Long-Term Prediction and Risk Factors for Incident Visual Field Defect in Nonpathologic High Myopia

Cong Li,[1] Yanping Chen,[1] Shaopeng Yang,[1] Ruilin Xiong,[1] Riqian Liu,[1] Ziyu Zhu,[1] Shida Chen,[1] Mingguang He,[1–4] and Wei Wang[1,5]

[1]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangdong Provincial Clinical Research Center for Ocular Diseases, Guangzhou, China
[2]Experimental Ophthalmology, The Hong Kong Polytechnic University, Hong Kong, China
[3]Research Centre for SHARP Vision (RCSV), The Hong Kong Polytechnic University, Kowloon, Hong Kong
[4]Centre for Eye and Vision Research (CEVR), 17W Hong Kong Science Park, Hong Kong
[5]Hainan Eye Hospital and Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, Haikou, China

Correspondence: Wei Wang, Zhongshan Ophthalmic Center, State Key Laboratory of Ophthalmology, Sun Yat-Sen University, Guangzhou, China;
wangwei@gzzoc.com.
Mingguang He, The Hong Kong Polytechnic University, Hong Kong, China;
mingguang.he@polyu.edu.hk.

CL, YC, and SY are co-first authors.

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Purpose. To investigate the long-term patterns and risk factors of visual field defect (VFD) development in nonpathologic high myopia (HM) over an 8-year follow-up.

Methods. This was an observational cohort study. The VFD classification adhered to the Glaucoma Suspects with High Myopia Study Group. Logistic regression models with generalized estimating equations were used to identify risk factors for VFD development.

Results. A total of 330 eyes from 194 patients were included. Among them, 49.4% of eyes developed VFD, with enlarged blind spot and nonspecific defect ranked as the most common VFDs, followed by partial arcuate defect, vertical step, nasal step, paracentral defect, and combined defects. Longer axial length (odds ratio [OR] = 1.43 per 1-mm increase; 95% CI, 1.04–1.95; $P = 0.026$), thinner central corneal thickness (OR = 1.01 per 1-µm decrease; 95% CI, 1.003–1.02; $P = 0.013$), worse mean deviation of visual field (OR = 1.51 per 1-dB decrease; 95% CI, 1.14–2.00; $P = 0.004$), and the presence of peripapillary γ-zone (OR = 5.57; 95% CI, 3.06–10.15; $P < 0.001$) at baseline correlated with the development of any VFD. By incorporating these factors, the prediction models achieved area under the curves of 0.789 (95% CI, 0.726–0.853) and 0.828 (95% CI, 0.714–0.943) for discriminating the development of any VFD and moderate/severe VFD, respectively, with good calibration power.

Conclusions. The development of VFD occurred frequently in individuals with nonpathologic HM and can be effectively predicted using relevant metrics. The findings will aid in expanding our knowledge of optic neuropathy in HM.

Keywords: nonpathologic high myopia, visual field defect, optic neuropathy

By 2050, approximately 938 million individuals (9.8% of the global population) will develop high myopia (HM) and are at a risk of vision loss and blindness.[1] Beyond myopic macular degeneration, optic neuropathy was another most common cause for visual impairment in the highly myopic population, and its prevalence increased with greater refractive error and older age.[2] Visual field defect (VFD) is an important functional indicator of evaluating optic neuropathy, which has been used as the primary outcome in prominent trials.[3–5] Considering the progressive essence of optic neuropathy, it is imperative to determine the natural trajectory of VFD development in the HM population without myopic macular degeneration.

We previously reported on the classification of VFD for high/pathologic myopia, but the impact of myopic macular degeneration on VFD was not excluded.[6] Recently, the Glaucoma Suspects with High Myopia Study Group has proposed a novel classification system to describe VFD for nonpathologic HM.[7] This classification system provides a standardized means of distinguishing glaucoma-like VFD from nonglaucomatous VFD in highly myopic eyes. Nevertheless, to our knowledge, none of the studies has employed this classification to explore the longitudinal patterns of VFD development in nonpathologic HM, which potentially enhances subsequent optimization of detecting and monitoring the optic neuropathy in HM.

Individuals with HM who are affected by irreversible visual impairment tend to have extra physical and financial burdens owing to the loss of productivity and independence.[8] Therefore, it is of paramount importance to clarify risk factors for VFD development and establish corresponding prediction models in the HM population, which facilitates identifying those high-risk individuals for early targeted intervention. However, due to limited longitudinal studies of investigating VFD aiming at the HM population,[9–11] risk

factors associated with the development of VFD in HM have not been well documented.

To fill the knowledge gap, the purposes of this study were as follows: (1) to investigate the patterns of VFD development in nonpathologic highly myopic individuals over an 8-year follow-up, (2) to determine the factors associated with VFD development, and (3) to establish the prediction models for discriminating the VFD development.

Methods

Study Participants

This cohort study was conducted at the Zhongshan Ophthalmic Center (ZOC), Sun Yat-Sen University, Guangzhou, China (ISRCTN56368396). This study was approved by the Ethics Committee of ZOC (2012KYNL002 and 2023KYPJ090), adhering to the tenets of the Declaration of Helsinki. Signed informed consent was obtained from all the patients or their legal guardians.

In total, 315 patients with bilateral HM (spherical error of −6.00 diopters or greater) were recruited from ZOC–Brien Holden Vision Institute High Myopia Cohort. Those patients were followed for a minimum of 8 years. The exclusion criteria were as follows: (1) presence of pathologic changes, including myopic maculopathy ≥ category 2 or "plus lesions" at baseline or follow-up, which was defined by the International Meta-Analysis for Pathological Myopia classification[12]; (2) presence of posterior staphyloma at baseline or follow-up; (3) best-corrected visual acuity (BCVA) <20/40 at baseline; (4) intraocular pressure (IOP) >21 mm Hg at baseline; (5) ocular surgery or laser treatment during the follow-up; (6) the absence or poor quality of visual field (VF) tests; (7) presence of VFD at baseline; (8) IOP-lowering medication; and (9) other ocular or systemic diseases such as severe cataract, age-related macular degeneration, and multiple sclerosis that may cause VFD.

VFD Assessments

All the patients underwent standard automatic perimetry (Zeiss Humphrey Visual Field 750i; Carl Zeiss Meditec, Dublin, CA, USA), using the 24-2 Swedish Interactive Threshold Algorithm protocol. Following the comprehensive examinations at baseline, the participants were scheduled to return to our hospital voluntarily for subsequent examinations every 24 months, including VF testing (from November 2011 to December 2021).[13] The VF tests were performed in a solitary dark room with no distractions (ambient light <5 lux). In this study, the reliable VF tests should meet three criteria: false-positive rate <15%, false-negative rate <15%, and fixation loss rate <20%. The unreliable VF tests or any abnormal VF were repeated instantly (up to two times). Accordingly, eyes with VFD would have at least two and up to three reliable VF tests, while those eyes with normal VF during the initial VF test would not undergo repeated testing.

After adhering to the Glaucoma Suspects with High Myopia Study Group's classification for VF abnormalities in HM without pathologic changes, a VFD was defined when a pattern deviation plot of VF (at least two consecutive reliable VF examinations) presented a reproducible decrease in sensitivity at a cluster of at least three adjacent test points with a P value of <5% loss or more or a cluster of at least two adjacent test points with a P value of <1% loss or more in the inferior or superior arcuate regions.[7] Alternatively, the total deviation plot presenting a 10-dB difference across the nasal horizontal midline at a cluster of at least two adjacent test points was considered.[7] The VFD patterns were divided into glaucoma-like defects (paracentral defect, nasal step, partial arcuate defect, arcuate defect), HM-related defects (enlarged blind spot, vertical step, partial peripheral rim, nonspecific defect), and combined defects (nasal step with enlarged blind spot).[7] The VF test with the least severe VFD (according to the mean deviation [MD] of VF) was selected for the further analysis if those patients had repeated VF tests.[7] In this study, any VFD consisted of glaucoma-like defects, HM-related defects, and combined defects. For the eyes with newly developed VFD, the severity of VFD was stratified into −6.00 dB or more for mild VFD and −6.01 dB or less for moderate/severe VFD (MS-VFD) based on the MD of VF at the 8-year follow-up.[14] The classification of VFD was evaluated by a trained ophthalmologist (CL) without knowledge of other data regarding study participants supervised by a panel of glaucoma specialists (WW, MH).

Ophthalmic Examinations

All the patients accepted the comprehensive ocular examinations. IOP was assessed using Goldmann applanation tonometry. The ocular biometric parameters, including axial length (AL), central corneal thickness (CCT), corneal curvature, anterior chamber depth, corneal diameter, and lens thickness, were obtained using optical low-coherence reflectometry (Lenstar LS900; Haag-Streit AG, Koeniz, Switzerland). If AL exceeded the measurement range of Lenstar (up to 32 mm), AL was measured using IOL-Master (Carl Zeiss Meditec, Oberkochen, Germany). After pupil dilation, determined by at least 6 mm in diameter and the absence of light reflex, refraction was collected with automatic refractometry (KR8800; Topcon, Tokyo, Japan). Spherical equivalent was calculated by summing spherical power and half of cylindrical power. The BCVA was assessed using a logarithm of the minimum angle of resolution Tumbling E chart (Precision Vision, La Salle, IL, USA). Detailed examinations of the anterior segment and fundus were conducted using the slit-lamp microscope and three-mirror contact lens.

Standard 45° color fundus photography, centered on the macula and optic nerve head, was captured using a digital fundus camera (Canon CX-1; Canon, Tokyo, Japan) after pupil dilation. Color fundus photography images were graded according to the meta-analysis for pathologic myopia (META-PM) classification, including "no myopic retinal degenerative lesion" (category 0), "tessellated fundus" (category 1), "diffuse chorioretinal atrophy" (category 2), "patchy chorioretinal atrophy" (category 3), "macular atrophy" (category 4), and "plus" lesions such as myopic choroidal neovascularization, lacquer cracks, and Fuch's spot.[12] The presence of a peripapillary γ-zone was defined by a whitish region presenting clearly visible sclera at the temporal optic disc margin without underlying choriocapillaris, middle-sized choroidal arteries, and signs of retinal pigment epithelium.[15–17] The staphyloma was defined as an outpouching of a circumscribed area in the posterior segment of the eyeball and displayed a smaller curvature radius compared to surrounding areas.[18,19]

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Statistical Analysis

The data distribution was examined using a Shapiro–Wilk test. Continuous variables with normal distribution were presented as mean (standard deviation); otherwise, they were presented as median (min, max). Categorical variables were expressed as number (percentage). Generalized estimating equations (exchangeable correlation matrix) were used to account for the correlation between pairs of eyes for each patient. Logistic regression models with generalized estimating equations were used to assess the association of clinical characteristics with the development of any VFD-, MS-VFD-, and HM-related defects and glaucoma-like defects, respectively. The univariable model was used to explore the association of clinical characteristics with the development of any VFD. Odds ratios (ORs) with 95% confidence interval (CIs) were calculated.

A data set comprising 194 eyes from 194 patients was used to construct the prediction models of the incidence of any VFD and MS-VFD. The assessment of model performance was evaluated based on discrimination and calibration. Using fivefold cross-validation, the receiver operating characteristic and average of the area under the curve (AUC) were performed to quantify predictive discrimination. Meanwhile, calibration plots were built to visualize the goodness of model fit and evaluated using the Hosmer–Lemeshow test where a P value greater than 0.05 indicates an acceptable fit. All analyses were conducted with Stata version 17 (StataCorp LP, College Station, TX, USA) and R software (version 4.3.1; R Project for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < 0.05$ unless otherwise indicated.

Results

Clinical Characteristics

The flowchart of the study is shown in Figure 1. A total of 330 eyes with nonpathologic HM from 194 patients were included in the analysis (Table 1). Compared to the excluded eyes, the included eyes tended to be younger, be less myopic, and have a deeper anterior chamber depth, a thinner lens thickness, and a better visual function at baseline (Supplementary Table S1). For the included eyes, the median (min, max) age of them was 17.09 (8.01, 66.30) years at baseline, and 61.52% were female. A total of 163 eyes (49.4%) developed any VFD over an 8-year follow-up. Among them, 55 eyes (16.7%) developed MS-VFD (Fig. 1). Compared with non-VFD eyes, the eyes with newly developed VFD tended to have a longer AL, a thinner CCT, greater vertical corneal curvature radius, worse BCVA, worse MD, a higher pattern standard deviation (PSD), and a lower visual field index (VFI) at baseline (all $P < 0.05$). The clinical characteristics of included eyes after an 8-year follow-up are shown in Supplementary Table S2.

Distribution of Incident VFD Patterns

Figure 2 shows the distribution and representative cases of newly developed VFD patterns and corresponding color fundus photography over an 8-year follow-up. The most common VFDs were enlarged blind spot (15.5%) and nonspecific defect (14.5%), followed by partial arcuate defect (5.5%), vertical step (4.8%), nasal step (4.6%), paracentral

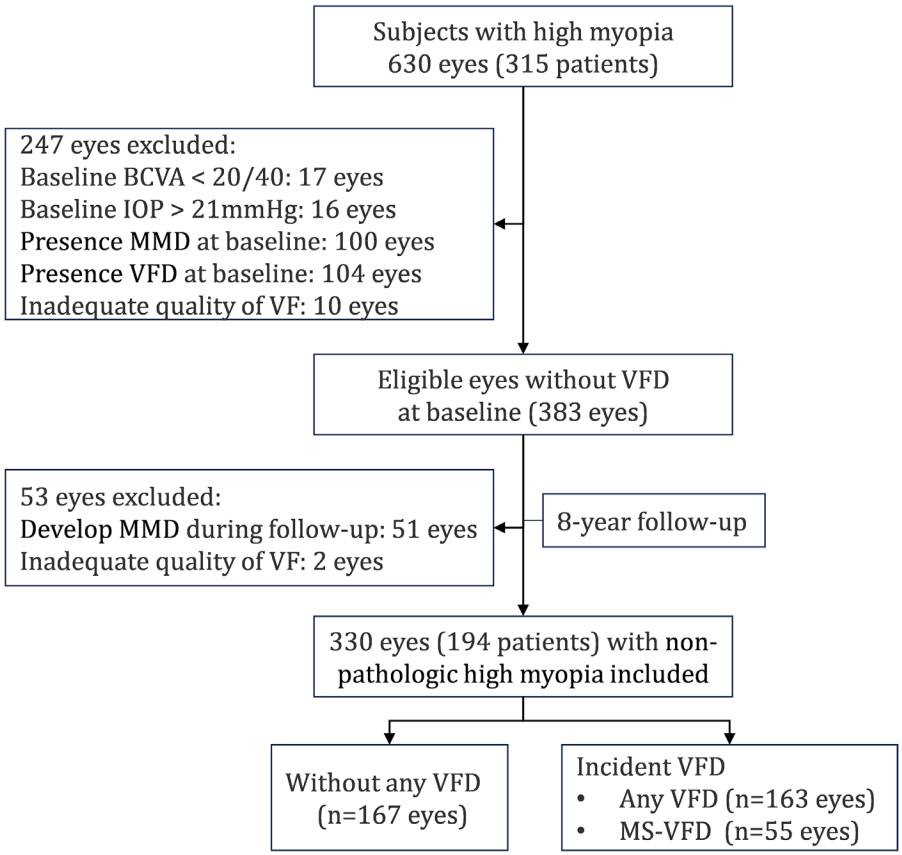

Figure 1. Inclusion and exclusion flowchart of the study. MMD, myopic macular degeneration.

Table 1. Baseline Characteristics of Included Eyes With Nonpathologic High Myopia

Characteristic	All Eyes (n = 330)	Newly Developed VFD		P Value*
		Yes (n = 163)	No (n = 167)	
Age, y	17.09 (8.01, 66.30)	17.88 (8.78, 62.60)	16.04 (8.01, 66.30)	0.055
Female, n (%)	203 (61.52%)	94 (57.67%)	109 (65.27%)	0.156
High school or higher education, n (%)	201 (60.91%)	101 (61.96%)	100 (59.88%)	0.698
Current smoker, n (%)	9 (2.73%)	7 (4.29%)	2 (1.20%)	0.106
Intraocular pressure, mm Hg	15.67 (10.00, 20.67)	15.67 (10.00, 20.67)	15.33 (10.33, 19.67)	0.206
Spherical equivalent, diopter	−8.13 (−16.88, −6.00)	−8.38 (−16.88, −6.00)	−8.00 (−14.75, −6.13)	0.084
Axial length, mm	26.77 (24.57, 31.05)	27.10 (24.89, 31.05)	26.49 (24.57, 28.88)	**0.011**
Central corneal thickness, µm	547 (473, 632)	541 (473, 626)	553 (476, 632)	**0.009**
Anterior chamber depth, mm	3.18 (0.25)	3.14 (0.26)	3.21 (0.23)	0.063
Lens thickness, mm	3.49 (3.00, 5.43)	3.53 (3.00, 4.98)	3.48 (3.09, 5.43)	0.179
Horizontal corneal curvature radius, mm	7.83 (0.27)	7.87 (0.24)	7.78 (0.28)	0.652
Vertical corneal curvature radius, mm	7.55 (0.27)	7.61 (0.26)	7.50 (0.27)	**0.017**
Corneal diameter, mm	12.04 (0.48)	12.08 (0.49)	12.01 (0.46)	0.419
Best-corrected visual acuity, logMAR	0 (−0.08, 0.30)	0 (−0.08, 0.30)	0 (−0.08, 0.20)	**0.018**
Mean deviation of visual field, dB	−1.78 (1.20)	−2.12 (1.10)	−1.45 (1.20)	**<0.001**
Pattern standard deviation of visual field, dB	1.47 (0.96, 4.69)	1.51 (1.05, 4.69)	1.40 (0.96, 4.69)	**0.034**
Visual field index of visual field, %	99 (96, 100)	99 (96, 100)	99 (96, 100)	**0.021**
Myopic maculopathy classification, n (%)				**<0.001**
Category 0 based on META-PM system	183 (55.45%)	73 (44.79%)	110 (65.87%)	
Category 1 based on META-PM system	147 (44.55%)	90 (55.21%)	57 (34.13%)	

Continuous variables with normal distribution are presented as mean (standard deviation); otherwise, they are presented as median (min, max). Categorical variables are expressed as number (%). META-PM, meta-analysis for pathologic myopia classification.
*P Value was obtained with a generalized estimating equation.

defect (2.4%), and combined defects (2.1%), while arcuate defect and partial peripheral rim were not observed during the follow-up. Overall, glaucoma-like VFD, HM-related VFD, and combined defects accounted for 12.5%, 34.8%, and 2.1% of all eyes, respectively.

Predictors for Incident VFD

The univariable model showed that the development of any VFD significantly correlated with baseline AL, CCT, BCVA, MD of VF, PSD of VF, VFI of VF, and the presence of a peripapillary γ-zone (Table 2). After adjusting for other factors, the development of any VFD was significantly associated with longer AL (OR = 1.43 per 1-mm increase; 95% CI, 1.04–1.95; P = 0.026), thinner CCT (OR = 1.01 per 1-µm decrease; 95% CI, 1.003–1.02; P = 0.013), worse MD of VF (OR = 1.51 per 1-dB decrease; 95% CI, 1.14–2.00; P = 0.004), and the presence of a peripapillary γ-zone (OR = 5.57; 95% CI, 3.06–10.15; P < 0.001) at baseline. Similarly, the development of MS-VFD significantly correlated with longer AL (OR = 2.81 per 1-mm increase; 95% CI, 1.91–4.14; P < 0.001), thinner CCT (OR = 1.01 per 1-µm decrease; 95% CI, 1.002–1.03; P = 0.025), worse MD of VF (OR = 1.80 per 1-dB decrease; 95% CI, 1.20–2.70; P = 0.004), and the presence of a peripapillary γ-zone (OR = 3.01; 95% CI, 1.43–6.34; P = 0.004) at baseline. In Tables 3 and 4, these predictors consistently showed a significant correlation with the development of HM-related defects and glaucoma-like defects after multivariable adjustment, respectively.

Predictive Modeling for Incident VFD

By incorporating AL, CCT, MD of VF, and the presence of a peripapillary γ-zone at baseline, the prediction model demonstrated a robust ability to discriminate the development of any VFD and achieved an average AUC of 0.789 (95% CI, 0.726–0.853) (Fig. 3A). For MS-VFD, the prediction model's efficacy was higher, with an average AUC of 0.828 (95% CI, 0.714–0.943) (Fig. 3B). Calibration plots (Figs. 3C, 3D) showed excellent calibration power (P = 0.297 and P = 0.358), indicating the strong concordance between predicted and observed probabilities for the development of any VFD and MS-VFD, respectively.

Discussion

Main Findings

This study demonstrated that 49.4% of eyes with nonpathologic HM developed VFD over an 8-year follow-up, with enlarged blind spot and nonspecific defect ranked as the most common VFDs. Longer AL, thinner CCT, worse MD of VF, and the presence of a peripapillary γ-zone at baseline were main predictors for VFD development. By incorporating these variables, the prediction model had an AUC of 0.789 for discriminating the development of any VFD and excellent calibration power. To our knowledge, this study first reported the long-term patterns of VFD development in individuals with nonpathologic HM according to the latest classification system.

Longitudinal Patterns of Incident VFD

Currently, HM-associated optic neuropathy is already one of the most frequent causes of irreversible vision loss in East Asia.[20] Despite this, limited studies have been involved in this topic,[2,21] particularly among highly myopic individuals without pathologic change. The novel classification for VF abnormalities is expected to open new avenues for effectively monitoring and predicting the development of VFD in nonpathologic HM, which facilitates a comparison of investigation in future studies.

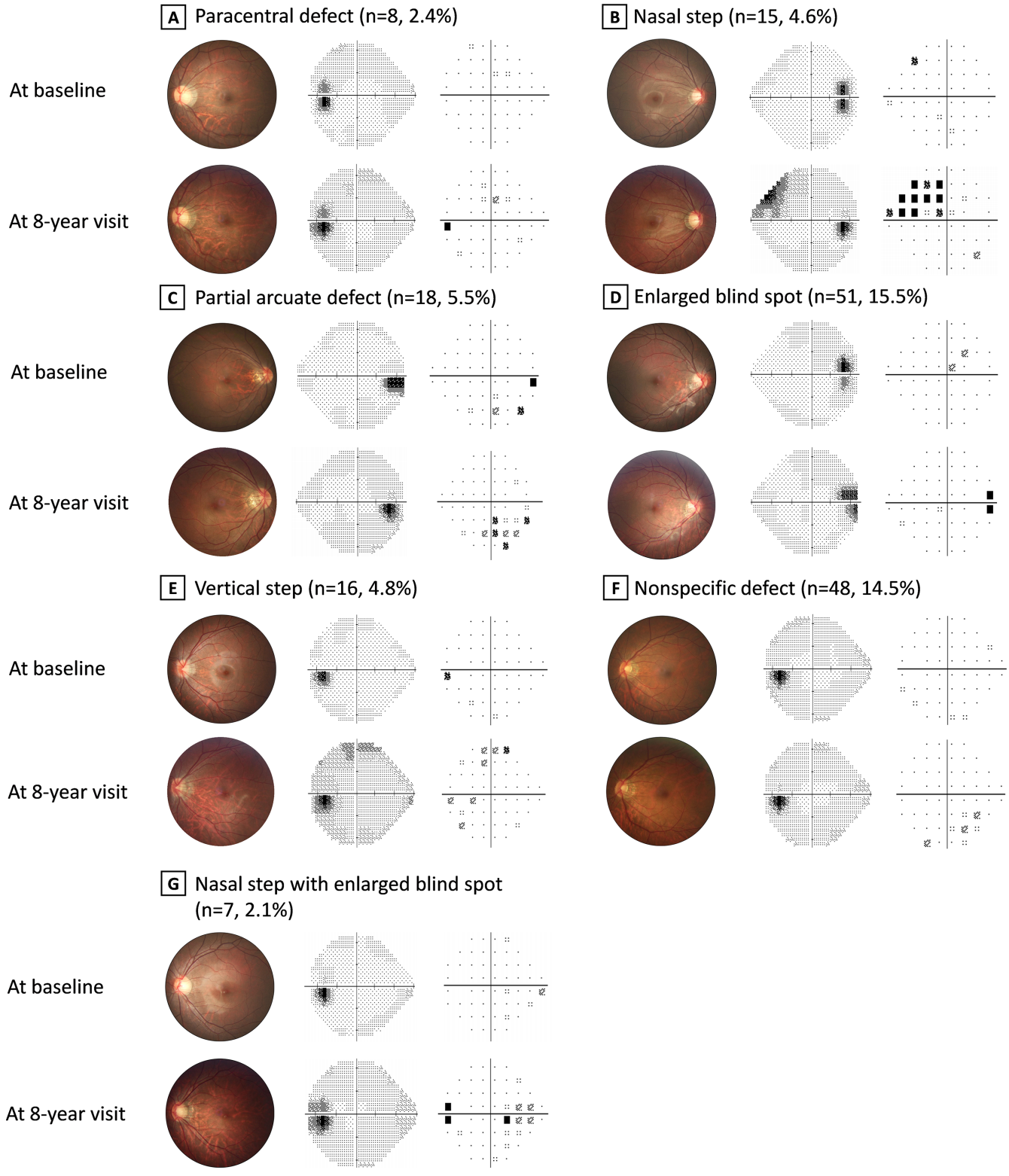

Figure 2. The distribution and representative cases of newly developed visual field defect patterns and corresponding color fundus photography in eyes with nonpathologic high myopia over an 8-year follow-up.

Table 2. Association of Clinical Characteristics With the Development of VFD in Eyes With Nonpathologic High Myopia

	Univariable Model		Multivariable Model 1*		Multivariable Model 2*	
Characteristic	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Baseline age, per 1 year older	1.03 (0.999–1.05)	0.055	1.005 (0.97–1.04)	0.770	0.997 (0.96–1.04)	0.878
Sex, female vs. male	0.72 (0.42–1.24)	0.243	NA		NA	
Educational level at baseline						
Primary school and below	Reference					
High school and above	1.09 (0.65–1.84)	0.744	NA		NA	
Baseline AL, per 1-mm increase	1.80 (1.37–2.38)	**<0.001**	1.43 (1.04–1.95)	**0.026**	2.81 (1.91–4.14)	**<0.001**
Baseline IOP, per 1-mm Hg increase	1.07 (0.96–1.19)	0.223	NA		NA	
Baseline CCT, per 1-µm decrease	1.01 (1.001–1.02)	**0.029**	1.01 (1.003–1.02)	**0.013**	1.01 (1.002–1.03)	**0.025**
Baseline ACD, per 1-mm increase	0.34 (0.11–1.03)	0.056	0.62 (0.15–2.56)	0.509	0.71 (0.18–2.88)	0.634
Baseline LT, per 1-mm increase	1.96 (0.77–5.03)	0.160	NA		NA	
Baseline BCVA, per 0.1-logMAR unit increase	1.82 (1.23–2.68)	**0.002**	1.28 (0.84–1.96)	0.246	1.15 (0.73–1.80)	0.552
Baseline MD of VF, per 1-dB decrease	1.67 (1.33–2.10)	**<0.001**	1.51 (1.14–2.00)	**0.004**	1.80 (1.20–2.70)	**0.004**
Baseline PSD of VF, per 1-dB increase	1.40 (1.04–1.87)	**0.024**	1.08 (0.75–1.54)	0.686	1.30 (0.82–2.07)	0.271
Baseline VFI of VF, per 1% increase	0.71 (0.55–0.92)	**0.010**	1.03 (0.67–1.56)	0.899	1.39 (0.84–2.31)	0.200
Presence of γ-zone at baseline, yes vs. no	5.88 (3.35–10.29)	**<0.001**	5.57 (3.06–10.15)	**<0.001**	3.01 (1.43–6.34)	**0.004**

Bold indicates statistical significance. ACD, anterior chamber depth; LT, lens thickness; NA, not applicable.
* Factors with a *P* value less than 0.10 in the univariable model were considered for the multivariable model. Model 1 examined any VFD as the outcome, whereas model 2 focused on moderate/severe VFD.

Table 3. Risk Factors for the Development of High Myopia-Related Defects In Eyes With Nonpathologic High Myopia

	Univariable Analysis		Multivariable Analysis*	
Characteristic	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Baseline age, per 1 year older	1.03 (0.997–1.06)	0.073	1.01 (0.98–1.05)	0.590
Sex, female vs. male	0.67 (0.38–1.18)	0.167	NA	
Educational level at baseline				
Primary school and below	Reference			
High school and above	1.16 (0.66–2.03)	0.613	NA	
Baseline AL, per 1-mm increase	1.88 (1.40–2.53)	**<0.001**	1.53 (1.09–2.15)	**0.013**
Baseline IOP, per 1-mm Hg increase	1.09 (0.97–1.22)	0.137	NA	
Baseline CCT, per 1-µm decrease	1.01 (1.00–1.02)	**0.044**	1.01 (1.001–1.02)	**0.031**
Baseline ACD, per 1-mm increase	0.29 (0.09–0.92)	**0.036**	0.76 (0.17–3.47)	0.724
Baseline LT, per 1-mm increase	1.64 (0.60–4.47)	0.335	NA	
Baseline BCVA, per 0.1-logMAR unit increase	1.76 (1.14–2.70)	**0.010**	1.50 (0.94–2.38)	0.091
Baseline MD of VF, per 1-dB decrease	1.59 (1.25–2.02)	**<0.001**	1.46 (1.09–1.95)	**0.010**
Baseline PSD of VF, per 1-dB increase	1.46 (1.09–1.96)	**0.011**	1.12 (0.76–1.66)	0.559
Baseline VFI of VF, per 1% increase	0.78 (0.59–1.03)	0.079	1.03 (0.66–1.61)	0.907
Presence of γ-zone at baseline, yes vs. no	6.45 (3.64–11.41)	**<0.001**	5.39 (2.89–10.06)	**<0.001**

Bold indicates statistical significance. ACD, anterior chamber depth; LT, lens thickness; NA, not applicable.
* Factors with a *P* value less than 0.10 in the univariable analysis were considered for the multivariable analysis.

Although some longitudinal studies have investigated the VFD in individuals with HM, the long-term patterns of VFD development remain unclear. In a study conducted in Japan, Ohno-Matsui et al.[9] reported that 13.2% of highly myopic eyes developed significant VFD using Goldmann kinetic perimetry during a mean follow-up of 11.6 years. In the other study over a 10-year period, Fledelius et al.[10] found that 42% of individuals with HM had VFD by using Goldmann kinetic perimetry in a Danish population, but the sample size of the study was quite limited. In this study, we reported that 49.4% and 16.7% of eyes developed any VFD and MS-VFD over an 8-year follow-up, respectively. Our findings suggested that the development of VFD occurred frequently in highly myopic individuals without pathologic change. Enlarged blind spot was the most common VFD in eyes with nonpathologic HM, which may be attributed to peripapillary atrophy and/or a tilted optic nerve insertion mapping beyond the normal blind spot on static perimetry.[6] Several studies have reported that peripapillary atrophy (41.5–81.2%)[22–24] and tilted optic disc (56.6–57.4%)[22,24] were highly prevalent in HM. Meanwhile, nonspecific defect was the second most common VFD, which advanced the cross-sectional study by Lin et al.[7] The occurrence of nonspecific defect may be due to the irregular stretching and bending of the retinal nerve fiber layer within the progression of HM.[7,9]

We observed that 12.5% of eyes developed glaucoma-like defects, including partial arcuate defect (5.5%), nasal step (4.6%), and paracentral defect (2.4%). This suggested that the initial location of optic nerve damage in highly myopic glaucoma may differ from nonmyopic glaucoma, as HM alters the normal trajectory of retinal nerve fiber bundles temporal to the macula.[25] Among seven eyes that developed the combined defects, four eyes with normal fundus at baseline progressed to tessellated fundus, indicating that HM

Table 4. Risk Factors for the Development of Glaucoma-Like Defects in Eyes With Nonpathologic High Myopia

	Univariable Analysis		Multivariable Analysis*	
Characteristic	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Baseline age, per 1 year older	1.03 (0.99–1.06)	0.158	NA	
Sex, female vs. male	0.96 (0.44–2.10)	0.917	NA	
Educational level at baseline				
Primary school and below	Reference			
High school and above	1.07 (0.51–2.26)	0.855	NA	
Baseline AL, per 1-mm increase	1.96 (1.35–2.83)	**<0.001**	1.52 (1.03–2.24)	**0.037**
Baseline IOP, per 1-mm Hg increase	1.02 (0.86–1.20)	0.852	NA	
Baseline CCT, per 1-µm decrease	1.01(1.002–1.03)	**0.026**	1.02 (1.001–1.03)	**0.032**
Baseline ACD, per 1-mm increase	0.13 (0.02–0.74)	**0.022**	0.25 (0.04–1.71)	0.159
Baseline LT, per 1-mm increase	2.40 (0.70–8.26)	0.166	NA	
Baseline BCVA, per 0.1-logMAR unit increase	1.70 (0.999–2.89)	0.050	1.20 (0.73–1.98)	0.478
Baseline MD of VF, per 1-dB decrease	1.66 (1.23–2.23)	**0.001**	1.51 (1.02–2.23)	**0.038**
Baseline PSD of VF, per 1-dB increase	1.21 (0.86–1.70)	0.285	NA	
Baseline VFI of VF, per 1% increase	0.70 (0.51–0.97)	**0.030**	0.98 (0.60–1.59)	0.930
Presence of γ-zone at baseline, yes vs. no	4.54 (2.17–9.53)	**<0.001**	3.50 (1.57–7.84)	**0.002**

Bold indicates statistical significance. ACD, anterior chamber depth; LT, lens thickness; NA, not applicable.
* Factors with a *P* value less than 0.10 in the univariable analysis were considered for the multivariable analysis.

progression and glaucoma may not be separate but interacting disorders,[26] yet the intricate nature of this relationship necessitates further investigation.

In one study, Lin et al.[7] reported the prevalence of various VFD patterns and found that enlarged blind spot and nonspecific defect were the most frequent VFDs, followed by nasal step, partial arcuate defect, paracentral defect, and other VFDs, which echoed the findings of this longitudinal study to a great extent. In the same study, Lin et al.[7] also reported that the partial peripheral rim accounted for less than 0.5% of all eyes with nonpathologic HM.[7] In the other study, Ding et al.[6] found that rim artifacts were detected in 2.5% of highly myopic eyes. These findings suggested that this type of VFD may be uncommon in HM, and thus it seemed reasonable that partial peripheral rim was not observed in our study.

Factors Associated With VFD Development

Predictors for the development of VFD in HM have not been well determined, as current insights into VFD in the HM population mainly derived from cross-sectional studies. Prior studies have revealed that longer AL is a risk factor for glaucomatous optic neuropathy in HM,[27,28] collaborating to support our findings. In a study conducted in Russia, Bikbov et al.[21] reported that a higher prevalence of nonglaucomatous optic nerve atrophy was associated with longer AL and wider peripapillary γ-zone. Furthermore, it was suggested that the peripapillary γ-zone strongly correlated with longer AL, generally starting beyond an AL of 25 mm, and its size increased when AL exceeded 26.5 mm.[29–31] This study found that longer AL and the presence of a peripapillary γ-zone significantly correlated with the development of VFD in patients with nonpathologic HM. A larger peripapillary γ-zone was associated with marked vertical optic disc rotation, leading to a stretching of the temporal peripapillary scleral flange.[15,16,32] Thus, it may be inferred that axial elongation and the peripapillary γ-zone cause the stretching of retinal nerve fiber layer due to the increasing distance between the optic disc and retinal ganglion cells, consequently contributing to optic nerve damage and VFD.

We found that worse MD of VF at baseline significantly correlated with the development of VFD. Aung et al.[33] found that MD decreased by 0.33 dB with each 1-mm increase in AL, suggesting that MD could serve as a functional indicator reflecting the severity of myopia. Moreover, in a retrospective study with a duration of 24 to 64 months, nearly 50% of highly myopic eyes with glaucoma showed a significant decrease in MD.[34] Considering the progressive essence of optic neuropathy in HM, it is recommended to incorporate VF testing as a routine assessment, with MD serving as an indicator of functional loss for monitoring HM, especially at the initial visit.

We also found that thinner CCT at baseline was significantly associated with the development of VFD. Wang et al.[35] reported that thinner CCT was related to an increased incidence of open-angle glaucoma in individuals with HM. Medeiros et al.[36] reported patients with a CCT of <545 µm had more than a twofold higher risk of developing VFD compared to patients with a CCT of ≥545 µm. Jin et al.[37] found that CCT showed a continuous downward trend as AL increased in a highly myopic population. Given that scleral thickness decreases with longer AL within the course of myopia (especially HM) progression, we assumed that the corneal stroma may exhibit a comparable thinning pattern to the sclera.

Implications of Prediction Models

By incorporating AL, CCT, MD of VF, and the peripapillary γ-zone at baseline, the prediction models achieved good performance in discriminating the development of any VFD and MS-VFD, respectively. Notably, we found that longer AL was a potent predictor of incident MS-VFD. Rozema et al.[38] indicated that newly myopic children exhibited greater AL growth rates than emmetropes. Moreover, Fledelius et al.[39] found that continued axial elongation also occurs among individuals aged 13 to 18 years. This study highlights the necessity of comprehensive myopia management for monitoring and controlling excessive axial elongation in children and adolescents. Currently, the pathophysiologic mechanism in HM that affects VF is still unclear, and thus our results would be help-

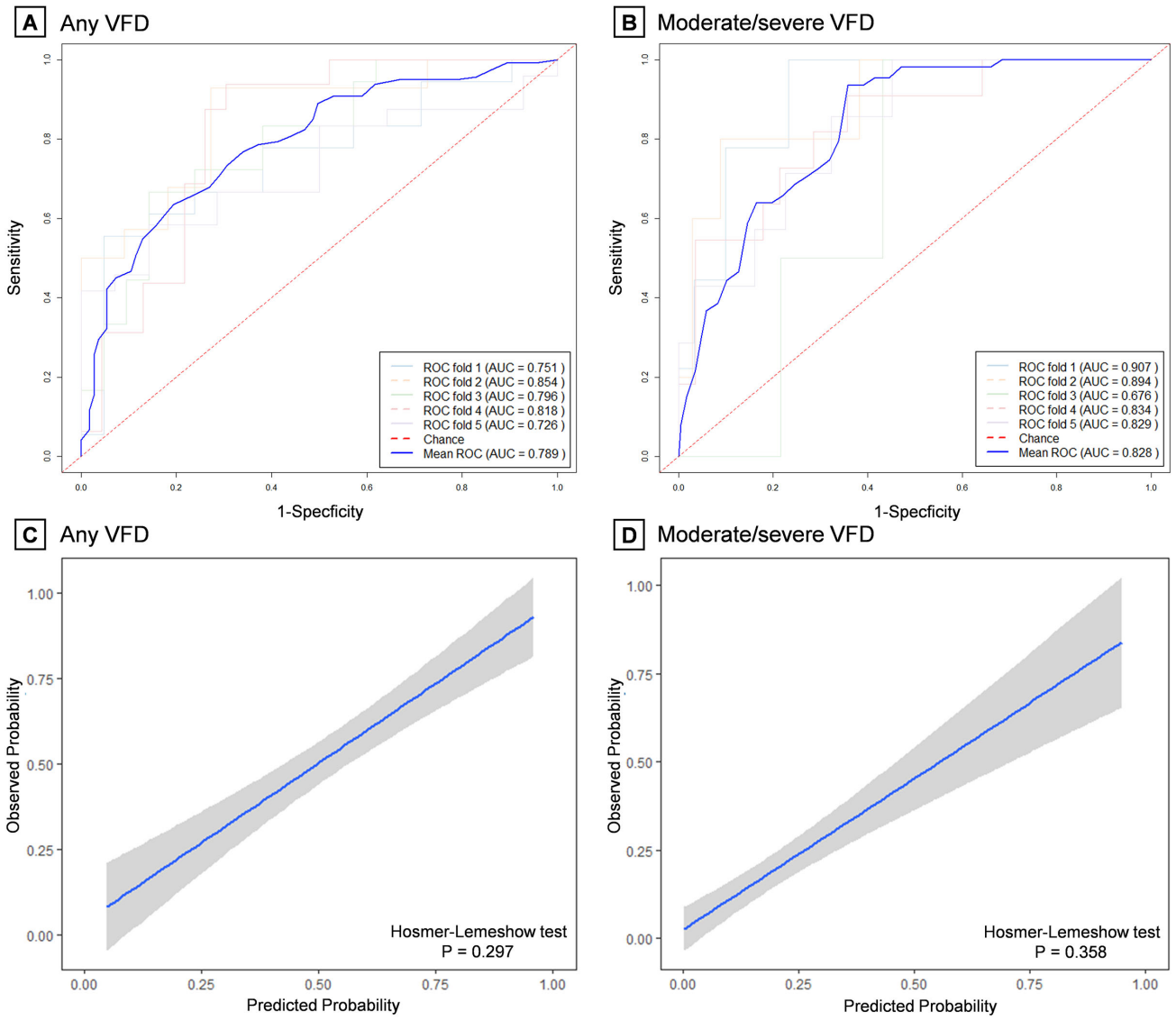

Figure 3. Receiver operating characteristic curves and calibration plots of prediction models for predicting the development of VFD in eyes with nonpathologic high myopia. (A) The prediction model achieves the mean AUC of 0.789 for discriminating the development of any VFD. (B) The prediction model achieves the mean AUC of 0.828 for discriminating the development of moderate/severe VFD. (C, D) The calibration plots reveal that both prediction models possess good calibration power (all $P > 0.05$), suggesting a strong agreement between the predicted probability and observed probability.

ful in identifying high-risk individuals and facilitating timely interventions.

Strengths and Limitations

The strengths of this study lie in the longitudinal cohort design, comprehensive exploration, and adjustment of potential confounders. In addition, the study participants were relatively young, and thus our results would be less influenced by other confounders such as cataract, age-related macular degeneration, and so on. However, several limitations of our study should be considered. First, since our participants came from a single territory center, recruitment-based population bias may exist. Thus, it is unclear whether our results can be generalized to other highly myopic individuals from different ethnic backgrounds. Second, the peripapillary γ-zone was assessed on color fundus photography since optical coherence tomography (OCT) imaging of the optic nerve head was not available at baseline. Third, we found that the risk factors for the development of HM-related defects and glaucoma-like defects were consistent. Nevertheless, this finding needs further investigation since certain systemic factors (e.g., blood pressure, glycated hemoglobin levels, and body mass index) and parameters of multimodal ocular imaging (e.g., OCT and OCT angiography) were not included in this study. Fourth, due to the lack of external validation, it should be noted that the observed levels of predictive performance may not be applicable to patients from other hospitals or regions.

Conclusions

In conclusion, this study found that about half of eyes developed VFD in individuals with nonpathologic HM over an

8-year follow-up. Among them, enlarged blind spot and nonspecific defect were the most common VFDs. Longer AL, thinner CCT, worse MD of VF, and the presence of the peripapillary γ-zone at baseline were risk factors for VFD development. Utilizing these factors, the prediction models showed good discrimination and calibration power for the development of any VFD and MS-VFD. Further studies involving other ethnicities are warranted.

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