

Factors Associated With Differences in the Initial Location of Structural Progression in Normal-Tension Glaucoma

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Précis: Different clinical factors are associated with the location of the first structural progression in glaucoma.

Purpose: The aim was to investigate the underlying clinical parameters affecting the location of the initial structural progression of glaucoma in patients with normal-tension glaucoma (NTG).

Methods: This retrospective study included 228 eyes of 228 patients with NTG. In total, 130 eyes of 130 patients demonstrated structural progression (as determined by event-based guided progression analysis using Cirrus HD-optical coherence tomography) in the peripapillary retinal nerve fiber layer (ppRNFL) or macular ganglion cell inner plexiform layer (mGCIPL). Depending on where the progression occurred first, it was defined as either ppRNFL first progression or mGCIPL first progression. Clinical parameters associated with each first progression were identified using logistic regression.

Results: In total, 50 eyes showed ppRNFL first progression and 64 eyes showed mGCIPL first progression. ppRNFL first progression was significantly associated with female sex [odds ratio (OR)=5.705, $P=0.015$], lack of systemic hypertension (OR=0.199, $P=0.014$), disc hemorrhage (OR=4.188, $P=0.029$), higher mean intraocular pressure (OR=1.300, $P=0.03$), and lower pattern SD (OR=0.784, $P=0.028$). In contrast, male sex (OR=0.450, $P=0.043$), lower central corneal thickness (OR=0.987, $P=0.032$), higher intraocular pressure fluctuation (OR=1.753, $P=0.047$), lower systolic blood pressure fluctuation (OR=0.839, $P=0.002$), and higher diastolic blood pressure fluctuation (OR=1.208, $P=0.015$) were significantly associated with mGCIPL first progression.

Conclusions: Different clinical factors were associated with the initial site of structural glaucoma progression in patients with NTG depending on its peripapillary or macular location, and these findings suggest possible differences in underlying mechanisms of glaucoma damage.

Key Words: structural progression, guided progression analysis, peripapillary retinal nerve fiber first progression, macular ganglion cell inner plexiform layer first progression, normal-tension glaucoma

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Glaucoma develops as a result of the dysfunction of retinal ganglion cells (RGCs).¹ To diagnose and evaluate the progression of glaucoma, it is important to assess alterations in the structure and function of RGCs. Optical coherence tomography (OCT) can be used to measure the thickness of the peripapillary retinal nerve fiber layer (ppRNFL, consisting of the axons of RGCs) and the macular ganglion cell inner plexiform layer (mGCIPL, containing the cell bodies, dendrites, and axons of RGCs).² Therefore, OCT plays an important role in assessing structural alterations in RGCs.

The guided progression analysis (GPA) software package—available for the Cirrus HD-OCT platform—can be used to estimate structural progression in RGSs by analyzing the serial data obtained by OCT scans. This software provides the event and trend analyses for detecting glaucoma progression in the ppRNFL and mGCIPL. GPA compares the mean of the 2 baseline images with those of other scans obtained from the patient. This comparison is conducted without using a normative database, which reduces the possibility of errors related to anatomical variation, age, race, and refractive errors. The changes in the ppRNFL or mGCIPL play complementary roles in determining the glaucoma status; therefore, it is necessary to evaluate the structural alterations in both locations simultaneously. Interestingly, evaluating the structural changes in these 2 locations can reveal the differences in the location where the initial glaucomatous structural changes occur.

Few studies have been conducted to identify the factors influencing the location of structural changes associated with the initial occurrence of glaucoma. Marshall et al³ investigated the clinical factors that influence the location of the earliest stages of glaucomatous structural progression in the ppRNFL and mGCIPL. Their study found that a lower pretreatment intraocular pressure (IOP) and lower ppRNFL thickness were significantly associated with glaucoma progression being detected in the mGCIPL earlier than in the ppRNFL. However, the aforementioned study included a large number of glaucoma patients with an IOP ≥ 25 mm Hg. The group with initial progression on the ppRNFL also showed a significantly higher pretreatment

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IOP than the group with initial progression on the mGCIPL. In addition, other clinical factors associated with the location of the structural progression were not investigated. Therefore, we conducted this study to identify the clinical parameters that affect the location of the first structural progression of glaucoma in patients with normal-tension glaucoma (NTG).

METHODS

This retrospective study was conducted at the Department of Ophthalmology, Severance Hospital, Yonsei University, Seoul, Korea, with the approval of the Institutional Review Board of Yonsei University Severance Hospital, Seoul, Korea. The study adhered to the tenets of the Declaration of Helsinki. The requirement for written informed consent was waived because of the retrospective study design. We carefully reviewed the medical records of patients who visited the glaucoma clinic from November 2012 to August 2019. Following the routine protocol of our clinic, all patients underwent the following ophthalmic investigations during the follow-up period: slit-lamp examination, best-corrected visual acuity, IOP measurement using Goldmann applanation tonometry, autokeratometry (KR-8800; Topcon, Tokyo, Japan), axial length measurement using the IOL Master (Carl Zeiss Meditec AG, Jena, Germany), and central corneal thickness (CCT) measurement using an ultrasonic pachymeter (DGH-100; DGH Technology, Frazer, PA). Glaucoma was diagnosed and the progression was estimated using a +90 diopter lens, gonioscopy, color disc and red-free photographs (VISUCAM 200; Carl Zeiss Meditec AG), spectral-domain OCT (Cirrus HD-OCT; Carl Zeiss Meditec AG), and a visual field (VF) test using the 24-2 Swedish Interactive Threshold Algorithm of Humphrey Visual Field analyzer (Carl Zeiss Meditec AG). OCT examinations were conducted once or twice a year. To reconfirm whether patients had NTG, the examination results were carefully reviewed by 2 glaucoma specialists (S.Y.L. and H.Y.) who verified open-angle glaucoma with the presence of glaucomatous changes in the optic disc, ppRNFL and mGCIPL defects, and/or glaucomatous VF defects. To confirm glaucomatous VF defects, there had to be at least 2 of Anderson criteria with reliable results (false-positive errors <15%, false-negative errors <15%, and fixation loss <20%). In addition, according to the Hodapp-Parrish-Anderson criteria,⁴ the severity of glaucoma was classified as early or moderate to severe. If the 2 glaucoma specialists disagreed in their decision regarding NTG, a third glaucoma specialist (H.W.B.) performed the final determination. In addition to these ophthalmic examinations, each patient's blood pressure (BP) was measured in a sitting position from their right arm according to the standard clinical protocol at every follow-up visit.

The inclusion criteria were as follows: patients aged above 20 years with NTG, best-corrected visual acuity \geq 20/30, axial length <24.5 mm, spherical equivalent between -3.0 and +3.0 diopters, a cylindrical refractive error within 3 diopters, and IOPs during the follow-up period (including the maximum pretreatment IOP) <21 mm Hg. The pretreatment IOP had to be <21 mm Hg on 3 repeated measurements at different times on separate visits.⁵ In addition, all included patients with glaucoma were required to have been diagnosed with NTG for the first time and have started treatment at our clinic. All included patients were followed-up for at least 3 years. Patients with other types of glaucoma

(such as secondary or angle closure glaucoma), a history of ocular surgery, and any systemic or ophthalmic conditions influencing OCT measurements were excluded. The eye that had the most severe glaucoma status was selected for measurements. If both eyes showed the same degree of severity of glaucoma, the eye used for the study was randomly selected.

IOP and BP Parameters

Four IOP parameters were used in this study.⁶ The IOP measured before the medical treatment was defined as the pretreatment IOP (pre-IOP). The average and maximum of the IOP values measured during follow-up after starting the medical treatment were recorded as the mean IOP and peak IOP, respectively. IOP fluctuation was defined as the SD of all IOP values during the follow-up periods, excluding the pretreatment IOP. The mean systolic BP (SBP) and mean diastolic BP (DBP) were calculated as the respective averages of the SBP and DBP measured during the follow-up periods. SBP and DBP fluctuations were defined as respective the SDs of the SBP and DBP measured during the follow-up periods.

Optic Disc Parameters

The ImageJ software (v1.52; National Institutes of Health, Bethesda, MD) was used to measure the optic disc tilt ratio and torsion angle following previously published methods.⁷ The ratio between the longest and shortest diameters of the optic disc was defined as the disc tilt ratio. The vertical meridian was defined as a line perpendicular to the line connecting the fovea and the center of the optic disc. To measure the optic disc torsion angle, we calculated the angle of deviation of the long axis of the optic disc from the vertical meridian. Two investigators (S.Y.L. and H.Y.) calculated these optic disc parameters using color fundus images, and the average values calculated by each investigator were used.

Evaluation of Glaucoma Progression Using GPA of Optical Coherence Tomography

We used an event-based algorithm provided by the GPA software for the Cirrus HD-OCT platform to evaluate the structural progression of glaucoma in the ppRNFL and mGCIPL. The GPA OCT images were obtained from the optic disc cube scan and macular scan protocols in Cirrus HD-OCT. For the optic disc cube scan, we used an RNFL map (size, 6×6 mm; 200×200 pixels) centered on the optic disc. In addition, ppRNFL thickness was verified by a measurement circle with a diameter of 3.46 mm. For the macular cube scan, we used a GCIPL map (size, 6×6 mm; 512×128 pixels) centered on the fovea. Using this scan mode, the thickness of the mGCIPL was measured in an annulus-shaped measurement area with internal vertical and horizontal diameters of 1 and 1.2 mm, respectively, and external vertical and horizontal diameters of 4 and 4.8 mm, respectively. OCT images with a signal strength of \geq 6 were included in this study. In addition, at least 5 reliable OCT images had to be obtained at each visit for inclusion in the study. Scans with artefacts that affect OCT results—such as segmentation errors or poor centration—were excluded. All OCT images were obtained under pupil dilation.

To detect glaucoma progression, event analysis was conducted by analyzing deviations from the 2 baseline measurements. If the difference exceeded the test-retest variability compared with the baseline, the superpixels

(4×4 pixels=1 superpixel) were marked in orange as “possible loss.” Superpixels that showed thinning beyond the test-retest reliability were marked in red as “likely loss.” These markings were shown if the change was confirmed in 20 or more adjacent superpixels. The structural progression of glaucoma was defined as a case where “likely loss” was identified on the GPA event-based analysis and the change was also confirmed on the most recent OCT result.⁵ Cases where the progression in the ppRNFL preceded that in the mGCIPL were defined as ppRNFL first progression, and cases where the progression in the mGCIPL preceded that in the ppRNFL were defined as mGCIPL first progression. For patients with nonprogressive glaucoma, no progression should have been observed during the follow-up period of at least 5 years.

Statistical Analysis

The R statistical software v3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses. The comparison between groups was conducted using independent 2-sample *t* tests and χ^2 tests. To identify the clinical parameters associated with the location of initial structural progression, we performed univariate and multivariate logistic regression analyses and calculated the odds ratio (OR) and 95% confidential interval (95% CI). Logistic regression analysis was conducted to identify the parameters associated with ppRNFL first progression, and the dependent variables were coded as follows: 1=patients with ppRNFL first progression, 0=patients with structural progression but without ppRNFL first progression. Similar analyses with corresponding parameters were used to identify the parameters associated with mGCIPL first progression. Statistical significance was defined as *P*-value <0.05.

RESULTS

Baseline Characteristics

In total, 228 patients with NTG were enrolled and 228 eyes (1 from each patient) were used in this study. Ninety-eight eyes of 98 patients had nonprogression and 130 eyes of 130 patients showed progression. All patients with NTG included in this study were Korean. Table 1 shows the baseline characteristics of the nonprogression and progression groups. The mean follow-up period of patients with NTG was 71.29 ± 10.73 months. There were significant differences in hypertension or not, diabetes mellitus, and disc hemorrhage ratios and pattern standard deviation (PSD) of the VF between the 2 groups (*P*=0.042, 0.011, 0.003, and 0.048, respectively). Among eyes with progression, 50 eyes showed ppRNFL first progression and 64 showed mGCIPL first progression. The remaining 16 eyes showed similar progression at the same time in both locations. Table 2 shows the baseline characteristics of the ppRNFL first progression and mGCIPL first progression groups. There were significant differences in the ratio of sex and PSD of VF between the 2 groups (*P*=0.005 and 0.048, respectively).

Clinical Parameters Associated With the Location of First Progression

Table 3 shows the results of logistic regression for analyzing the clinical parameters associated with ppRNFL first progression. In the univariate analysis, ppRNFL first progression was significantly associated with female sex

(OR=2.83, 95% CI=1.388-5.711, and *P*=0.006), axial length (OR=1.439, 95% CI=1.001-2.069, and *P*=0.049), disc hemorrhage (OR=5.127, 95% CI=1.487-17.474, and *P*=0.013), torsional angle of the optic disc (OR=1.041, 95% CI=1.006-1.078, and *P*=0.023), mean IOP (OR=1.205, 95% CI=1.041-1.396, and *P*=0.013), PSD (OR=0.79, 95% CI=0.625-0.935, and *P*=0.043), VF index (OR=0.98, 95% CI=0.962-0.999, and *P*=0.039), SBP fluctuation (OR=1.168, 95% CI=1.034-1.319, and *P*=0.013), and DBP fluctuation (OR=1.073, 95% CI=1.011-1.190, and *P*=0.039). In the multivariate logistic regression, ppRNFL first progression was significantly associated with female sex (OR=5.705, 95% CI=1.407-23.129, and *P*=0.015), disc hemorrhage (OR=4.188, 95% CI=1.154-15.204, and *P*=0.029), mean IOP (OR=1.300, 95% CI=1.025-1.649, and *P*=0.03), and PSD (OR=0.784, 95% CI=0.631-0.975, and *P*=0.028).

In the univariate analysis, mGCIPL first progression was significantly associated with diabetes mellitus (OR=2.463, 95% CI=1.236-4.907, and *P*=0.01), CCT (OR=0.988, 95% CI=0.979-0.997, and *P*=0.009), torsion angle of the optic disc (OR=1.059, 95% CI=1.024-1.095, and *P*=0.001), mean IOP (OR=1.115, 95% CI=1.025-1.212, and *P*=0.011), IOP fluctuation (OR=1.66, 95% CI=1.122-2.456, and *P*=0.011), PSD (OR=1.087, 95% CI=1.011-1.168, and *P*=0.023), VF index (OR=0.981, 95% CI=0.966-0.997, and *P*=0.021), mean DBP (OR=0.933, 95% CI=0.891-0.978, and *P*=0.004), SBP fluctuation (OR=0.788, 95% CI=0.599-0.993, and *P*=0.043), and DBP fluctuation (OR=1.512, 95% CI=1.123-2.145, and *P*=0.011) (Table 4). In the multivariate analysis, mGCIPL first progression was significantly associated with CCT (OR=0.987, 95% CI=0.975-0.999, and *P*=0.032), IOP fluctuation (OR=1.753, 95% CI=1.007-3.052, and *P*=0.047), SBP fluctuation (OR=0.839, 95% CI=0.749-0.940, and *P*=0.002), and DBP fluctuation (OR=1.208, 95% CI=1.037-1.407, and *P*=0.015).

DISCUSSION

OCT technology allows objective and quantitative evaluation of glaucomatous structural damage. The RNFL is composed of the axons of RGCs in the peripapillary area, whereas the GCIPL includes the cell body, dendrites, and axons of the RGCs in the macular region.² Therefore, since glaucoma is characterized by damage to the RGCs, glaucomatous structural damage can be evaluated by using OCT scans to measure the thickness of the RNFL and GCIPL. It is important to perform structural evaluations of these two areas individually as well as simultaneously, as simultaneous evaluations play a complementary role in the diagnosis and detection of glaucoma progression.^{8,9} However, the alterations in the two areas do not always occur at the same time. Therefore, identifying the clinical factors associated with locational differences may help prevent further glaucoma damage by predicting the site of structural progression in glaucoma. A previous prospective longitudinal study investigated the clinical factors influencing the location of glaucomatous structural progression³ and evaluated the progression using GPA with Cirrus HD-OCT scans. The results showed that a lower pretreatment IOP and thinner baseline ppRNFL thickness were associated with earlier structural progression on the mGCIPL compared with that on the ppRNFL. However, pretreatment IOP and baseline ppRNFL thickness were significantly different between

TABLE 1. Comparison of Demographic and Clinical Characteristics of Patients With and Without Progression of Normal-tension Glaucoma

	Nonprogression (N = 98)	Progression (N = 130)	P*
Age (age)	61.31 ± 12.1	61.66 ± 12.93	0.658
Sex (male:female)	45:53	51:79	0.311
Time until progression (mo)		68.54 ± 24.55	
HTN (no:yes)	63:35	66:64	0.042
DM (no:yes)	87:11	98:32	0.011
Axial length (mm)	23.93 ± 1.38	23.79 ± 1.17	0.470
SE (D)	-0.33 ± 1.63	-0.55 ± 1.92	0.206
CCT (µm)	537.87 ± 35.83	528.8 ± 33.8	0.075
Disc hemorrhage (no:yes)	83:15	88:42	0.003
Tilt ratio	1.12 ± 0.14	1.11 ± 0.13	0.316
Torsion angle (°)	-0.24 ± 6.96	6.36 ± 10.08	0.711
Pre-IOP (mm Hg)	14.77 ± 2.35	16.36 ± 3.86	0.754
Mean IOP (mm Hg)	12.91 ± 1.92	13.97 ± 2.25	0.185
Peak IOP (mm Hg)	15.38 ± 2.41	17.72 ± 3.95	0.954
IOP fluctuation (mm Hg)	1.56 ± 0.57	1.99 ± 0.99	0.367
Glaucoma severity (early:moderate to severe)	52:46	70:60	0.226
MD (dB)	-5.02 ± 5.07	-6.38 ± 6.61	0.079
PSD (dB)	4.98 ± 3.65	5.13 ± 4.03	0.048
VFI (%)	88.41 ± 14.99	85.47 ± 20.42	0.143
ppRNFL thickness (µm)	77.97 ± 10.76	78.2 ± 11.42	0.151
mGCIPL thickness (µm)	73.07 ± 7.72	72.37 ± 10.49	0.330
Mean SBP (mm Hg)	122.98 ± 12.8	124.63 ± 12.71	0.506
Mean DBP (mm Hg)	71.81 ± 8.72	71.15 ± 8.7	0.725
SBP fluctuation (mm Hg)	10.57 ± 4.7	10.39 ± 4.55	0.527
DBP fluctuation (mm Hg)	7.09 ± 2.91	7.72 ± 3.11	0.678

*Independent *t* test or χ^2 test.

CCT indicates central corneal thickness; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension or not; IOP, intraocular pressure; MD, mean deviation; mGCIPL, macular ganglion cell inner plexiform layer; ppRNFL, peripapillary retinal nerve fiber layer; PSD, pattern standard deviation; SBP, systolic blood pressure; SE, spherical equivalent; VFI, visual field index.

groups with first structural progression on the ppRNFL versus on the mGCIPL. In addition, the study included glaucoma patients with IOP values ranging from low (~10 mm Hg) to high (≥ 35 mm Hg). Since IOP is closely related to glaucoma progression, a wide distribution of IOP values is likely a confounding factor. Therefore, the present study identified clinical factors associated with the location of first glaucomatous structural progression in patients with NTG. In the present study, the ppRNFL first progression group and the mGCIPL first progression group were not significantly different in terms of variables other than the sex ratio and the PSD of the VF. However, there were notable differences in the clinical factors associated with the location of first structural progression.

Among the factors included in this study, the female sex showed a significant correlation with ppRNFL first progression. The relatively high proportion of females in the ppRNFL first progression group likely influenced these findings. Although the effect of sex on open-angle glaucoma is unclear,¹⁰ several studies have demonstrated that macular thickness is lower^{11,12} and ppRNFL thickness is higher in females than in males.¹³⁻¹⁵ The initial thickness of the macula or ppRNFL can be an important factor influencing the rate and location of thickness reduction.^{3,16} Recent studies using deep learning algorithms have predicted sex with a high level of accuracy using only fundus photographs.^{17,18} The regions used for sex prediction were the fovea, optic disc, and proximal retinal vascular arcade. These findings suggest that the structural differences between sexes may not be limited to thickness of macula or ppRNFL and may include areas that yet unknown. However, further studies are required to determine whether our

findings related to sex are because of intersex morphologic differences in peripapillary and macular thickness or a result of bias because of the retrospective study design.

Disc hemorrhage, a higher mean IOP, and lower PSD values were associated with the occurrence of first structural progression in the ppRNFL. However, a thinner CCT, higher IOP and DBP fluctuation, and lower SBP fluctuation were associated with the occurrence of first structural progression in the mGCIPL. These results show that different factors determine the location of glaucomatous structural changes and highlight the need to establish a more effective treatment strategy depending on the location of first structural progression in clinical practice. These results were verified despite few significant differences in clinical parameters between the 2 groups (Table 2), which demonstrates the high reliability of our study.

Among the IOP parameters, mean IOP and IOP fluctuation were significantly associated with ppRNFL first progression and mGCIPL first progression, respectively, in our study. Compressive injury caused by a high IOP can cause retrograde deterioration of the RGC axons at the level of the lamina cribrosa, and this is a well-known mechanism for the development and progression of glaucoma.^{8,9} The superior and inferior regions of the lamina cribrosa have thin connective tissue septa and large pores, which make these areas vulnerable to mechanical deformation.^{19,20} Regional differences in susceptibility to mechanical stress in the lamina cribrosa can explain the occurrence of focal RNFL damage in the superior and inferior peripapillary areas. Therefore, a high mean IOP is likely to first affect structural changes in the ppRNFL rather than the mGCIPL. In addition, this result was confirmed even when

TABLE 2. Comparison of Demographic and Clinical Characteristics of Patients Showing Peripapillary Retinal Nerve Fiber Layer First Progression and Ganglion Cell Inner Plexiform Layer First Progression

	ppRNFL First Progression (N = 50)	mGCIPL First Progression (N = 64)	P*
Age (age)	61.12 ± 11.57	62.22 ± 14.23	0.658
Sex (male:female)	12:38	32:32	0.005
Time until progression (mo)	71.14 ± 25.01	66.34 ± 25.08	0.313
HTN (no:yes)	27:23	32:32	0.671
DM (no:yes)	39:11	45:19	0.355
Axial length (mm)	23.73 ± 1.16	23.93 ± 1.21	0.470
SE (D)	-0.33 ± 1.94	-0.8 ± 1.95	0.206
CCT (μm)	534.42 ± 32.6	522.59 ± 35.43	0.075
Disc hemorrhage (no:yes)	36:14	44:20	0.707
Tilt ratio	1.1 ± 0.12	1.12 ± 0.14	0.316
Torsion angle (°)	6.32 ± 9.48	6.95 ± 10.79	0.711
Pre-IOP (mm Hg)	16.36 ± 3.37	16.13 ± 4.37	0.754
Mean IOP (mm Hg)	14.2 ± 2.02	13.66 ± 2.26	0.185
Peak IOP (mm Hg)	17.69 ± 3.08	17.73 ± 4.66	0.954
IOP fluctuation (mm Hg)	1.88 ± 0.74	2.06 ± 1.22	0.367
Glaucoma severity (early:moderate to severe)	30:20	35:29	0.521
MD (dB)	-5.46 ± 6.22	-7.72 ± 7.08	0.079
PSD (dB)	4.47 ± 3.79	6.01 ± 4.22	0.048
VFI (%)	87.95 ± 20.01	81.62 ± 21.85	0.143
ppRNFL thickness (μm)	79.24 ± 11.88	76.11 ± 11.14	0.151
mGCIPL thickness (μm)	70.48 ± 11.05	72.46 ± 10.37	0.330
Mean SBP (mm Hg)	123.38 ± 12.17	125.01 ± 13.54	0.506
Mean DBP (mm Hg)	71.28 ± 9.55	70.69 ± 8.05	0.725
SBP fluctuation (mm Hg)	10.72 ± 5.22	10.15 ± 4.19	0.527
DBP fluctuation (mm Hg)	7.97 ± 3.31	7.72 ± 3.14	0.678

*Independent *t* test or χ^2 test.

CCT indicates central corneal thickness; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension or not; IOP, intraocular pressure; MD, mean deviation; mGCIPL, macular ganglion cell inner plexiform layer; ppRNFL, peripapillary retinal nerve fiber layer; PSD, pattern standard deviation; SBP, systolic blood pressure; SE, spherical equivalent; VFI, visual field index.

TABLE 3. Univariate and Multivariate Logistic Regression Analysis of Factors for Eyes Showing Peripapillary Retinal Nerve Fiber Layer First Progression

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.997 (0.972-1.022)	0.804		
Sex (reference: male)	2.830 (1.388-5.771)	0.006	5.705 (1.407-23.129)	0.015
HTN	1.143 (0.609-2.148)	0.677		
DM	1.287 (0.595-2.781)	0.521		
Axial length (mm)	1.439 (1.001-2.069)	0.049		
SE (D)	1.053 (0.883-1.256)	0.567		
CCT (μm)	1.002 (0.993-1.011)	0.674		
Disc hemorrhage	5.127 (1.487-17.474)	0.013	4.188 (1.154-15.204)	0.029
Tilt ratio	0.289 (0.022-3.844)	0.347		
Torsion angle (°)	1.041 (1.006-1.078)	0.023	1.054 (0.992-1.119)	0.088
Pre-IOP (mm Hg)	1.075 (0.983-1.176)	0.114		
Mean IOP (mm Hg)	1.205 (1.041-1.396)	0.013	1.300 (1.025-1.649)	0.030
Peak IOP (mm Hg)	1.094 (0.938-1.191)	0.326		
IOP fluctuation (mm Hg)	1.136 (0.812-1.590)	0.458		
MD (dB)	1.012 (0.958-1.070)	0.663		
PSD (dB)	0.790 (0.625-0.935)	0.043	0.784 (0.631-0.975)	0.028
VFI (%)	0.980 (0.962-0.999)	0.039	0.984 (0.948-1.021)	0.384
ppRNFL thickness (μm)	1.012 (0.984-1.041)	0.412		
mGCIPL thickness (μm)	0.970 (0.939-1.002)	0.065		
Mean SBP (mm Hg)	0.996 (0.971-1.021)	0.733		
Mean DBP (mm Hg)	0.997 (0.962-1.034)	0.882		
SBP fluctuation (mm Hg)	1.168 (1.034-1.319)	0.013	1.160 (0.987-1.363)	0.072
DBP fluctuation (mm Hg)	1.073 (1.011-1.190)	0.039	0.933 (0.747-1.166)	0.541

CCT indicates central corneal thickness; CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension or not; IOP, intraocular pressure; MD, mean deviation; mGCIPL, macular ganglion cell inner plexiform layer; OR, odds ratio; ppRNFL, peripapillary retinal nerve fiber layer; PSD, pattern standard deviation; SBP, systolic blood pressure; SE, spherical equivalent; VFI, visual field index.

TABLE 4. Univariate and Multivariate Logistic Regression Analysis of Factors for Eyes Showing Macular Ganglion Cell Inner Plexiform Layer First Progression

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.006 (0.983-1.030)	0.593		
Sex (reference: male)	0.640 (0.358-1.145)	0.133		
HTN	1.448 (0.810-2.587)	0.212		
DM	2.463 (1.236-4.907)	0.010	2.028 (0.797-5.160)	0.138
Axial length (mm)	1.086 (0.799-1.476)	0.599		
SE (D)	0.865 (0.736-1.016)	0.077		
CCT (μm)	0.988 (0.979-0.997)	0.009	0.987 (0.975-0.999)	0.032
Disc hemorrhage	1.560 (0.820-2.968)	0.175		
Tilt ratio	2.125 (0.250-18.063)	0.490		
Torsion angle (°)	1.059 (1.024-1.095)	0.001	1.034 (0.992-1.077)	0.119
Pre-IOP (mm Hg)	1.054 (0.969-1.146)	0.218		
Mean IOP (mm Hg)	1.115 (1.025-1.212)	0.011	1.041 (0.855-1.268)	0.687
Peak IOP (mm Hg)	1.043 (0.914-1.191)	0.532		
IOP fluctuation (mm Hg)	1.660 (1.122-2.456)	0.011	1.753 (1.007-3.052)	0.047
MD (dB)	0.986 (0.953-1.020)	0.421		
PSD (dB)	1.087 (1.011-1.168)	0.023	1.067 (0.956-1.190)	0.249
VFI (%)	0.981 (0.966-0.997)	0.021	0.987 (0.966-1.009)	0.254
ppRNFL thickness (μm)	0.977 (0.952-1.004)	0.092		
mGCIPL thickness (μm)	0.997 (0.966-1.028)	0.832		
Mean SBP (mm Hg)	1.009 (0.987-1.032)	0.421		
Mean DBP (mm Hg)	0.933 (0.891-0.978)	0.004	0.981 (0.934-1.030)	0.434
SBP fluctuation (mm Hg)	0.788 (0.599-0.993)	0.043	0.839 (0.749-0.940)	0.002
DBP fluctuation (mm Hg)	1.512 (1.123-2.145)	0.011	1.208 (1.037-1.407)	0.015

CCT indicates central corneal thickness; CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; GCIPL, ganglion cell inner plexiform layer; HTN, hypertension or not; IOP, intraocular pressure; MD, mean deviation; OR, odds ratio; PPRNFL, peripapillary retinal nerve fiber layer; PSD, pattern standard deviation; SBP, systolic blood pressure; SE, spherical equivalent; VFI, visual field index.

the pretreatment IOP was not high. This indicates that even if the IOP is not high, it is important to sufficiently reduce the IOP. Whether IOP fluctuation is an independent risk factor for the progression of glaucoma is currently controversial. In the Advanced Glaucoma Intervention Study^{21,22} and Collaborative Initial Glaucoma Treatment study,^{23,24} IOP fluctuation was found to be significantly associated with glaucoma progression. However, other studies such as the Early Manifest Glaucoma Trial²⁵ and Diagnostic Innovations in Glaucoma Study²⁶ failed to find this association. These contrasting results are thought to be because of the differences in definition of IOP fluctuation and limitation in continuous IOP measurement.^{27,28} In a recent meta-analysis where the effects of short-term and long-term IOP fluctuation were considered separately,²⁷ long-term IOP fluctuation showed a significant correlation with glaucoma progression. In our study, long-term IOP fluctuation was used as a clinical parameter and was associated with mGCIPL first progression. The impairment of blood flow because of IOP fluctuation likely affected the mGCIPL first progression. The multivariate analysis showed that SBP and DBP fluctuation were significantly associated with only mGCIPL first progression. The smaller the SBP fluctuation and the larger the DBP fluctuation, the higher is the risk of mGCIPL first progression. Low ocular perfusion pressure is also a risk factor for glaucoma onset and progression. Although SBP, DBP, and IOP fluctuation were not directly used to calculate ocular perfusion pressure in our study, fluctuation in the ocular perfusion pressure can induce structural changes in relation to the poor perfusion. However, IOP fluctuation can also cause mechanical damage. Therefore, further studies are needed to identify the reasons underlying the significant correlation between IOP

fluctuation and changes in the macular area but not the lamina cribrosa, which is vulnerable to pressure-related damage.

Previous studies have shown disc hemorrhage to be an independent risk factor associated with glaucoma progression.^{29,30} Pressure-related structural alteration of the lamina cribrosa³¹ or the dysfunction of autoregulation can cause vascular damage, which likely causes the development of disc hemorrhage.³² However, the mechanism has not been confirmed. In our study, disc hemorrhage was significantly associated only with ppRNFL first progression. Disc hemorrhage frequently occurs in regions adjacent to locations of prior damage, such as the edges of RNFL defects around the optic disc.³³ Therefore, our findings reasonably confirmed the significant association between ppRNFL first progression and disc hemorrhage.

In our study, a thin CCT was significantly associated with mGCIPL first progression but not with ppRNFL first progression. CCT is a well-known predictive factor for glaucoma progression,³⁴⁻³⁷ and affects IOP measurement using a Goldmann applanation tonometry. This effect may explain the association between CCT and glaucoma progression. However, several studies have shown that CCT is an independent risk factor for glaucoma.³⁸⁻⁴⁰ These studies also suggest that CCT may be associated with increased vulnerability to glaucomatous damage through the alteration of the biochemical properties of the peripapillary sclera or lamina cribrosa. It is unknown whether the alteration of biomechanical properties is related to mechanical or vascular damage for glaucomatous structural progression. Clinical parameters known to better reflect biomechanical properties, such as corneal hysteresis, were not measured in this study. However, our findings are significant because

they indicate the importance of ocular biomechanical properties for determining the location of first structural progression in glaucoma.

Our study has several limitations. We confirmed the clinical factors associated with structural progression in glaucoma using only by the event-based algorithm of GPA for Cirrus HD-OCT scans. Therefore, further research is needed to confirm these results even when functional progression is included. In addition, this was a retrospectively designed study that included only Koreans. Therefore, long-term prospective studies on various races are required that include a larger number of patients.

In conclusion, our study demonstrates that disc hemorrhage, high mean IOP, and low PSD are significantly associated with the first structural progression of glaucoma in the ppRNFL. In contrast, thin CCT, high IOP fluctuation, low SBP fluctuation, and high DBP fluctuation are clinical factors significantly associated with the location of first structural progression of glaucoma in the mGCIPL. Our findings suggest that clinical factors can help predict the location where glaucomatous structural progression would occur first. In addition, these results would be helpful for further studies investigating the pathophysiology of glaucoma.

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