**Article**

# Correlation Between Enlargement of Retinal Nerve Fiber Defect Angle in En Face Imaging and Visual Field Progression

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**Purpose:** Retinal nerve fiber layer defects (RNFLDs) become enlarged with glaucoma progression. We measured the RNFLD angle and investigated whether it was correlated with deterioration of the visual field in patients with glaucoma.

**Methods:** This study included 84 eyes of 84 patients with open-angle glaucoma (mean deviation [MD] = $-6.51 \pm 5.91$ dB, follow-up period = $2.82 \pm 0.74$ years) with the RNFLDs, who underwent en face swept-source optical coherence tomography (SS-OCT) wide scans ($12 \times 9$ mm) at least 6 times. The RNFLD angle was measured as the intersection between the RNFLD and a circle centered on the disc with a radius half the distance between the disc and the fovea. Slopes for the RNFLD angle, macular ganglion cell layer thickness (GCCT), and circumpapillary RNFL thickness (cpRNFLT) were compared with the MD slope, as measured with the Humphrey field analyzer 24-2 program.

**Results:** The correlation coefficients with MD slope were $-0.67$ for the RNFLD angle slope ($P < 0.001$), 0.15 for the macular GCCT slope ($P = 0.163$), and 0.04 for the cpRNFLT slope ($P = 0.719$). The RNFLD angle tended to increase as the number of disc hemorrhage occurrences increased (rs = 0.31, $P = 0.004$). The RNFLD angle slope also had good predictive power for glaucoma progression (area under the receiver operating characteristic curve = 0.88, 95% confidence interval = 0.81–0.95).

**Conclusions:** We found that the RNFLD angle slope was more closely associated with the MD slope than were other OCT parameters. This suggests that measurement of the RNFLD angle with en face OCT images could be effective in evaluating glaucoma progression.

**Translational Relevance:** Our study provides a method for monitoring glaucoma progression with SS-OCT.

## Introduction

Glaucoma is an irreversible, chronic cause of visual field (VF) impairment worldwide,[1] and is considered as a multifactorial disease: high intraocular pressure (IOP),[2] age,[3] myopia,[3] low ocular perfusion,[4,5] and oxidative stress.[6,7] These factors are believed to lead to damage of the optic nerve fibers of the retinal ganglion cells (RGCs) at the site of the lamina cribrosa.[8] Clinically, these events can be detected as retinal nerve fiber layer (RNFL) defects (RNFLDs), localized areas of the retina that appear darker than their surroundings. In an aging society, it is important to detect

glaucoma and its progression with high sensitivity and specificity.

VF examination is critical for diagnosis and assessing the progression of glaucoma, however, this type of subjective glaucoma examination has poor reproducibility and accuracy, especially in older patients. Recently, quantitative, objective techniques for using optical coherence topography (OCT) to assess the RNFLDs have been introduced.[9] OCT enables the precise evaluation of changes in various aspects of retinal thickness, such as circumpapillary RNFL (cpRNFL) thickness (cpRNFLT), macular RNFL thickness, and macular ganglion cell complex (GCC) thickness (GCCT). We previously reported that OCT measurements of the papillomacular nerve fiber bundle (PMB), which is located between the optic disc and the macula, are useful to assess visual acuity (VA) in patients with glaucoma.[10–12] OCT is a powerful tool for the detection of early glaucoma, including preperimetric glaucoma, and assessment of its progression.[13]

Swept-source OCT (SS-OCT), with its long wavelength of 1050 nm, provides higher resolution images and allows more detailed analysis of retinal structure than spectral-domain OCT (SD-OCT).[14] SS-OCT also has a faster imaging speed, providing images with good reproducibility and accuracy.[15] This improvement has made it possible to obtain high quality en face OCT images, which represent a flattened view of the internal limiting membrane (ILM), with the brightness of the ILM superimposed over the deeper layers. These images enable us to observe subtle structural changes in glaucoma.[16,17]

As previously described, RNFLDs are a major diagnostic symptom of glaucoma, and as glaucoma progresses, the RNFLDs become enlarged.[18,19] Many cross-sectional studies have demonstrated the correlation between glaucomatous damage and VF loss.[20,21] However, in terms of progression, the relationship between structure and function is not strong (especially in summary metrics that are widely used in daily practice), a finding that has attracted research interest.[22] Therefore, it is an important goal to establish an objective and effective method of assessing glaucoma progression with OCT.

We previously reported that the RNFLD angle measured in en face OCT images was highly correlated with mean deviation (MD) in patients with glaucoma.[23] Given this result, we hypothesized that measuring the RNFLD angle would also be useful to assess glaucoma progression. In this study, we investigated the extent to which enlargement of the RNFLD was correlated with VF progression and whether the RNFLD angle could be used by itself to assess glaucoma progression. Our results indicate that SS-OCT may be a new method to assess glaucoma progression.

## Material and Methods

### Patients

This study included 84 eyes of 84 patients with primary open-angle glaucoma (POAG) or normal-tension glaucoma (NTG) for whom en face OCT images were available with particularly easy to identify RNFLDs. All patients were recruited at Tohoku University Hospital and underwent at least 6 VF and SS-OCT examinations performed over an observation period of at least 24 months. The exclusion criteria were as follows: axial length more than 28.0 mm, other ocular diseases that might affect retinal thickness or visual function, and ambiguous or difficult-to-identify RNFLDs.

Baseline clinical parameters for each patient were recorded, including sex, age, refractive error, and best-corrected visual acuity (BCVA). IOP was measured with Goldmann applanation tonometry. Central corneal thickness (CCT) was measured with anterior-segment OCT (Casia, Tomey Corporation, Nagoya, Japan). The MD was measured with the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, CA, USA) with the Swedish Interactive Threshold Algorithm (SITA)-standard strategy of the 24-2 program. MD (a logarithmic scale) was converted to 1/Lambert (a linear scale) with the following formula:

$$dB = 10 \times \log_{10}(1/Lambert).$$

Axial length was measured with ocular biometry (IOLMaster; Carl Zeiss Meditec). Medication score was counted as one per component. BCVA was measured with a standard Japanese decimal visual acuity chart and converted to the logarithm of the minimum angle of resolution (logMAR). All the examination data were obtained within a 2-month period, without interrupting the use of medication for glaucoma. Only reliably measured MD values were used (<20% fixation errors, <15% false-positive results, and <33% false-negative results).

Glaucoma was defined in this study by the presence of an abnormal glaucomatous optic disc (with diffuse or focal thinning of the neuroretinal rim) and a corresponding glaucomatous VF defect, defined according to the Anderson-Patella criteria[24] by the presence of one or more of the following: (1) a cluster of three points with reduced sensitivity at a probability of <5% on the pattern deviation map in at least one hemifield (including ≥1 point at a probability of <1% or a cluster of 2 points at a probability of <1%, (2) glaucomatous hemifield test results outside the normal limits, or (3) a pattern standard deviation beyond 95% of normal limits, as confirmed in at least 2 reliable examinations.

For glaucoma progression, three glaucoma specialists (authors T.N., O.K., and N.T.) made a comprehensive, blind decision, referring to IOP, fundus photographs, OCT images, and VF examinations. If our decisions differed, we resolved the difference through discussion.

Each retinal thickness parameter was measured with SS-OCT (DRI OCT Triton, Topcon). Average macular GCCT was measured in 6 × 6 mm macular scans, as well as in quadrant cpRNFLT scans. The RNFLD angle was measured in en face images, averaged from the ILM plane down to 52 μm beneath it. The resulting slab was thick enough to assess glaucomatous damage on the relatively thinner temporal side of the disc. If the slab had been any thicker, it would have reached the ganglion cell layer (GCL) and reduced the clarity of the en face image by increasing the noise level.[16] The en face images were created from 12 × 9 mm OCT wide scans, which were obtained at the same time as the other scans. The center of the disc and the fovea were aligned for each patient to measure RNFLD angle consistently. For the measurement of the RNFLD angle, we adopted the same method as we reported previously.[23] Briefly, the RNFLD angle was defined as the intersection between the RNFLD and a circle centered on the disc having a radius half the distance between the disc and the fovea (Supplementary Fig.). If there was more than one RNFLD, all were added together.

## Analysis

Continuous clinical variables ware compared with the Wilcoxon rank sum test and categorical clinical variables were compared with the chi-squared test. For each measurement parameter, the first measurement was set as the baseline and subsequent changes were converted into slopes: the cpRNFLT slope, the macular GCCT slope, and the RNFLD angle slope. We analyzed the association between each slope and other clinical measurements with Spearman's rank correlation coefficient. Spearman's correlation determines the strength and direction of the monotonic relationship between pairs of variables, in contrast to Pearson's correlation, which determines the strength and direction of the linear relationship between pairs of variables. We also used logistic regression analysis to calculate the odds ratio with the 95% confidence interval (CI) and evaluated the discrimination between the progressive glaucoma group and the nonprogressive glaucoma group with the area under the receiver operating curve (ROC-AUC). The analyses used JMP software (version 14.3.0; SAS Institute Japan Inc., Tokyo, Japan) and R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).
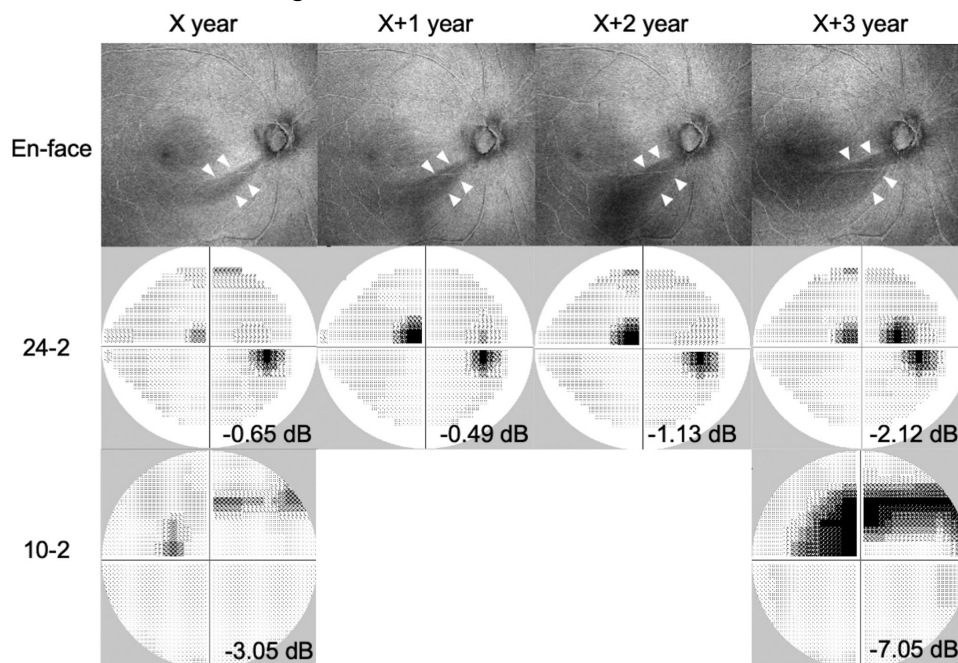
This study adhered to the tenets of the Declaration of Helsinki and the protocols were approved by the Clinical Research Ethics Committee of the Tohoku University Graduate School of Medicine (study 2020-1-455).

## Results

Figure 1 shows a representative glaucoma case. The RNFLD was located in the lower temporal optic disc



**Figure 1.** Representative case. The retinal nerve fiber layer defect (RNFLD) gradually became enlarged, resulting in visual field progression.

**Table 1.** Patient Characteristics

| | Non Progressive | | Progressive | | |
|---|---|---|---|---|---|
| | Mean | ±SD | Mean | ±SD | *P* Value |
| No. of eyes | 47 | | 37 | | |
| Types of glaucoma (POAG/NTG) | 11/36 | | 10/27 | | 0.704 |
| Age, y | 59.02 | 10.83 | 63.97 | 10.34 | 0.040 |
| Sex (male/female) | 18/29 | | 14/23 | | 0.966 |
| BCVA (logMAR) | −0.06 | 0.12 | −0.06 | 0.18 | 0.474 |
| Axial length (mm) | 24.85 | 1.32 | 24.74 | 1.47 | 0.728 |
| CCT (μm) | 512.36 | 29.53 | 509.95 | 36.20 | 0.598 |
| DH within the period (eyes) | 9 | | 17 | | 0.008 |
| Base line | | | | | |
| IOP (mm Hg) | 14.15 | 3.31 | 13.36 | 3.19 | 0.306 |
| MD (dB) | −6.45 | 6.06 | −6.57 | 5.79 | 0.712 |
| 1/Lambert (m$^2$/cd) | 0.41 | 0.34 | 0.37 | 0.28 | 0.711 |
| cpRNFLT (μm) | 76.04 | 11.86 | 75.25 | 11.43 | 0.957 |
| Macular GCCT (μm) | 83.14 | 10.87 | 81.98 | 10.66 | 0.379 |
| RNFLD angle (degree) | 39.55 | 30.47 | 38.22 | 27.49 | 0.835 |
| Medication score (*n*) | 2.41 | 1.36 | 3.05 | 1.25 | 0.039 |
| End point | | | | | |
| IOP (mm Hg) | 12.68 | 3.04 | 13.49 | 3.56 | 0.337 |
| MD (dB) | −6.55 | 6.10 | −8.37 | 6.37 | 0.127 |
| 1/Lambert (m$^2$/cd) | 0.40 | 0.34 | 0.29 | 0.28 | 0.127 |
| cpRNFLT (μm) | 74.24 | 10.94 | 70.85 | 10.02 | 0.284 |
| Macular GCCT (μm) | 81.59 | 10.06 | 79.21 | 9.72 | 0.183 |
| RNFLD angle (degree) | 41.34 | 30.19 | 45.27 | 28.91 | 0.483 |
| Medication score (*n*) | 2.89 | 1.25 | 3.49 | 1.22 | 0.032 |
| Slopes | | | | | |
| MD slope (dB/y) | 0.05 | 0.33 | −0.68 | 0.48 | <0.001 |
| 1/Lambert slope (m$^2$/cd/y) | 0.01 | 0.04 | −0.03 | 0.05 | <0.001 |
| cpRNFLT slope (μm/y) | −1.03 | 1.30 | −1.69 | 1.67 | 0.047 |
| Macular GCCT slope (μm/y) | −0.50 | 0.92 | −1.24 | 1.43 | 0.004 |
| RNFLD angle slope (degree/y) | 0.67 | 0.74 | 2.56 | 1.71 | <0.001 |

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; CCT, central corneal thickness; DH, disc hemorrhage; IOP, intraocular pressure; MD, mean deviation; cpRNFLT, circumpapillary retinal nerve fiber layer thickness; GCCT, ganglion cell complex thickness; RNFLD, retinal nerve fiber layer defect.

and gradually grew larger, resulting in VF progression. Table 1 shows the systemic characteristics of the subjects. The average follow-up period was $2.82 \pm 0.74$ years. There was a significant difference between the progressive and nonprogressive groups in age ($P = 0.040$), disc hemorrhage (DH; $P = 0.008$), baseline medication score (0.039), end point medication score ($P = 0.032$), MD slope ($P < 0.001$), cpRNFLT slope ($P = 0.047$), macular GCCT slope ($P = 0.004$), and RNFLD angle slope ($P < 0.001$). The root mean square residuals (RMSRs) of MD, 1/Lambert, cpRNFLT, macular GCCT, and RNFLD angle were 0.89 dB, 0.07 m$^2$/cd, 2.13 μm, 1.37 μm, and 1.44 degrees, respectively.

**Table 2.** Correlation Between Visual Field Mean Deviation and Other Parameters

| | Non Progressive | | Progressive | |
|---|---|---|---|---|
| | rs | *P* Value | rs | *P* Value |
| BCVA (logMAR) | −0.14 | 0.336 | −0.41 | 0.013 |
| CCT | 0.10 | 0.516 | 0.47 | 0.003 |
| Axial length | −0.23 | 0.116 | −0.01 | 0.948 |
| cpRNFLT | 0.59 | <0.001 | 0.72 | <0.001 |
| Macular GCCT | 0.41 | 0.004 | 0.47 | 0.003 |
| RNFLD angle | −0.66 | <0.001 | −0.80 | <0.001 |

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; CCT, central corneal thickness; cpRNFLT, circumpapillary retinal nerve fiber layer thickness; GCCT, ganglion cell complex thickness; RNFLD, retinal nerve fiber layer defect.
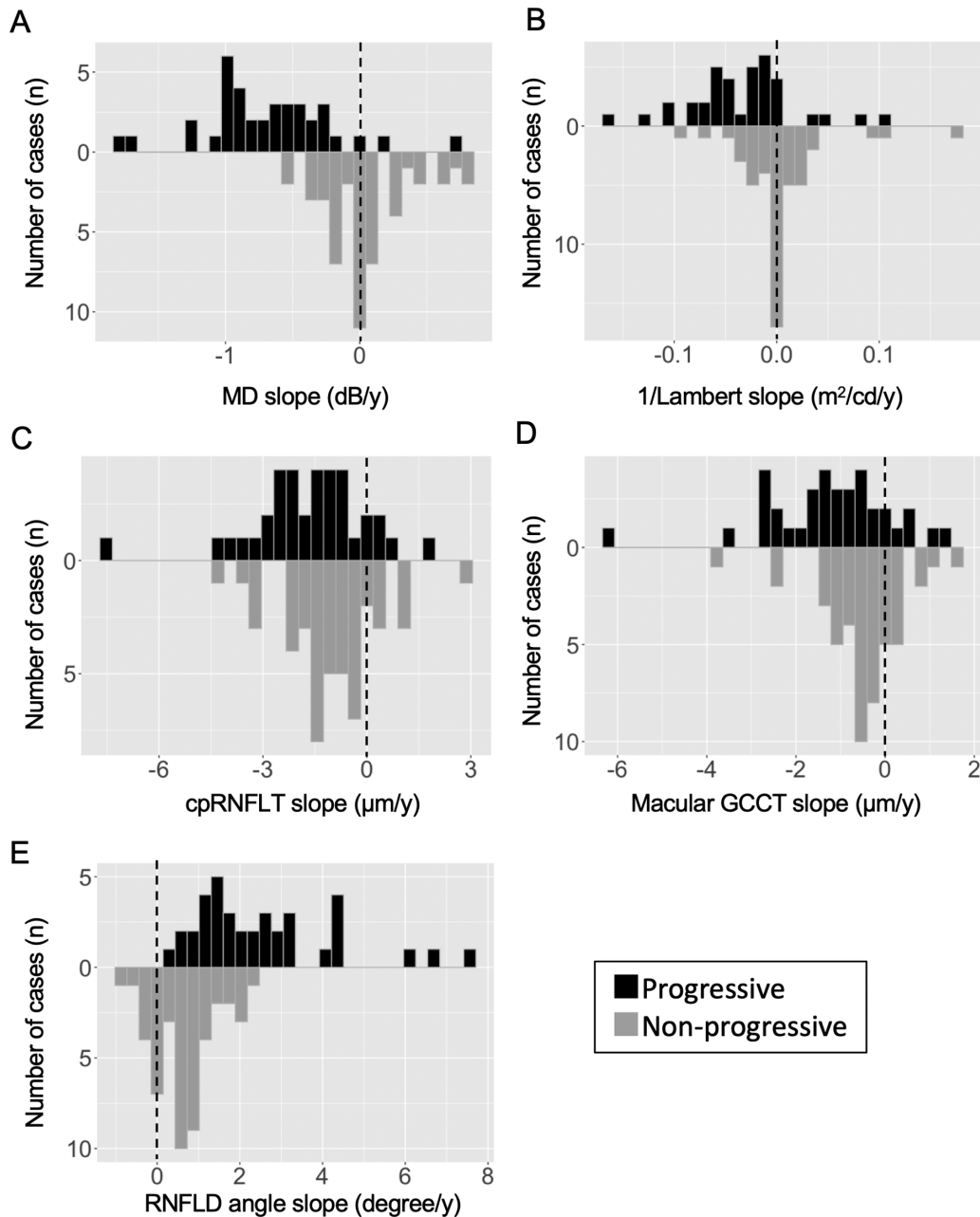
**Figure 2.** Histograms of each slope. (**A**) Mean deviation (MD) slope, (**B**) 1/Lambert slope, (**C**) circumpapillary retinal nerve fiber layer thickness (cpRNFLT) slope, (**D**) macular ganglion cell complex thickness (GCCT) slope, and (**E**) retinal nerve fiber layer defect (RNFLD) angle slope. The *black bar* and the *gray bar* show glaucoma progressive and nonprogressive groups, respectively.

Table 2 shows the results of a cross-sectional analysis of the correlation coefficient between the MD and other parameters in the nonprogressive and progressive groups. In the nonprogressive group, there were significant correlations with cpRNFLT ($rs = 0.59$, $P < 0.001$), macular GCCT ($rs = 0.41$, $P = 0.004$), and RNFLD angle ($rs = -0.66$, $P < 0.001$). In the progressive group, there were significant correlations with the CCT ($rs = 0.47$, $P = 0.003$), cpRNFLT ($rs = 0.72$, $P < 0.001$), macular GCCT ($rs = 0.47$, $P = 0.003$), and RNFLD angle ($rs = -0.80$, $P < 0.001$).

Figure 2 shows histograms for each slope, including MD, 1/Lambert, cpRNFLT, GCCT, and RNFLD angle in the nonprogressive and progressive groups. Overall, as Table 1 shows, deterioration tended to be faster in the progressive group, especially in the MD slope and RNFLD angle slope.

Next, we investigated the correlation between the 1/Lambert and MD slopes and other slopes. An overall
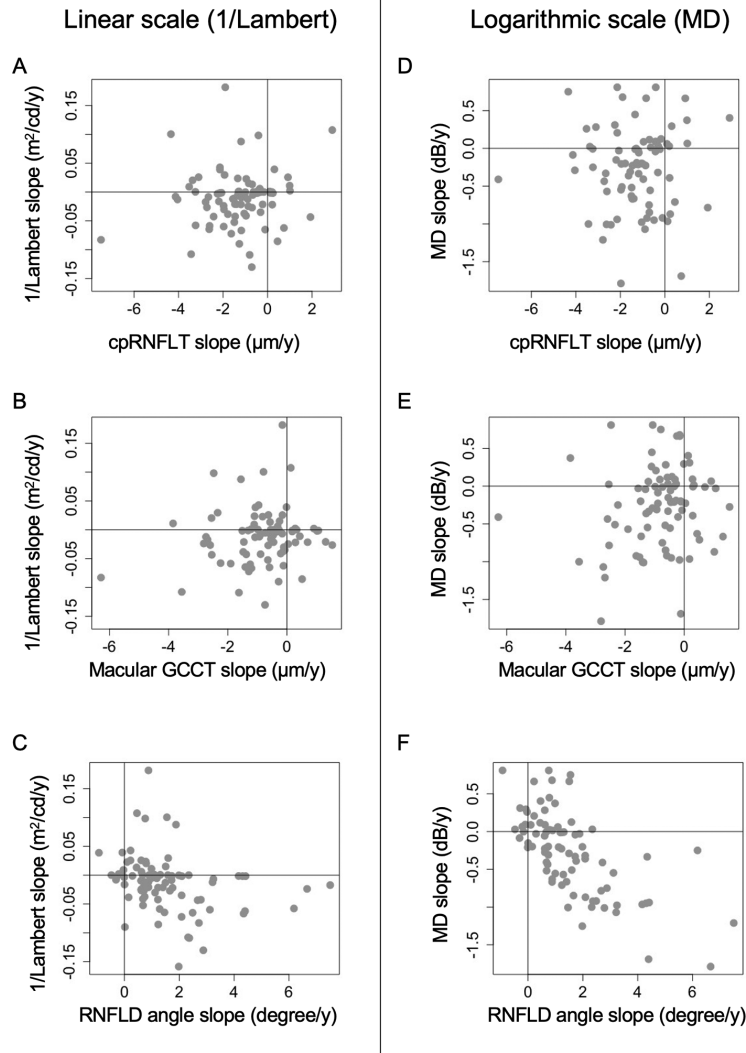
**Figure 3.** Scatter plot showing the relationship between visual field slopes and each parameter. *Left column*: Linear scale; *right column*: logarithmic scale. (**A, D**) circumpapillary retinal nerve fiber layer thickness (cpRNFLT) slope, (**B, E**) macular ganglion cell complex thickness (GCCT) slope, and (**C, F**) retinal nerve fiber layer defect (RNFLD) angle slope.

comparison showed that the RNFLD angle slope was significantly correlated with both the 1/Lambert and MD slopes (1/Lambert slope: rs = −0.43, $P < 0.001$ and MD slope: rs = −0.67, $P < 0.001$), whereas the cpRNFLT slope (1/Lambert slope: rs = 0.12, $P = 0.297$ and MD slope: rs = 0.04, $P = 0.719$) and macular GCCT slope (1/Lambert slope: rs = 0.13, $P = 0.237$ and MD slope: rs = 0.15, $P = 0.163$) were not. We also divided the subjects into mild (MD $\geq$ −6 dB) and moderate/severe (MD < −6 dB) glaucoma groups. Only the RNFLD angle slope showed a trend toward a significant correlation with the visual field slope, and this did not differ with glaucoma stage (Fig. 3, Table 3).

We also examined the number of occurrences of DH during the study period and investigated the correlation with the cpRNFLT slope, macular GCCT slope, and RNFLD angle slope (Fig. 4). Of 26 eyes with

**Table 3.** Correlation Between Visual Field Mean Deviation Slope and Other Slopes

| | 1/Lambert Slope | | MD Slope | |
|---|---|---|---|---|
| | rs | *P* Value | rs | *P* Value |
| cpRNFLT slope | | | | |
|   Overall | 0.12 | 0.297 | 0.04 | 0.719 |
|   Mild stage | 0.05 | 0.743 | −0.01 | 0.979 |
|   Moderate/sever stage | 0.30 | 0.088 | 0.11 | 0.542 |
| Macular GCCT slope | | | | |
|   Overall | 0.13 | 0.237 | 0.15 | 0.163 |
|   Mild stage | 0.19 | 0.194 | 0.22 | 0.120 |
|   Moderate/severe stage | 0.09 | 0.626 | 0.08 | 0.635 |
| RNFLD angle slope | | | | |
|   Overall | −0.43 | <0.001 | −0.67 | <0.001 |
|   Mild stage | −0.53 | <0.001 | −0.62 | <0.001 |
|   Moderate/severe stage | −0.49 | 0.003 | −0.74 | <0.001 |

cpRNFLT, circumpapillary retinal nerve fiber layer thickness; GCCT, ganglion cell complex thickness; RNFLD, retinal nerve fiber layer defect; Mild, mean deviation (MD) $\geq$−6dB; moderate/severe, MD <−6dB.
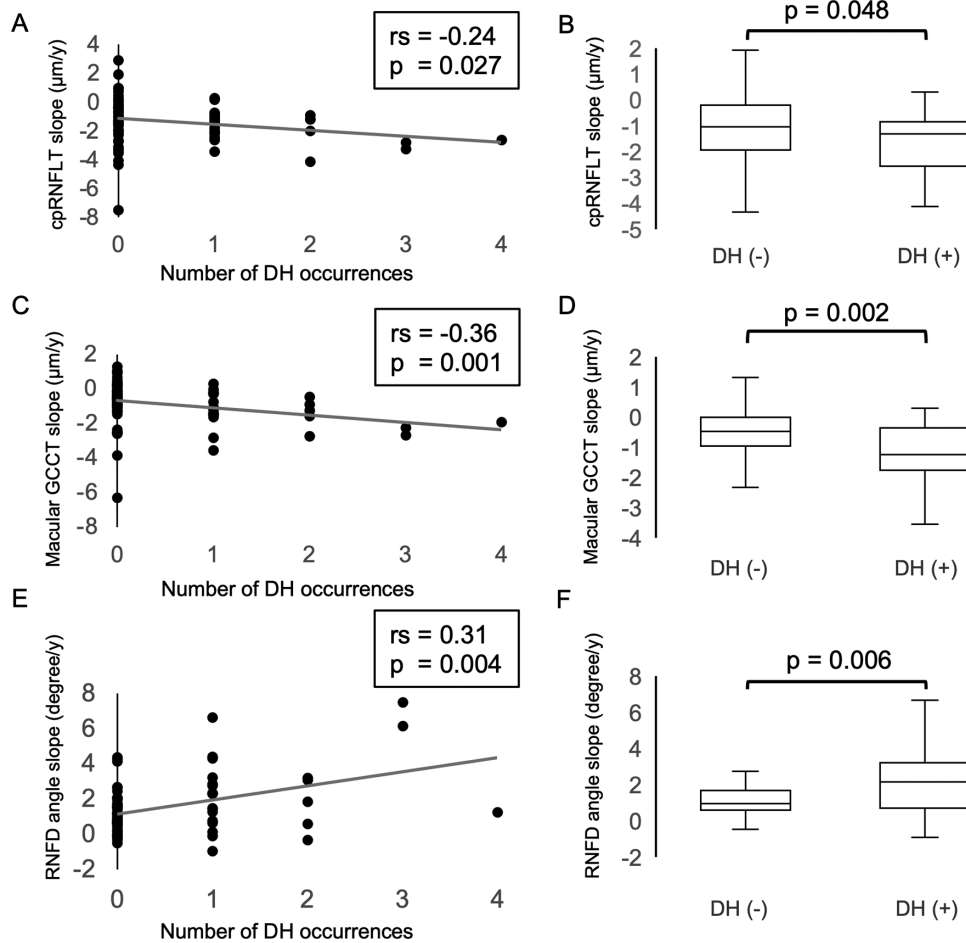
**Figure 4.** *Left column*: Relationship between number of occurrences of disc hemorrhage (DH) and each slope. (**A**) Circumpapillary retinal nerve fiber layer thickness (cpRNFLT) slope; rs = −0.24, *P* = 0.027, (**C**) macular ganglion cell complex thickness (GCCT) slope; rs = −0.36, *P* = 0.001, and (**E**) retinal nerve fiber layer defect (RNFLD) angle slope; rs = 0.31, *P* = 0.004. *Right column*: Relationship between presence and absence of DH occurrence during follow up (**B**) cpRNFLT slope; *P* = 0.048, (**D**) macular GCCT slope; *P* = 0.002 and (**F**) RNFLD angle slope; *P* = 0.006.

**Table 4.** Odds Ratio and Area Under the Receiver Operating Curve (ROC-AUC) to Predict Visual Field Progression

|  | Odds Ratio | 95% CI | *P* Value | ROC-AUC | 95% CI |
|---|---|---|---|---|---|
| **cpRNFLT slope** | | | | | |
| Overall | 0.80 | 0.60–1.04 | 0.121 | 0.62 | 0.50–0.74 |
| Mild stage | 0.83 | 0.59–1.12 | 0.249 | 0.63 | 0.47–0.79 |
| Moderate/severe stage | 0.71 | 0.38–1.24 | 0.240 | 0.62 | 0.43–0.82 |
| **Macular GCCT slope** | | | | | |
| Overall | 0.76 | 0.51–1.04 | 0.119 | 0.67 | 0.54–0.79 |
| Mild stage | 0.72 | 0.42–1.07 | 0.160 | 0.74 | 0.59–0.89 |
| Moderate/severe stage | 0.82 | 0.43–1.50 | 0.523 | 0.56 | 0.35–0.77 |
| **RNFLD angle slope** | | | | | |
| Overall | 6.26 | 3.03–16.07 | <0.001 | 0.88 | 0.81–0.95 |
| Mild stage | 6.94 | 2.72–24.50 | <0.001 | 0.87 | 0.77–0.97 |
| Moderate/severe stage | 5.59 | 2.09–31.22 | 0.010 | 0.90 | 0.80–0.99 |

CI, confidence interval; cpRNFLT, circumpapillary retinal nerve fiber layer thickness; GCCT, ganglion cell complex thickness; RNFLD, retinal nerve fiber layer defect; Mild, mean deviation (MD) $\geqq$−6dB; moderate/severe, MD <−6dB.

DH, 18 eyes (69.2%) had only one occurrence of DH, whereas 8 eyes (30.8%) had multiple occurrences. As the number of DH occurrences increased, all slopes tended to worsen: cpRNFLT slope (rs = −0.24, $P$ = 0.027), macular GCCT slope (rs = −0.36, $P$ = 0.001), and RNFLD angle slope (rs = 0.31, $P$ = 0.004).

We performed a logistic regression analysis (Table 4). Overall, the RNFLD angle slope showed a good ability to predict progression (ROC-AUC = 0.88, 95% CI = 0.81 − 0.95), whereas the cpRNFLT slope and macular GCCT slope did not (ROC-AUC = 0.62 and 0.67, 95% CI = 0.50 – 0.74 and 0.54 – 0.79).

## Discussion

In the current study, we set up a method to assess RNFLD angle in en face OCT wide scans. We investigated the usefulness of this method to measure and predict glaucoma progression and compared it with the traditional parameters, the cpRNFLT and macula GCCT. We found that a widening RNFLD angle predicted glaucomatous structural progression in patients with DH, and, interestingly, that the RNFLD angle slope was highly correlated with the MD slope (rs = −0.67, $P$ < 0.001), but not the cpRNFLT slope or the macular GCCT slope. The AUC for glaucoma progression of the RNFLD angle slope was 0.88, with an odds ratio of 6.26 ($P$ < 0.001). These results suggest that the RNFLD angle may be useful for monitoring glaucoma progression. In daily clinical practice, we sometimes encounter patients who cannot easily complete subjective VF examinations, such as those with dementia, intellectual disabilities, or an inability to focus on the test. Measurement of the RNFLD angle is performed objectively and would thus be advantageous in these situations.

In the current study, we decided to assess glaucoma progression according to expert opinion. It is important to acknowledge that there is no gold standard in glaucoma studies, because there is no universally accepted definition of glaucoma progression. Guided progression analysis (GPA) of the VF, which is a common and widespread method, is affected by many false positive errors over time.[25] In addition, GPA can be affected by false negatives and miss progression, most frequently fast focal progressive damage.[26] Although clinical judgments are subjective compared to GPA, clinicians make their own judgments every day, and these judgments are the most clinically relevant measure.

To our knowledge, there are few reports on measuring the RNFLD angle in en face OCT images as a method of assessing glaucoma progression. We previously developed software to measure the RNFLD angle in en face OCT wide scans, and found that there was a high correlation coefficient between the RNFLD angle and MD.[23] Although the RNFLD angle can be slightly affected by head position and rotation, we consider that because of its low RMSR, this method had good reproducibility. Nitta et al. reported that the average increase in the RNFLD angle in red-free fundus photographs was 1.7 degrees/year in the early and moderate stages of NTG.[18] This result was similar to the current en face image-based results. Although we did not include a comparison with red-free fundus photography in this study, en face images have the advantage of making it easy to distinguish RNFLDs even when conditions such as myopia make them difficult to detect in fundus photography.

A significant body of evidence suggests that there are strong associations between structure and function in cross-sectional analyses,[20,21] however, the structure and function relationship is not considered strong enough for the evaluation of glaucoma progression.[25] Our results for cpRNFLT and macular GCCT were consistent with these reports, but we found that the RNFLD angle had a stronger association with VF progression. There are three factors that might explain this. First, the loss of cpRNFLT and macular GCCT generally precedes VF progression, as has been widely reported.[13,22,26] Second, as we previously reported, the correlation between cpRNFLT and MD is affected by optic disc type, as classified according to Nicolela et al.'s system.[27] Disc type affects whether structural damage is diffuse or local, and, in our previous report, we confirmed that this affected the structure-function relationship. Third, the macular map reflects only the central 10 degrees of the VF.[28] Compared to the cpRNFLT and macular GCCT, which are difficult to measure precisely enough to reveal small changes, the RNFLD angle is measured in very small units (in single degrees), which makes it possible for measurements of the RNFLD angle to reveal VF progression with high sensitivity. This means that the RNFLD angle can detect localized progression that corresponds to VF deterioration. We consider that these factors may explain the strong correlation we found between the RNFLD slope and MD slope. Contrary to previous methods, our method has the potential to assess VF progression independently of subjective methods. Leung et al.[9] reported that 85.7% of eyes with glaucoma show a widening RNFL progression pattern, so it is reasonable to focus on the RNFLD angle as a diagnostic parameter.

We saw some cases in which progression was not apparent in the results of HFA 24-2, which is

commonly used in daily practice, but was apparent in RNFLD angle. Figure 1 shows a representative case of mild open-angle glaucoma that might help understand this finding. In this case, the RNFLD angle was clearly expanding, even though HFA 24-2 findings showed only gradual VF progression. However, HFA 10-2 revealed that central VF progression was significant. This case illustrates that in mild glaucoma, it is difficult to assess progression with HFA 24-2, which tests at 6-degree intervals. This shortcoming of the HFA 24-2 program has previously been noted by Hood.[21] Therefore, the RNFLD angle may be more sensitive than the general VF examination to identify VF progression.

Many reports have found that DH is a strong risk factor for glaucoma progression. Kim et al.[29] reported that RNFL thickness decreased after the appearance of a DH (i.e. they found that DH was an indicator of glaucoma progression). The present study also found that DH was related to glaucoma deterioration, and that as the number of DH occurrences increased, glaucoma worsened more quickly. This tendency was confirmed for all the slopes we examined: cpRNFLT slope, macular GCCT slope, and RNFLD angle slope. The RNFLD angle slope had a very similar relationship to DH as the other slopes. Thus, our results were consistent with previous reports that DH is a risk factor for glaucomatous structural progression.

We acknowledge that there were several limitations in this study. First, it had a small number of patients and used a retrospective design with participants of a single ethnicity. A second limitation was a relatively short observation period for glaucoma, which is a disease with a long, chronic course. Third, OCT parameters are affected by patient data. In particular, myopic enlargement causes thinning of the retina. This had the potential to introduce bias, so we excluded patients with high myopia (axial length <28.0 mm). OCT parameters are also affected by image quality (IQ); low-IQ images make it too difficult to measure retinal thickness and RNFLD angle. To prevent this issue, we also excluded images with IQ of less than 30, which was recommended by the manufacturer of the OCT device. Fourth, we only evaluated a single aspect of RNFLDs, their angle, even though they have a complex, three-dimensional structure. In the future, we hope technological innovation will allow us to evaluate other aspects of RNFLDs. Fifth, MD is a logarithmic scale and cannot be analyzed by a simple linear regression of OCT parameters.[30] According to Bhattacharya et al.,[31] the relationship between neuroretinal rim area and perimetric measures is not always linear or curvilinear, and the results are influenced by the composi-

tion of the sample and by the statistical method of analysis. Therefore, the present study was conducted using the Spearman's correlation coefficient, which can be applied to both linear and nonlinear lines as long as they are monotonic. Our results showed that the correlation with RNFLD angle was good for both logarithmic (MD) and linear (1/Lambert) scales; this did not affect the results. It is particularly interesting that the correlation with the MD slope, which is widely used in clinical practice, was high. We believe that our finding of this correlation with visual field progression will open up new possibilities for OCT examination.

In conclusion, the RNFLD angle slope, measured with SS-OCT, was highly correlated with the MD slope and could be used to accurately detect VF progression. It has previously been believed that the relationship between structure and function is strong in cross-sectional evaluations of glaucoma, but not strong enough for the evaluation of VF progression. Here, we found that there was a high correlation coefficient between the RNFLD angle slope and the MD slope, suggesting that this structural parameter should be useful to assess the progression of glaucoma. In addition, because OCT can be used to evaluate structural changes objectively, it might be possible to use it in animal studies, such as those based on monkeys. Normally, it is difficult to assess disease progression in these models. Our proposed technique can detect glaucoma deterioration with high sensitivity and reflects VF progression, suggesting that it may contribute to improving the quality of glaucoma treatment.

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