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Regression Analysis of Optical Coherence Tomography Disc Variables for Glaucoma Diagnosis

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Abstract

Purpose—To report diagnostic accuracy of optical coherence tomography (OCT) disc variables using both time-domain (TD) and Fourier-domain (FD) OCT, and to improve the use of OCT disc variable measurements for glaucoma diagnosis via regression analyses that adjust for optic disc size and axial length-based magnification error

Design—Observational, cross-sectional

Participants—180 normal eyes of 112 participants and 180 eyes of 138 participants with perimetric glaucoma from the Advanced Imaging for Glaucoma (AIG) Study

Methods—Diagnostic variables evaluated from TD-OCT and FD-OCT were: disc area, rim area, rim volume, optic nerve head volume, vertical cup-to-disc ratio (CDR), and horizontal CDR.

These were compared to overall retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC). Regression analyses were performed that corrected for optic disc size and axial length. Area-under-receiver-operating curves (AUROC) were used to assess diagnostic accuracy before and after the adjustments. An index based on multiple logistic regression that combined

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optic disc variables with axial length was also explored with the aim of improving diagnostic accuracy of disc variables.

Main Outcome Measure—Comparison of diagnostic accuracy of disc variables, as measured by area-under-receiver operating curves

Results—The unadjusted disc variables with the highest diagnostic accuracies were: rim volume for TD-OCT (AUROC=0.864) and vertical CDR (AUROC=0.874) for FD-OCT. Magnification correction significantly worsened diagnostic accuracy for rim variables, and while optic disc size adjustments partially restored diagnostic accuracy, the adjusted AUROCs were still lower. Axial length adjustments to disc variables in the form of multiple logistic regression indices led to a slight but insignificant improvement in diagnostic accuracy.

Conclusions—Our various regression approaches were not able to significantly improve disc-based OCT glaucoma diagnosis. However, disc rim area and vertical CDR had very high diagnostic accuracy, and these disc variables can serve to complement additional OCT measurements for diagnosis of glaucoma.

Introduction

Glaucomatous optic neuropathy is characterized by progressive loss of retinal ganglion cells and axons with corresponding visual field defects. Once clinicians identify the disease, they can slow its progression by implementing intraocular pressure reduction therapies. Structural damage to the optic nerve head and retinal nerve fiber layer may precede detectable glaucomatous visual field abnormalities.¹ The Ocular Hypertension Treatment Study reported that disc change was detected earlier than visual field defects in more than half of those patients who were eventually diagnosed with glaucoma.² Medeiros et al. recently reported that significant retinal ganglion cell loss occurs prior to the earliest detectable visual field loss in glaucoma patients.³ Refining the use of imaging modalities that can accurately identify the onset of early glaucomatous nerve damage could greatly improve a clinician's ability to begin preventative therapies that reduce the risk of blindness.

Optical coherence tomography (OCT) uses low-coherence interferometry to measure time-of-flight delay of backscattering light and thus determines the depth of reflections from retinal layers. The result is high-resolution, cross-sectional images that have greatly improved the diagnosis and management of several retinal and optic nerve diseases.⁴ OCT has been widely used to measure retinal nerve fiber layer (RNFL) thickness as a means of diagnosing and monitoring the progression of glaucoma.⁵ However, it is important to recognize that RNFL thinning is present in all optic neuropathies⁶, and thus RNFL measurements are not as specific to glaucomatous optic neuropathy as disc measurements that aim to quantify “cupping”. Additionally, while OCT RNFL thickness has been clinically useful, it still misses some perimetric glaucoma cases. For example, the sensitivity of global RNFL thickness by various spectral-domain OCTs have been reported as 62.1–65.6% at a fixed specificity of 95%,⁷ so improving our use of optic disc topographic variables such as cup and rim measurements may complement RNFL thickness and further improve our diagnostic abilities.

In this study, we report the diagnostic accuracy of OCT disc variables of both time-domain (TD) and Fourier-domain (FD) OCT, using age-matched subjects from the Advanced Imaging for Glaucoma (AIG) Study. We also aimed to improve the use of OCT optic disc variable measurements for the diagnosis of glaucoma via regression analyses that adjusted for (1) optic disc size and (2) axial length-based magnification error. The justification for these adjustments is as follows. (1) It is well known that normal patients with larger optic disc size also have greater optic nerve cup and rim measurements.^{8–12} Wollstein et al. developed a linear regression model (known as the “Moorefield’s Regression Analysis”) for optic disc rim and cup measurements from the confocal laser scanning ophthalmoscope (cSLO, specifically the Heidelberg Retina Tomograph, or HRT, by Heidelberg Engineering) that adjusted for optic disc size variation and thus improved the diagnostic accuracy of cSLO in detection of early glaucoma cases.⁸ This adjustment was explored for OCT topographic disc variables in this study. (2) Huang et al. have previously shown that axial length variation causes magnification errors that account for the observed relationship among normal subjects of increased (apparent) disc size and increased overall RNFL thickness, and, in fact, there is no significant association between true optic disc area and overall RNFL thickness.¹³ Based on these prior findings, in addition to reporting unadjusted diagnostic accuracies of OCT disc variables, we investigated whether taking axial length and optic disc size into account could improve the diagnostic accuracy further.

Methods

Clinical Procedures and Definitions

The detailed methodology for the Advanced Imaging for Glaucoma (AIG) Study have previously been reported in full. [Le P, Francis B, Zhang X, et al. Advanced Imaging for Glaucoma (AIG) Study: design, baseline characteristics, and inter-site comparison. Submitted to *Ophthalmology*.] Briefly, written informed consent was obtained from all participants, and institutional review board (IRB) approval was obtained from all participating institutions. The described study is HIPAA compliant and adheres to the tenets of the Declaration of Helsinki. The AIG Study is a prospective longitudinal trial that began enrollment in 2004, and data from the baseline visits were used in the present investigation.

Participants were between the ages of 40 and 79. The complete inclusion and exclusion criteria are listed in the AIG Study Manual of Procedures posted on www.AIGStudy.net. Participants were assigned to the normal group if both eyes had intraocular pressure of <21mmHg, a normal Humphrey Swedish Interactive Threshold Algorithm (HVF) 24-2 visual field (defined as having mean deviation [MD], pattern standard deviation [PSD] within 95% limits of the normal reference, and a glaucoma hemifield test within 97% limits), a central corneal thickness >500 microns, an open anterior chamber angle, normal-appearing optic nerve head and retinal nerve fiber layer (RNFL) by ophthalmoscopy, and no history of chronic corticosteroid use or corneal surgery. Participants were classified to the perimetric glaucoma (PG) group if one or more eyes fulfilled criteria for abnormal HVF 24-2 (defined as an abnormal PSD [$P<0.05$] or glaucoma hemifield test [$P<0.01$] in a consistent glaucomatous pattern on 2 qualifying visual fields) and RNFL or optic nerve head abnormality detected on slit-lamp biomicroscopy (defined as diffuse or localized rim

thinning, splinter hemorrhage, a notch in the neuroretinal rim, or a vertical cup-to-disc ratio (CDR) 0.2 more than the fellow eye). Glaucoma staging is reported based on the enhanced Glaucoma Staging System 2, which is based on visual field mean deviation and pattern standard deviation.¹⁴

OCT Measurements

The diagnostic variables evaluated in this study were disc area, rim area, rim volume, optic nerve head volume, vertical cup-to-disc ratio (CDR), and horizontal CDR. Additionally, overall retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC) thickness were measured. These measurements were obtained from experienced photographers who were certified by the AIG Study, and were taken from both time-domain OCT (TD-OCT) and Fourier-domain OCT (FD-OCT). The TD-OCT used in this study was the Stratus OCT (Carl Zeiss Meditech, Inc. Dublin, CA, software version 4.0), which has a scan rate of 400 A-scans/second and 10 micron depth resolution; the FD-OCT used in this study was the RTVue 100 (Optovue Inc, Fremont, CA, software version 6.0), which had a scan rate of 26,000 A-scans/second and 5 micron depth resolution.

For TD-OCT, disc parameters were obtained using the algorithm "Fast Optic Disc Scan", which contained 6 radial lines, 4 millimeters in length, that were centered at the optic disc and were within 30-degree intervals.¹⁵ Inner limiting membrane (ILM) and retinal pigment epithelium (RPE) were detected on each radial line scan. Topographies of ILM and RPE were interpolated from the 6 radial lines. The disc boundary was defined by the two end tips of RPE in the OCT image for each radial line scan, and then a smooth boundary was fit based on the 12 RPE end tips (Figure 1). Similarly, the cup boundary was defined as the two cross points of ILM and a straight-line which was parallel and 150 microns higher than the connection line between the two corresponding RPE end tips. A smoothed boundary was fit for the 12 cross points and used as the cup boundary. Rim was defined as the nerve fiber layer (NFL) between the cup boundary and the disc boundary. Disc area was the area within the disc boundary, while cup area was the area within cup boundary. Rim area was the area between disc boundary and cup boundary. The ratio of the largest cup size and largest disc size in the vertical direction was defined as vertical CDR, while the ratio in the horizontal direction was defined as horizontal CDR. The ratio of cup area and disc area was defined as CDR area.

For TD-OCT, RNFL thickness was obtained using the Fast RNFL thickness scan, which contained 3 repeated circles (D=3.4mm) around the optic disc. RNFL thickness was defined by the distance from inner limited membrane and outer boundary of nerve fiber layer.^{16,17}

For FD-OCT, both disc parameters and RNFL thickness were obtained using the optic nerve head (ONH) scan, which contained 12 radial lines (D=3.4mm) and 13 concentric circles (D=1.3~4.9mm), all centered at the optic disc.¹⁸ The definition of boundaries and parameters were similar to TD-OCT. But the disc boundary was firstly detected on an independent 3D disc scan, which is a volume scan (6mm×6mm) centered on the optic disc. Retinal pigment complex (RPC) end tips were automatically detected and saved as the baseline in 3D disc scan. Retinal pigment complex was the combination of RPE and Bruch membrane. The boundary defined by RPC end tips was equal to Bruch membrane opening

(BMO) in other literature, in which BMO was defined as the innermost edge of Bruch's membrane. BMO may be a better anatomic landmark than RPE tips because BMO is not affected by peripapillary atrophy. The tested ONH scan was registered with the 3D disc scan, and the baseline disc boundary was mapped to the ONH scan as the disc margin. Then the ILM, RNFL, and RPE were detected for each radial line. RPC end tips were determined based on cross points of detected RPC and mapped disc margin. With boundaries and RPC tips, cup, rim, and disc parameters were calculated in the same way in TD-OCT. RNFL thickness map were interpreted using the RNFL thickness profiles from the 13 concentric circles. The NFL thickness map is then re-centered according to the detected disc margin. RNFL thickness profile at D=3.4mm was extracted from the re-centered NFL thickness map.

For FD-OCT, GCC thickness was obtained from a GCC scan, which is a raster scan covering a 7mm×7mm area and centered 1mm temporal to the fovea. GCC thickness is defined as the distance between the ILM and the outer boundary of the inner plexiform layer. A 6mm×6mm GCC thickness map was interpolated from 15 vertical lines and registered by detection of the fovea.¹⁹

Statistical analysis

The area-under-receiver-operator-characteristic curves (AUROC) for diagnostic accuracy of optic disc variables for glaucoma are reported both before and after the various adjustments, described below.

The studied correction formula for axial length-based magnification error is as follows, and was applied to rim area, disc size, rim volume, and FD-OCT ONH volume.¹³

$$A = A_m * (L/L_a)^2$$

- A is the true/adjusted value.
- A_m is the apparent/measured value
- L is the axial length of the eye
- L_a is the average axial length from emmetropic eyes. Emmetropic eyes had a spherical equivalent refraction of -1.00 to +1.00 with no history of cataract surgery, and the average value of axial length of the emmetropic group was 23.6mm.

No magnification correction was warranted for the CDR values because these values represent ratios that are not affected by axial length.

The studied adjustment to disc variables for disc size was applied to rim area, rim volume, FD-OCT ONH volume, horizontal CDR, vertical CDR, and area CDR. It was important that this adjustment be performed after the magnification adjustment.

If Y is the target variable and X is the respective disc size, the adjustment procedure was as follows:

- Perform linear regression of log(Y) on log(X) among normal patients.

- Determine the regression coefficient: $\log(Y) = \beta * \log(X) + \alpha$
- Calculate the average of $\log(X)$ among normal patients.
- The adjusted Y is defined as:
 - o $Y_{adj} = \exp(\log(Y) - \beta * \{\log(X) - \log(X)_{avg}\})$.

An additional axial length adjustment was explored. The magnification – corrected disc variables as well as axial length were included in a multiple logistic regression model through stepwise selection to find the best model consisting of optimal combination of the disc variables. The diagnostic accuracy of the best model was then evaluated by calculating the AUROC using the leave-one-out-cross-validation (LOOCV) method. On each LOOCV run, one subject was left out to serve as the test set; the model was built on the remaining subjects and evaluated on the one-subject test set. The use of LOOCV ensures that model building and evaluation are done on separate data sets, thus reducing evaluation bias. The LOOCV model AUROC was also compared to the AUROCs before and after various adjustments.

When applicable, the statistical analyses were done using the generalized estimating equation method, which adjusted for potential inter-eye correlation. All of the statistical analyses were performed with SAS system 9.2 (SAS Institute Inc., Cary, NC).

Results

180 eyes of 112 participants from the normal group of the AIG Study and 180 glaucomatous eyes of 138 participants from the perimetric glaucoma group of the AIG Study were studied and frequency-matched on age, gender and ethnicity (African American or non-African American). The characteristics of this study population are summarized in Table 1. While there was no significant difference for age, gender, ethnicity, cataract history, or (treated) intraocular pressure, participants with glaucoma had a longer axial length, thinner central corneal thickness, abnormal visual field results, and thinner RNFL and GCC thicknesses. Most of the perimetric glaucoma (PG) subjects were in the earlier stages, with only 21.1% in stages 4 and 5 by the Enhanced Glaucoma Staging System (GSS2). 11.1% of the PG subjects were classified as stage 0 or borderline because they had normal VF MD values but had consistent focal VF damage detected by GHT. 2.2% in the normal group were classified as Stage 1 by GSS2 due to high VF MD, which may have resulted from cataracts and other causes of visual field loss not specific to glaucoma.

After using the mathematical model to correct the disc variables for axial length-based magnification error, univariate linear regression to identify association with disc size were evaluated, and results are shown in Table 2a and 2b. For TD-OCT, rim area, vertical CDR, horizontal CDR, and CDR area were all positively correlated with disc area, but rim volume was not significantly correlated. For FD-OCT, rim area, vertical CDR, horizontal CDR, and CDR area were also positively correlated with disc area, but the rim volume and ONH volume were not significantly correlated with disc area. The linear regression parameters from Table 2 were used for adjustments in later analyses (Tables 3–5).

The OCT disc variables were adjusted for axial length-based magnification error and then disc size adjustment based on our models described above; these results are shown in Table 3. Magnification correction had essentially no effect on the disc rim variables in the normal subjects, but increased the average rim area of glaucoma subjects due to their longer axial lengths. This effect was partially offset by the disc size adjustment, which reduced the average rim area of the glaucoma subjects because they tended to have larger discs. After both magnification and disc size adjustment steps, the contrast between normal and glaucoma groups were essentially unchanged. The CDR variables are not affected by magnification because the magnification applies to both the numerator and denominator of the ratio and cancels out. However, the CDR variables were affected by disc size adjustment, with reduced contrast between glaucoma and normal subjects, because glaucomatous eyes tend to have larger discs.

Following this procedure, the diagnostic accuracies as measured by area-under-the-receiver-operator-curve (AUROC) values were calculated for each of the adjusted disc variables, as shown in Table 4, and these adjusted values were compared to AUROC measurements for the disc variables before the adjustments. For all of the rim variables, magnification correction significantly worsened diagnostic accuracy. Disc size adjustment partially restored diagnostic accuracy for the rim variables, but the AUROC values were still below the original variables. For the CDR variables, disc size adjustment reduced diagnostic accuracy, and the difference was statistically significant for FD-OCT.

Without adjustment (Table 4), the optic disc variable with the highest diagnostic accuracy for TD-OCT was rim volume, with an AUROC of 0.864, followed by rim area (AUROC=0.857), vertical CDR (AUROC=0.855), CDR area (AUROC=0.842), and horizontal CDR (AUROC=0.810). The diagnostic accuracy of the best TD-OCT disc variable, rim volume, was slightly lower than that for the average overall RNFL thickness (AUROC=0.886), but there was no significant difference ($p=0.14$).

For FD-OCT (Table 4), the optic disc variable with the highest diagnostic accuracy was vertical CDR (AUROC=0.874), followed by rim volume (AUROC=0.857), ONH volume (AUROC=0.857), CDR area (AUROC=0.857), rim area (AUROC=0.874), and horizontal CDR (AUROC=0.795). This is compared to an AUROC of 0.893 for overall RNFL thickness, and an AUROC of 0.846 for overall GCC thickness. There was no significant difference between diagnostic accuracy of vertical CDR compared to overall RNFL thickness ($p=0.40$) or overall GCC thickness ($p=0.24$).

In order to better understand the diagnostic thresholds, the one percentile and five percentile cut-off points for each of the disc variables were calculated for the unadjusted values, after magnification correction, and after disc size adjustment (Table 5). Magnification correction raised the diagnostic threshold of rim variables by correcting the predominantly myopic refractive errors, which minified images. Disc size adjustment tended to lower the one and five percentile diagnostic thresholds for CDR, especially for FD-OCT. By adjusting for very low CDR values in small discs, and very high CDR in large discs, disc size adjustment narrowed the range of CDR in the normal group.

Because the linear regression approach above did not improve the diagnostic accuracy of disc variables, we investigated a second approach based on multivariate logistic regression analysis. These took magnification-corrected disc variables as input. Stepwise selection was performed to find the optimal multivariate logistic regression (MLR) model for glaucoma diagnosis. The candidate variables included the disc variables for each OCT device, as well as axial length, rim area, and vertical CDR. For TD-OCT, the optimized model (Table 6) included vertical CDR, rim area, and axial length. For FD-OCT, the model included vertical CDR and axial length.

The MLR approach for both TD-OCT and FD-OCT yielded an optimized Disc Index that did improve diagnostic accuracy (Table 7), but only to a small extent, which was not statistically significantly better than the best unadjusted single disc variables. The TD-OCT Disc Index had an AUROC of 0.866 and diagnostic sensitivity of 62.5% (at 95% specificity), compared to the unadjusted rim volume, which had an AUROC of 0.864 and sensitivity of 65.0%. The FD-OCT Disc Index had an AUROC of 0.881 and sensitivity of 70.0%, compared to vertical CDR, which had an AUROC of 0.874 and sensitivity of 62.2%. The AUROC and sensitivity of the Disc Indices were not significantly different from the overall RNFL thickness variables for both TD-OCT and FD-OCT.

Discussion

To date, overall RNFL thickness is the most widely used OCT variable by glaucoma clinicians. Lu et al. showed that overall RNFL thickness had the highest diagnostic accuracy (AUROC value =0.89) of all single RNFL variables evaluated by the Advanced Imaging for Glaucoma Study.²⁰ Rao et al. compared RNFL, ONH, and macular thickness measurements using the RTVue OCT from the Diagnostic Innovations in Glaucoma Study (DIGS) and reported that RNFL and inner retinal macula thickness measurements performed better than ONH variables at detecting glaucomatous eyes.²¹ Mwanza et al. reported on the ability of various ONH variables and RNFL thickness from the Cirrus HD-OCT to diagnose glaucoma and found no significant difference between the two.²² In this study, we report diagnostic accuracy of ONH variables for TD-OCT and FD-OCT compared to overall RNFL thickness in patients from the AIG Study; and because such previous studies on ONH variables had not considered disc size and/or axial-length based adjustments^{23–25}, as is done with HRT measurements of ONH variables^{8, 26–28}, we explored the impact that these adjustments have on diagnostic accuracy.

The ONH variable with the best diagnostic accuracy was rim area for TD-OCT and vertical CDR for FD-OCT in our study. In both cases, diagnostic accuracies were slightly lower than overall RNFL thickness (for TD-OCT and FD-OCT) and similar to overall GCC thickness (for FD-OCT), with no statistically significant difference detected (Table 4, Figure 2). Our finding that vertical CDR provided the greatest diagnostic accuracy, both on its own and even more so when taking into account axial length, is consistent with previous studies of FD-OCT optic disc variables. Kim et al. recently showed that vertical CDR, as measured by TD-OCT and FD-OCT, exhibits excellent diagnostic agreement with both horizontal CDR measured by OCT, and stereoscopic photography analyzed by glaucoma specialists.²⁹ Lisboa et al. recently used a case control design of pre-perimetric glaucoma patients

compared to normal controls and reported ONH variables with the highest diagnostic accuracies were vertical CDR, rim area, and rim volume for FD-OCT (RTVue).²⁵ This is consistent with findings in this report. The finding that rim area was the best for TD-OCT but vertical CDR was best for FD-OCT is likely due to chance, as the difference between their AUROC values were small. Interestingly, Lisboa et al. reported a statistically significant improvement in diagnostic accuracy with overall RNFL thickness compared to vertical CDR or GCC thickness, which has been supported by a separate study by Huang et al.³⁰ Since the size of these studies are similar, the lack of statistical difference between the diagnostic accuracies of disc and RNFL variables in this study is most likely attributable to differences in subject characteristics.

In our approach to adjust for disc size variation in the disc diagnostic variables, we began with the linear regression approach taken by Wollstein et al. in developing the Moorefield's Regression Analysis for the HRT system.⁸ Our task was more complex because neither the TD or FD-OCT systems compensated for magnification difference between eyes. In contrast, HRT software automatically adjusted for magnification differences by the use of refraction information. Therefore our first step was to correct for magnification effects on the disc size by the use of axial length information. Unfortunately, magnification correction reduced the diagnostic accuracy (AUROC) of disc based variables (Table 4). This is likely because glaucomatous eyes tend to be longer and so the magnification correction served to increase the rim area and volume for glaucomatous eyes. Although the subsequent step of disc size adjustment improved the AUROC for the rim variables, it was not sufficient to compensate for the loss in the magnification correction step. The loss of diagnostic accuracy in the magnification correction step most likely explains why we were not able to demonstrate overall improvement in diagnostic accuracy for rim variables using the linear regression approach, in contrast to the success of the Moorefield's Regression Analysis for the HRT.⁸

In a second approach that utilized MLR to construct optimized disc indices, we were able to improve diagnostic accuracy compared to single disc variables. However, the improvements were not statistically significant, therefore we are not able to recommend the use of the disc indices over the best single disc variables, which were the vertical CDR and rim area. It is interesting to note that the optimized disc indices for both TD-OCT and FD-OCT included the axial length. Presumably this is due to the fact that longer axial length (myopia) is correlated with glaucoma in both our study and other studies.³¹⁻³⁴ Our results show that axial length may be a complementary diagnostic variable that could boost the performance of OCT diagnostic variables when used in regression analysis.

A limitation of the current study is the older method used by the Stratus OCT and RTVue OCT algorithms to measure the disc and cup margins. The disc margin was measured using RPE tips in Stratus OCT and BMO on RTVue OCT, and the cup margin was measured as where the ILM edge bisects a line 150 microns anterior and parallel to the line of RPE/RPC tips on both systems (Figure 1). Recently, Chauhan et al. had developed a newer method to define the disc margin at BMO. They further defined the neuroretinal rim based on the minimal rim width (MRW) from the BMO.³⁵ The BMO-MRW was found to have higher diagnostic accuracy than even RNFL thickness.³⁶ Unfortunately, because the BMO-MRW

parameter is not available with the Optovue RTVue or the Zeiss Stratus software, we are unable to analyze that parameter in this paper. We hypothesize that even if we had measured BMO-MRW, our results that magnification and disc size adjustments not improving diagnostic accuracy would most likely be unchanged, because both BMO-MRW and the older disc rim parameters would be similarly affected by myopia and magnification variation. However it is possible that BMO-MRW would provide better diagnostic accuracy than the disc variables presented here, such as rim area and vertical CDR. Analysis of AIG Study data showed that combining RNFL, GCC, and ONH measurements can improve diagnostic accuracy.³⁷ It is possible that the combined diagnostic index could be further improved by incorporating BMO-MRW.

Although we were not able to significantly improve disc-based OCT glaucoma diagnosis using various regression approaches, our study demonstrated strong diagnostic performance for disc rim area and vertical CDR, which provides preliminary evidence supporting continued interest in disc variables for glaucoma diagnosis. While many optic neuropathies cause RNFL thinning⁶, progressive disc “cupping” is an important diagnostic finding that is most often associated with glaucoma,³⁸ and as discussed above, incorporation of OCT disc measurements is likely to continue to improve our ability to diagnose glaucoma using the OCT. This study further supports the use of disc variables in glaucoma diagnosis, in combination with other diagnostic information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

On each radial line scan, two RPE tips were detected as demonstrated here. Two cup points were also detected where the ILM bisected a line 150 microns anterior to the disc boundary.

Figure 2.

The receiver operating characteristic curve for FD-OCT disc index, vertical CDR, and RNFL thickness from FD-OCT shows similar diagnostic accuracy.

Table 1

Demographic and Ocular Characteristics of the Study Population

	Normal Eyes	Eyes with Perimetric Glaucoma	P-value
	N= 180	N= 180	
Age	59.4 ± 10.1	60.9 ± 9.7	0.11
Female	115 (63.9%)	115 (63.9%)	1
African American Origin	14 (7.8%)	23 (11.9%)	0.28
Cataract Extraction Surgery	11 (6.11%)	11 (6.11%)	1
Axial Length (mm)	23.7 ± 1.0	24.5 ± 1.3	<.001
Central Corneal Thickness (microns)	560 ± 31	544 ± 39	<.001
Intraocular Pressure (mm Hg)	14.7 ± 2.6	14.0 ± 4.0	0.16
Mean Deviation on HVF	−0.1 ± 1.1	−4.7 ± 4.6	<.001
Pattern Standard Deviation on HVF	1.4 ± 0.2	5.7 ± 4.2	<.001
Visual Field Index (%)	99.6 ± 0.5	88.3 ± 13.5	<.001
TD-OCT RNFL Thickness Overall (microns)	99.3 ± 9.9	76.9 ± 15.8	<.001
FD-OCT RNFL Thickness Overall (microns)	99.8 ± 8.0	82.0 ± 12.0	<.001
FD-OCT GCC Thickness Overall (microns)	96.6 ± 7.1	84.2 ± 10.4	<.001
Glaucoma Stage *			
Stage 0	140 (77.8%)	6 (3.3%)	
Borderline	36 (20.0%)	14 (7.8%)	
Stage 1	4 (2.2%)	56 (31.1%)	
Stage 2	0	37 (20.6%)	
Stage 3	0	29 (16.1%)	
Stage 4	0	31 (17.2%)	
Stage 5	0	7 (3.9%)	

Values described are mean ± standard deviation or frequency (percent)

* The glaucoma stage is based on the Enhanced Glaucoma Staging System. HVF = Humphrey Visual Field Standard Automated Perimetry; TD=time-domain; FD=Fourier-domain; OCT=optical coherence tomography; RNFL=retinal nerve fiber layer; GCC=ganglion cell complex

Table 2**a. Linear Regression Parameters for Time-Domain Optical Coherence Tomography (OCT) Disc Variables Against Disc Area**

TD-OCT Parameters	Slope β	P-value	R-Square
Rim Area	0.378	<.001	0.125
Rim Volume	−0.216	0.33	0.0054
Vertical CDR	0.522	<.001	0.089
Horizontal CDR	0.603	<.001	0.113
CDR Area	1.117	<.001	0.105

b. Linear Regression Parameters for Fourier-Domain Optical Coherence Tomography (OCT) Disc Variables Against Disc Area

FD-OCT Parameters	Slope β	P-value	R-Square
Rim Area	0.337	<.001	0.066
Rim Volume	−0.407	0.065	0.019
ONH Volume	−0.327	0.107	0.1
Vertical CDR	0.637	0.001	0.064
Horizontal CDR	0.738	<.001	0.114
CDR Area	1.38	<.001	0.121

TD=time-domain; OCT=optical coherence tomography; FD=Fourier-domain; CDR= cup to disc ratio

Table 3

Disc Variables with Magnification Correction and Disc Size Adjustment

	Original		After Magnification Correction		After Disc Size Adjustment	
	Normal	Glaucoma	Normal	Glaucoma	Normal	Glaucoma
<i>TD-OCT Disc variables</i>						
Disc Size (mm ²)	2.34 ± 0.45	2.43 ± 0.49	2.35 ± 0.43	2.61 ± 0.63	-	-
Rim Area (mm ²)	1.60 ± 0.39	1.04 ± 0.44	1.61 ± 0.38	1.11 ± 0.46	1.64 ± 0.29	1.07 ± 0.43
Rim Volume (mm ³)	0.45 ± 0.31	0.19 ± 0.21	0.45 ± 0.30	0.20 ± 0.22	0.46 ± 0.31	0.20 ± 0.22
ONH Volume (mm ³)	-	-	-	-	-	-
Vertical CDR	0.50 ± 0.14	0.71 ± 0.15	-	-	0.50 ± 0.14	0.68 ± 0.14
Horizontal CDR	0.56 ± 0.17	0.75 ± 0.15	-	-	0.56 ± 0.16	0.71 ± 0.14
CDR Area	0.31 ± 0.17	0.56 ± 0.19	-	-	0.30 ± 0.17	0.50 ± 0.18
<i>FD-OCT Disc Variables</i>						
Disc Size (mm ²)	2.00 ± 0.41	2.10 ± 0.43	2.01 ± 0.40	2.26 ± 0.55	-	-
Rim Area (mm ²)	1.31 ± 0.35	0.81 ± 0.39	1.32 ± 0.34	0.86 ± 0.42	1.31 ± 0.31	0.83 ± 0.38
Rim Volume (mm ³)	0.16 ± 0.09	0.06 ± 0.07	0.16 ± 0.09	0.06 ± 0.07	0.16 ± 0.10	0.07 ± 0.07
ONH Volume (mm ³)	0.30 ± 0.17	0.13 ± 0.12	0.30 ± 0.17	0.14 ± 0.12	0.30 ± 0.17	0.14 ± 0.13
Vertical CDR	0.54 ± 0.18	0.81 ± 0.16	-	-	0.55 ± 0.16	0.76 ± 0.17
Horizontal CDR	0.63 ± 0.21	0.83 ± 0.15	-	-	0.63 ± 0.18	0.77 ± 0.17
CDR Area	0.33 ± 0.17	0.61 ± 0.19	-	-	0.32 ± 0.15	0.53 ± 0.22

TD=time-domain; OCT=optical coherence tomography; FD=Fourier-domain; CDR= cup to disc ratio

Table 4
Area Under the Receiver Operating Characteristic Curve with Magnification Correction and Disc Size Adjustment

	Time Domain OCT			Fourier Domain OCT		
	Original	Magnification Correction	Disc Size Adjustment	Original	Magnification Correction	Disc Size Adjustment
Rim Area (mm ²)	0.857	0.828 (<.001)*	0.863 (.27)	0.855	0.831 (<.01)	0.848 (.30)
Rim Volume (mm ³)	0.864	0.850 (.001)	0.849 (.005)	0.857	0.842 (<.01)	0.837 (<.01)
ONH Volume (mm ³)	-	-	-	0.857	0.840 (<.01)	0.836 (<.01)
Vertical CDR	0.855	-	0.843 (.26)	0.874	-	0.833 (0.02)
Horizontal CDR	0.810	-	0.782 (.04)	0.795	-	0.715 (<.01)
CDR area	0.842	-	0.821 (.09)	0.857	-	0.802 (<.01)
Overall RNFL	0.886	-	-	0.893	-	-
Overall GCC	-	-	-	0.846	-	-

* P-values in the parentheses indicate tests against original

OCT= optical coherence tomography; CDR=cup-to-disc ratio; RNFL=retinal nerve fiber layer; GCC=ganglion cell complex

Table 5

One and Five Percentile Cut-Off Points for Healthy Eyes

	Original		After Magnification Correction		After Disc Size Adjustment	
	1%	5%	1%	5%	1%	5%
TD-OCT Variables						
Disc Size (mm ²)	1.33	1.67	1.41	1.69	-	-
Rim Area (mm ²)	0.98	1.10	1.03	1.11	1.03	1.14
Rim Volume (mm ³)	0.13	0.17	0.13	0.18	0.13	0.18
ONH Volume (mm ³)	-	-	-	-	-	-
Vertical CDR	0.84	0.74	-	-	0.85	0.68
Horizontal CDR	0.96	0.84	-	-	0.89	0.70
CDR Area	0.70	0.58	-	-	0.71	0.49
FD-OCT Variables						
Disc Size (mm ²)	1.32	1.43	1.36	1.48	-	-
Rim Area (mm ²)	0.50	0.85	0.66	0.86	0.63	0.82
Rim Volume (mm ³)	0.03	0.06	0.04	0.05	0.04	0.05
ONH Volume (mm ³)	0.06	0.11	0.09	0.11	0.09	0.11
Vertical CDR	0.90	0.79	-	-	0.86	0.76
Horizontal CDR	0.98	0.90	-	-	0.95	0.88
CDR Area	0.73	0.61	-	-	0.72	0.56

TD=time-domain; OCT=optical coherence tomography; FD=Fourier-domain; ONH=optic nerve head; CDR=cup to disc ratio

Table 6

Optimized Multivariate Logistic Regression Models

		Coefficient	P-value
TD-OCT	Axial Length	0.45	0.001
	Rim Area	−1.14	0.037
	Vertical CDR	6.61	<.001
FD-OCT			
	Axial Length	0.52	<.001
	Vertical CDR	9.1	<.001

TD=time-domain; OCT=optical coherence tomography;
FD=Fourier-domain; CDR= cup to disc ratio

Table 7

Diagnostic Performance of Logistic Regression-Based Disc Indices Compared to Best Single Diagnostic Disc Variables

	AUROC	Sensitivity at 95% Specificity
TD-OCT Disc Index	0.866 (0.825, 0.898)	62.5%
FD-OCT Disc Index	0.881 (0.843, 0.912)	70.0%
TD-OCT Rim Volume	0.864 (0.824, 0.897)	65.0%
FD-OCT Vertical CDR	0.874 (0.837, 0.907)	62.2%
TD-OCT Overall RNFL Thickness	0.885 (0.849, 0.917)	66.7%
FD-OCT Overall RNFL Thickness	0.893 (0.857, 0.923)	61.1%

AUROC= Area-under-receiver-operating-characteristic curve; TD=time-domain; OCT=optical coherence tomography; FD=Fourier-domain; RNFL=retinal nerve fiber layer. Leave-one-out cross validation was used in computing the AUROC of the optimized TD-OCT and FD-OCT Disc Indices.