Longitudinal Macular Ganglion Cell–Inner Plexiform Layer Measurements to Detect Glaucoma Progression in High Myopia

JOONG WON SHIN, MIN KYUNG SONG, AND KYUNG RIM SUNG

• PURPOSE: To investigate whether progressive macular ganglion cell–inner plexiform layer (GCIPL) and peripapillary retinal nerve fiber layer (RNFL) thinning are predictive for detecting visual field (VF) progression in eyes with high myopia.

• DESIGN: Cohort study.

• METHODS: A total of 104 primary open-angle glaucoma (POAG) eyes with high myopia and 104 age- and VF severity-matched POAG eyes without high myopia (mean follow-up, 5.4 years) were included. High myopia was defined as a spherical equivalent <-6.0 diopters or axial length >26.5 mm. Progressive GCIPL, RNFL, and VF deterioration were determined by Guided Progression Analysis (GPA) in optical coherence tomography and standard automated perimetry. The risk of VF progression was evaluated using Cox proportional hazard models.

• RESULTS: Highly myopic eyes with progressive GCIPL thinning had a significantly higher risk of developing VF progression after adjusting for the baseline intraocular pressure (HR 4.00; $P = .001$) or peak intraocular pressure (HR 3.11; $P = .011$) in the multivariable Cox proportional hazard model, whereas highly myopic eyes with progressive RNFL thinning were not significantly associated with VF progression. In eyes without high myopia, both progressive GCIPL (HR 4.67 or 3.62; $P = .008$ or .037, respectively) and RNFL (HR 6.60 or 3.97; $P = .001$ or .016, respectively) thinning were associated with a significantly higher risk of developing VF progression after adjusting for the baseline or peak intraocular pressure.

• CONCLUSIONS: Monitoring macular GCIPL thickness was effective for predicting glaucoma progression regardless of the presence of high myopia (Am J Ophthalmol 2021;223:9–20. © 2020 Elsevier Inc. All rights reserved.)

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Department of Ophthalmology, College of Medicine, University of Ulsan, Asan Medical Center, Seoul, Korea.

Inquiries to Kyung Rim Sung, Department of Ophthalmology, College of Medicine, University of Ulsan, Asan Medical Center, 388-1 Pungnap-2-dong, Songpa-gu, Seoul 138-736, Korea; e-mail: sungeye@gmail.com

INTRODUCTION

DIAGNOSING AND MONITORING GLAUCOMA IN high myopia are challenging because of structural deformation in the peripapillary area. The peripapillary retinal nerve fiber layer (RNFL) of a highly myopic eye tends to be thinner than that of a normal eye, and optic disc changes such as tilting, oval configuration, and peripapillary atrophy may cause variations in RNFL measurements.[1–3] Axial elongation not only contributes to the temporalization of RNFL distribution but also leads to the inherent RNFL measurement error due to magnification effect and scan circle misalignment on the optic disc.[1,4,5] These may lower the diagnostic accuracy of RNFL thickness for detecting glaucoma in highly myopic eyes.[6] Macular ganglion cell–inner plexiform layer (GCIPL) measurement can be useful for detecting glaucomatous structural loss in highly myopic eyes, wherein the macular region has been less affected by optic disc variation.[7,8] Previous studies have reported macular measurements as effective for detecting glaucoma regardless of the degree of myopia, with a higher diagnostic accuracy than both optic disc and RNFL measurements in highly myopic eyes.[6,9] However, little is known about the ability of GCIPL and RNFL measurements to identify glaucomatous progression in high myopia.

Guided Progression Analysis (GPA; Carl Zeiss Meditec, Dublin, CA, USA) was developed to expedite the monitoring of structural changes in optical coherence tomography (OCT). Detecting progressive GCIPL and RNFL thinning using GPA is useful for predicting visual field (VF) progression among patients with glaucoma.[10–13] A recent study reported that the repeatability of OCT parameters in highly myopic eyes, including GCIPL and RNFL measurements, was comparable to that in emmetropic eyes.[14] This may imply that monitoring OCT parameters can be useful for detecting disease progression in glaucoma patients with high myopia. Therefore, this study aimed to investigate the performance of progressive GCIPL and RNFL thinning in detecting VF progression in eyes with high myopia.

METHODS

• PARTICIPANTS: This study recruited subjects from an ongoing Asan Glaucoma Progression Study, which is a

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retrospective cohort study conducted at the Asan Medical Center (Seoul, Korea). The data were collected by reviewing medical records from April 2009 through May 2019. The Institutional Review Board of Asan Medical Center approved the present study, and all procedures were carried out in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

All participants underwent complete ophthalmologic examinations at the baseline visit, including the measurement of best-corrected visual acuity, intraocular pressure (IOP) using Goldmann applanation tonometry, refractive error using an autorefractor (KR-890; Topcon Corp, Tokyo, Japan), axial length (IOLMaster; Carl Zeiss Meditec), central corneal thickness (CCT; DGH-550; DGH Technology, Exton, PA, USA), slit-lamp biomicroscopy, and gonioscopy. Participants were followed up at 6-month intervals (±3 months depending on patients' condition) for stereoscopic optic disc and red-free RNFL photography (AFC-210; Nidek, Aichi, Japan), RNFL and GCIPL imaging (Cirrus HD-OCT; Carl Zeiss Meditec), and VF testing (Humphrey Field Analyzer [HFA], Swedish Interactive Threshold Algorithm 24-2; Carl Zeiss Meditec).

For inclusion in the present study, all participants had to have POAG and meet the following criteria: a best-corrected visual acuity ≥20/30 and a normal anterior chamber and open-angle on slit-lamp and gonioscopic examinations. At least 6 reliable VF and OCT examinations at separate visits and at least 3 years of follow-up were required for inclusion. Glaucoma was defined as the presence of RNFL defects or glaucomatous optic disc changes (eg, neuroretinal rim thinning, disc excavation, or disc hemorrhage on stereoscopic optic disc photography) with compatible glaucomatous VF defects. Glaucoma was determined by an experienced glaucoma expert (K.R.S.). A glaucomatous VF defect was defined as follows: (1) a cluster of ≥3 nonedged contiguous points with a less than 5% probability in pattern deviation plot hemifield, at least 1-point with a less than 1% probability; (2) a pattern standard deviation with *P* less than 5%; or (3) outside normal limits glaucoma hemifield test results, as confirmed on 2 consecutive VF tests. Only reliable VF test results (false-positive errors <15%, false-negative errors <15%, and a fixation loss <20%) were included in the analysis. The glaucomatous patients who met our inclusion criteria were classified into 2 groups: highly myopic eyes or not. High myopia was defined as a spherical equivalent (SE) <–6.0 diopters (D) or axial length >26.5 mm.[15] Eyes without high myopia were selected and matched to highly myopic eyes for age (≤2 years) and VF mean deviation (MD, ≤2 dB) to minimize the influence of these variables on glaucoma progression because older age and worse VF MD at initial presentation are known to be associated with glaucoma progression.[16,17] Patients were excluded from the study if they had a history of intraocular or refractive surgery and any ophthalmic (eg, myopic maculopathy) or neurologic disease known to affect the optic nerve head, macular structure, or VF. If surgical or laser treatment was performed during the study follow-up period, only data obtained in the period before the treatment were analyzed. If both eyes of a patient were eligible, 1 eye was selected at random.

OCT IMAGING

THE MACULAR AND OPTIC DISC CUBE SCANS MEASURED GCIPL and RNFL thicknesses, using Cirrus HD-OCT (software version 10.0), at the macular and peripapillary regions (6×6-mm^2) centered at the fovea and optic disc, respectively. The average macular GCIPL thickness was measured within an annulus with inner vertical and horizontal diameters of 1 and 1.2 mm, respectively, and outer vertical and horizontal diameters of 4 and 4.8 mm, respectively. The average peripapillary RNFL thickness was measured in a circle, 3.46 mm in diameter. Only images with a signal strength ≥6 in both macular and optic disc cube scans were included. Images with motion artifacts, poor centering, or segmentation errors were checked and discarded by the operator, and rescanning was performed during the same visit. If unobtainable or erroneous thickness data existed within a 4-mm-diameter circle in peripapillary images and a 5-mm-diameter circle in macular images, these images were excluded in the final analysis. Seventeen OCT images (pairs of GCIPL and RNFL thickness maps) from 9 eyes were excluded because of insufficient signal strength, 25 OCT images from 13 eyes were excluded because of uncorrectable segmentation errors, and 104 OCT images from 28 eyes were excluded because of unobtainable scan data. The mean number of OCT examinations per eye was 10.2 (range, 6-20). In total, 2,120 OCT images were included in the final analysis.

• **PROGRESSIVE THINNING OF THE GCIPL AND RNFL:** Progressive GCIPL and RNFL thinning were evaluated using OCT GPA, which provides a color-coded classification for abnormal GCIPL and RNFL changes exceeding the normal test-retest variability range. The built-in software automatically aligns, registers, and compares baseline and follow-up OCT images and presents abnormal changes as yellow and red codes in a 6×6-mm^2 (50×50 superpixels) map. A yellow code (ie, "possible progression" in the OCT GPA) indicates the first detection of an abnormal GCIPL or RNFL change in the GCIPL or RNFL thickness change map. A red code (ie, "likely progression" in the OCT GPA) indicates that an abnormal GCIPL or RNFL change has been confirmed in a subsequent follow-up examination. In the present study, progressive thinning was defined as when at least 20 contiguous red superpixels were detected in the GCIPL or RNFL thickness change map, and the same changes were observed in the latest

follow-up visit.[10–12,18] The rate of change in GCIPL and RNFL thicknesses over time was determined by linear regression using GPA.

• **REFERENCE OF GLAUCOMA PROGRESSION:** In the present study, VF progression was determined by the Early Manifest Glaucoma Trial criteria using HFA GPA and was regarded as the reference for glaucoma progression.[19] Progressive VF change (eg, "likely progression" in the HFA GPA) was defined when there were 3 or more locations that showed significant decreases exceeding test-retest variability in VF sensitivity compared with 2 baseline examinations in 3 consecutive tests. These changes also should be observed in all the subsequent follow-up visits. The trend-based analysis, such as linear regression using VF index, was not adopted as criteria in determining VF progression, because visual field patterns may be more appropriate than quantitative indices to assess the visual field in highly myopic patients.[20]

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using the statistical package R (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria) and SPSS software (version 20; IBM Corp, Armonk, NY). Demographic and clinical characteristics were compared between progressors and non-progressors according to the presence of high myopia. Continuous variables were compared using independent *t* test or Mann-Whitney *U* test depending on the result of normality test (Shapiro-Wilk test). Categorical variables were compared using the χ^2 test. Cox proportional hazard model was used to evaluate the risk factors for VF progression in eyes with and without high myopia. Univariable analysis was performed to find potential clinical variables associated with the VF progression. A backward elimination process was used to build a multivariable model incorporating variables with $P < .10$ in univariable analysis. Kaplan-Meier survival analysis and the log-rank test were used to compare the VF survival estimates in eyes with and without progressive GCIPL or RNFL thinning, according to the presence of high myopia.

RESULTS

A TOTAL OF 104 EYES OF 104 POAG PATIENTS (69 MEN AND 35 women) with high myopia and 104 age- and VF MD-matched eyes of 104 POAG patients (63 men and 41 women) without high myopia were included. The mean follow-up period was 5.4 ± 1.4 years (range, 3.0-9.4 years). Table 1 summarizes and compares the demographic and clinical characteristics of POAG eyes with and without high myopia. Eyes with high myopia had significantly thinner mean GCIPL (67.4 ± 9.3 μm vs 73.0 ± 9.3 μm at baseline and 65.0 ± 8.9 μm vs 70.8 ± 9.1 μm at final, all $P < .001$) and RNFL (68.6 ± 10.7 μm vs 76.9 ± 13.9 μm at baseline and 66.4 ± 9.7 μm vs 73.2 ± 12.6 μm, all $P < .001$) thicknesses than those without high myopia. There were no significant differences in the progressive changes of HFA, GCIPL, and RNFL GPA between eyes with and without high myopia. During follow-up period, subjects who underwent at least 2 refractive error or axial length measurements were 84 eyes and 21 eyes in high-myopia group, respectively. There were no significant differences between baseline and last measurements of refractive error (6.82 ± 2.03 D vs 6.79 ± 1.93 D, $P = .924$) or axial length (26.75 ± 1.12 mm vs 26.88 ± 1.21 mm, $P = .879$).

• **PERFORMANCE OF GUIDED PROGRESSION ANALYSIS FOR DETECTING GLAUCOMA PROGRESSION IN EYES WITH AND WITHOUT HIGH MYOPIA:** In eyes with high myopia, progressive GCIPL and RNFL thinning by GPA were detected in 31 eyes (29.8%) and 21 eyes (20.2%), respectively, and 26 eyes (25.0%) showed progressive VF deterioration according to the Early Manifest Glaucoma Trial criteria (Figure 1, left). The sensitivities of GCIPL and RNFL GPA for detecting VF progression were 57.7% and 34.6% at the specificities of 79.5% and 84.6%, respectively, and there was a significant difference ($P = .001$). Table 2 compares the demographic and clinical characteristics between the progressors and nonprogressors in eyes with high myopia. The progressors had a significantly higher baseline IOP (17.7 ± 3.3 mm Hg vs 15.8 ± 3.3 mm Hg, $P = .009$), higher peak IOP (22.4 ± 8.9 mm Hg vs 17.5 ± 2.7 mm Hg, $P < .001$), and faster rate of change in average GCIPL (0.80 ± 0.81 μm/y vs 0.26 ± 0.41 μm/y, $P < .001$) and RNFL (0.80 ± 1.06 μm/y vs 0.31 ± 0.76 μm/y, $P = .011$) thicknesses during the follow-up compared with nonprogressors.

In eyes without high myopia, progressive GCIPL and RNFL thinning by GPA were detected in 37 eyes (35.6%) and 24 eyes (23.1%), respectively, and 15 eyes (14.4%) showed progressive VF deterioration according to the Early Manifest Glaucoma Trial criteria (Figure 1, right). The sensitivities of GCIPL and RNFL GPA for detecting VF progression were 73.3% and 60.0% at the specificities of 70.1% and 83.2%, respectively, and there was no significant difference ($P = .059$). Table 3 compares the demographic and clinical characteristics between the progressors and nonprogressors in eyes without high myopia. The progressors had a significantly longer follow-up duration (6.2 ± 1.5 years vs 5.2 ± 1.4 years, $P = .011$), higher peak IOP (23.6 ± 9.7 mm Hg vs 19.0 ± 5.1 mm Hg, $P = .007$), and faster rate of change in average GCIPL (0.87 ± 0.54 μm/y vs 0.37 ± 0.48 μm/y, $P < .001$) and RNFL (1.38 ± 1.67 μm/y vs 0.41 ± 0.85 μm/y, $P = .001$) thicknesses during the follow-up compared with nonprogressors.

• **RISK OF GLAUCOMA PROGRESSION IN EYES WITH AND WITHOUT HIGH MYOPIA:** Table 4 shows the risk factors

TABLE 1. Comparison of Clinical Characteristics Between Glaucomatous Eyes With and Without High Myopia

	Eyes With High Myopia	Eyes Without High Myopia	*P* Value
Number of eyes	104	104	
Gender (male/female)	69/35	63/41	
Age (y)	49.0 ± 12.3	50.2 ± 9.3	.442
Refractive error (diopter)	–6.61 ± 1.96	–1.24 ± 1.34	**< .001**
Axial length (mm)	26.46 ± 1.08	23.82 ± 0.54	**< .001**
Central corneal thickness (μm)	536.6 ±32.8	527.6 ± 36.5	.137
Follow-up duration (y)	5.4 ± 1.3	5.4 ± 1.4	.829
Intraocular pressure (IOP, mm Hg)			
Baseline IOP	16.3 ± 3.4	16.6 ± 4.6	.490
Mean IOP	14.1 ± 2.1	14.3 ± 2.1	.501
Peak IOP	18.7 ± 5.4	19.7 ± 6.1	.239
Visual field measurement			
Baseline MD (dB)	–6.36 ± 6.22	–5.35 ± 5.11	.201
Baseline PSD (dB)	6.60 ± 4.63	6.24 ± 4.26	.553
Final MD (dB)	–6.88 ± 6.25	–5.24 ± 5.86	.071
Final PSD (dB)	7.71 ± 4.62	7.20 ± 4.49	.452
HFA GPA (progressive/stable)	26/78	15/89	.055
Macular GCIPL measurement			
Baseline average GCIPL thickness (μm)	67.4 ± 9.3	73.0 ± 9.3	**< .001**
Final average GCIPL thickness (μm)	65.0 ± 8.9	70.8 ± 9.1	**< .001**
GCIPL GPA (progressive/stable)	31/73	37/67	.375
Rate of change in the average GCIPL thickness (μm/y)	–0.39 ± 0.57	–0.44 ± 0.52	.466
Peripapillary RNFL measurement			
Baseline average RNFL thickness (μm)	68.6 ± 10.7	76.9 ± 13.9	**< .001**
Final average RNFL thickness (μm)	66.4 ± 9.7	73.2 ± 12.6	**< .001**
RNFL GPA (progressive/stable)	21/83	24/80	.613
Rate of change in the average RNFL thickness (μm/y)	–0.43 ± 0.87	–0.55 ± 1.06	.380

GCIPL = ganglion cell–inner plexiform layer, GPA = Guided Progression Analysis, HFA = Humphrey field analyzer, MD = mean deviation, PSD = pattern standard deviation, RNFL = retinal nerve fiber layer.

Statistically significant differences are shown in bold.

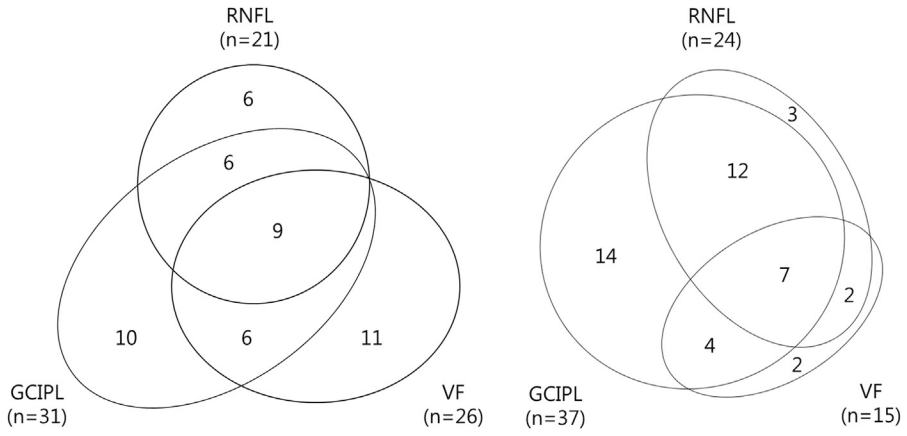

FIGURE 1. Proportional Venn diagrams representing the number of eyes detected with progressive thinning of the ganglion cell–inner plexiform layer (GCIPL) and retinal nerve fiber layer (RNFL), as well as with visual field (VF) progression in glaucomatous eyes with (left) and without (right) high myopia.

TABLE 2. Comparison of Clinical Characteristics Between Progressors and Nonprogressors in Glaucomatous Eyes with High Myopia

	Progressors	Nonprogressors	*P* Value
Number of eyes	26	78	
Gender (male/female)	21/5	48/30	.072
Age (y)	46.4 ± 12.8	49.9 ± 12.1	.212
Refractive error (diopter)	–6.40 ± 1.85	–6.68 ± 2.01	.602
Axial length (mm)	26.22 ± 1.01	26.53 ± 1.10	.348
Central corneal thickness (μm)	539.8 ± 29.4	535.5 ± 34.1	.629
Follow-up duration (y)	5.5 ± 1.6	5.4 ± 1.2	.621
Intraocular pressure (IOP, mm Hg)			
Baseline IOP	17.7 ± 3.3	15.8 ± 3.3	**.009**
Mean IOP	14.5 ± 2.5	13.9 ± 1.9	.229
Peak IOP	22.4 ± 8.9	17.5 ± 2.7	**< .001**
Visual field measurement			
Baseline MD (dB)	–7.26 ± 7.28	–6.06 ± 5.85	.395
Baseline PSD (dB)	6.62 ± 4.31	6.60 ± 4.76	.978
Final MD (dB)	–10.07 ± 6.91	–5.82 ± 5.65	**.003**
Final PSD (dB)	9.65 ± 3.34	7.06 ± 4.84	**.019**
Rate of change in the MD (dB/y)	–0.75 ± 0.58	0.04 ± 0.39	**< .001**
Rate of change in the PSD (dB/y)	0.62 ± 0.64	0.11 ± 0.31	**< .001**
Macular GCIPL measurement			
Baseline average GCIPL thickness (μm)	67.4 ± 8.0	67.4 ± 9.8	.971
Final average GCIPL thickness (μm)	63.9 ± 9.1	65.3 ± 8.9	.481
GCIPL GPA (progressive/stable)	15/11	16/62	**< .001**
Rate of change in the average GCIPL thickness (μm/y)	–0.80 ± 0.81	–0.26 ± 0.41	**< .001**
Peripapillary RNFL measurement			
Baseline average RNFL thickness (μm)	68.1 ± 10.2	68.8 ± 10.9	.788
Final average RNFL thickness (μm)	64.4 ± 10.3	67.1 ± 9.4	.233
RNFL GPA (progressive/stable)	9/17	12/66	**.034**
Rate of change in the average RNFL thickness (μm/y)	–0.80 ± 1.06	–0.31 ± 0.76	**.011**

GCIPL = ganglion cell–inner plexiform layer, GPA = Guided Progression Analysis, MD = mean deviation, PSD = pattern standard deviation, RNFL = retinal nerve fiber layer.

Statistically significant differences are shown in bold.

associated with VF progression in eyes with and without high myopia using Cox proportional hazard model. In eyes with high myopia, higher baseline IOP (hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.06-1.31; $P = .003$), higher peak IOP (HR 1.08, 95% CI 1.04-1.12; $P < .001$), and progressive GCIPL thinning (HR 4.00, 95% CI 1.77-9.02; $P = .001$) were significantly associated with the risk of VF progression in the univariable model, whereas progressive RNFL thinning (HR 1.99, 95% CI 0.85-4.69; $P = .114$) was not significantly associated with VF progression. To avoid multicollinearity between baseline IOP and peak follow-up IOP and between progressive GCIPL and RNFL thinning determined by GPA, these parameters were analyzed separately in the multivariable model. In the multivariable model using eyes with high myopia, progressive GCIPL thinning (HR 4.00 or 3.11, 95% CI 1.76-9.09 or 1.30-7.43; $P = .001$ or .011, respectively) was associated with a significantly higher risk of developing VF progression after adjusting for the baseline IOP or peak IOP.

In eyes without high myopia, higher peak IOP (HR 1.08, 95% CI 1.02-1.15; $P = .006$) and progressive GCIPL (HR 4.61, 95% CI 1.46-14.51; $P = .009$) and RNFL thinning (HR 5.22, 95% CI 1.86-14.67; $P = .002$) were significantly associated with the risk of VF progression in the univariable model. To avoid multicollinearity between baseline IOP and peak follow-up IOP and between progressive GCIPL and RNFL thinning determined by GPA, these parameters were analyzed separately in the multivariable model. In the multivariable model using eyes without high myopia, eyes with progressive GCIPL (HR 4.67 or 3.62, 95% CI 1.51-15.04 or 1.08-12.09; $P = .008$ or .037, respectively) and RNFL (HR 6.60 or 3.97, 95% CI 2.25-19.40 or 1.29-12.16; $P = .001$ or .016, respectively) thinning were

TABLE 3. Comparison of Clinical Characteristics Between Progressors and Nonprogressors in Glaucomatous Eyes without High Myopia

	Progressors	Nonprogressors	*P* Value
Number of eyes	15	89	
Gender (male/female)	9/6	54/35	.961
Age (y)	50.6 ± 8.0	50.1 ± 9.5	.465
Refractive error (diopter)	–0.83 ± 1.62	–1.31 ± 1.29	.235
Axial length (mm)	23.95 ± 0.36	23.76 ± 0.61	.535
Central corneal thickness (μm)	540.0 ± 50.4	524.7 ± 37.4	.194
Follow-up duration (y)	6.2 ± 1.5	5.2 ± 1.4	**.011**
Intraocular pressure (IOP, mm Hg)			
Baseline IOP	16.3 ± 5.0	16.7 ± 4.5	.777
Mean IOP	14.7 ± 2.1	14.2 ±2.1	.429
Peak IOP	23.6 ± 9.7	19.0 ± 5.1	**.007**
Visual field measurement			
Baseline MD (dB)	–4.99 ± 5.63	–5.41 ± 5.04	.772
Baseline PSD (dB)	4.98 ± 3.97	6.45 ± 4.29	.216
Final MD (dB)	–10.75 ± 8.35	–4.58 ± 5.19	**.002**
Final PSD (dB)	10.32 ± 3.55	6.83 ± 4.46	**.027**
Rate of change in the MD (dB/y)	–0.72 ± 0.69	0.14 ± 0.57	**< .001**
Rate of change in the PSD (dB/y)	0.75 ± 0.68	0.09 ± 0.48	**< .001**
Macular GCIPL measurement			
Baseline average GCIPL thickness (μm)	71.5 ± 9.2	73.3 ± 9.4	.508
Final average GCIPL thickness (μm)	67.0 ± 8.4	71.5 ± 9.1	.079
GCIPL GPA (progressive/stable)	11/4	26/63	**.001**
Rate of change in the average GCIPL thickness (μm/y)	–0.87 ± 0.54	–0.37 ± 0.48	**< .001**
Peripapillary RNFL measurement			
Baseline average RNFL thickness (μm)	78.7 ± 15.9	76.6 ± 13.6	.577
Final average RNFL thickness (μm)	70.8 ±11.3	73.6 ±12.8	.428
RNFL GPA (progressive/stable)	9/6	15/74	**< .001**
Rate of change in the average RNFL thickness (μm/y)	–1.38 ± 1.67	–0.41 ± 0.85	**.001**

GCIPL = ganglion cell–inner plexiform layer, GPA = Guided Progression Analysis, MD = mean deviation, PSD = pattern standard deviation, RNFL = retinal nerve fiber layer.

Statistically significant differences are shown in bold.

associated with a significantly higher risk of developing VF progression after adjusting for the baseline IOP or peak IOP.

In Kaplan-Meier survival analysis using eyes with high myopia, eyes with progressive GCIPL thinning had significantly lower VF survival estimates than eyes without GCIPL thinning (Figure 2, top left, $P < .001$), whereas VF survival estimates did not differ between eyes with and without progressive RNFL thinning (Figure 2, bottom left, $P = .107$). In eyes without high myopia, VF survival estimates were significantly lower in eyes with progressive GCIPL and RNFL thinning than in eyes without (Figure 2, top right and bottom right, all $P < .05$).

• **TEMPORAL RELATIONSHIP AMONG PROGRESSIVE GCIPL, RNFL, AND VF CHANGE:** Among 15 highly myopic eyes with progressive GCIPL and VF changes, 12 eyes (80.0%) detected progressive GCIPL thinning simultaneously or before VF progression (33.3% and 46.7%, respectively). There was no significant difference in the mean interval to the first detection of GCIPL and VF progression (41.6 ± 15.4 vs 47.2 ± 21.0 months, respectively, $P = .332$). Among 9 highly myopic eyes with progressive RNFL and VF changes, 7 eyes (77.8%) detected progressive RNFL thinning simultaneously or before VF progression (22.2% and 55.6%, respectively). There was no significant difference in the mean interval to the first detection of RNFL and VF progression (35.2 ± 13.1 vs 41.8 ± 19.0 months, respectively, $P = .493$).

Likewise, among 11 non–highly myopic eyes with progressive GCIPL and VF changes, progressive GCIPL thinning was detected before VF progression in 6 eyes (54.5%)

TABLE 4. Univariable and Multivariable Cox Proportional Hazard Models for the Risk of Visual Field (VF) Progression in Glaucomatous Eyes with and without High Myopia

	Univariable		Multivariable 1		Multivariable 2		Multivariable 3		Multivariable 4	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Eyes with High Myopia										
Age (y)	0.97 (0.94-1.01)	.131								
Refractive error (diopters)	1.03 (0.81-1.31)	.836								
Axial length (mm)	0.81 (0.47-1.40)	.456								
Central corneal thickness (μm)	1.01 (0.99-1.02)	.319								
Follow-up duration (y)	1.06 (0.89-1.26)	.549								
Baseline IOP (mm Hg)	1.17 (1.06-1.31)	**.003**	1.20 (1.06-1.35)	**.004**			1.18 (1.05-1.31)	**.004**		
Mean follow-up IOP (mm Hg)	1.14 (0.97-1.35)	.113								
Peak follow-up IOP (mm Hg)	1.08 (1.04-1.12)	**<.001**			1.05 (1.01-1.09)	**.010**			1.07 (1.03-1.11)	**<.001**
Baseline VF MD (dB)	0.96 (0.91-1.02)	.235								
Baseline GCIPL thickness (μm)	0.98 (0.94-1.03)	.432								
Baseline RNFL thickness (μm)	0.99 (0.95-1.02)	.462								
Progressive GCIPL thinning	4.00 (1.77-9.02)	**.001**	4.00 (1.76-9.09)	**.001**	3.11 (1.30-7.43)	**.011**				
Progressive RNFL thinning	1.99 (0.85-4.69)	.114					1.87 (0.79-4.40)	.153	1.55 (0.63-3.77)	.340
Eyes without high myopia										
Age (y)	1.00 (0.95-1.06)	1.000								
Refractive error (diopters)	1.30 (0.88-1.92)	.194								
Axial length (mm)	1.50 (0.21-1.50)	.687								
Central corneal thickness (μm)	1.02 (1.00-1.04)	.116								
Follow-up duration (y)	1.40 (0.86-2.26)	.174								
Baseline IOP (mm Hg)	0.99 (0.88-1.11)	.860	0.97 (0.87-1.08)	.606			0.93 (0.83-1.05)	.224		
Mean follow-up IOP (mm Hg)	1.17 (0.91-1.51)	.216								
Peak follow-up IOP (mm Hg)	1.08 (1.02-1.15)	**.006**			1.05 (0.99-1.12)	.082			1.05 (0.98-1.12)	.148
Baseline VF MD (dB)	1.02 (0.92-1.13)	.738								
Baseline GCIPL thickness (μm)	0.98 (0.93-1.03)	.443								
Baseline RNFL thickness (μm)	1.01 (0.97-1.04)	.708								
Progressive GCIPL thinning	4.61 (1.46-14.51)	**.009**	4.76 (1.51-15.04)	**.008**	3.62 (1.08-12.09)	**.037**				
Progressive RNFL thinning	5.22 (1.86-14.67)	**.002**					6.60 (2.25-19.40)	**.001**	3.97 (1.29-12.16)	**.016**

CI = confidence interval, GCIPL = ganglion cell–inner plexiform layer, IOP = intraocular pressure, MD = mean deviation, RNFL = retinal nerve fiber layer, VF = visual field.
Statistically significant differences are shown in bold.

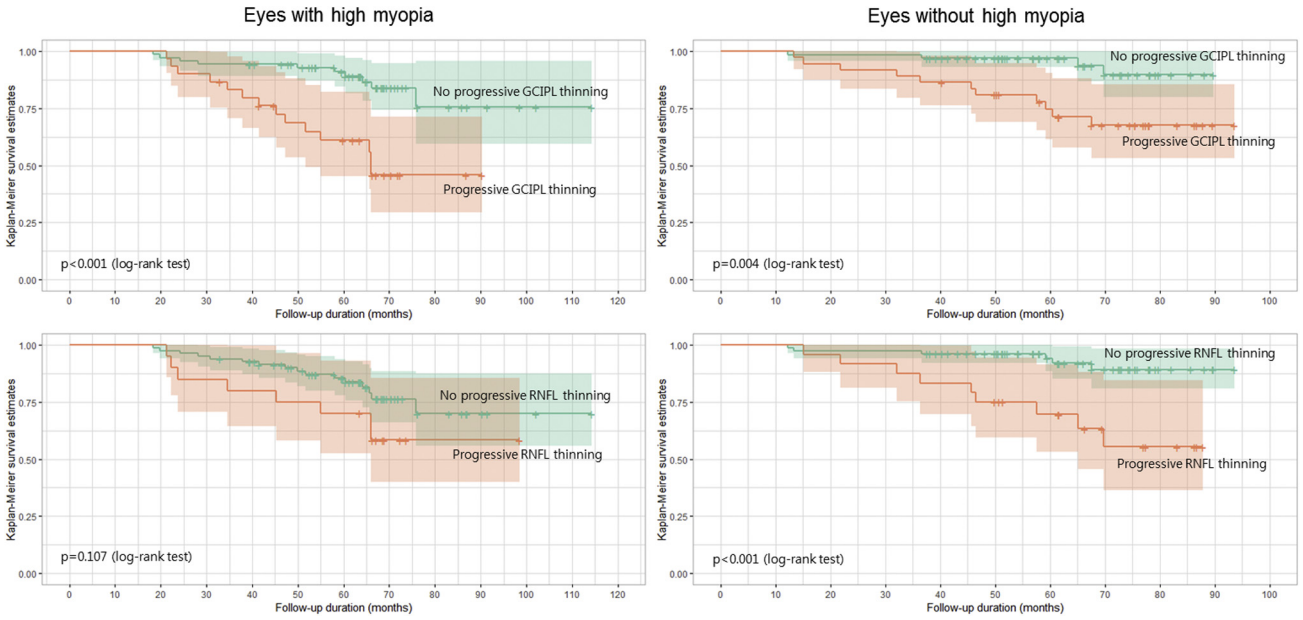

FIGURE 2. Kaplan-Meier curves for visual field (VF) survival estimates stratified according to the presence of progressive ganglion cell–inner plexiform layer (GCIPL) or retinal nerve fiber layer (RNFL) thinning in eyes with (top left and bottom left) and without (top right and bottom right) high myopia. The log-rank test was used to compare the VF survival estimates in eyes with and without progressive GCIPL or RNFL thinning.

or simultaneously in 3 eyes (27.3%). There was no significant difference in the mean interval to the first detection of GCIPL and VF progression (38.6 ± 18.0 vs 41.4 ± 19.1 months, respectively, $P = .620$). Among 9 non–highly myopic eyes with progressive RNFL and VF changes, progressive RNFL thinning was detected before VF progression in 4 eyes (44.4%) or simultaneously in 2 eyes (22.2%). There was no significant difference in the mean interval to the first detection of RNFL and VF progression (43.3 ± 18.8 months vs 46.8 ± 15.8 months, respectively, $P = .614$).

DISCUSSION

IN THE PRESENT STUDY, WE FOUND THAT MONITORING macular GCIPL thickness was predictive of VF progression in highly myopic eyes, whereas monitoring peripapillary RNFL thickness was less effective in predicting VF progression. In 104 eyes of 104 POAG patients with high myopia, eyes with progressive GCIPL thinning had a 3.11- or 4.00-fold increase (Table 4, depending on the multivariable models) in the risk of developing VF progression compared with eyes without progressive GCIPL thinning. In contrast, highly myopic eyes with progressive RNFL thinning did not show significant associations with VF progression. Additionally, the sensitivity of GCIPL GPA for detecting VF progression was 57.7% and significantly higher than that of RNFL GPA (34.6%) at the similar levels of specificities as 79.5% and 84.6%, respectively. The mean interval to the first detection of GCIPL (41.6 ± 15.4 months) was earlier than that of VF progression (47.2 ± 21.0 months), although there was no statistical significance. To our knowledge, this study revealed the first evidence demonstrating the validity of longitudinal follow-up with regular macular imaging with OCT to expedite the early detection of glaucoma progression in highly myopic eyes.

In eyes without high myopia, both progressive GCIPL and RNFL thinning were significantly associated with VF progression, and this finding is consistent with previous studies. Hou and associates[12] reported that progressive GCIPL (HR 3.48, 95% CI 1.51-8.01; $P = .003$) and RNFL (HR 3.66, 95% CI 1.68-7.97; $P = .001$) thinning were similarly predictive for detecting VF progression in 231 eyes with a mean SE of –3.4 D followed up for >5 years. In our previous study of 196 eyes (mean SE –2.13 D) followed up for a mean of 5.0 years, eyes with progressive GCIPL or RNFL thinning had significantly lower VF survival estimates than eyes without progressive GCIPL or RNFL thinning.[10] Considering similar predictive performance between GCIPL and RNFL monitoring for detecting VF progression in eyes without high myopia, it should be explored why GCIPL monitoring showed better performance in predicting VF progression than RNFL monitoring in high myopia.

The distribution pattern of glaucomatous RNFL defects is atypical in eyes with high myopia. Kim and associates[21]

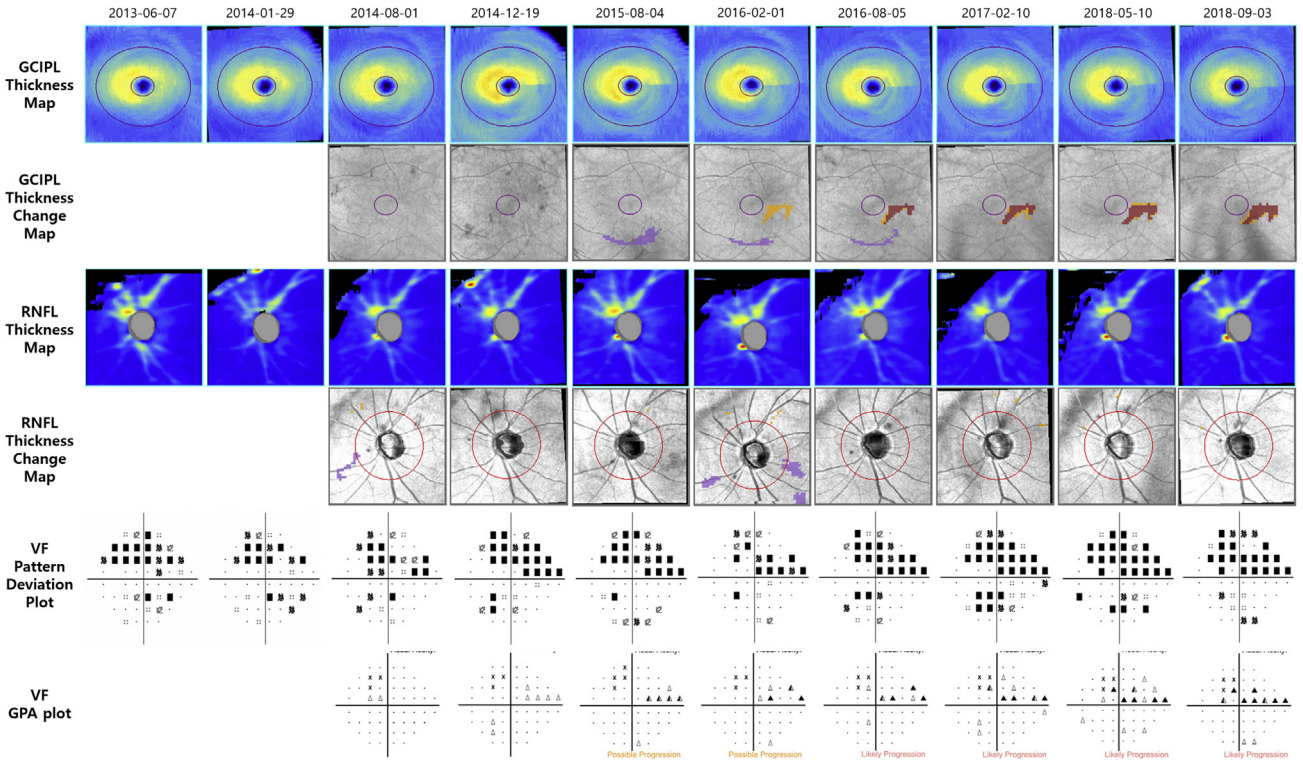

FIGURE 3. A representative case of a glaucomatous eye with high myopia. A 57-year-old man with high myopia (axial length, 27.14 mm) demonstrated simultaneous significant progressive macular ganglion cell–inner plexiform layer (GCIPL) thinning and visual field (VF) progression on August 5, 2016. Peripapillary retinal nerve fiber layer (RNFL) thickness did not change significantly over 5 years of follow-up. Because of the combined influence of highly myopic changes and glaucomatous damage, RNFL had already reached the measurement floor at his baseline examination and showed a discrepancy with GCIPL and VF damage.

reported that localized RNFL defects are wider and closer to the fovea in eyes with high myopia than those with mild to moderate myopia or emmetropia. Kimura and associates[22] reported that highly myopic eyes are more susceptible to papillomacular bundle damage in early stage of glaucoma and associated with the presence of paracentral scotomas. Among patients with high myopia, peripapillary assessment is challenging because of thinner RNFL, peripapillary atrophy, or optic disc variation. Optic disc variability, including optic disc torsion, can affect the pattern of distribution of peripapillary RNFL measurements, whereas the pattern of distribution of GCIPL measurements is less dependent on optic disc variability.[23] Progressive changes involving papillomacular bundles or areas close to the fovea may be efficiently detected with macular assessment. This may explain our finding that macular monitoring was effective for detecting glaucoma progression in eyes with high myopia.

A reliable test-retest variability is required to monitor disease progression using OCT parameters. Rao and associates[14] reported that the repeatabilities of GCIPL and RNFL measurements in highly myopic eyes (spherical refractive error between –6 D and –12 D) were good and comparable to those of emmetropic eyes. However, they also reported that the axial length was significantly associated with worse repeatability of the average RNFL thickness, while it did not affect the repeatability of the average GCIPL thickness. These imply that the repeatability of RNFL thickness may become unreliable in eyes with extremely long axial length and our study included highly myopic eyes up to 32.11 mm of axial length. Previous studies have reported lower repeatability of RNFL parameters in eyes with thinner RNFL,[24,25] and longer axial length is significantly associated with thinner RNFL.[14,26,27] Structural RNFL thinning along with axial elongation in highly myopic eyes can interfere with the accurate delineation of RNFL borders and may lead to greater variability in RNFL measurements.[14] This may explain our finding that monitoring RNFL thickness had limited value in predicting VF progression.

Lee and associates[28] recently reported that the rate of change in the average RNFL thickness was significantly faster in eyes with high myopia than in eyes without high myopia among subjects aged 40-49 years (−1.70 vs −0.48 μm/y, $P = .031$) and 50-59 years (−1.69 vs −0.63 μm/y, $P = .014$). They also reported similar findings in terms of the average GCIPL thickness for subjects aged 50-59 years (−0.81 vs −0.31 μm/y, $P < .001$).[29]

Although the reduction rate of GCIPL and RNFL thicknesses was accelerated among older patients with high myopia, a significant difference in the reduction rate of these parameters between eyes with and without high myopia was detected at younger ages for RNFL than for GCIPL measurements.[28,29] Additionally, the mean reduction rates of RNFL thickness (−0.31, −0.95, −1.70, and −1.69 μm/y, respectively) were faster than those of GCIPL thickness (−0.12, −0.28, −0.51, and −0.81 μm/y, respectively) in highly myopic eyes, regardless of age groups (20-29, 30-39, 40-49, and 50-59 years, respectively).[28,29] Considering this trend of longitudinal changes in GCIPL and RNFL in high myopia, RNFL is more likely to reach the measurement floor than GCIPL. It also should be taken into account that baseline RNFL thickness was thinner in eyes with high myopia than in eyes without high myopia, and it is more likely to reach the measurement floor. Consequently, monitoring GCIPL thickness may be advantageous for predicting glaucoma progression in high myopia than monitoring RNFL thickness. Figure 3 shows an exemplary case with progressive GCIPL thinning and VF progression in a 57-year-old man with highly myopic POAG over 5 years of follow-up; there was no further structural change in the RNFL thickness map resulting from the measurement floor effect.

In the present study, VF progression was detected more frequently in eyes with high myopia (26 eyes [25.0%]) compared with eyes without high myopia (15 eyes [14.4%]) when baseline age and VF MD were matched between the 2 groups. It still remains unclear whether myopia is a risk factor for VF progression,[30,31] or not.[32–35] Myopic glaucoma patients are usually younger than non–myopic glaucoma patients[36]; consequently, previous studies included relatively young subjects (mean age 40-50 years) and failed to demonstrate associations between VF progression and myopia or even demonstrate a protective effect of myopia against VF progression.[32–35] Because many population-based studies have reported an association between older age and glaucoma progression,[16,37,38] including only relatively young subjects with myopic glaucoma may lead to underestimates of the incidence of glaucoma progression. Although it remains to be clarified in further studies, higher incidence of VF progression in age-matched eyes with high myopia than in eyes without high myopia may suggest that POAG patients with high myopia are at greater risk of developing glaucomatous progression.

Our study had several limitations. Highly myopic eyes are likely to show various pathologic macular features, such as chorioretinal atrophy, posterior staphyloma, lacquer cracks, choroidal neovascular membrane, and retinoschisis.[39,40] Because these conditions may interfere with the accurate segmentation of the retinal layers, we excluded subjects with myopic maculopathy. Population-based studies reported the prevalence of myopic maculopathy in high myopia as 10% in a European population and 28.7% in an Asian population.[41,42] Our findings should be interpreted with caution considering that the current study may have overestimated the performance of GCIPL GPA, given the relatively high prevalence of myopic maculopathy among individuals with high myopia. The other limitation of our study was that myopia-related optic disc configuration change was recruited in the analysis. In a study of 888 highly myopic eyes, beta-zone peripapillary atrophy, optic disc tilting, and rotation were very common (81.2%, 48.3%, and 92.8%, respectively) and inevitable.[43] To minimize severe errors from optic disc deformation in determining progressive RNFL thinning, we excluded the peripapillary OCT images that have unobtainable or erroneous thickness data within a 4-mm-diameter circle. Nevertheless, this condition could have an impact on the underestimation of the performance of RNFL GPA in predicting VF progression. Temporal relationship should be interpreted with caution in the present study. The mean interval of the first detection of RNFL progression (35.2 ± 13.1 months, 9 eyes) seems to be earlier than that of GCIPL progression (41.6 ± 15.4 months) in highly myopic eyes. However, these intervals came from different groups (15 eyes with both GCIPL and VF progression and 9 eyes with both RNFL and VF progression, respectively), and direct comparison may lead to wrong interpretation.

In conclusion, monitoring macular GCIPL thickness using OCT was effective for predicting glaucoma progression regardless of the presence of high myopia. The increasing prevalence of high myopia has already been noted, and a recent meta-analysis estimated that 10% of the world (approximately 1 billion people) will have high myopia by 2050.[44] The need for proper management of glaucoma progression in eyes with high myopia is also increasing, although it is still challenging because there is structural and functional variation among highly myopic eyes. Regular macular imaging can be helpful for monitoring glaucoma progression in eyes with high myopia.

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