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Baseline Fourier-Domain OCT Structural Risk Factors for Visual Field Progression in the Advanced Imaging for Glaucoma Study

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Abstract

Purpose—To identify baseline structural parameters that predict the progression of visual field (VF) loss in patients with open angle glaucoma.

Design—Multicenter cohort study.

Methods—Participants from Advanced Imaging for Glaucoma (AIG) study were enrolled and followed-up. VF progression is defined as either a confirmed progression event on Humphrey Progression Analysis or a significant ($p < 0.05$) negative slope for VF index (VFI). Fourier-domain optical coherence tomography (FD-OCT) was used to measure optic disc, peripapillary retinal nerve fiber layer (NFL) and macular ganglion cell complex (GCC) thickness parameters.

Results—277 eyes of 188 participants were followed up for 3.7 ± 2.1 years. VF progression was observed in 83 eyes (30%). Several baseline NFL and GCC parameters, but not disc parameters,

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were found to be significant predictors of progression on univariate Cox regression analysis. The most accurate single predictors were the GCC focal loss volume (FLV), followed closely by NFL-GCC. An abnormal GCC-FLV at baseline increased risk of progression by a hazard ratio of 3.1. Multivariate Cox analysis showed that combining age and central corneal thickness with GCC-FLV in a composite index called “Glaucoma Composite Progression Index” (GCPI) further improved the accuracy of progression prediction. GCC-FLV and GCPI were both found to be significantly correlated with the annual rate of change in VFI.

Conclusion—Focal GCC and NFL loss as measured by FD-OCT are the strongest predictors for VF progression among the measurements considered. Older age and thinner central corneal thickness can enhance the predictive power using the composite risk model.

Introduction

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 could be followed more closely and treated more aggressively. Understanding an individual's risk profile would allow for the rational use of medical, laser and surgical treatments, all of which have significant cost, compliance, and safety issues. A number of risk factors have been previously identified, and these include intraocular pressure (IOP)^{1–3} and its variability,^{4,5} corneal thickness,^{6,7} cup-to-disc ratio, age, VF parameters,^{8,9} and optic disc hemorrhage.^{10,11} Family history and race also provide risk information. Photographic evidence of NFL defect¹ and evidence of disc rim defect¹² have also been recognized as risk factors for VF loss.^{13,14} In a recent meta-analysis,¹⁵ Ernest et al. identified a list of recognized baseline prognostic factors for future VF loss, including disc hemorrhage (for normal tension glaucoma), VF loss, IOP and exfoliation syndrome, while a definitive association was not proven for other factors, such as family history. However, none of these risk factors by themselves are reliable predictors of glaucoma progression, and clinicians must consider all of them in glaucoma patient management.

Advanced imaging technologies can quantify glaucomatous damage to retinal neural structures and may provide useful prognostic information, since structural damage often precedes VF damage.^{16,17} Fourier-domain optical coherence tomography (FD-OCT), in particular, provides 3-dimensional imaging that measures the neural structures of the retina and optic nerve head with excellent resolution.^{18,19}

The Advanced Imaging for Glaucoma (AIG) Study was designed to identify the role of quantitative imaging in evaluating the risk of glaucoma progression, and in early diagnosis of glaucoma and clinical decision-making.²⁰ The purpose of this article is to identify baseline FD-OCT structural predictors for the progression of glaucomatous visual field (VF) defects, using the longitudinal AIG Study perimetric glaucoma cohort.

Methods

Longitudinal Clinical Study

The Advanced Imaging for Glaucoma (AIG) study is a multi-center bioengineering partnership and longitudinal cohort study sponsored by the National Eye Institute

(ClinicalTrials.gov identifier: NCT01314326). The data analyzed in this article came from participants in the perimetric glaucoma (PG) arm of the AIG Study.²⁰ These participants were enrolled at the Bascom Palmer Eye Institute, University of Miami; the 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 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 NFL defect on fundus examination, and corresponding repeatable abnormal standard automated perimetry (SAP) defects with glaucoma hemifield test (GHT) or pattern standard deviation (PSD, $p < 0.05$) outside normal limits.

All study participants underwent a baseline examination²⁰ 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 published²⁰ and the manual of procedures could be found at www.aigstudy.net.

Visual Field Progression Detection

Two methods of visual field progression detection were adopted: (1) event-based progression analysis, and (2) trend-based progression analysis. Event-based visual field progression was determined using Guided Progression Analysis (GPA; Humphrey Field Analyzer; Software version 4.2, Carl Zeiss Meditec Inc, Dublin, CA). GPA uses statistical criteria designed for the Early Manifest Glaucoma Trial (EMGT) and compares the sensitivity values of individual test locations on follow-up visual fields to the sensitivity values of the same locations on an average of 2 baseline exams. An automated analysis identifies the locations that show change greater than the expected variability (at the 95% significance level). Event-based Progression was defined as a significant change detected in 3 test locations, and repeated at the same locations in 3 consecutive follow-up examinations, categorized by the GPA software as “Likely Progression”.

Trend-based visual field progression was defined as a significant ($p < 0.05$) negative slope in the annual rate of change in the visual field index (VFI). The VFI is a calculated index allocated to each visual field that determines the level of abnormality of the field.²¹ The VFI uses the pattern deviation (PD) probability map to identify the test locations that are considered either normal and scored as 100%, or absolute defect and scored as 0%. The remaining test locations with relative loss on PD plot are scored in percentage based on their total deviation (TD) value and age-corrected normal threshold.²¹ The occurrence of Trend-based Visual Field Progression was defined as the first follow-up visit reaching a significant

($p < 0.05$) negative VFI slope over time. Visual field progression endpoint was reached when either type of progression was observed.

Fourier-domain Optical Coherence Tomography

Participants were scanned every 6 months with a commercial FD-OCT system (RTVue-100, Optovue Inc., Fremont, CA, USA). During each visit, participants had three ganglion cell complex (GCC) and optic nerve head (ONH) scans. In the baseline visit, an extra 3D disc scan was also obtained to register ONH scans of same participant in all visits.

Raw data from all AIGS clinical centers were de-identified and transferred to the Casey Eye Institute OCT Reading Center. Certified graders used RTVue software Version 6.12 to analyze the data and generate disc, NFL, and GCC structural parameters. Scans were excluded if they had low signal strength, cropping artifact, or failed segmentation. Any ONH scan with a signal strength index (SSI) less than 37 and GCC scan less than 42 were excluded for analysis.²² Measurements from qualified scans in the same visit were averaged.

Macular GCC parameters were measured using GCC scans. The macular GCC scan covered a 7 by 7 mm square area, centered 0.75 mm temporal to the fovea, which is designed to improve the coverage of the temporal macula. The macular GCC thickness was defined as the combination of NFL, GCL, and inner plexiform layer.²³ The RTVue software derived a 6 mm diameter GCC thickness map centered 0.75 mm temporal to fovea (Figure 1). Based on the map, overall, superior and inferior hemisphere average of GCC were obtained. Two special pattern analyses parameters were also obtained: a) the global loss volume (GLV), which measures all negative deviation values normalized by the overall map area, and, b) the focal loss volume (FLV), which measures the negative deviation values in areas of significant focal loss in the foveal region.^{24,25}

Parameters for NFL were measured using ONH scans. The ONH scan covered 4.9mm round area centered at optic disc. It consisted of concentric (1.3–4.9 mm diameter) scans and radial scans (3.4 mm length). The ONH scans were automatically registered with the baseline 3D disc scan. The 3D disc scan also provided the disc margin information. The NFL thickness profile at 3.4 mm diameter was resampled on the NFL map re-centered according to detected optic disc center (figure 1 left). Based on the profile, overall, superior, and inferior quadrant averages of NFL thickness were obtained using the RTVue software. Pattern analysis was applied to the NFL thickness profile using custom software described in a previous publication.¹⁷ The NFL pattern analysis is analogous to the RTVue GCC pattern analysis that generates the GLV and FLV parameters, but based on the NFL profile instead of the GCC map.

Parameters for optic disc were also measured using ONH scans. The ONH scan was processed using RTVue software to delineate cup and disc boundaries (Figure 1). The horizontal cup-to-disc ratio (CDR) is the ratio of the diameter of the cup portion with the total diameter of the optic disc in horizontal direction. The vertical CDR is the ratio in vertical direction. The CDR of area is the ratio of cup area and disc areas.

In summary, the acquired measurements using FD-OCT included (1) the overall, superior and inferior hemisphere averages of the GCC thickness map, (2) the overall, superior and inferior quadrants averages of the NFL thickness profiles, (3) cup disc ratio and rim area, (4) FLV and GLV of GCC thickness map, (5) FLV and GLV of NFL thickness profile.

Statistical Analysis

Statistical analysis was performed using SAS software version 9.2 (SAS Inc., Cary, NC, USA) to detect progressive structural loss and visual field progression in PG patients. All tests were two-sided and a p-value of <0.05 was considered significant. The average of three high quality OCT measurements that met the inclusion criteria was used for the statistical analyses. Analysis of variance (ANOVA) was used to compare means for continuous variables and chi-square test for the categorical variables. When applicable, general estimating equation (GEE) method was used to adjust for correlation between the two eyes of the same patient.²⁶

The primary analysis used Cox regression⁹ which is suitable for time-to-event data. The participants had to have at least three follow-up visits in addition to the baseline visit to be eligible for inclusion in the analysis. For each of the covariates in the analysis, we provided a hazard ratio (HR) estimate and the corresponding p-value. We also provided the AUC for the covariate to compare its relative predictive accuracy for glaucomatous progression.

For NFL and GCC parameters, normal, borderline (1–5 percentile of normal population), and abnormal (below 1 percentile) classifications were provided by the RTVue device based on the normative database compiled by Optovue. These classifications are shown in yellow (borderline), red (abnormal), and green (normal) on the RTVue printout (Figure 1). For these categorical covariates, Kaplan-Meier survival curves were produced, and log-rank tests were used to compare risks among categories.

Because many participants had both eyes enrolled in this study, we used a robust sandwich covariance estimation method in the Cox regression to adjust for this potential correlation.

All of the potential covariates were evaluated to build an optimal multivariate Cox regression model through a combination of manual elimination and automatic stepwise selection processes. When the optimal combination of the covariates was determined, the linear form was transformed through a logistic function. The resulting value, which ranged from 0 to 1, was defined as the glaucoma composite progression index (GCPI). The GCPI closer to 1 implied a higher risk of progression.

Results

Characteristics of Participants: Progressors and Non-Progressors

Out of 277 perimetric glaucoma (PG) eyes of 188 participants, there were 194 non-progressor eyes (age 62.2 ± 10.1 years, followed 4.0 ± 1.6 years) from 132 patients and 83 progressor eyes (age 63.8 ± 8.3 years, followed 3.8 ± 1.6 years) from 66 patients ($p = 0.61$). Out of 5901 total follow-up scans, 289 (4.9%) GCC scans and 307 (5.2%) NFL scans were excluded due to poor signal strength; and 203 (3.4%) GCC and 243 (4.1%) NFL scans were

excluded due to cropping artifacts or failed segmentation. More progressors were identified using trend-based analysis rather than event-based analysis (Figure 2). Baseline IOP was slightly lower in progressors, although the difference was not significant (Table 1). The average IOP during the follow-up period was similar ($p = 0.13$) between non-progressors and progressors (14.1 ± 3.2 vs. 13.5 ± 2.7 mmHg). The peak IOP during the follow-up period was similar ($p = 0.28$) between non-progressors and progressors (16.9 ± 4.6 vs. 16.3 ± 3.9 mmHg). The IOP range during the follow-up period was also similar ($p = 0.74$) between non-progressors and progressors (5.1 ± 4.2 vs. 5.3 ± 3.8 mmHg). Central corneal thickness (CCT), baseline MD, PSD, and VFI were not significantly different between non-progressors and progressors ($p > 0.05$). The age distribution, sex, and number of patients with African origin, diabetes, systemic hypertension and family history of glaucoma were similar between non-progressor and progressor eyes (Table 1).

Among the baseline FD-OCT measurements, the following variables were significantly different between progressors and non-progressors: rim area, vertical CDR, NFL-FLV and GCC-FLV (Table 1). The following variables were not significantly different between progressors and non-progressors: horizontal CDR, NFL overall thickness, NFL inferior and superior quadrant thickness, NFL- GLV, GCC overall thickness, GCC inferior and superior hemisphere thickness and GCC-GLV. According to univariate Cox regression analyses (Table 2), significant baseline risk factors for VF progression include CCT, VF PSD, NFL inferior quadrant thickness, NFL-FLV, GCC overall thickness, GCC inferior hemisphere thickness, GCC-GLV and GCC-FLV. The following baseline factors were not statistically significant: IOP, VFI, rim area, CDRs, NFL overall thickness, NFL superior quadrant thickness, NFL- GLV, GCC overall thickness, and GCC superior hemisphere thickness. The following variables are of borderline statistical significance: VF MD ($p = 0.08$), NFL-GLV ($p = 0.07$). Among the significant risk factors, GCC-FLV is the strongest predictor with AUC = 0.632. NFL-FLV is the second strongest with AUC = 0.631, almost identical to GCC-FLV.

Although continuous parameters provide the fullest information, clinicians find it easiest to interpret the classifications of normal, borderline, and abnormal that are simple and highlighted in color in the device printout. Therefore, we calculated hazard ratios for these OCT classifications (Table 3). GCC-FLV was again the strongest predictor of VF progression. Eyes with abnormal GCC-FLV at the baseline had more than 3 times the hazard of significant VF progression compared to those with normal GCC-FLV.

We also calculated the slope of VFI change over time according to GCC-FLV classification at baseline (Table 4). Eyes with normal GCC-FLV at the baseline had, on the average, no change in VFI over time. Eyes with borderline or abnormal GCC-FLV at baseline had significantly faster VFI decline. The slope of VFI deterioration was on the average twice as fast for those with abnormal GCC-FLV at baseline, compared to those with borderline values. . Figure 3 shows the Kaplan-Meier analysis of cumulative probability of visual field progression in a group of PG eyes that had borderline or abnormal GCC-FLV at baseline versus the PG eyes that had normal GCC-FLV at baseline. At 6 years follow-up, eyes with abnormal or borderline GCC-FLV values doubled the risk for VF progression, comparing to eyes with normal GCC-FLV at baseline (Log rank test $p < 0.001$).

We created the Glaucoma Composite Progression Index (GCPI) by combining the available demographic, clinical, and FD-OCT continuous variables. First, baseline VF, CCT, and FD-OCT parameters with univariate Cox regression HRs at a significance level of $p < 0.1$ were included (Table 2), along with demographic parameters that were different between progressors and non-progressors (Table 1). Next, these candidate covariates were run through an automatic stepwise selection/elimination process, where the p -value for elimination was set at 0.05. The final components that made up the GCPI included age, CCT and GCC-FLV. The components were added together with the optimized weight coefficients (Table 5), and then went through logistic transformation to produce the composite index with a value ranging from 0 to 1. The GCPI AUC of 0.653 performed better than any single variable, including GCC-FLV, which had an AUC of 0.632 (Table 3). The Cox model predicts that the risk of VF progression varies smoothly with GCPI value, with a predicted 6 year progression risk ranging from 0 to 1 for GCPI values from 0.1 to 0.9 (Figure 4).

Quartile analysis (Table 6) confirmed that GCPI had significant predictive power for the risk of VF progression ($p < 0.001$, likelihood ratio test) and the rate of VFI decline ($p < 0.001$). Eyes in the lowest quartile had much lower progression risk than the higher three quartiles. The cutoff value of GCPI that maximized the accuracy of predicting progression with sensitivity at 60.2 and specificity at 65.5 was 0.23, which is at the 55% percentile of the study eyes. The speed of progression, as measured by VFI slope, could also be predicted by GCPI (Table 6, $p < 0.001$). Eyes in the bottom quartile of GCPI showed no trend toward progression in the average, while eyes in the top quartile had average VFI progression rate more than twice that of the middle 2 quartiles.

Discussion

The therapeutic goal for any glaucoma patient is to stabilize the disease and prevent progression of optic nerve damage and visual field loss. The rate of progression over time provides the most definitive 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. Based on the finding from a number of studies,¹⁻⁸ clinicians already use IOP and CCT in stratifying the risk and rate of progression. The severity and location of VF damage is also a well-established guide to glaucoma management, based on the logic that evidence of past damage predicts future progression. However, due to the variability of VF performance, a single VF test at the baseline may not be reliable guide.^{27,28} Therefore objective tests to establish the severity of optic nerve damage may provide more reliable initial predictors of progression risk.

Measures of focal loss in the peripapillary NFL and macular GCC were the strongest OCT predictors of glaucoma progression in our study. A possible explanation is that focal defects are more reliable indicators of glaucoma damage than overall thinning. An overall thinning of the NFL or GCC could be due to normal population variation, magnification effects (NFL appear thinner in longer eyes),^{29,30} myopic retinal degeneration,³¹ or aging.³² A focal defect, however, would be highly unlikely in the absence of glaucoma or other specific diseases. In our univariate analysis, several GCC and NFL parameters that measured global

average and inferior damage were significant predictors of VF progression. However, NFL-FLV and GCC-FLV were even better predictors as judged by AUC. Multivariable analysis showed that GCC-FLV, the parameter that measures focal loss in the macular ganglion cells, was the only OCT parameter needed in the optimized Glaucoma Composite Progression Index (GCPI) which also included age and the CCT. In clinical practice, it is reasonable to assume that most clinicians would not have the facility to compute the GCPI. However, clinicians could look at the GCC-FLV classification alone for the simplest strong predictor. Eyes with baseline GCC-FLV classification as borderline or abnormal have a hazard ratio of ~3 in our Cox model, and a doubling of VF progression rate to 60% over an average follow-up period of 4 years in our study population.

An interesting finding (Tables 2 and 3) is that GCC seems more robust than NFL in predicting progression. In particular, decreased inferior hemispheric GCC thickness average carried stronger relative risk than decreased inferior quadrant NFL thickness. One possible reason is that GCC is measured in the macular area that fall within the 24-2 VF, while the peripapillary NFL supplies the entire retina, some of which fall outside the VF testing area and therefore may not correlate as well. Another possible reason is that NFL is more susceptible to decentration error. The thickness of NFL is approximately inversely proportional to the radial distance from disc center.²⁹ Therefore decentration error could bias the measurement of NFL thickness in a quadrant (i.e. a superiorly decentered sampling circle would artifactually increase the inferior NFL thickness and decrease the superior NFL thickness). The decentration-related error is relatively significant for a quadrantic measurement of NFL thickness because the sampling circle is relatively small (3.4 mm diameter). Furthermore, the center of the disc is difficult to establish accurately due to anatomic variations (shape variation, tilt, peripapillary atrophy, etc.) On the other hand, the GCC thickness varies slowly outside parafoveal region, and the GCC analytic area (6 mm circle) is relatively large compared to parafoveal area. Furthermore, the centration of the GCC scan is easily established relative to foveal fixation. Therefore hemispheric GCC thickness parameters are relatively robust to decentration error.

In a recent publication, we had analyzed the baseline OCT parameters that predicted development glaucomatous VF defects (converting to perimetric glaucoma) in the glaucoma suspects and pre-perimetric glaucoma cohort of the AIG Study.¹⁷ We found that GCC-FLV was also the most powerful predictor converting to perimetric glaucoma. More baseline OCT parameters, including NFL, GCC, and disc parameters, were significant predictors of conversion. And the AUC values were generally higher for predicting conversion, with the AUC of GCC-FLV at 0.753. This compares with an AUC of 0.632 for prediction progression with the same parameter in this paper. The comparison suggests that OCT assessment may be most powerful in the earliest stages of glaucoma.

Several prior studies have looked at ocular hypertensives or glaucoma suspects and the role of imaging at baseline to predict conversion to glaucoma. Abnormal baseline measurements using confocal scanning laser ophthalmoscope (cSLO) scans³³, scanning laser polarimetry³⁴, and NFL thickness with OCT³⁵ have all been shown to predict glaucomatous visual field change in ocular hypertensive glaucoma suspects. In a report analysing early data from the AIG Study with time-domain OCT, scanning laser polarimetry and cSLO,

abnormal baseline ONH topography and thin inferior retinal NFL were reported to be predictive of VF progression in a smaller sample of glaucoma suspects and patients.³⁶ These studies showed that NFL loss as measured by advanced imaging modalities could be used to predict future VF conversion.

The importance of the focal macular structural parameter in predicting visual field progression in our analysis suggests that macular damage may be more common and occur earlier than previously believed. It has recently been shown that macula GCC parameters measured with OCT can be used to measure the glaucomatous damage in the macula.³⁷ Studies have also shown that FLV and GLV demonstrate a higher diagnostic accuracy than average GCC thickness.^{24,38} In a retrospective study, baseline macular GCC thickness of the inferior hemifield was shown to be predictive of VF progression in POAG³⁹. Interestingly, Sung et al. also proposed that in advanced glaucoma, changes in average macula thickness measured with spectral domain OCT may improve the ability to detect progression.⁴⁰ This is also supported by recent literature that showed more than 50% of eyes with mild to moderate glaucoma have field loss within the central 3 degrees, when tested using the 10-2 central VF algorithm.⁴¹ However, it is a significant time burden to conduct routine 10-2 VF testing in addition to the standard 24-2 VF testing in the clinical practice of glaucoma. Macular GCC mapping (or other types of ganglion cell related mapping) by OCT is faster and may be a more practical way of evaluating glaucoma damage in the central regions.

Our multivariate Cox analysis showed age and CCT to be synergistic with GCC-FLV in predicting progression. Age is a well-known factor associated with both the higher prevalence of glaucoma^{1,8} as well as faster progression.^{3,4} CCT has been established as a significant risk factor for glaucoma in a population-base study⁴² and for glaucoma conversion in ocular hypertensives.⁸ Therefore it is not surprising that age and CCT are significant independent risk factors included in the GCPI in the current study. What is more interesting is that IOP and VF parameters were not found to be significant in the multivariate analysis. While a considerable body of evidence supports the role of IOP as a strong predictor of VF progression,^{2,6} this association may have been masked in our study by the use of pressure-lowering glaucoma eye drops. Due to ethical considerations, it was not possible to randomize treatment in the AIG study nor blind the treating physicians to IOP measurements. Therefore IOP values in both progressors and non-progressors groups were well controlled throughout the study. The lack of eyes with untreated high IOP took away the contrast necessary for the study to detect any IOP effect. Finally, since physicians were allowed to treat according to their clinical judgment and current practice in the study, different patterns of care depending on cornea thickness as well might also have had an impact on our results. VF parameters, on the other hand, offered a wide range of contrast in our study population. Furthermore, VF PSD was found to a significant univariate predictor of progression, as would be expected from past studies.³ The fact that all VF parameters dropped out in the multivariate analysis suggests that GCC-FLV was a more reliable measure of glaucoma damage, therefore VF parameters became redundant when these parameters were analyzed together.

In the present study, optic nerve rim area at baseline was not a statistically significant predictor of future field progression. Studies have not consistently shown a clear association

between rim area and VF change.^{36,43,44} However, it has been suggested that optic disc topography analysis based on identification of Bruch's membrane opening-minimum rim width showed good correlation with VF sensitivities, therefore supporting the role of this parameter as a strong predictor of VF change.⁴⁵ The integration of new algorithms in disc topography analysis with OCT may improve the diagnostic abilities of this parameter.

In conclusion, this study demonstrated that, in a large cohort of perimetric glaucoma patients followed for 1.5 to 6.5 years, FD-OCT measurements of peripapillary NFL and macular GCC are significant predictors of VF progression, in addition to known risk factors of age and CCT. GCC-FLV was the most significant predictive factor in multivariate Cox analysis. The Glaucoma Composite Prediction Index (GCPI) calculated from 3 most important risk factors - age, CCT, and GCC-FLV - increased the accuracy of predicting progression compared to any single factor. It has predictive value in terms of both risk of significant VF progression and rate of VFI change over time. These parameters may be useful in the baseline evaluation of glaucoma and initial determination of relative progression risk, which is relevant to the the planning of treatment intensity (i.e. setting target IOP) and follow-up frequency. However, the absolute predictive accuracy of these baseline factors are not high and there is room for further improvement in the development of novel predictive measurements. Baseline factors are indicators of disease severity. Greater disease severity could be due to faster disease progression, but could also be due to great disease duration. Therefore a baseline measurement alone can never be a very accurate predictor of progression, and longitudinal monitoring is always needed to establish the rate of disease progression. Furthermore, 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 2.

The number of progressing eyes identified using trend-based analysis and event-based analysis

Figure 3. Kaplan-Meier plot of visual field progression probability in perimetric glaucoma eyes, stratified according to baseline macular ganglion cell complex focal loss volume (GCC FLV) status.

Figure 4.

Probability of visual field progression in perimetric glaucoma eyes stratified according to the Glaucoma Composite Progression Index (GCPI) based on a Cox proportional hazard model = glaucoma composite progression index (range 0.1 to 0.9).

Table 1

Baseline Characteristics of the participants who had glaucomatous progression compared to the participants who had not experienced progression

	Non-Progressors 194 Eyes	Progressors 83 Eyes	p-Value
Age (year)	62.23 ± 10.08	63.75 ± 8.27	0.61
Female	116 (59.8%)	49 (59.0%)	0.91
African Origin	20 (10.3%)	8 (9.6%)	0.31
Systemic Hypertension	72 (37.1%)	31 (37.3%)	0.97
Diabetes Mellitus	20 (10.3%)	11 (13.3%)	0.48
Family History of Glaucoma	79 (40.7%)	44 (53.0%)	0.61
# Eye Drop Used	1.4 ± 1.2	1.5 ± 1.1	0.42
Central Corneal Thickness (μm)	549 ± 37	535 ± 35	0.12
IOP at Baseline (mmHg)	14.6 ± 4.7	13.5 ± 3.6	0.16
VF Mean Deviation (db)	-4.76 ± 5.13	-4.99 ± 4.21	0.97
VF Pattern Standard Deviation (db)	5.36 ± 4.02	6.61 ± 4.39	0.20
VFI (%)	87.9 ± 15.0	86.8 ± 12.5	0.92
Follow-up time (years) *	3.8 ± 2.2	3.7 ± 1.9	0.72
Fourier-Domain Optical Coherence Tomography Parameters			
Rim Area (mm ²)	0.80 ± 0.38	0.69 ± 0.31	0.01
CDR, Vertical	0.80 ± 0.16	0.85 ± 0.13	0.02
CDR, Horizontal	0.84 ± 0.15	0.85 ± 0.17	0.54
CDR, Area	0.60 ± 0.19	0.63 ± 0.19	0.27
NFL Overall (μm)	81.4 ± 12.5	78.5 ± 10.7	0.19
NFL Inferior Q (μm)	94.8 ± 19.9	88.8 ± 16.3	0.15
NFL Superior Q (μm)	97.6 ± 18.7	95.2 ± 18.3	0.20
NFL-GLV (%)	20.24 ± 10.66	22.79 ± 8.74	0.21
NFL-FLV (%)	6.79 ± 4.64	8.84 ± 4.53	0.01
GCC Overall (μm)	83.9 ± 11.1	81.5 ± 9.0	0.38
GCC Inferior H (μm)	81.9 ± 12.9	78.1 ± 11.5	0.10
GCC Superior H (μm)	85.8 ± 11.7	84.3 ± 10.2	0.74
GCC-GLV (%)	12.91 ± 9.46	15.2 ± 7.7	0.24
GCC-FLV (%)	4.75 ± 4.16	6.61 ± 4.36	0.01

Cell contents are mean ± standard deviation. CCT=central corneal thickness; IOP=intraocular pressure; VF= visual field; MD=mean deviation, PSD=pattern standard deviation; VFI=visual field index; CDR=cup-to-disc ratio, Q=quadrant average thickness; H=hemispheric average thickness; NFL=nerve fiber layer; GCC=ganglion cell complex; GLV=global loss volume; FLV=focal loss volume

* Follow-up time is calculated over the entire follow-up for the participant.

Table 2

Significant Baseline Continuous Variables for Predicting Visual Field Progression

	Unit	HR	P-value	AUC
Central Corneal Thickness (μm)	20 μm thinner	1.14	0.012	0.621
VF PSD (dB)	1 db higher	1.06	0.013	0.587
Fourier-Domain Optical Coherence Tomography Parameters				
NFL Inferior Quadrant (μm)	10 μm thinner	1.15	0.020	0.585
NFL-FLV (%)	5% higher	1.46	0.002	0.631
GCC Overall (μm)	10 μm thinner	1.29	0.013	0.576
GCC Inferior Hemisphere (μm)	10 μm thinner	1.26	0.006	0.590
GCC-GLV (%)	5% higher	1.18	0.003	0.597
GCC-FLV (%)	5% higher	1.50	<0.001	0.632

Univariate Cox regression analysis. HR = Hazard Ratio; AUC = area under receiver-operating curve; VF = visual field; PSD = pattern standard deviation.

Table 3

Significant Baseline FD-OCT Categorical Variables for Predicting Visual Field Progression

	Classification	Number of Eyes (%)	Hazard Ratio	P-value
NFL Inferior Quadrant (μm)	Borderline	28 (10.1%)	1.18	0.33
	Abnormal	86 (31.1%)	1.25	0.04
NFL-FLV %	Borderline	55 (19.9%)	1.50	0.17
	Abnormal	108 (39.0%)	2.07	0.007
GCC Overall	Borderline	59 (21.3%)	1.39	0.27
	Abnormal	107 (38.6%)	1.86	0.02
GCC Inferior Hemisphere	Borderline	37 (13.4%)	1.52	0.21
	Abnormal	135 (48.7%)	1.88	0.007
GCC-GLV %	Borderline	63 (22.7%)	2.05	0.04
	Abnormal	123 (46.2%)	2.31	0.003
GCC-FLV %	Borderline	34 (12.3%)	2.69	0.007
	Abnormal	149 (53.8%)	3.07	<.0001

Univariate Cox regression analysis.

Table 4

Visual Field Progression Rate Stratified by Baseline Ganglion Cell Complex Status

Baseline GCC-FLV	VFI Slope
Normal	-0.03% $\pm$ 1.27% (N= 64)
Borderline	-0.20% $\pm$ 1.03% (N=25)
Abnormal	-0.43% $\pm$ 1.56% (N=109)

The visual field index (VFI) slopes are calculated only for eyes with 6 visits. The rates are significantly ($p < 0.001$) different for the 3 groups stratified by macular ganglion cell complex-focal loss volume (GCC-FLV).

Table 5

Glaucoma Composite Progression Index Based on Multivariate Cox Regression Model

	Unit	Coefficient	Hazard Ratio	P-value
Age	10 years older	0.21	1.24	0.047
Central Corneal Thickness	20 μm thinner	0.11	1.14	0.049
GCC-FLV	5% higher	0.35	1.42	0.001

The AUC for the Glaucoma Composite Progression Index (GCPI) was 0.653, larger than the AUC for any of the individual variables.

Table 6

Glaucoma Composite Progression Index Quartile and Risk of Visual Field Progression

Quartile	GCPI Range	Actual Progression Proportion	VFI Slope* (per year)
0% – 25%	0.08 – 0.18	15.7%	0.04 ± 1.47
25% – 50%	0.18 – 0.22	27.5%	–0.25 ± 1.45
50% – 75%	0.22 – 0.28	37.7%	–0.22 ± 1.32
75% — 100%	0.28 – 0.54	39.1%	–0.57 ± 1.42

Perimetric glaucoma eyes were divided into quartiles according to their Glaucoma Composite Progression Index values.

* VFI slope was calculated from eyes with 6 or more visits (N=198)