Published in final edited form as:

J Glaucoma. 2014 ; 23(8): 487–493. doi:10.1097/IJG.0b013e31827b155b.

Diagnostic Specificities of Retinal Nerve Fiber Layer, Optic Nerve Head, and Macular Ganglion Cell-Inner Plexiform Layer Measurements in Myopic Eyes

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Abstract

Purpose—To evaluate and compare the diagnostic specificities of peripapillary retinal nerve fiber layer (RNFL) thickness, macular ganglion cell-inner plexiform layer (GC-IPL) thickness, and optic nerve head (ONH) measurements in non-glaucomatous myopic individuals.

Methods—In a prospective, cross-sectional study, participants underwent a complete ophthalmic examination, a screening automated visual field test, and axial length measurement. The study eye then underwent optic nerve and macular scanning using spectral-domain optical coherence tomography (OCT) instrumentation to determine RNFL thickness, GC-IPL thickness, and ONH measurements. False positive rates for each of the OCT-derived parameters, using pre-defined criteria for an abnormal test, were calculated. Comparative analysis was performed using the McNemar test.

Results—Data from 43 eligible subjects were analyzed. The mean age was 30 ± 6.8 years (range: 22 to 50) with average axial length of 25.26 ± 1.21 mm (range: 23.06 to 29.07) and mean spherical equivalent of -4.50 ± 1.93 diopters (range: -1.00 to -9.00). The false positive rate was higher when using RNFL parameters compared to both ONH (47% vs. 7%, respectively; $P < 0.001$) and GC-IPL (47% vs. 26%, respectively; $P = 0.049$) parameters. The false positive rate was higher when using GC-IPL parameters, compared to ONH parameters (26% vs. 7%, respectively; $P = 0.039$).

Conclusions—Caution should be exercised when relying on OCT-derived RNFL and GC-IPL thickness values to diagnose glaucoma in myopic individuals. OCT-derived ONH parameters perform better than RNFL and GC-IPL parameters and may increase diagnostic specificity in this population.

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Conflicts of interest: None.

Presented as a scientific poster at: The American Glaucoma Society Annual Meeting, March 2, 2012, New York, New York

Keywords

Optical coherence tomography; Imaging; Myopia; Retinal nerve fiber layer; Optic nerve; Ganglion cell

INTRODUCTION

Glaucoma is an optic neuropathy characterized by the death of retinal ganglion cells and their accompanying axons.¹ Optical coherence tomography (OCT) aids in the diagnosis and management of glaucoma by allowing for the direct measurement and quantification of retinal nerve fiber layer (RNFL) thickness, which has been found to correlate with the presence² and severity³ of the disease. However, OCT-measured RNFL thickness may vary significantly with factors other than glaucoma, such as age, ethnicity, axial length, and optic disc area.⁴ Prior studies have also shown that OCT-measured RNFL thickness correlates inversely with myopic refractive error, confounding glaucoma diagnosis.^{5, 6} The clinical diagnosis of glaucoma is also challenging in myopic individuals due to a higher prevalence of optic disc tilting⁷ and presence of non-progressive visual field defects that may simulate glaucomatous disease.⁸

It has been proposed that the measurement of macular ganglion cell layer thickness in glaucoma diagnosis may be less sensitive to variability with axial length and refractive error.⁹ The higher resolution capability of spectral-domain OCT now allows for segmentation and thickness measurement of the macular ganglion cell and inner plexiform layers (GC-IPL).^{10,11} The objectives of this study were to evaluate and compare the diagnostic specificities of peripapillary RNFL, optic nerve head (ONH), and macular GC-IPL thickness measurements using spectral-domain OCT in healthy, non-glaucomatous myopic individuals.

METHODS

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the institutional review board of the University of Miami Miller School of Medicine. After a discussion of the nature and purpose of the study, written informed consent was obtained from all participants. The study was performed in accordance with the Health Insurance Portability and Accountability Act of 1996 regulations.

Myopic subjects 18 years of age without other ocular pathology were invited to participate. The more myopic eye was selected as the study eye. Eligible participants underwent a thorough ophthalmic examination (A.A.A.) to confirm the lack of ocular pathology other than refractive error. This examination included measurement of Snellen visual acuity, intraocular pressure (IOP) measurement by applanation tonometry, and slit-lamp biomicroscopy with a +90-D lens to assess optic nerve cup-to-disc ratio (CDR). The study eye underwent an automated visual field test using the screening mode of frequency doubling technology (FDT; software version 4.00.0, Welch Allyn, Humphrey Systems, Carl Zeiss Meditec Inc., Dublin, CA) followed by axial length biometry (IOL Master, Carl Zeiss

Meditec, Dublin, CA). Subjects enrolled in the study did not undergo pharmacologic pupillary dilation.

Exclusion criteria included diabetes, cataract, any history of ocular surgery, best corrected visual acuity worse than 20/40, IOP ≥ 18 mm Hg, past history of raised IOP, optic nerve CDR ≥ 0.5 , CDR interocular asymmetry ≥ 0.2 , evidence or history of non-glaucomatous neuropathy or other optic nerve abnormalities, and retinal diseases including diabetic retinopathy, macular edema, or other vitreoretinal disease. Abnormal FDT results, defined as one or more locations identified as abnormal at the $P < 5\%$ level or less at the same location(s) on repeated testing and OCT scan signal strength score < 6 were also exclusion criteria. Following the screening examination, the study eye underwent macular and peripapillary OCT scanning using the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA). The data was analyzed using a pre-release version of software intended for release with the 6.0 software version for Cirrus OCT. Three scans centered on the optic disc were acquired through an undilated pupil to obtain the ONH measurements and peripapillary RNFL thickness. The Cirrus HD-OCT produces an RNFL thickness map by acquiring a 6×6 mm cube of signal data in the peripapillary region. Each cube of data consists of 40,000 data points (200×200 A-scans). HD-OCT software then extracts a 3.46 mm peripapillary circle of data points centered on the optic disc from the cube of acquired data to construct a peripapillary RNFL map. This analysis is displayed as quadrant and clock-hour sector maps, both of which are color-coded according to relative RNFL thickness in that area compared with a normative age-matched database. Green, yellow, and red colors signify a 5% to 95%, a 1% to 5%, and a less than 1% chance that the measured RNFL thickness is within normal range for an age-matched population, respectively. A white color designates an RNFL thickness that is thicker than 95% of age-matched normal controls. The RNFL thickness parameters were measured using the Cirrus HD-OCT segmentation algorithm, which automatically detects the borders of the internal limiting membrane and outer RNFL in each A-scan of each OCT frame.¹² RNFL thickness is then calculated as the distance between these two boundaries.

ONH parameters were measured using the same scanning protocol (using the same 6×6 mm data cube) as that used for RNFL analysis. The Cirrus HD-OCT automatically identifies the termination of Bruch's membrane and considers this to be the optic disc edge. The Cirrus HD-OCT algorithm measures optic disc rim area by measuring the rim width within the circumference of the optic disc edge. Average CDR and optic disc cup volume are also automatically determined by this algorithm. The ONH parameters are statistically compared with a normative age-matched database and displayed in a data table. This table is color-coded in a manner similar to that employed for RNFL analysis.

Each study eye then underwent three macular scans centered on the fovea to obtain the GC-IPL series. The protocol used in this study performs 200 horizontal B-scans comprising of 200 A-scans per B-scan within a 6×6 mm cube of acquired signal data centered on the fovea. The GC-IPL software algorithm automatically identifies the outer boundary of the RNFL and the outer boundary of the IPL. The GC-IPL thickness is calculated as the distance between these two boundaries. The overall mean GC-IPL thickness, minimum thickness (lowest GC-IPL thickness over a single meridian crossing the annulus), and sectoral (supero-

temporal, superior, supero-nasal, infero-nasal, inferior, infero-temporal) thicknesses are measured in an elliptic annulus (vertical radius of 2.0 mm, horizontal radius of 2.4 mm) centered on the fovea. The GC-IPL parameters are displayed in a data table (mean and minimum GC-IPL thicknesses) and sectoral map (Figure 1). The data table and sectoral map are color-coded according to relative GC-IPL thickness compared with a normative age-matched database. Green, yellow, and red colors signify a 5% to 95%, a 1% to 5%, and a less than 1% chance that the measured GC-IPL thickness is within normal range for an age-matched population, respectively. A white color designates a GC-IPL thickness that is thicker than 95% of age-matched normal controls.

All scans were obtained by a single operator with over 2 years of experience with full-time OCT operation at the Bascom Palmer Eye Institute (F.E.S.). The RNFL parameters that were considered for analysis included the average, quadrant, and clock-hour sectoral thicknesses. The ONH parameters that were considered for analysis included rim area, average CDR, and optic disc cup volume. The GC-IPL parameters that were considered for analysis were the average, minimum, and sectoral perimacular thicknesses. Each scan was reviewed for quality, and scans showing algorithm segmentation failure, signal strength < 6, or artifacts due to eye movements or blinking were excluded from the study.

We classified an RNFL thickness scan as “outside normal limits” if at least two of the following three criteria was met: 1) At least 2 of the 3 peripapillary RNFL scans demonstrating an average RNFL thickness with borderline or severe thinning (as indicated by yellow or red overlay coloring, respectively), 2) At least 2 of the 3 RNFL scans demonstrating one or more of the same peripapillary quadrants with borderline or severe thinning, or 3) At least 2 of the 3 peripapillary RNFL scans demonstrating one or more of the same or directly adjacent clock-hour segments with borderline or severe thinning. We classified an OCT scan as “outside normal limits” on the basis of ONH analysis if at least two of the following three criteria were met: 1) At least 2 of the 3 optic nerve scans demonstrating a rim area measurement with borderline or severe reduction (as indicated by yellow or red overlay coloring, respectively), 2) At least 2 of the 3 scans demonstrating a CDR at the level of borderline or severe enlargement, or 3) At least 2 of the 3 scans demonstrating a cup volume measurement with borderline or severe reduction. We classified a GC-IPL scan as “outside normal limits” if at least two of the following three criteria were met: 1) At least 2 of the 3 macular scans demonstrating an average GC-IPL thickness with borderline or severe thinning (as indicated by yellow or red overlay coloring, respectively), or 2) At least 2 of the 3 macular scans demonstrating a minimum GC-IPL thickness suggestive of borderline or severe thinning, or 3) At least 2 of the 3 macular scans demonstrating one or more GC-IPL sectors with borderline or severe thinning.

The false positive rates of the RNFL and GC-IPL scanning methods were calculated for each of the criteria used to define an imaging series as “outside normal limits”. The overall false positive rate of each scanning method was also calculated considering a test to be positive if at least 2 of the 3 respective criteria were met. The false positive rate was defined as the total number of participants with an imaging series considered to be “outside normal limits” divided by the total number of participants. Specificities of each scanning method were compared using the McNemar test. Linear regression was used to determine the

correlation between average GC-IPL thickness, average RNFL thickness, and optic nerve rim area with axial length and spherical equivalent. Significance was set at $P < 0.05$.

RESULTS

Fifty-five subjects volunteered for the study protocol. Five subjects did not complete 3 imaging scans for both the RNFL and GC-IPL imaging series and were excluded from final analysis. Two subjects were excluded due to algorithm failure noted in at least one of the acquired OCT scans. One subject was excluded in each case for the following reasons: OCT scan signal strength score < 6 , history of cataract extraction in the study eye, CDR > 0.5 discovered on ophthalmic examination, visual field defect discovered on automated visual field testing, and incomplete clinical ophthalmic examination. Therefore, data from 43 eligible subjects were analyzed. Of these subjects, 56% were female. The mean age was 30 ± 6.8 years (range: 22 to 50) with an average axial length of 25.26 ± 1.21 mm (range: 23.06 to 29.07). Fifty-three percent of subjects had axial length ≥ 25 mm. Mean spherical equivalent was -4.50 ± 1.93 diopters (range: -1.00 to -9.00). CDR by funduscopy was 0.23 and mean IOP was 13.2 ± 2.27 mm Hg (range: 9 to 17).

Twenty subjects (47%) had RNFL thickness scans that were classified as “outside normal limits”. The false positive rates when using average RNFL thickness, peripapillary RNFL quadrant thicknesses, or peripapillary RNFL clock-hour segment thicknesses to classify a test as “outside normal limits” were 5%, 19%, and 47%, respectively. The number and percentage of subjects with zero, one, two, or three abnormal scans for average RNFL thickness and RNFL quadrant thickness parameters are displayed in the Table. Three subjects (7%) had scans that were classified as “outside normal limits”. The false positive rates when using rim area, average CDR, or cup volume to classify a test as “outside normal limits” were 5%, 7%, and zero, respectively. The number and percentage of subjects with zero, one, two, or three abnormal scans for ONH rim area, average CDR, vertical CDR, and cup volume parameters are displayed in the Table.

Eleven subjects (26%) had GC-IPL thickness scans that were classified as “outside normal limits”. The false positive rates when using average GC-IPL thickness, minimum GC-IPL thickness, or GC-IPL sector thicknesses to classify a test as “outside normal limits” were 9%, 7%, and 26%, respectively. The number and percentage of subjects with zero, one, two, or three abnormal scans for average GC-IPL, minimum GC-IPL, and sectoral thickness parameters are displayed in the Table.

Overall diagnostic specificity was higher when using ONH parameters to classify an imaging series as positive when compared to both RNFL ($P < 0.001$) and GC-IPL ($P = 0.039$) parameters. Overall diagnostic specificity was higher when using GC-IPL parameters, compared to RNFL parameters ($P = 0.049$).

No significant association was found between axial length ($R = -0.094$, $P > 0.05$, Figure 2) or spherical equivalent ($R = 0.11$, $P > 0.05$, Figure 3) and average RNFL thickness. No significant association was found between axial length ($R = 0.055$, $P > 0.05$, Figure 4) or spherical equivalent ($R = 0.154$, $P > 0.05$, Figure 5) and optic disc rim area. No significant

association was found between axial length ($R = -0.29$, $P > 0.05$, Figure 6) or spherical equivalent ($R = 0.24$, $P > 0.05$, Figure 7) and average GC-IPL thickness.

While not statistically significant, logistic regression suggested an increased risk of detection of a false positive for each additional millimeter of axial length by RNFL with odds ratio 1.4 (95% confidence interval: 0.8, 2.4; $p=0.20$) and GC-IPL with odds ratio 1.5 (95% confidence interval: 0.9, 2.8; $p=0.14$), but not by ONH (odds ratio 0.6, 95% confidence interval: 0.2, 2.0). The wide confidence interval around the odds ratio for ONH is not surprising considering there were only three false positives by these criteria.

DISCUSSION

The challenge of distinguishing otherwise healthy myopic eyes from those afflicted with glaucoma is complex, especially when considering that myopic refractive error is a risk factor for open-angle glaucoma.¹³ Clinical differentiation between the two entities is confounded by the presence of larger and more ovally configured discs in myopic eyes,¹⁴ larger beta and alpha-zones of peripapillary atrophy,¹⁵ and the presence of visual field defects similar to those seen in glaucomatous eyes.⁸ Although OCT imaging technology has been shown to be of great clinical utility in the diagnosis and follow-up of glaucomatous eyes, the results of such testing may also be inaccurate in myopic eyes.^{5, 16–18}

In our study, we investigated the diagnostic specificities of 3 different OCT scanning protocols in order to determine which may have the lowest false-positive rate (and therefore the greatest clinical utility) in a non-glaucomatous myopic population. Specifically, we compared the false-positive rates of peripapillary RNFL, ONH, and macular GC-IPL parameters. To our knowledge, and based on a literature search of the Medline database, there are no published studies comparing the diagnostic specificities of these OCT-derived parameters in a non-glaucomatous, myopic population using the Cirrus HD-OCT system.

Our results indicate that measurement of the ONH parameters, particularly rim area, average CDR, and cup volume, results in higher overall specificity than measurement of the peripapillary RNFL or GC-IPL with spectral-domain OCT in non-glaucomatous myopic individuals. In the current study, classifying a test on the basis of RNFL clock-hour analysis resulted in a false positive rate approaching 50%. This exceedingly high rate likely relates not only to thinner RNFL in myopic eyes, but also to a different topographic RNFL profile in this population. Indeed, Kim et al¹⁶ reported that high myopes had significantly thinner mean RNFL measurements in the non-temporal parapapillary sectors, but thicker RNFL thickness in the temporal quadrant. With more pronounced RNFL thinning in the nasal regions (and thickening in the temporal regions), OCT-derived quadrant and clock-hour analyses may be subject to error when using only an abnormal region to classify a test as positive. Our study revealed a lower false-positive rate when relying on average RNFL thickness alone. This has two likely causes. First, regions of thicker peripapillary RNFL may balance the thinner regions, allowing for a somewhat normalized average thickness result. Second, the examination of 12 separate clock-hours provides 12 opportunities for a chance of false positive to occur. For these reasons, we recommend that caution be exercised when

relying on the RNFL quadrant and/or clock-hour map to diagnose glaucoma in myopic subjects and recommend that the clinician place little weight on these analyses.

Our study also found a relatively high false-positive rate when using novel GC-IPL parameters in our healthy, myopic population. This finding may relate to an association between RNFL and GC-IPL thicknesses. In a study investigating the predictors of normal GC-IPL thickness, Mwanza and colleagues¹¹ found that RNFL thickness was the strongest determinant of GC-IPL thickness ($R = 0.646$, $P < 0.001$). Macular GC-IPL thickness values may therefore correlate with myopic refractive error and spherical equivalent, and limit utility in myopic individuals, in the same manner as previously shown for peripapillary RNFL thickness values.^{4,5,19–22}

Our study found that OCT-derived ONH parameters had the lowest false-positive rates in non-glaucomatous myopic individuals. When using the criterion of at least 2 of 3 scans indicating abnormal cup volume, not a single subject's imaging series was deemed to be positive. The Cirrus HD-OCT system measures ONH parameters using a 200×200 optic disc cube protocol centered on the optic disc. The system considers the termination of Bruch's membrane as the disc edge. The rim width around the entire circumference of the optic disc is determined by measuring the three-dimensional thickness of the neuroretinal tissue in the optic nerve as it turns to exit through the opening in Bruch's membrane.²³ Since measurements are performed within this three-dimensional volume, optic nerve rim area, CDR, and cup volume are all measured in the plane of the ONH, along the axis of nerve exit, rather than the axis of examination. This method allows for a more accurate quantification of optic nerve variables in myopic eyes with tilted discs.

In the current study, a given imaging series was considered as a positive test based on meeting at least 2/3 pre-defined, reproducible criteria for a given OCT-derived parameter. By these criteria, ONH parameters, which are not subdivided into quadrants, clock-hours, or sectors, were less likely to produce a false-positive test result. We recognize that these pre-defined criteria may not be employed by all practitioners interpreting OCT results in myopic individuals. The Table provides the frequency of observed false-positive test results of individual RNFL, GC-IPL, and RNFL parameters, allowing for interpretation with respect to an individual practitioner's criteria for classifying an OCT scan series as positive. The Table does suggest that the false positive rates of these individual parameters, excluding the RNFL clock-hour analysis, are similar. We therefore recommend caution in using pre-defined criteria to classify an OCT scan series as positive in myopic individuals.

Each subject in this study underwent 3 separate ONH and macular scans in order to ensure reproducibility of our results. Although peripapillary RNFL and ONH parameters have been shown to demonstrate excellent intravisit reproducibility, test-retest standard deviation has been shown to range from 1.18 microns for average RNFL to 3.62 microns for sectoral RNFL thicknesses at clock-hours 8 and 4, in right and left eyes, respectively.²³ We therefore recommend that 3 OCT scans per eye per scanning protocol be obtained in routine clinical practice for the purposes of glaucoma assessment.

The purpose of our study was to determine the false positive rates for diagnosis of glaucoma on the basis of 3 different OCT-derived parameters in myopic individuals. We chose a younger patient population in order to decrease any likelihood of glaucomatous damage or other factors that could have affected RNFL measurements and confounded our study results. For the same reason, we also excluded all subjects with CDR > 0.5 or CDR interocular asymmetry > 0.2. Myopic eyes may have larger disc sizes with corresponding larger CDRs,¹⁴ so exclusion of study subjects based on these criteria may have lead to underestimation of the false positive rates using the OCT-derived parameters. Although our younger patient population and conservative exclusion criteria likely excluded subjects with glaucomatous optic neuropathy, there exists a possibility that some subjects in our study may have been afflicted with pre-perimetric disease, and longitudinal follow-up would be necessary to ensure the accuracy of our reported diagnostic specificity values. Our study was not designed to determine the abilities of OCT-derived ONH, peripapillary RNFL, and GC-IPL parameters to diagnose glaucoma in myopic individuals. Therefore, diagnostic sensitivities and AUROCs are not reported and should not be extrapolated from our data. Rather, our study helps the clinician decipher which OCT-derived parameter is least likely to give a false-positive result in an otherwise healthy myopic individual.

The instrument used to measure retinal thickness in this study was the Cirrus HD-OCT system. Prior studies have shown that thickness measurements obtained by different spectral domain instruments may not be entirely compatible and interchangeable.²⁴ Results from this study should not be generalized to spectral domain instrumentation other than the Cirrus HD-OCT system. Prior studies have found that RNFL measurements obtained by the Cirrus HD-OCT system are unaffected by pupil size,²⁵ so although subjects enrolled in our study did not undergo pharmacologic pupillary dilation, we do not believe that this had any impact on our results.

In conclusion, spectral-domain OCT continues to improve our ability to diagnose and monitor glaucomatous disease. The ability to measure ganglion cell layer thickness aids our diagnostic abilities. However, interpretation of OCT results in myopic eyes deserves careful attention by the clinician. Peripapillary RNFL and ganglion cell layer thickness measurements in myopic eyes may not be comparable to those of a standard normative age-matched control group and generates false-positive test results. Quantitative OCT-derived ONH measurements are associated with a lower false-positive rate in this population. The clinician should place greater weight on these measurements in myopic individuals.

Acknowledgments

Source of funding: Unrestricted grant to the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, from Research to Prevent Blindness, Inc., New York, NY; NIH P30 EY014801 awarded to the Bascom Palmer Eye Institute

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Figure 1. Ganglion cell-inner plexiform (GC-IPL) layer sectoral thickness map, as obtained by Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) ganglion cell analysis (GCA) software. Each of the six perimacular GC-IPL sectors is color-coded to indicate relative thickness compared to an age-matched control population.

Figure 2. Linear regression analysis of the relationship between overall average retinal nerve fiber layer thickness and axial length.

Figure 3. Linear regression analysis of the relationship between overall average retinal nerve fiber layer thickness and spherical equivalent.

Figure 4.
Linear regression analysis of the relationship between optic nerve rim area and axial length.

Figure 5.
Linear regression analysis of the relationship between optic nerve rim area and spherical equivalent.

Figure 6. Linear regression analysis of the relationship between average ganglion cell-inner plexiform layer thickness and axial length.

Table

Optical coherence tomography scan results in non-glaucomatous myopic individuals.

Parameter	# (%) yellow/3 replicates				# (%) red/3 replicates			
	0	1	2	3	0	1	2	3
GC-IPL Average	38 (88)	1 (2)	1 (2)	3 (7)	42 (98)	0	1 (2)	0
GC-IPL Minimum	37 (86)	3 (7)	1 (2)	2 (5)	41 (95)	1 (2)	1 (2)	0
GC-IPL Sup-Temp	35 (81)	4 (9)	2 (5)	2 (5)	42 (98)	0	0	1 (2)
GC-IPL Sup	39 (91)	0	1 (2)	3 (7)	42 (98)	1 (2)	0	0
GC-IPL Sup-Nasal	36 (84)	2 (5)	2 (5)	2 (5)	42 (98)	0	1 (2)	0
GC-IPL Inf-Nasal	29 (67)	4 (9)	1 (2)	9 (21)	40 (93)	0	1 (2)	2 (5)
GC-IPL Inferior	34 (79)	4 (9)	0	5 (12)	38 (88)	2 (5)	1 (2)	2 (5)
GC-IPL Inf-Temp	41 (95)	0	1 (2)	1 (2)	43 (100)	0	0	0
ONH Rim area	41 (95)	1 (2)	0	1 (2)	43 (100)	0	0	0
ONH Average CDR	40 (93)	0	1 (2)	2 (5)	43 (100)	0	0	0
ONH Vertical CDR	41 (95)	1 (2)	0	1 (2)	43 (100)	0	0	0
ONH Cup Volume	41 (95)	2 (5)	0	0	43 (100)	0	0	0
RNFL Average	41 (95)	0	0	2 (5)	43 (100)	0	0	0
RNFL Temporal	42 (98)	0	0	1 (2)	43 (100)	0	0	0
RNFL Superior	41 (95)	0	0	2 (5)	41 (95)	1 (2)	1 (2)	0
RNFL Nasal	40 (93)	0	0	3 (7)	41 (95)	0	0	2 (5)
RNFL Inferior	40 (93)	1 (2)	0	2 (5)	41 (95)	0	1 (2)	1 (2)

GC-IPL indicates ganglion cell-inner plexiform layer thickness; ONH, optic nerve head; CDR, cup-disc ratio; RNFL, retinal nerve fiber layer thickness.