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

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• 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 of −1%/year or a mean deviation slope of −0.5 dB/year, confirmed at 2 consecutive follow-up visits. Slow progression was defined as VFI slope greater than −0.5%/year or a mean deviation slope of −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 mean deviation 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, 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 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. (Am J Ophthalmol 2019;202:62–71. © 2019 Elsevier Inc. All rights reserved.)

Abbreviations: CRSP = confirmed rapid significant progression; FLV = focal loss volume; GCC = ganglion cell complex; GLV = global loss volume; NFL = nerve fiber layer; OCT = optical coherence tomography; ONH = optic nerve head; VF = visual field; VFI = VF index

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

THE ADVANCED IMAGING FOR GLAUCOMA STUDY (AIGS; NCT01314326) was a National Eye Institute-funded bioengineering partnership established to develop novel imaging technology to aid the diagnosis and monitoring of glaucoma. The AIGS was a multicenter longitudinal

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prospective observational study 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 carried out in accordance with the Health Insurance Portability and Accountability Act (HIPPA) of 1996 privacy and security regulations.

Eyes enrolled in the PG group had glaucomatous optic neuropathy as shown 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 baseline examinations 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 examinations with repeat testing every 6 months. During the follow-up period, each patient was treated at the discretion of the attending physician. The AIGS design and baseline participant characteristics were previously published, and the manual of procedures can be found at the Advanced Imaging for Glaucoma Web site (Casey Eye Institute, Portland, Oregon).[7] The VF was assessed by standard automated perimetry using a Humphrey field analyzer (HFA II; Carl Zeiss Meditec, Inc., Dublin, California) and 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 using Fourier-domain OCT (RTVue; Optovue, Inc., Fremont, California). During each visit, participants underwent 3 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- × 7-mm square area in the macula. Scans were centered 0.75 mm temporal to the fovea to improve coverage of the temporal macula. The GCC scan consisted of the combination of NFL, ganglion cell layer, and inner plexiform layer.[9,10] The automated Optovue software covered a 6-mm-diameter GCC thickness map centered 0.75 mm temporal to the fovea. The ONH concentric (1.3- to 4.9-mm diameter) scans were centered on the optic disc. In postprocessing, the ONH scan was automatically registered with a baseline 3-dimensional (3D) 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, recentered according to the 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, including the GCC global loss volume (GCC-GLV), which measured all negative deviation values normalized by the overall map area, and 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 made software described previously.[2,11] Two parameters were generated, the NFL-GLV and the NFL focal loss volume (NFL-FLV). Note that NFL-GLV and NFL-FLV values 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 of age for the mean deviation (MD) and VF index (VFI). We wanted 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 an MD slope more negative than −0.5 dB/year or a 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 a zero slope. A confirmed rapid significant progression (CRSP) was reached when 2 consecutive MD or VFI slopes were both rapid and significant. Because the regression analysis started from the fourth visit, the earliest visit at which VF CRSP endpoint could be reached was the fifth visit. Our intention was to define CRSP so that it was a clinically meaningful event, a time point at which sufficient VF information had 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 an MD slope ≥−0.25 dB/year and a VFI slope ≥−0.5%/year, that is, 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,[12] 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 fifth visit up to the ninth visit, whereas the slow progression status was determined at the ninth visit. Examinations beyond the ninth 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 worsening of visual acuity confirmed by 2 or more lines at 2 or more follow-up visits and confirmed clinical cataract progression assessment at 2 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 scale[13] in which early glaucoma was defined as MD >-6 dB, moderate glaucoma was defined as an MD between -12 dB and -6 dB, and late stage glaucoma was defined as MD <-12 dB.

The primary statistical model used for the analysis was logistic regression with the general estimating equation[14] method to adjust for the correlation between 2 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 an entry P value of <0.15 and a stay P value of <0.05. In addition to the logistic regression analysis, we also performed ordinary linear regression of MD and VFI slopes on the baseline risk factors. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

AMONG THE 377 EYES OF 249 PATIENTS IN THE PG GROUP, 150 eyes from 103 patients were qualified for analysis in this study 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 characteristics included in the analyses of this study were summarized and stratified by the 3 progression rate categories (rapid [CRSP], slow, and intermediate) (Table 2). There were no statistically significant differences in age, sex, race, or ethnicity. Progression

TABLE 1. Progression Rate Categories by Glaucoma Severity

Glaucoma Severity	CRSP 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)

CRSP = confirmed rapid significant progression rate.

in eyes that progressed slowly tended to be shorter than in 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 were no significant differences 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 3 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 (Figure 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. Other significant variables included baseline GCC-FLV, PSD, and central cornea thickness. The number of occurrences of disc hemorrhage during

TABLE 2. Characteristics of Eyes Classified by Glaucoma Progression Rate

	Progression Rate	Rapid	Intermediate	Slow	Intermedian[a]	P[b]
	Number of eyes	23	47	80	-	-
Baseline predictive variables						
Demographic	Mean age ± SD (y)	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 ± SD (mm)	24.7 ± 1.3	24.8 ± 1.7	24.2 ± 1.2	24.2	0.053
	Central cornea thickness ± SD (μm)	528 ± 36	544 ± 40	548 ± 34	545	0.186
	Intraocular pressure ± SD (mm Hg)	13.7 ± 2.2	13.6 ± 3.2	14.9 ± 3.9	14.4	0.157
Visual field	Deviation ± SD (dB)	-5.18 ± 4.27	-4.92 ± 4.13	-4.15 ± 4.09	-3.7	0.535
	Pattern standard deviation ± SD (dB)	7.25 ± 4.73	6.44 ± 4.38	5.00 ± 3.62	4.9	0.090
	Visual field index ± SD (%)	78.7 ± 14.8	83.5 ± 13.8	90.4 ± 13.0	88.5	0.008
Nerve fiber layer thickness	Superior quadrant ± SD (μm)	98.4 ± 13.0	96.0 ± 17.4	99.1 ± 19.8	101.6	0.375
	Inferior quadrant ± SD (μm)	85.8 ± 17.5	93.2 ± 16.9	93.2 ± 16.1	88.1	0.160
	Overall ± SD (μm)	81.0 ± 8.4	81.1 ± 10.8	81.3 ± 12.3	82.2	0.598
	Global loss volume ± SD (%)	21.26 ± 6.47	20.57 ± 9.02	20.30 ± 10.30	19.9	0.370
	Focal loss volume ± SD (%)	10.39 ± 4.80	8.47 ± 4.05	6.18 ± 3.90	8.5	0.001
Ganglion cell complex thickness	Superior hemisphere ± SD (μm)	89.5 ± 7.5	87.1 ± 11.2	86.5 ± 11.1	89.0	0.415
	Inferior hemisphere ± SD (μm)	78.0 ± 12.3	80.5 ± 11.5	82.4 ± 10.9	80.6	0.320
	Overall ± SD (μm)	83.8 ± 6.5	83.8 ± 9.8	84.5 ± 9.4	84.5	0.868
	Global loss volume ± SD (%)	13.32 ± 5.29	13.41 ± 7.91	12.33 ± 8.06	12.4	0.654
	Focal loss volume ± SD (%)	7.41 ± 4.52	5.53 ± 3.76	4.75 ± 4.18	5.53	0.063
Optic disc	Rim area ± SD (mm^2)	1.96 ± 0.35	2.04 ± 0.39	1.98 ± 0.49	1.93	0.692
	Vertical cup/disc ratio ± SD	0.84 ± 0.13	0.85 ± 0.09	0.81 ± 0.14	0.85	0.185
Longitudinal predictive variables						
Intraocular pressure (mm Hg)	Average ± SD	13.1 ± 1.5	13.0 ± 2.4	13.5 ± 2.8	13.4	0.675
	Peak ± SD	16.9 ± 3.2	16.2 ± 3.2	17.7 ± 4.8	16.8	0.227
	±SD	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 ± SD		0.70 ± 0.97	0.36 ± 0.76	0.06 ± 0.24	0	0.0084
Number of glaucoma medications ± SD		1.5 ± 1.1	2.0 ± 1.0	1.4 ± 1.0	1.5	0.127

CRSP = confirmed rapid significant progression; FD-OCT = Fourier-domain optical coherence tomography; NFL = nerve fiber layer.

Cell contents values are mean ± SD unless otherwise noted. The circumpapillary NFL thickness, macular ganglion cell complex thickness, and disc parameters were measured using FD-OCT.

[a]The intermedian is the midpoint between the medians of the CRSP group and the slow progression group. The intermedian is used later to dichotomize continuous variables.

[b]The *P* values compare 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 the Visual Field Progression Trend Analysis in Various Glaucoma Stages

		Mild	Moderate	Advanced
	Number of Eyes, n	105	32	13
Summary of visual field index slope	Mean %/y	−0.24	−1.11	−0.24
	±SD %/y	0.88	1.56	1.94
	Maximum, %/y	1.77	1.50	2.68
	Minimum, %/y	−1.23	−1.76	−1.19
	Residual, %[a]	1.76	3.41	4.78
	CRSP defined by VFI, n (%)	6 (5.7)	6 (18.7)	2 (15.4)
Summary of Mean Deviation Slope	Mean, dB/year	−0.085	−0.45	−0.087
	Standard deviation. dB/y	0.41	0.64	0.57
	Maximum, dB/y	1.25	0.82	1.13
	Minimum, dB/y	−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)

CRSP = confirmed rapid significant progression; MD = mean deviation; VFI = visual field index.

[a]The residual value is the pooled root-mean-square residual of linear regression representing the residual size after the main effect is removed.

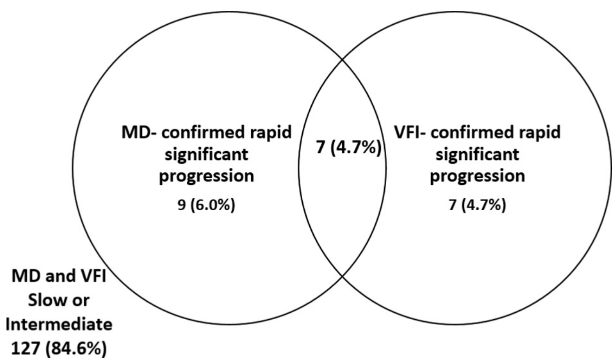

FIGURE 1. Venn diagram shows the detection rate of confirmed rapid significant progression by MD and VFI. MD = mean deviation; VFI = visual field index.

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 (Figure 2), with the peak probability for rapid progression occurring at a VFI of 67%. The AUC of the quadratic model was 0.747 with an Akaike Information Criterion of 124.3 units, only minimally improved over the linear model, which had an AUC of 0.745 with an Akaike Information Criterion of 125.4 units. Quadratic models for MD, NFL thickness, and GCC thickness also showed U-shaped dependencies, but the quadratic terms 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 a 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 consisted 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 value for predicting CRSP was 0.752 and 0.800 for slow progression.

The logistic regression analysis so far used discrete classifications of VF progression speed, designated 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

TABLE 4. Univariate Analysis of Significant Baseline Continuous Predictive Variables

Variable Type	Predictive Variables	Unit[a]	CRSP			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 μm	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

[a]Units for predictive variables in the logistic regression analysis were set to ±1 SD in the population of eyes analyzed. AUC = area under the receiver operating curve; CRSP = confirmed rapid significant progression; OR = odds ratio.

regression analysis were central corneal thickness, IOP, VFI, GCC-FLV, and NFL-FLV (Table 7). NFL-FLV appeared to be the most significant variable, which agrees with Table 4 data. The baseline IOP was a significant predictor in the continuous model but not in the discrete model, whereas VF-PSD was a significant predictor in the discrete model but not in 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.

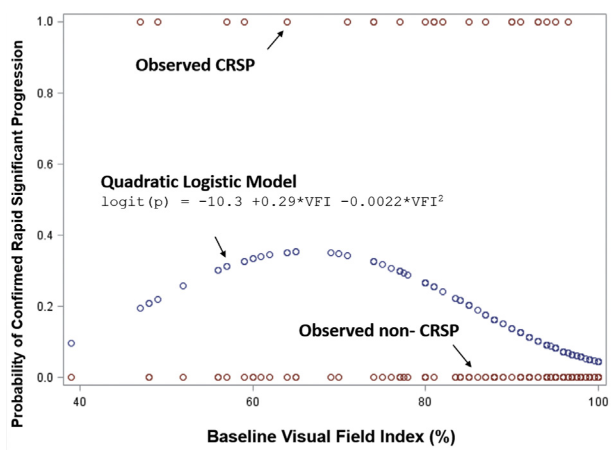

FIGURE 2. The probability plot of a logistic model of CRSP on baseline visual field index with quadratic terms (both linear and quadratic terms are significant) and the observed CRSP. CRSP = confirmed rapid significant progression.

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 experiencing 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 investigated the factors that predict the risk of developing statistically significant VF progression,[2,5,6,15–20] or the factors that influence the average rate of progression in a group of patients,[21] few studies have examined factors that predict which glaucoma patients or eyes are more likely to have rapid versus slow rate of VF deterioration.[22–24] Furthermore, none of the studies have related the speed of VF progression to baseline OCT findings. This study identified 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.[5,6,16,20,25–28] There is no clear consensus yet on what speed of progression should be considered rapid. The range of MD slopes between −0.5 and −2.0 dB/year has been considered clinically significant.[12,29,30] In the AIGS, 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 the sample size and contrast needed for statistical analysis. This cutoff value 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

TABLE 5. Univariate Analysis of Significant Dichotomous Predictive Variables

Variable Type	Predictive Variables	Cutoff[a]	% of High-Risk Eyes Meeting Cutoff Values	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 μm	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

OR = odds ratio.

[a]The cutoff value was set to the midpoint between the medians of the confirmed rapid significant progresson and the slow progression groups.

TABLE 6. Multivariate Analyses of Significant Predictive Variables

	Units	Coefficients	*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.

slope of worse than −1%/year as an alternative definition that was roughly equivalent to an MD slope of −0.5 dB/year. These 2 VF parameters are synergistic because MD does not suffer from the "ceiling effect" of VFI,[31–33] whereas on the other hand, VFI is more sensitive to central and focal loss due to the way it is defined and computed.[34] 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.

At 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 alternative definition that is roughly equivalent to an MD slope of −0.25 dB/year.

Our primary finding is that measurements of focal loss in the peripapillary NFL and macular GCC were the strongest OCT predictors of glaucoma progression rate. Interestingly, among the VF parameters, measurements that emphasize focal loss such as VFI and PSD were also strong predictors, although measurements 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 (ie, the NFL appears thinner in longer eyes[35–37]), myopic retinal degeneration,[37] or aging.[38] 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,[31] dry eye,[39] or lack of attentiveness,[40] whereas VFI and PSD would be less affected by these nonglaucomatous factors. Clear evidence of glaucoma damage at baseline would indicate past glaucoma progression. If we assume that each patient has a characteristic

TABLE 7. Baseline Variables with Significant Linear Correlations 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

GCC = ganglion cell complex; FLV = focal loss volume; NFL = nerve fiber layer.

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 would be correlated with faster future progression, at least in the short term.

Although a positive correlation between glaucoma severity and progression rate existed for most of the AIGS 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 approximately 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 examinations was not a significant factor in this study, probably because in most AIGS 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 corneas and were taking 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 AIGS 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.[2,4–6,15–24,41,42]

Previously, we found that GCC-FLV was the most powerful baseline OCT parameter that predicted glaucoma conversion, that is, the development of glaucomatous VF defects in glaucoma suspects and pre-PG patients,[11] as well as statistically significant glaucoma progression.[2] In the current study, we found that NFL-FLV was an even stronger predictor of the rate of progression than GCC-FLV, although the difference was not significant (P = 0.69). The detection of GCC-FLV is already commercially available. Although 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 study need validation by an independent sample outside of the AIGS. The results could vary with a different OCT device, a different patient population, or a 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 values) 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.

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