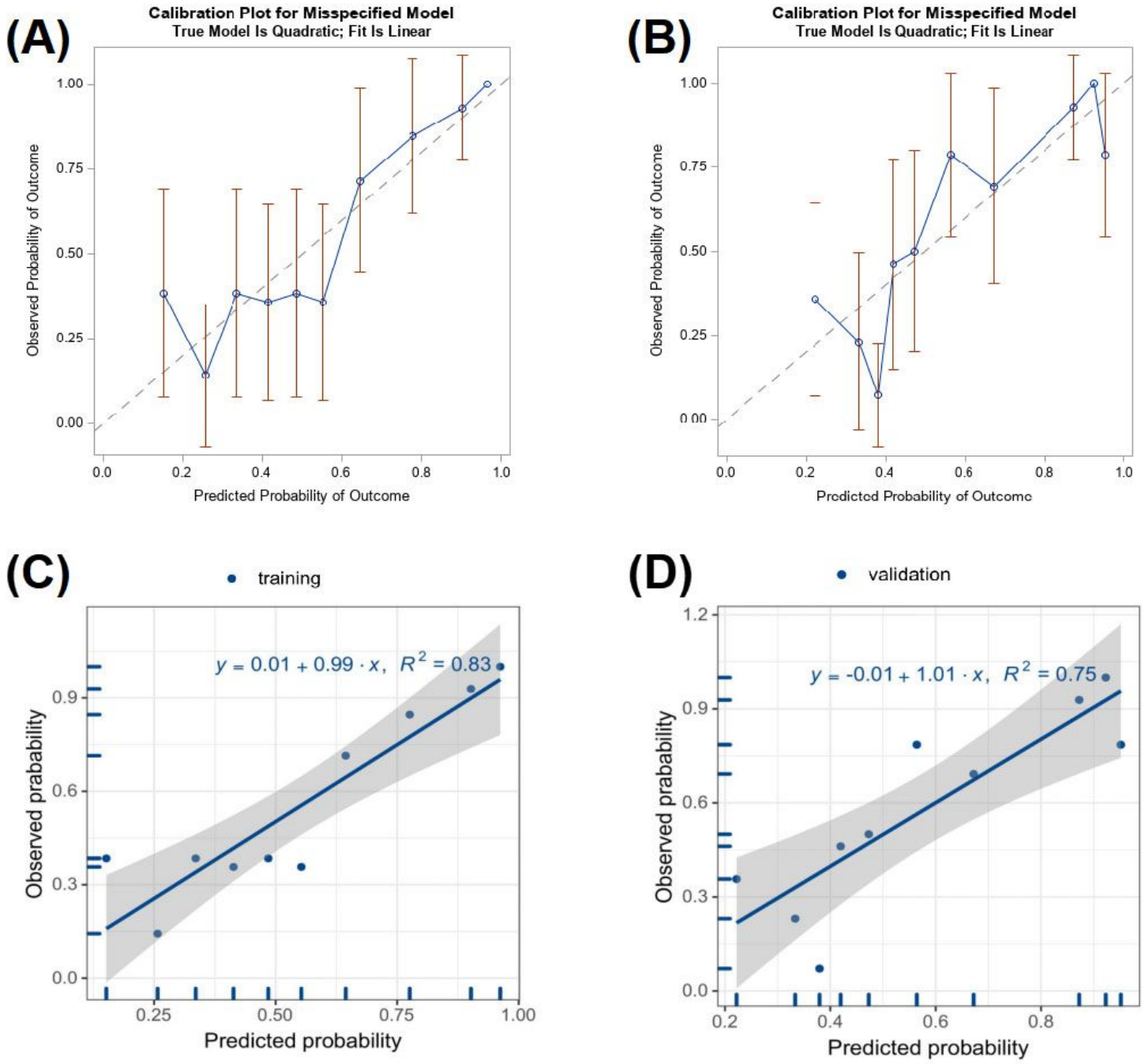

Figure 4

Plotting deciles of the predicted probability of DR-worsening against the observed proportions for the model: (A)(C) the training cohort; (B)(D) the validation cohort. The x-axis is the predicted risk and the y-axis is the actual risk. The grey dotted lines indicate a perfect prediction by an ideal model. The blue solid lines indicate the performance of the model, and a closer fit to the diagonal dotted lines indicate a better prediction.

Supplementary Files

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