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Predictive Factors for the Rate of Visual Field Progression in the Advanced Imaging for Glaucoma Study

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Abstract

Purpose: To investigate predictive factors associated with the rate of visual field (VF) loss in open-angle glaucoma.

Design: Prospective multicenter cohort study.

Methods: Perimetric glaucoma patients of the Advanced Imaging for Glaucoma study were selected for analysis if they had 9 completed visits. Confirmed rapid significant progression (CRSP) of VF was defined as a significant ($P < 0.05$) negative VF index (VFI) slope $< -1\%$ /year or a mean deviation (MD) slope < -0.5 dB/year, confirmed at 2 consecutive follow-up visits. Slow progression was defined as VFI slope $> -0.5\%$ /year or MD slope > -0.25 dB/year. Fourier-domain optical coherence tomography (FD-OCT) measured optic disc, peripapillary retinal nerve fiber layer (NFL), and macular ganglion cell complex (GCC) thicknesses. Logistic regression was used to identify baseline predictors for CRSP and slow progression. Linear regression was used to identify baseline predictors for the VFI and MD slope.

Results: Eyes ($n=150$) of 103 participants were included. Slow progression was observed in 80 eyes (53.3%) and CRSP in 23 eyes (15.3%). Larger NFL and GCC baseline focal loss volume (FLV), thinner central corneal thickness (CCT), and lower VFI were significant ($p < 0.05$) baseline predictors of more rapid progression on univariate analysis. The predictor with the highest odds ratio (OR) was NFL-FLV, which was also the most significant non-VF predictor in the multivariate

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analysis. Eyes with NFL-FLV > 8.5% had an OR of 2.67 for CRSP and 0.42 for slow progression. Disc hemorrhage during the follow up was also important, with an OR of 2.61 for CRSP and 0.23 for slow progression for each occurrence.

Conclusions: Focal loss measured by FD-OCT or VF, along with CCT, are strong baseline predictors for the rate of glaucoma progression.

Keywords

visual field; glaucoma; progression; optical coherence tomography; imaging

Introduction

Glaucoma is a leading cause of irreversible blindness worldwide.¹ In the initial evaluation of glaucoma patients, it is important to evaluate the risk of disease progression and the likely rate of visual field (VF) loss. Patients with higher risk of rapid progression should be followed more closely and treated more aggressively. This would allow for the rational use of medical, laser, and surgical treatments, all of which have significant cost, compliance, and safety issues.

Most studies of glaucoma progression have focused on predicting which eyes will have statistically significant VF progression,^{2–6} and optical coherence tomography (OCT) structural measurements are useful in predicting that progression.² However, to identify patients at high risk of experiencing clinically significant VF loss, it is necessary to make predictions on whether the rate of VF loss will be rapid or slow. The purpose of this article is to identify predictive factors for rapid or slow VF progressions among glaucoma participants in the *Advanced Imaging for Glaucoma* (AIG) study.^{2,7}

Methods

Advanced Imaging for Glaucoma was a National Eye Institute-funded bioengineering partnership (NIH R01 EY013516) to develop novel imaging technology to aid the diagnosis and monitoring of glaucoma. The AIG study is a multi-center longitudinal prospective observational study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01314326) identifier: NCT01314326). The data analyzed in this article came from participants in the perimetric glaucoma (PG) arm of the AIG study.⁷ These participants were enrolled at the Bascom Palmer Eye Institute, University of Miami; Doheny Eye Institute (then affiliated with University of Southern California); and the University of Pittsburgh Medical Center Eye Institute. The Institutional Review Board (IRB) of each participating university approved the study protocol. The study was conducted in agreement with the provisions of the Declaration of Helsinki. Informed consent was obtained from all subjects using the consent forms approved by the IRBs of the participating institutions. The study was in accordance with The Health Insurance Portability and Accountability Act of 1996 (HIPPA) privacy and security regulations.

Eyes enrolled in the PG group had glaucomatous optic neuropathy as evidenced by diffuse or localized thinning of the neuroretinal rim or a nerve fiber layer (NFL) defect on fundus examination. There were also corresponding repeatable abnormal standard automated

perimetry defects with glaucoma hemifield test or pattern standard deviation (PSD, $P < 0.05$) outside normal limits.

All study participants underwent a baseline examination consisting of a complete ophthalmic examination with VF and advanced glaucoma imaging (OCT, confocal scanning laser ophthalmoscopy, and scanning laser polarimetry) and had follow-up visits with repeat testing every six months. During the follow-up period, each patient was treated at the discretion of the attending physician. The study design and baseline participant characteristics have been previously published⁷ and the manual of procedures can be found at www.aigstudy.net.

The visual field was assessed by standard automated perimetry on the Humphrey Field Analyzer (HFA II; Carl Zeiss Meditec, Inc, Dublin, California, USA) using the Swedish Interactive Thresholding Algorithm 24–2. The minimum requirement for reliability included less than 15% fixation losses, less than 33% false positives, and less than 33% false negatives.”

The peripapillary NFL and macular ganglion cell complex (GCC) were imaged and measured by Fourier-domain OCT (RTVue, Optovue, Inc., Fremont, CA, USA). During each visit, participants had three GCC and optic nerve head (ONH) scans. Only ONH scans with a signal strength index above 37 and GCC scans above 44 were selected for analysis.⁸ Measurements of qualified scans in the same visit were averaged. The macular GCC scan covered a 7 by 7 mm square area in the macula. Scans were centered 0.75 mm temporal to the fovea to improve the coverage of the temporal macula. The GCC consisted of the combination of NFL, ganglion cell layer, and inner plexiform layer.^{9,10} The automated Optovue software derived a 6-mm diameter GCC thickness map centered 0.75 mm temporal to fovea. The ONH concentric (1.3–4.9 mm diameter) scans were centered on the optic disc. In post processing, the ONH scan was automatically registered with a baseline three-dimensional disc scan to provide the disc margin information. The NFL thickness profile at a diameter of 3.4 mm was resampled on the NFL thickness map re-centered according to detected optic disc center. The RTVue software (version 6.12) was used to provide the OCT image-derived measurements of the GCC thickness map and the NFL thickness profile.

Based on the GCC thickness map, overall, superior, and inferior hemisphere averages of the GCC thickness were obtained. Two special pattern analysis parameters were also obtained: (a) the GCC global loss volume (GCC-GLV), which measured all negative deviation values normalized by the overall map area, and (b) the GCC focal loss volume (GCC-FLV), which measured the negative deviation values in areas of significant focal loss in the macular region.¹⁰ Based on the NFL thickness profile, overall, superior, and inferior quadrant thickness averages of the NFL were obtained using the RTVue software. Pattern analysis was also applied to the NFL thickness profile using custom software described previously.^{11,12} Two parameters were generated: (a) NFL global loss volume (NFL-GLV) and (b) NFL focal loss volume (NFL-FLV). Note that NFL-GLV and NFL-FLV were based on analysis of the 3.4-mm diameter NFL thickness profile rather than the entire 4.9-mm diameter NFL thickness map.

The speed of VF progression was measured by the slope of ordinary linear regressions on age for the mean deviation (MD) and VF index (VFI). We wish to detect statistically significant rapid progression as soon after the baseline as possible. Therefore we performed regression analyses using partial VF series between the baseline (first) visit up to the Nth visit, starting from N=4, and repeating the analysis after adding successive follow-up visits up to N=9 (entire series). VF rapid progression was defined as a MD slope more negative than -0.5 dB/year or VFI slope more negative than -1% /year. Significant progression was defined as a significant ($P<0.05$) negative slope compared to the null hypothesis of zero slope. A confirmed rapid significant progression (CRSP) was reached when two consecutive MD or VFI slopes were both rapid and significant. Because the regression analysis started from the 4th visit, the earliest visit at which VF CRSP endpoint could be reached was the 5th visit. Our intention is to define CRSP so that it is a clinically meaningful event – a time point at which sufficient VF information have been obtained to show rapid disease progression with sufficient statistical reliability for the clinician to recommend more intensive treatment or follow-up.

A slow progression rate was defined as the absence of CRSP and a MD slope greater than or equal to -0.25 dB/year and a VFI slope greater than or equal to -0.5% /year, i.e., slower than half of the minimum rapid progression rates.

Because the number of visits had a large effect on the chance of detecting significant progression,¹³ this analysis included only participants who had completed at least 9 visits, for a total follow-up period of 4 years. The CRSP status was determined at any visit from the 5th visit up to the 9th visit, whereas the slow progression status was determined at the 9th visit. Visits beyond 9th visit were not used for eyes with longer follow-up durations. At the end of the 4-year follow-up, the VF progression rate for each eye was classified as either CRSP, slow ($MD > -0.25$ dB/year and $VFI > -0.5\%$ /year), or intermediate (neither CRSP nor slow).

To eliminate the interference of cataract on the VF measurements, we also excluded eyes that experienced significant cataract progression any time during the follow up. A significant cataract progression was defined as confirmed worsening of visual acuity by two or more lines at two or more follow-up visits, and confirmed clinical cataract progression assessment at two or more follow-up visits. The glaucoma severity of the PG eyes included in the study were further classified based on their average MD measurements over the entire follow up using the modified Hodapp-Parrish-Anderson grading scale¹⁴: early glaucoma, defined as $MD > -6$ dB; moderate glaucoma, defined as MD between -12 dB and -6 dB; and late stage glaucoma, defined as $MD < -12$ dB.

The primary statistical model used for the analysis was logistic regression with the general estimating equation¹⁵ method to adjust for the correlation between two eyes from the same participant. The primary outcomes were CRSP and slow progression, in contrast to an intermediate rate of progression. The predictive factors for CRSP and slow progression were analyzed separately. For multivariate model building we used a stepwise selection method with entry p-value of <0.15 and stay p-value of <0.05 . In addition to the logistic regression,

we also performed ordinary linear regression of MD/VFI slopes on the baseline risk factors. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Among the 377 eyes of 249 patients in the PG group, 150 eyes from 103 patients were qualified for analysis in this paper based on sufficient length of follow-up and absence of significant cataract progression. CRSP was observed in 23 eyes (15.3%) and slow progression in 80 eyes (53.3%) after 4 years of follow up. The distribution of the progression rates was significantly different among glaucoma stages ($P = 0.003$, Table 1).

The demographics and the characteristics included in the analyses of this study were summarized and stratified by the three progression rate categories (rapid [CRSP], slow, and intermediate; Table 2). There were no statistically significant differences in age, sex, race, or ethnicity. Eyes that progressed slowly tended to be shorter than eyes that progressed faster. Eyes that progressed rapidly had a thinner corneal thickness ($P = 0.034$) than eyes that progressed slowly or at an intermediate rate, but there was no significant difference in corneal thickness between the intermediate and slow groups. More rapid progressors tended to have a lower VFI, but there were no significant differences in MD or PSD. Among the OCT parameters analyzed, only the NFL-FLV and the GCC-FLV were significantly higher in eyes with more rapid progression rates. Intraocular pressure (IOP) at baseline and during the follow-up period did not have a significant correlation with progression rates. Disc hemorrhage was rare in slow progressors and significantly more common in eyes with more rapid progression.

The MD and VFI trends were summarized and stratified by three stages of glaucoma disease severity (Table 3). The rate of VF progression, as measured by both MD ($P = 0.02$) and VFI ($P = 0.015$), was by far the highest in eyes with moderate glaucoma, whereas eyes with either mild or advanced stages of glaucoma had slower average rates of progression. This finding suggests that progression rates follow an inverted “U” shape on the scale of glaucoma severity. The test-retest variability of VF parameters, as measured by the linear regression residual, increased with disease severity. In early and moderate glaucoma, most cases of CRSP were detected by MD, whereas in advanced glaucoma, most cases were detected by VFI. When all glaucoma stages were combined, MD detected slightly more CRSP than VFI, with moderate overlap (Fig. 1).

The baseline continuous variables were individually fitted in univariate logistic regression models to evaluate their predictive power for CRSP or slow progression (Table 4). Baseline VFI was the strongest individual predictive variable with the highest area under the receiver characteristic curve (AUC) for both CRSP and slow progression. The baseline NFL-FLV had the second highest AUC for both CRSP and slow progression, and it had the strongest odds ratio (OR). Other significant variables included baseline GCC-FLV, PSD, and central cornea thickness. The number of occurrences of disc hemorrhage during the study period was also a significant predictor of progression rate.

When the respective quadratic terms for the baseline variables were also added to the logistic models, we found that VFI had significant linear and quadratic terms for both CRSP and slow progression. The plot of the model fit showed that the probability of CRSP had an inverted U-shaped dependence on baseline VFI (Fig. 2), with the peak probability for rapid progression occurring at a VFI of 67%. The AUC of the quadratic model was 0.747 with AIC = 124.3, only minimally improved over the linear model, which had AUC of 0.745 with AIC = 125.4. Quadratic models for MD, NFL thickness, and GCC thickness also showed U-shaped dependencies, but the quadratic term for these variables were not statistically significant.

Although continuous parameters provide the fullest information, using them to calculate odds ratios requires a computing device. Dichotomization of variables using a cutoff threshold makes them easier to use in a clinical setting. Examples of significant dichotomous predictive variables included VF parameters, OCT focal loss volume parameters, central corneal thickness, and disc hemorrhage (Table 5). Note that the high-risk interval for VFI has both an upper and lower cutoff due to the U-shaped distribution. The occurrence of disc hemorrhage anytime during the study period significantly increased the risk for CRSP and made slow progression less likely. The presence of disc hemorrhage at the baseline was a rare occurrence (3.2%) and was not a significant predictor.

The relevant variables (Table 2) were used in a stepwise selection process to build a multivariate model (Table 6) that further increased the predictive power on progression rate classification. To stay in the model, a variable must have had a P-value of at least 0.1. The best multivariate model for predicting CRSP was comprised of only the NFL-FLV and the longitudinal disc hemorrhage status during the follow up (Table 6). It was surprising that VFI was not a significant contributor to the multivariate model. On the other hand, the best model to predict slow progression rate included both linear and quadratic terms of the VFI (Table 6). The AUC for predicting CRSP was 0.752, and for slow progression it was 0.800.

The logistic regression analysis so far used discrete classifications of VF progression speed - rapid, intermediate, or slow. We also analyzed the speed of progression as continuous variables using the slope of change of VFI and MD over time. The baseline variables that were significant predictors of progression speed on univariate linear regression analysis were central corneal thickness, IOP, VFI, GCC-FLV, and NFL-FLV (Table 7). NFL-FLV appeared to be the most significant one, which agrees with Table 4. The baseline IOP was a significant predictor in the continuous model but not the discrete model, while VF-PSD was a significant predictor in the discrete model but not the continuous model. The IOP correlation was counterintuitive, as higher IOP was associated with more positive MD and VFI slopes (slower glaucoma progression). Overall, the continuous model agreed well with the discrete model except for their respective weakest significant predictive variables. The significant baseline predictive variables common to both models were central corneal thickness, VFI, GCC-FLV, and NFL-FLV.

Discussion

The therapeutic goal for glaucoma management is to prevent progression of optic nerve damage and VF loss. The treatment should be sufficient to prevent the patient from suffering the visual impairments associated with advanced glaucoma, and yet not entail excessive cost and risk of complications. The rate of progression over time, in the context of baseline damage and life expectancy, provides a rational guide to treatment decisions. However, longitudinal information is not available for a newly diagnosed glaucoma patient. Therefore methods for using baseline data to stratify the risk of future progression would be most helpful in planning the monitoring frequency and treatment strategy in this situation. While many studies have looked at the factors that predict the risk of developing statistically significant VF progression,^{2,5,6,16–21} or the factors that influence the average rate of progression in a group of patients,²² few studies have examined factors that predict which glaucoma patients or eyes are more likely to have rapid versus slow rate of VF deterioration.^{23–25} Furthermore, none have related the speed of VF progression to baseline OCT findings. In this paper, we sought to identify the baseline OCT measurements and other clinical variables that could help make such predictions.

We used the rate of change of global VF variables to define the speed of progression because this is the best established standard.^{5,6,17,21,26–29} There is no clear consensus yet on what speed of progression should be considered rapid. The range of MD slopes between -0.5 to -2.0 dB/year has been considered clinically significant.^{13,30,31} In the AIG study, very few subjects had progression rates worse than -2.0 dB/year, perhaps due to the close follow up and management. Therefore we chose to use an MD slope of worse than -0.5 dB/year as the primary definition for rapid progression because it afforded us the sample size and contrast needed for statistical analysis. This cutoff is also clinically reasonable because, in less than 12 years, an eye that changed faster than -0.5 dB/year would progress from mild glaucoma to moderate, and in less than 24 years would progress from mild to advanced glaucoma. We also chose a VFI slope of worse than -1% /year as an alternate definition that is roughly equivalent to a MD slope of -0.5 dB/year. These two VF parameters are synergistic because MD does not suffer from the “ceiling effect” of VFI,^{32–34} while, on the other hand, VFI is more sensitive to central and focal loss due to the way it is defined and computed.³⁵ This synergy was confirmed by the only moderate overlap between CRSP detected by MD and VFI. In early and moderate glaucoma, CRSP was more likely to be detected using MD slope, as would be expected due to the ceiling effect impediment of the VFI.

On the other end of the spectrum, clinicians are also interested in identifying eyes with rates of glaucoma progression that are sufficiently slow to preclude the possibility of functionally important visual loss over the patient’s lifetime. These patients could be safely followed without imposing more aggressive treatment regimens. We chose a cutoff of the MD slope slower than -0.25 dB/year to define slow progression. At this rate, it would take more than 24 years to progress from mild to moderate glaucoma, and more than 48 years to progress from mild to severe glaucoma. We also chose a VFI slope worse than -0.5% /year as an alternate definition that is roughly equivalent to MD slope of -0.25 dB/year.

Our primary finding is that measures of focal loss in the peripapillary NFL and macular GCC were the strongest OCT predictors of glaucoma progression rate. Interestingly, among the VF parameters, measures that emphasize focal loss such as VFI and PSD were also strong predictors, while measures of general loss such as MD were not significant predictors. A possible explanation is that focal defects are more reliable indicators of glaucoma damage than overall thinning. A thin overall NFL or GCC could be due to glaucoma, but could also be due to normal population variation, magnification effects, i.e., the NFL appears thinner in longer eyes,^{36–38} myopic retinal degeneration,³⁸ or aging.³⁹ A focal defect, however, would be highly unlikely in the absence of glaucoma or other specific diseases. Similarly, a more negative VF MD could be due to cataract,³² dry eye,⁴⁰ or lack of attentiveness,⁴¹ while VFI and PSD would be less affected by these non-glaucomatous factors. Clear evidence of glaucoma damage at baseline would indicate past glaucoma progression. If we assume that each patient has a characteristic rate of progression that is maintained throughout the course of the disease, if treatment is not modified, then patients with more rapid rates of progression would be more likely to exhibit evidence of more severe glaucoma damage. According to Bayes' rule, evidence of more severe glaucoma should be statistically correlated with faster prior progression, which would in turn be correlated with faster future progression, at least in the short term.

While a positive correlation between glaucoma severity and progression rate existed for most of the AIG study participants, it did not apply to those with the most severe disease. Eyes with advanced glaucoma were actually less likely to have rapid progression. The rate of progression appeared to have a U-shaped relationship to disease severity. The highest chance for rapid progression occurred at a VFI value of around 72%. Thus there is evidence that glaucoma progression appears to decelerate in the advanced stages, at least as measured by the global VF parameters. This may be due to the greater intensity of treatment for advanced glaucoma patients. The greater test-retest variability of VF in more advanced stages of glaucoma also impedes the detection of significant change. Of course, these results need to be interpreted with care in terms of clinical practice, as patients with advanced glaucoma have little visual reserve and are at greater risk of progressive functional impairment even without rapid decline in MD and VFI.

IOP during the follow-up visits was not a significant factor in this study, probably because in most AIG participants it was well controlled by medication. Therefore little variation in IOP remained to serve as statistical contrast for detecting its effect. Baseline IOP was a weak predictor of the speed of VF progression in the continuous model. The correlation was counterintuitive as higher baseline IOP was associated with slower progression. This could be attributed to the fact that the eyes with slower progression as a group had thicker cornea and were on fewer glaucoma medications. To adequately assess the effect of IOP on the speed of glaucoma progression, treatment would need to be either withheld or randomly assigned. The AIG study was not so designed out of ethical concerns given what is already known. Therefore the findings in this study should not be construed as contradicting the known positive association between elevated IOP and faster glaucoma progression found in earlier studies.^{2,4–6,12,16–25,42,43}

Previously, we had found that GCC-FLV was the most powerful baseline OCT parameter that predicted glaucoma conversion, i.e., the development of glaucomatous VF defects in glaucoma suspects and pre-PG patients,⁴⁴ as well as statistically significant glaucoma progression.² In the current study, we found that NFL-FLV is an even stronger predictor of the rate of progression than was GCC-FLV, though the difference was not significant ($P=0.69$). The detection of GCC-FLV is already commercially available. While the detection of NFL-FLV is not yet available in commercial software, it could be implemented with similar ease from a normative database.

The predictive models developed in this paper need validation on an independent sample outside of the AIG study. The results could vary with a different OCT device, a different patient population, or different clinical management regime.

In conclusion, this study demonstrated that, in a large cohort of PG patients with medically well-controlled IOP (average 13.4 mm Hg) followed for over 4 years, several OCT and VF parameters were predictive of the speed of VF progression. These parameters may be useful in the baseline evaluation of glaucoma and initial determination of treatment intensity (i.e., setting target IOP) and follow-up frequency. However, the absolute predictive accuracies of these baseline parameters were not high, and there is room for further improvement in the development of novel predictive measurements. Because glaucoma is mostly a chronic disease spanning many years, patient risk factors can change over time, and the risk assessment is likely to require continual updates and follow-on longitudinal analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Venn diagram for the detection of confirmed rapid significant progression by mean deviation (MD) and visual field index (VFI).

Figure 2.

The probability plot of a logistic model of confirmed rapid significant progression (CRSP) on baseline visual field index with quadratic term (both linear and quadratic terms are significant) and the observed CRSP.

Table 1.

Progression Rate Categories by Glaucoma Severity

Glaucoma Severity	Confirmed Rapid Significant Progression Rate	Intermediate Progression Rate	Slow Progression Rate
Mild, n (%)	11 (10.5%)	28 (26.7%)	66 (62.9%)
Moderate, n (%)	10 (31.3%)	14 (43.8%)	8 (25%)
Advanced, n (%)	2 (15.4%)	5 (38.5%)	6 (46.2%)

Table 2.

Characteristics of Eyes as Classified by Glaucoma Progression Rate

	Progression Rate	Rapid	Intermediate	Slow	Inter-median *	P**
	Number of eyes	23	47	80	-	-
Baseline Predictive Variables						
Demographic	Age (years)	61.7 ± 7.1	62.5 ± 9.3	60.2 ± 10.3	-	0.835
	Sex (% female)	69.6%	66.0%	57.5%	-	0.46
	Race (% black)	8.7%	4.3%	11.3%	-	0.4
	Ethnicity (% Hispanic)	8.7%	21.3%	15%	-	0.38
Ocular	Axial length (mm)	24.7 ± 1.3	24.8 ± 1.7	24.2 ± 1.2	24.2	0.053
	Central cornea thickness (μm)	528 ± 36	544 ± 40	548 ± 34	545	0.186
	Intraocular Pressure (mm Hg)	13.7 ± 2.2	13.6 ± 3.2	14.9 ± 3.9	14.4	0.157
Visual Field	Mean deviation (dB)	-5.18 ± 4.27	-4.92 ± 4.13	-4.15 ± 4.09	-3.7	0.535
	Pattern standard deviation (dB)	7.25 ± 4.73	6.44 ± 4.38	5.00 ± 3.62	4.9	0.090
	Visual field index (%)	78.7 ± 14.8	83.5 ± 13.8	90.4 ± 13.0	88.5	0.008
Nerve Fiber Layer Thickness	Superior quadrant (μm)	98.4 ± 13.0	96.0 ± 17.4	99.1 ± 19.8	101.6	0.375
	Inferior quadrant (μm)	85.8 ± 17.5	93.2 ± 16.9	93.2 ± 16.1	88.1	0.160
	Overall (μm)	81.0 ± 8.4	81.1 ± 10.8	81.3 ± 12.3	82.2	0.598
	Global loss volume (%)	21.26 ± 6.47	20.57 ± 9.02	20.30 ± 10.30	19.9	0.370
	Focal loss volume (%)	10.39 ± 4.80	8.47 ± 4.05	6.18 ± 3.90	8.5	0.001
Ganglion Cell Complex Thickness	Superior hemisphere (μm)	89.5 ± 7.5	87.1 ± 11.2	86.5 ± 11.1	89.0	0.415
	Inferior hemisphere (μm)	78.0 ± 12.3	80.5 ± 11.5	82.4 ± 10.9	80.6	0.320
	Overall (μm)	83.8 ± 6.5	83.8 ± 9.8	84.5 ± 9.4	84.5	0.868
	Global loss volume (%)	13.32 ± 5.29	13.41 ± 7.91	12.33 ± 8.06	12.4	0.654
	Focal loss volume (%)	7.41 ± 4.52	5.53 ± 3.76	4.75 ± 4.18	5.53	0.063
Optic Disc	Rim area (mm ²)	1.96 ± 0.35	2.04 ± 0.39	1.98 ± 0.49	1.93	0.692
	Vertical cup/disc ratio	0.84 ± 0.13	0.85 ± 0.09	0.81 ± 0.14	0.85	0.185
Longitudinal Predictive Variables						
Intraocular Pressure (mm Hg)	Average	13.1 ± 1.5	13.0 ± 2.4	13.5 ± 2.8	13.4	0.675
	Peak	16.9 ± 3.2	16.2 ± 3.2	17.7 ± 4.8	16.8	0.227
	Standard deviation	1.9 ± 1.1	1.9 ± 0.8	2.1 ± 1.1	1.8	0.265
Disc Heme, n (%)		9 (39.1%)	13 (27.7%)	6 (7.5%)	-	0.004
Disc Hemorrhage Occurrence (0–3) During Follow-up		0.70 ± 0.97	0.36 ± 0.76	0.06 ± 0.24	0	0.0084
Glaucoma Medication, n		1.5 ± 1.1	2.0 ± 1.0	1.4 ± 1.0	1.5	0.127

The cell contents are mean±standard deviation unless otherwise noted. The circumpapillary nerve fiber layer (NFL) thickness, macular ganglion cell complex thickness, and disc parameters were measured by Fourier-domain optical coherence tomography (FD-OCT).

* The intermedian is the midpoint between the medians of the confirmed rapid significant progression (CRSP) group and the slow progression group. The intermedian is used later to dichotomize continuous variables.

** The P-value compares the 3 groups. Means were compared using general estimating equation method. Categorical variables were compared using Chi-square tests.

Table 3.

Summary of the Rate of Change from Visual Field Progression Trend Analysis in Various Glaucoma Stages

		Mild	Moderate	Advanced
	Number of Eyes, n	105	32	13
	Mean, %/year	-0.24	-1.11	-0.24
	Standard deviation, %/y	0.88	1.56	1.94
Summary of Visual	Maximum, %/year	1.77	1.50	2.68
Field Index Slope	Minimum, %/year	-1.23	-1.76	-1.19
	Residual, % *	1.76	3.41	4.78
	CRSP defined by VFI, n (%)	6 (5.7%)	6 (18.7%)	2 (15.4%)
	Mean, dB/year	-0.085	-0.45	-0.087
	Standard deviation, dB/y	0.41	0.64	0.57
Summary of Mean	Maximum, dB/year	1.25	0.82	1.13
Deviation Slope	Minimum, dB/year	-1.23	-1.76	-1.19
	Residual, dB	0.91	1.32	1.74
	CRSP defined by MD, n (%)	8 (7.6%)	8 (25%)	0 (0%)
CRSP	Defined by either MD or VFI, n (%)	11 (10.5%)	10 (31.3%)	2 (15.4%)

* Residual is the pooled root-mean-square residual of linear regression, representing the residual size after the main effect is removed. The abbreviations are: VFI - visual field index; CRSP - confirmed rapid significant progression; MD - mean deviation.

Table 4.

Univariate Analysis of Significant Baseline Continuous Predictive Variables

Variable Type	Predictive Variables	Unit*	Confirmed Rapid Significant Progression			Slow Progression Rate		
			OR	P	AUC	OR	P	AUC
Visual Field	Visual Field Index	14.2%	0.57	0.0013	0.721	1.73	0.012	0.745
	Pattern Standard Deviation	4.1 dB	1.57	0.037	0.608	0.72	0.055	0.604
Focal Loss Volume	Nerve Fiber Layer	4.4%	2.26	0.0016	0.708	0.54	0.0011	0.697
	Ganglion Cell Complex	4.2%	1.98	0.0084	0.657	0.73	0.0703	0.606
Thickness	Central Cornea	37 μ m	0.58	0.045	0.623	1.28	0.157	0.562
Longitudinal	Disc Hemorrhage During Follow-up	Each occurrence	2.6	0.004	0.658	0.23	0.0007	0.622

* The units for predictive variables in the logistic regression analysis were set to one standard deviation in the population of eyes analyzed; OR, odds ratio; AUC, area under the receiver operating curve.

Table 5.

Univariate Analysis of Significant Dichotomous Predictive Variables

Variable Type	Predictive Variables	Cutoff*	High Risk (% eyes meeting cutoff)	Confirmed Rapid Significant Progression		Slow Progression Rate	
				OR	P	OR	P
Visual Field	Visual field index (Quadratic)	60%–84.5%	50%	3.43	0.007	0.26	0.001
	Pattern standard deviation	>4.9 dB	44.0%	2.29	0.097	0.61	0.17
Focal Loss Volume	Nerve fiber layer	>8.5%	36.7%	2.67	0.023	0.42	0.004
	Ganglion cell complex	>5.5%	44.7%	1.86	0.20	0.60	0.104
Thickness	Central Cornea	<545 μ m	45.3%	3.15	0.013	1.89	0.085
Logitudinal	Disc Hemorrhage During Follow-up	>0	17.3%	2.61	0.004	0.23	0.001

* The cutoff was set to the midpoint between the medians of the confirmed rapid significant progression and slow progression groups; OR, odds ratio.

Table 6.

Multivariate Analyses of Significant Predictive Variables

	Units	Coefficient	P	AUC
Model for Confirmed Rapid Significant Progression				
NFL-FLV	%	0.19	0.0011	0.752
Disc Hemorrhage During Follow-up	Yes	1.7	0.0014	
Model for Slow Progression				
NFL-FLV	%	−0.09	0.1	0.800
VFI (linear)	%	−0.27	0.015	
VFI (quadratic)	%	0.0021	0.008	
Disc Hemorrhage During Follow-up	Yes	−1.61	0.0004	

AUC, area under the receiver operating curve; NFL-FLV, nerve fiber layer focal loss volume; VFI, visual field index

Table 7.

Baseline Variables with Significant Linear Correlation with the Speed of Visual Field Progression

	Slope of Mean Deviation		Slope of Visual Field Index	
	Pearson's r	p-Value	Pearson's r	p-Value
Central Corneal Thickness (μm)	0.221	0.008	0.136	0.105
Intraocular Pressure (mm Hg)	0.198	0.018	0.177	0.035
Visual Field Index (%)	0.209	0.012	0.303	0.0002
GCC-FLV (%)	-0.136	0.11	-0.204	0.015
NFL-FLV (%)	-0.234	0.005	-0.335	<0.0001

Abbreviations: GCC - ganglion cell complex; FLV - focal loss volume; NFL - nerve fiber layer.