Initial Retinal Nerve Fiber Layer Loss and Risk of Diabetic Retinopathy Over a Four-Year Period

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Purpose. The purpose of this study was to investigate whether the rapid rate of peripapillary retinal nerve fiber layer (pRNFL) thinning in short-term is associated with the future risk of developing diabetic retinopathy (DR).

Methods. This prospective cohort study utilized 4-year follow-up data from the Guangzhou Diabetic Eye Study. The pRNFL thickness was measured by optical coherence tomography (OCT). DR was graded by seven-field fundus photography after dilation of the pupil. Correlations between pRNFL thinning rate and DR were analyzed using logistic regression. The additive predictive value of the prediction model was assessed using the C-index, net reclassification index (NRI), and integrated discriminant improvement index (IDI).

Results. A total of 1012 patients with diabetes (1012 eyes) without DR at both baseline and 1-year follow-up were included in this study. Over the 4-year follow-up, 132 eyes (13%) developed DR. After adjusting for confounding factors, a faster rate of initial pRNFL thinning was significantly associated with the risk of DR (odds ratio per standard deviation [SD] decrease = 1.15, 95% confidence interval [CI] = 1.08 to 1.23, $P < 0.001$). Incorporating either the baseline pRNFL thickness or its thinning rate into conventional prediction models significantly improved the discriminatory power. Adding the rate of pRNFL thinning further enhanced the discriminative power compared with models with only baseline pRNFL thickness (C-index increased from 0.685 to 0.731, $P = 0.040$). The IDI and NRI were 0.114 and 0.463, respectively ($P < 0.001$).

Conclusions. The rate of initial pRNFL thinning was associated with DR occurrence and improved discriminatory power of traditional predictive models. This provides new insights into the management and screening of DR.

Keywords: diabetic retinopathy (DR), retinal neurodegeneration (NR), optical coherence tomography (OCT), prospective cohort

With the global diabetic population projected to exceed 1.31 billion by 2050, identifying predictive markers for diabetic retinopathy (DR) is crucial.[1] Although the duration of diabetes and the level of glycemic exposure are known to significantly influence the development of diabetic complications, established risk factors remain relatively poor predictors of DR development or progression.[2] Genetic association studies have also yielded disappointing results.[3] Historically viewed as a microvascular disease, DR is now defined by the American Diabetes Association as a "highly tissue-specific neurovascular complication."[4] However, the precise sequence of events—whether DR initiates with vasculopathy or neuropathy—remains unclear. Currently, reliable evidence is lacking regarding the role of retinal neurodegeneration (RN) in the onset and progression of microvascular disease.[2,3,5]

RN is characterized by the thinning of the ganglion cell-inner plexiform layers (GCIPLs) and the peripapillary retinal nerve fiber layer (pRNFL), which can be precisely quantified in vivo using optical coherence tomography (OCT).[2,3,5,6] Studies have shown that pRNFL in patients with diabetes without DR (non-DR) is thinner than in healthy controls.[7,8] Our previous study found that a 1-standard deviation (SD) decrease in baseline pRNFL increased the risk of DR by 82% over 2 years.[9] However, due to the variability of pRNFL among healthy individuals, establishing a definitive cutoff value is challenging. Quantifying the rate of pRNFL thinning offers a precise measure

of RN and disease progression. For instance, in glaucoma, the initial rate of pRNFL thinning predicts future disease progression and visual field loss.[10,11] Regular OCT screenings to monitor pRNFL thinning are essential for predicting glaucoma progression and adjusting treatment plans.[10,11]

Given the significance of pRNFL thinning in glaucoma, it may also hold predictive value for the DR development. However, it remains uncertain whether the rate of pRNFL decline is a more reliable metric for assessing DR risk than baseline pRNFL thickness. We hypothesize that accelerated pRNFL thinning precedes the onset of DR and that initial pRNFL thinning rates can more accurately predict future DR development. Therefore, this 4-year cohort study of patients with type 2 diabetes mellitus (T2DM) aims to evaluate the relationship between initial pRNFL thinning rates and long-term DR incidence.

Methods

Subjects

The Guangzhou Diabetes Eye Study (GDES) is an ongoing cohort study initiated at the Zhongshan Ophthalmic Center in China in November 2017. This study adheres to the principles of the Declaration of Helsinki and has received approval from the Ethics Committee of Zhongshan Ophthalmic Center (2017KYPJ094). All participants provided written informed consent.

The methodology of the GDES has been detailed in previous reports.[12–14] In brief, subjects with T2DM underwent thorough examinations at baseline and during annual follow-ups. Figure 1 illustrates the study's overall workflow. To ensure accurate assessment of initial pRNFL thinning preceding DR onset, we excluded cases that developed DR within the first study year, as it would be unclear whether pRNFL thinning occurred before, concurrently with, or after the clinical manifestation of DR. Thus, only participants without DR at both baseline and the 1-year follow-up were included. The risk of DR development in these individuals over the subsequent 3 years was then evaluated.

Basic Information and Systemic Examinations

Demographic and clinical information, including age, gender, duration of diabetes, chronic illness history, and medication history, were collected via standardized questionnaires. Comprehensive examinations were conducted during initial and follow-up visits. Trained nurses measured systolic blood pressure (SBP) and diastolic blood pressure (DBP), height, and weight. Laboratory analyses of urine and blood samples assessed biochemical markers, including glycated hemoglobin (HbA1c), serum creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL-C),

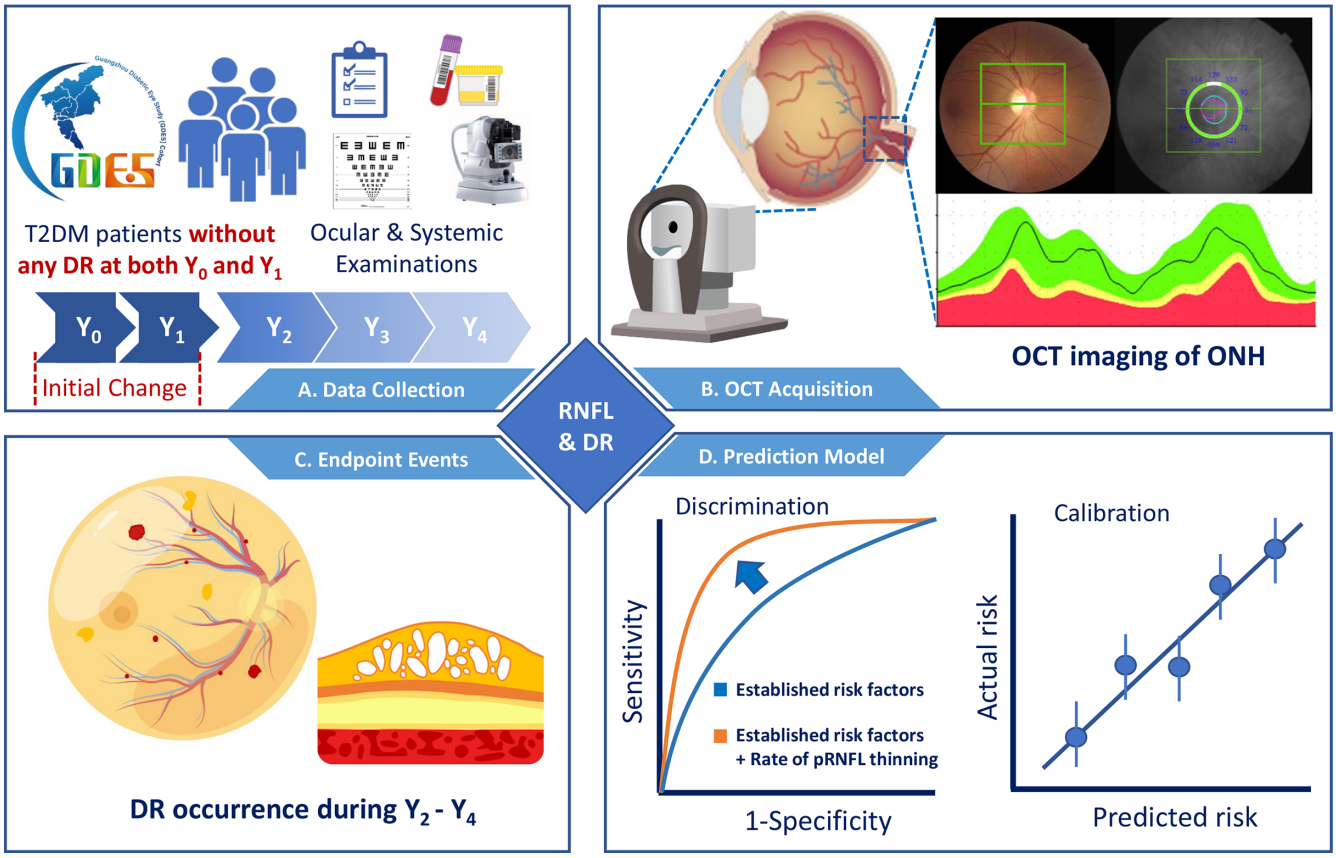

Figure 1. Workflow and study design. (**A**) Patients with T2DM were recruited in GDES and followed up annually for 4 years. The questionnaire was administered, and sample tests and ocular and systemic examinations were conducted. (**B**) OCT imaging was used quantify the pRNFL measurements. (**C**, **D**) The ROC curves and calibration analyses were performed to assess the incremental predictive value of pRNFL to predict DR development. T2DM, type 2 diabetes mellitus; GDES, Guangzhou Diabetic Eye Study; DR, diabetic retinopathy; ROC, receiver operating characteristic.

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low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs).

Ocular Examinations

Participants underwent a comprehensive ocular examination at baseline and throughout the 4-year follow-up, adhering to a standardized protocol. The examination included slit-lamp biomicroscopy, best corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) LogMAR E chart (Precision Vision, Villa Park, IL, USA), refraction measurements using the KR-8800 Auto Refractometer (Topcon, Tokyo, Japan), intraocular pressure (IOP) assessment with the CT-1 Non-contact Tonometer (Topcon), and ocular biometric measurements using the Lenstar LS900 (Haag-Streit, Koeniz, Switzerland).

Definition of Outcomes

Standard seven-field fundus photographs were taken for each eye using a digital fundus camera (Canon CX-1; Canon, Tokyo, Japan) after pupil dilation at baseline and each follow-up. DR was assessed following the ETDRS guidelines. Two trained ophthalmologists graded the images according to the Diabetic Retinopathy Preferred Practice Pattern guidelines. DR severity was classified into five categories: (1) no DR, (2) mild nonproliferative diabetic retinopathy (NPDR), (3) moderate NPDR, (4) severe NPDR, and (5) proliferative DR. The primary outcome was the onset of DR between years 1 and 4, defined as the development of DR in patients who had no DR at both baseline and year 1.

OCT Imaging for pRNFL Thickness

Following pupil dilation, optic disc structural images were acquired using a OCT device (DRI OCT Triton; Topcon). This instrument features a scan speed of 100,000 A-scans per second and the longitudinal resolutions of 8 µm, making it suitable for analyzing neural structures. A 3-dimensional optic disc scanning mode centered the disc, and the built-in software automatically segmented the images. The pRNFL thickness was determined by measuring the vertical distance between the inner limiting membrane and the inner border of the retinal ganglion cell layer. The scanning region was subdivided into four quadrants: superior, inferior, temporal, and nasal. The average pRNFL thickness and the thickness in each quadrant were automatically calculated. Two trained technicians reviewed the images to verify segmentation accuracy, making manual adjustments as necessary. Images compromised by blurring, motion artifacts, or a signal strength index below 60 were excluded from the study.

Statistical Analysis

The rate of initial pRNFL thinning was defined as the difference in pRNFL thickness between the first year of follow-up and the baseline measurement. The incidence of DR was evaluated using data collected over the subsequent 3-year follow-up period. This approach enabled comprehensive analysis of the correlation between initial pRNFL thinning rates and subsequent development of DR. Only data from the right eyes were included.

Continuous variables were summarized as means and SDs, whereas categorical variables were presented as frequencies and percentages. Normality of distribution was verified using the Kolmogorov-Smirnov test. The independent sample *t*-test and χ^2 test were used to evaluate normally distributed data and categorical variables, respectively. Multivariable logistic regression models were constructed to evaluate the impact of the rate of initial pRNFL thinning on the incidence of DR. The odds ratio (OR) and its 95% confidence interval (95% CI) per SD decrease in rate of progression were calculated for quantifying the associative degree. For confounders, we considered established risk factors (age, HbA1c level, and duration of diabetes) and referred to traditional DR prediction models from previous studies.[2,15–17] The multivariable model was adjusted for age, gender, body mass index (BMI), SBP, DBP, HbA1c, duration of diabetes, total cholesterol, and axial length (AL).

Receiver operating characteristic (ROC) curves were constructed for both traditional and new models, with the area under the curve (AUC) used to assess the C-index. The C-index ranges from 0.5 to 1.0, with values closer to 1.0 indicating superior discriminative ability. The models' discriminative power was further evaluated by the net reclassification index (NRI) and the integrated discriminant improvement index (IDI). An NRI and IDI greater than 0 indicate that the new model possesses better discriminative power than the old model. The calibration of the models was assessed by the Hosmer-Lemeshow goodness-of-fit test, with a P value < 0.05 indicating a significant difference between expected and observed probabilities, suggesting poor calibration. In addition, Brier scores were calculated to evaluate overall performance, including calibration, and to compare the impact of individual components on predictive ability. Scores close to 0 indicate perfect predictive performance, whereas scores close to 1 indicate poor predictive performance. All statistical analyses were performed using Stata/MP version 17.0 (StataCorp, College Station, TX, USA). Statistical significance was defined as $P < 0.05$, except for where specified.

Results

Baseline Characteristics

A total of 1012 patients with diabetes (1012 eyes) without DR at both baseline and 1-year follow-up were included in the analysis. Table 1 shows the demographics and baseline clinical characteristics of the participants. The mean age of participants was 64.0 ± 7.2 years and 567 (56%) were women. During the following 3-year period, 132 eyes (13%) developed DR. The participants who developed DR had poor BCVA, higher SBP and DBP, greater HbA1c, and more use of insulin in comparisons with those who had stable non-DR status (all $P < 0.05$). Other characteristics distributed similarly between the groups, such as age, sex, duration of diabetes, BMI, lipid profiles, and ocular conditions (see Table 1).

Baseline and Longitudinal Rates of pRNFL Thickness

Table 2 presents the baseline and longitudinal rates of pRNFL thickness among patients who developed DR during the follow-up period. The average pRNFL thickness at baseline was 105.53 µm (95% CI = 103.83 to 107.23) for patients who developed DR and 110.64 µm (95% CI = 109.96 to 111.33) for those who did not develop DR ($P < 0.001$).

Table 1. Demographic and Baseline Clinical Characteristics of Study Participants Stratified by Outcomes

Characteristic	Overall	Development of DR During 2–4 y		*P* Value*
		No	Yes	
No. of subjects, eyes	1012	880 (87%)	132 (13%)	—
Age, y	64.0 ± 7.2	64.1 ± 7.1	64.8 ± 7.6	0.755
Female (%)	567 (56)	497 (56)	70 (53)	0.457
Duration of diabetes, year	8.09 ± 6.66	7.98 ± 6.65	8.87 ± 6.70	0.150
Education attainment				0.748
< High school (%)	588 (58)	513 (58)	75 (57)	
≥ High school (%)	424 (42)	367 (42)	57 (43)	
Alcohol drinker (%)	108 (11)	96 (11)	12 (9)	0.528
Current smoker (%)	123 (12)	106 (12)	17 (13)	0.785
Spherical equivalent, diopter	0.40 ± 1.94	0.42 ± 1.94	0.28 ± 1.95	0.449
Best-corrected visual acuity, LogMAR	0.15 ± 0.13	0.14 ± 0.13	0.19 ± 0.17	**<0.001**
Intraocular pressure, mm Hg	16.19 ± 2.48	16.20 ± 2.46	16.12 ± 2.64	0.713
Central corneal thickness, µm	546.69 ± 33.04	547 ± 33	545 ± 34	0.521
Anterior chamber depth, mm	2.42 ± 0.39	2.42 ± 0.39	2.43 ± 0.36	0.830
Axial length, mm	23.46 ± 0.97	23.45 ± 0.95	23.46 ± 1.10	0.930
Body mass index, kg/m^2	24.38 ± 3.02	24.33 ± 3.00	24.72 ± 3.12	0.165
Waist to hip ratio	0.90 ± 0.06	0.90 ± 0.06	0.90 ± 0.06	0.692
Systolic blood pressure, mm Hg	132.59 ± 17.60	131.87 ± 17.47	137.43 ± 17.75	**<0.001**
Diastolic blood pressure, mm Hg	70.14 ± 10.07	69.83 ± 10.05	72.24 ± 10.02	**0.010**
Glycosylated hemoglobin, HbA1c, %	6.90 ± 1.21	6.83 ± 1.14	7.38 ± 1.57	**<0.001**
Triglycerides, mmol/L	2.37 ± 1.75	2.37 ± 1.74	2.37 ± 1.84	0.967
Total cholesterol, mmol/L	4.86 ± 1.10	4.86 ± 1.10	4.86 ± 1.14	0.973
Low-density lipoprotein cholesterol, mmol/L	3.03 ± 0.98	3.03 ± 0.98	3.09 ± 0.99	0.511
High-density lipoprotein cholesterol, mmol/L	1.30 ± 0.41	1.31 ± 0.41	1.27 ± 0.37	0.269
Serum creatine, mmol/L	70.86 ± 19.66	70.67 ± 19.02	72.15 ± 23.53	0.420
C-reactive protein, mg/L	2.30 ± 6.69	2.28 ± 7.04	2.41 ± 3.60	0.824
Microalbuminuria, mg/mL	3.35 ± 11.11	3.26 ± 11.42	3.70 ± 8.56	0.670
Use of insulin (%)	193 (19)	157 (18)	36 (27)	**0.010**

* Bold values indicate statistical significance.

Table 2. Baseline and Rates of Peripapillary Retinal Nerve Fiber Layer Average Thinning and the Risk of Incident DR

	Development of DR During 2–4 y		Difference (95% CI)	*P* Value*
	No	Yes		
Baseline pRNFL thickness (95% CI), µm				
Superior	135.34 (134.21 to 136.47)	126.84 (123.89 to 129.78)	−8.50 (−11.62 to −5.37)	**<0.001**
Inferior	143.27 (142.02 to 144.52)	136.17 (133.37 to 138.97)	−7.10 (−10.50 to −3.71)	**<0.001**
Nasal	82.54 (81.63 to 83.46)	80.72 (78.00 to 83.43)	−1.83 (−4.40 to 0.75)	0.164
Temporal	81.28 (80.46 to 82.11)	78.26 (75.82 to 80.70)	−3.02 (−5.35 to −0.70)	**0.011**
Average	110.64 (109.96 to 111.33)	105.53 (103.83 to 107.23)	−5.11 (−7.00 to −3.24)	**<0.001**
Rate of pRNFL thinning (95% CI), µm/y				
Superior	−0.60 (−1.04 to −0.16)	−0.53 (−1.63 to 0.57)	0.07 (−1.15 to 1.29)	0.913
Inferior	−1.65 (−2.09 to −1.22)	−3.44 (−4.91 to −1.96)	−1.78 (−3.03 to −0.53)	**0.005**
Nasal	−0.09 (−0.60 to 0.42)	−2.03 (−3.93 to −0.12)	−1.94 (−3.45 to −0.43)	**0.012**
Temporal	−0.23 (−0.70 to 0.25)	0.36 (−1.01 to 1.73)	0.59 (−0.75 to 1.93)	0.387
Average	−0.67 (−0.82 to −0.52)	−1.44 (−2.11 to −0.77)	−0.77 (−1.23 to −0.31)	**0.001**

DR, diabetic retinopathy; NA, not applicable; pRNFL, peripapillary retinal nerve fiber layer.
* Bold values indicate statistical significance.

Significant differences were also observed in the pRNFL thickness across the superior, inferior, and temporal quadrants ($P < 0.05$). The average rate of initial pRNFL thinning was –0.67 µm/year (95% CI = –0.82 to –0.52) for patients without DR and –1.44 µm/year (95% CI = –2.11 to –0.77) for those with DR, resulting in an inter-group difference of –0.77 µm/year (95% CI = –1.23 to –0.31, $P = 0.001$). This result indicates that patients with DR had an initial pRNFL thinning rate approximately 2.14 times faster than those patients without DR. Furthermore, patients with DR also showed a significantly faster rate of initial pRNFL thinning in the inferior quadrant (–1.78 µm/year [95% CI = –3.03 to –0.53], $P = 0.005$) and nasal quadrant (–1.94 µm/year [95% CI = –3.45 to –0.43], $P = 0.012$).

Rates of Initial pRNFL Loss and the DR Risk

Table 3 shows the association between the rate of initial pRNFL thinning and the risk of developing DR. After adjusting for confounding factors, a faster rate of average pRNFL loss was significantly associated with 15% higher odds of DR occurrence (OR = 1.15, 95% CI = 1.08 to 1.23, $P < 0.001$). Consistent results were observed in the subregional analyses

Table 3. Associations of Initial Rate of pRNFL Thinning and the Risk of Incident DR

	Univariable Model		Multivariable Model*	
Rate of pRNFL Thinning (μm/y)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Superior	1.00 (0.97 to 1.03)	0.912	1.00 (0.97 to 1.03)	0.913
Inferior	1.04 (1.01 to 1.07)	**0.005**	1.05 (1.02 to 1.08)	**0.001**
Nasal	1.03 (1.01 to 1.05)	**0.012**	1.03 (1.00 to 1.05)	**0.028**
Temporal	0.99 (0.96 to 1.01)	0.386	0.99 (0.97 to 1.02)	0.570
Average	1.12 (1.05 to 1.20)	**0.001**	1.15 (1.08 to 1.23)	**<0.001**

Bold values indicate statistical significance.
DR, diabetic retinopathy; pRNFL, peripapillary retinal nerve fiber layer; OR, odds ratio.
* Adjusted for age, sex, duration of diabetes, body mass index, systolic blood pressure, diastolic blood pressure, HbA1c level, total cholesterol, axial length, and pRNFL thickness at baseline.

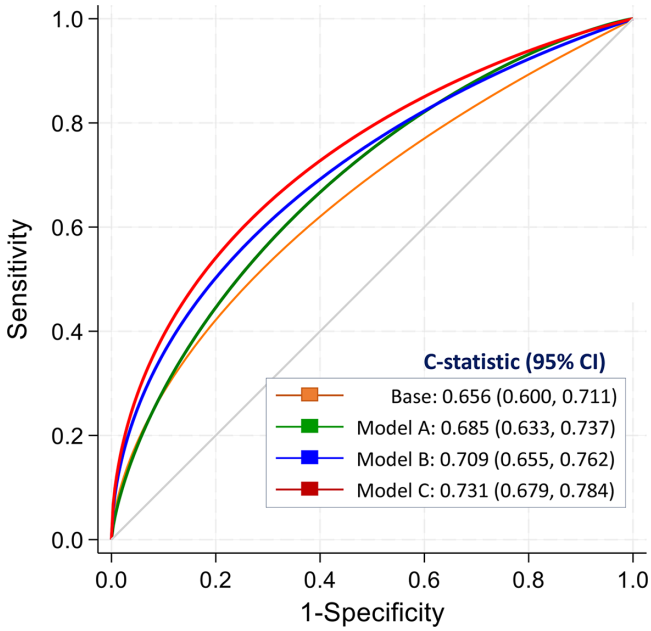

Figure 2. Discrimination ability of receiver operating characteristic (ROC) curve for prediction models of DR development. Base model included established risk factors, such as age, sex, duration of diabetes, HbA1c, systolic blood pressure, diastolic blood pressure, and total cholesterol. Model A was base model plus average pRNFL thickness at baseline. Model B was base model plus initial rate of average pRNFL thinning overtime. Model C was Model A plus initial rate of average pRNFL thinning overtime.

of the inferior quadrants (OR = 1.05, 95% CI = 1.02 to 1.08, $P = 0.001$) and nasal quadrants (OR = 1.03, 95% CI = 1.00 to 1.05, $P = 0.028$). Furthermore, we also analyzed the relationship between baseline pRNFL and the risk of developing DR (Supplementary Table S1).

Predictive Value of Incorporating pRNFL Metrics

Figure 2 illustrates the ROC curves for predictive models of DR occurrence. Incorporating either the average pRNFL thickness at baseline or its longitudinal rate of thinning into conventional prediction models—based on age, sex, duration of diabetes, HbA1c, SBP, DBP, and total cholesterol levels—significantly improved discriminatory power. The C-index increased from 0.656 (95% CI = 0.600 to 0.711) to 0.685 (95% CI = 0.633 to 0.737) with the addition of baseline pRNFL thickness ($P = 0.026$) and to 0.709 (95% CI = 0.655 to 0.762) with the rate of initial pRNFL thinning ($P = 0.043$). Furthermore, the new prediction models exhibited *P* values < 0.001 for both the NRI and the IDI (Table 4). Incorporating the rate of initial pRNFL decline further enhanced the discriminative power compared with models including only the baseline pRNFL thickness, with the C-index improving from 0.685 (95% CI = 0.633 to 0.737) to 0.731 (95% CI = 0.679 to 0.784). The corresponding IDI was 0.114 ± 0.020 ($P < 0.001$) and the NRI was 0.463 ± 0.099 ($P < 0.001$), indicating that the rate of pRNFL decline significantly improved the predictive accuracy for DR occurrence beyond what baseline pRNFL thickness alone could offer. The Brier scores of all models were low, and the Hosmer-Lemeshow test *P* values exceeded 0.05, suggesting excellent overall performance of the new models.

Table 4. Discrimination and Calibration of Prediction Models Incorporating Baseline and Rate of Average pRNFL Thickness for DR Risk

	C-Statistic		IDI		NRI			
Models	Mean (95% CI)	*P* Value	Mean ± SE	*P* Value	Mean ± SE	*P* Value	Brier Score	Hosmer-Lemeshow Test
Base model*	0.656 (0.600 to 0.711)	—	—	—	—	—	0.108	$P = 0.493$
Model A†	0.685 (0.633 to 0.737)	**0.026**	0.016 ± 0.005	**0.002**	0.232 ± 0.099	**0.019**	0.106	$P = 0.851$
Model B‡	0.709 (0.655 to 0.762)	**0.043**	0.087 ± 0.019	**<0.001**	0.302 ± 0.099	**0.002**	0.097	$P = 0.859$
Model C§	0.731 (0.679 to 0.784)	**0.005**	0.114 ± 0.020	**<0.001**	0.463 ± 0.099	**<0.001**	0.094	$P = 0.071$

DR, diabetic retinopathy; IDI, integrated discrimination improvement index; NRI, net reclassification index; pRNFL, peripapillary retinal nerve fiber layer; SE, standard error.
Bold values indicate statistical significance ($P < 0.05$).
* Base model included established risk factors, such as age, sex, duration of diabetes, HbA1c, systolic blood pressure, diastolic blood pressure, and total cholesterol.
† Model A was base model plus average pRNFL thickness at baseline.
‡ Model B was base model plus initial rate of average pRNFL thinning overtime.
§ Model C was model A plus initial rate of average pRNFL thinning overtime.

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Discussion

This study represents the first large-scale prospective analysis assessing the relationship between the rate of initial pRNFL thinning and the onset of DR. The results demonstrated that the rate of initial pRNFL thinning was approximately 2.14 times faster in patients who developed DR compared with those who did not. After adjusting for confounding factors, the rate of initial pRNFL thinning was independently associated with an increased risk of future DR. Furthermore, incorporating either baseline pRNFL thickness or its longitudinal rate of thinning significantly enhanced the prediction of DR occurrence, with the rate of initial pRNFL decline providing the most substantial improvement. This suggests that accelerated RN, as quantified by OCT, may serve as a potential biomarker for risk stratification, confirming that RN precedes retinal vascular alterations in DR progression.

The Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) studies revealed that HbA1c values accounted for only 11% of the risk of developing DR, leaving 89% unexplained.[2,5,18] Several prospective cohort studies have demonstrated that patients with diabetes without DR have thinner pRNFL compared with healthy controls.[19,20] Lim et al.[7,21] found that the rates of pRNFL thinning were 2.9 and 3.3 times faster in non-DR and NPDR groups, respectively, than in healthy controls. This study advances previous findings by revealing that patients who developed DR exhibited a faster rate of initial pRNFL thinning compared with those who did not develop DR.

The accelerated pRNFL thinning observed before the clinical diagnosis of DR suggests that RN occurs prior to microvascular abnormalities, indicating that RN is an initial event in DR pathogenesis. The "neurovascular unit," comprising neuroglial cells, neurons, and vascular cells, is central to maintain retinal function.[22] In this context, both RN and microvascular abnormalities are crucial in DR pathogenesis. Astrocyte damage, indicated by RNFL thinning, impacts superficial capillaries, potentially leading to microaneurysms and fluid leakage.[2] Hyperglycemia-induced metabolic changes in the retina cause an imbalance of growth factors, cytokines, and inflammatory molecules, damaging retinal vasculature and neurons and contributing to DR.[22]

Due to retinal ganglion cell axons that converge on the optic disc, scanning the thickness of the pRNFL is the most commonly used protocol for OCT in screening and monitoring patients with optic neuropathy.[23] The macula comprises up to 7 layers of retinal ganglion cell bodies, accounting for 50% of the total, with cell bodies being larger and easier to measure than axons, and exhibiting relatively small variation in morphology between individuals. However, the Diagnostic Innovations in Glaucoma Study found that pRNFL progressed faster than macular GCIPL, indicating that pRNFL is a more sensitive diagnostic indicator of glaucomatous damage.[24] A meta-analysis demonstrated that mean macular ganglion cell complex (GCC) thickness was less sensitive than the pRNFL thickness for glaucoma diagnosis, especially in RTVue OCT and high definition OCT (HD-OCT).[25] Furthermore, diabetic macular edema affects GCIPL measurements. Therefore, this study selected pRNFL as the primary index for assessing RN.

Notably, after adjusting for other confounders, the pRNFL decline in the inferior and nasal sector was significantly associated with DR occurrence. This suggests that optic nerve damage in the inferior and nasal zone may occur earlier in the pathophysiologic process of DR development. This may be due to the embryological closure of the optic nerve and choroidal fissure in the inferior region at around 7 weeks of gestational age.[23] Furthermore, this region corresponds to the papillomacular bundle, which consists of small ganglion cell axons, making it more susceptible to hypoxia or ischemia. Although the average differences in pRNFL thickness between baseline and 1 year later are small, the OCT device is only suitable for large-scale cohort analyses. For single patients or smaller groups, this technique would not be sufficient. Future studies with larger sample sizes are needed to replicate these results and uncover the complex mechanisms involved in this process.

Our study has implications. An accelerated rate of initial pRNFL thinning can help identify patients at higher risk of progression, thereby focusing healthcare resources on this population and reducing the follow-up burden on patients with more stable disease. For instance, incorporating pRNFL changes into screening programs could lead to shorter screening intervals and timely referrals for high-risk patients.[5] Because the elevated HbA1c level was significantly associated with rapid thinning, this suggest that patients with poorly controlled diabetes or elevated blood pressure (BP) should be prioritized for screening and monitoring.[19] This study provides a more accurate pathophysiologic profile of DR, indicating that future study should also focus on neurodegeneration. Furthermore, experimental studies have shown that GLP-1 receptor agonists and DPP-4 inhibitors provide neuroprotection.[1] In clinical trials, topical brimonidine has shown potential for protection of preexisting retinal neurologic dysfunction.[26] Further study is needed to explore the impact of these neuroprotective agents on the predictive efficacy of pRNFL and to validate their cost-effectiveness and acceptability in clinical practice.

This study has several strengths. First, it is the first large-scale prospective study to assess the relationship between the rate of initial pRNFL thinning and the risk of developing DR in patients with T2DM, providing novel evidence that RN precedes DR-related microvascular abnormalities. Second, using seven-field fundus color photographs to evaluate DR at baseline and during follow-up reduced the possibility of missing or misidentifying mild disease. Third, this study included a relatively large sample of patients with T2DM without a history of ocular treatment, thereby eliminating potential influences of treatments on pRNFL, with all participants coming from a homogeneous community. Fourth, the study adjusted for various potential confounders, minimizing systematic and random errors, and ensuring the study's credibility.

This study also has some limitations. First, it was not conducted on a broad population, which might introduce selection bias. However, given the study's relatively large sample size, its findings still hold significant value. Second, the study included only Chinese patients with T2DM, necessitating validation of the predictive model's efficacy and applicability to patients with type 1 diabetes mellitus and other ethnic groups. Third, the follow-up duration was relatively short, whereas DR development may occur over a longer period, potentially underestimation the correlation between retinal neurons and DR. Indeed, the subtle associations observed within a short follow-up period suggest that the predictive power of initial pRNFL thinning rate

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for DR onset could be more robust in studies with larger samples and longer follow-up periods. Finally, the study exclusively used OCT, although it is important to note that dysfunction often precedes morphological changes. Functional tests would enable early identification of RN, which may be reversible.[27] Further study is needed to investigate the predictive value of multifocal electroretinography and microperimetry in screening for RN in the development of DR.

Conclusions

In summary, this prospective longitudinal study indicates that patients who develop DR exhibit accelerated thinning of the pRNFL in the initial stages. A significant association between the rate of initial pRNFL thinning and the risk of developing DR, and it could improve discriminatory power of traditional predictive models. These findings demonstrate that RN precedes the microvascular abnormalities associated with DR. This provides new insights into the management of DR and supports the use of RN parameters for assessing DR risk and predicting disease progression. Further study on RN in diabetic eye disease may enhance understanding of DR pathogenesis, prognosis, and treatment.

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