American Chinese Glaucoma Imaging Study: A Comparison of the Optic Disc and Retinal Nerve Fiber Layer in Detecting Glaucomatous Damage

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Purpose. To compare the relationships between optic nerve structural measures and visual function, as well as the diagnostic sensitivity for glaucoma detection between the retinal nerve fiber layer (RNFL) and neuroretinal rim measurements.

Methods. A total of 101 normal and 156 glaucomatous eyes of 257 enrolled subjects were examined. RNFL thickness was measured by optical coherence tomography, and the neuroretinal rim (rim area, rim/disc area, and rim volume) was measured with a confocal scanning laser ophthalmoscope. The relationship between the structural measures and visual field sensitivity was evaluated with linear and non–linear-regression (quadratic and logarithmic) models. The coefficient of determination (R^2) was calculated, and the regression models were compared with Alkaike's information criteria and the F test. The diagnostic sensitivity for glaucoma detection in each structural measure was determined by the area under the receiver operating characteristic curve (AUC).

Results. The relationship of the RNFL, rim area, rim/disc area, and rim volume with visual function was best described with nonlinear regression models (quadratic regression for the RNFL [$R^2 = 0.383$]), rim area [$R^2 = 0.303$]), and rim/disc area [$R^2 = 0.265$]; and logarithmic regression for rim volume [$R^2 = 0.175$]). The change of visual sensitivity at each level of structural damage was highest for the RNFL. The AUC for the RNFL also was higher than the neuroretinal rim measures. In this study population, at 90% specificity, the diagnostic sensitivities for detecting glaucomatous damage was 82.7%, 67.3%, 67.3%, and 52.6% for the RNFL, rim area, rim/disc area, and rim volume, respectively. (These values would apply only to a group with inclusion criteria and disease severity similar to those of the present cohort.)

Conclusions. The RNFL showed a stronger structure–function association and a higher diagnostic sensitivity for glaucoma detection than did the neuroretinal rim. (*Invest Ophthalmol Vis Sci.* 2007;48:2644–2652) DOI:10.1167/iovs.06-1332

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Supported in part by National Eye Institute Grants EY11008 (LMZ) and EY08208 (PAS).

Submitted for publication November 6, 2006; revised December 18, 2006; accepted April 16, 2007.

Disclosure: **C.K. Leung**, Heidelberg Engineering (R); **F.A. Medeiros**, Carl-Zeiss Meditec, Inc. (F); **L.M. Zangwill**, Carl-Zeiss Meditec, Inc., and Heidelberg Engineering (F); **P.A. Sample**, Carl-Zeiss Meditec, Inc. (F); **C. Bowd,** None; **D. Ng**, None; **C. Yim Lui Cheung**, None; **D.S.C. Lam**, None; **R.N. Weinreb**, Carl-Zeiss Meditec, Inc., and Heidelberg Engineering (F, R)

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Glaucoma is characterized by progressive degeneration of retinal ganglion cells with loss of the retinal nerve fiber layer (RNFL), thinning of the neuroretinal rim, and subsequent increase in the cup-to-disc ratio. Clinical examination of the optic disc and the RNFL is the key component in establishing the diagnosis and monitoring the course of the disease. Although the cup-to-disc ratio has been commonly documented in clinical practice, neuroretinal rim measurement has been reported to be more related to functional damage and predictive of future functional loss.[1] It has been shown that loss of neuroretinal rim graded by the Disc Damage Likelihood Scale (a clinical disc-grading system based on the radial width of the rim measured at its thinnest point) is highly associated with loss of visual function and is closely correlated with rim measurements obtained with a confocal scanning laser ophthalmoscope.[2]

Clinical assessment of the RNFL, in contrast, often requires red-free photography for optimal visualization. Quantification of RNFL thickness has been problematic until the relatively recent advent of imaging instruments. Recent studies have confirmed the role of RNFL measurement in the detection of suspected glaucoma or glaucoma with the use of optical coherence tomography (OCT) and scanning laser polarimetry (SLP).[3–5] Significant correlation between RNFL thickness and visual function has also been reported.[6–7] Nevertheless, it is uncertain whether the RNFL or the neuroretinal rim represents a more sensitive surrogate for detecting glaucomatous change and which one correlates better with visual function. Although the relationship between visual field sensitivity and the RNFL-neuroretinal rim has been described as curvilinear,[5–7] almost all previous studies involved analysis of both normal and glaucomatous eyes. It could be argued that the flatter portion of the curve represents the wide variations of the RNFL/neuroretinal rim in normal individuals thereby giving a false impression of the curvilinear fit. In addition, the different units of measurement of the RNFL (in micrometers) and neuroretinal rim area (in square millimeters) or volume (in cubic millimeters) may render a direct comparison of the structure–function regression profiles difficult. In the present study, we standardized the units and compared the diagnostic performance for glaucoma detection and the structure–function relationship between the neuroretinal rim and the RNFL measured with a confocal scanning laser ophthalmoscope and an optical coherence tomographer.

Investigative Ophthalmology & Visual Science, June 2007, Vol. 48, No. 6

MATERIALS AND METHODS

Subjects

This study was collaborative, with subjects recruited from the Hamilton Glaucoma Center Diagnostic Innovations in Glaucoma Study (DIGS) at the University of California, San Diego, and the Department of Ophthalmology and Visual Sciences of The Chinese University of Hong Kong (CUHK). The data in the present study were obtained from the databases in CUHK and DIGS. These databases were established for a prospective longitudinal study designed to evaluate optic nerve structure and visual function in glaucoma. Data meeting the inclusion criteria in this study were exported from the databases for analyses. One eye was selected randomly from 101 normal individuals and 156 patients with glaucoma. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and approved by the respective Institutional Review Boards.

All subjects underwent a full ophthalmic examination, including visual acuity, refraction, intraocular pressure measurement with Goldmann tonometry, gonioscopy, dilated fundus examination with stereoscopic biomicroscopy of the optic nerve head under slit lamp and indirect ophthalmoscopy. The inclusion criteria were best corrected visual acuity of not worse than 20/40, spherical refractive error within the range of −6.00 to + 3.00 D, and <5.00 D of cylinder. Individuals were excluded if they had a history of any retinal disease, surgery or laser procedures, diabetes mellitus, or neurologic diseases. Normal subjects were individuals with no ocular or intraocular diseases. In particular, they had no abnormal visual fields based on reliable visual field perimetry results (SITA standard, Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, CA) and no history of intraocular pressure higher than 21 mm Hg. A reliable visual field perimetry result is defined as fixation losses less than 30% and false-positive and -negative errors each less than 33%. Eyes were classified as glaucomatous if they had at least two consecutive abnormal visual field test results, defined as a pattern SD (PSD) outside the 95% normal confidence limits and/or a Glaucoma Hemifield Test (Carl Zeiss Meditec, Inc.) result outside normal limits, regardless of the appearance of the optic disc. Twenty-one eyes from the DIGS were also classified as glaucomatous because of a history of documented evidence of progressive glaucomatous change in the appearance of the optic disc as assessed by simultaneous stereoscopic optic disc photographs, regardless of visual field test results. The evidence of progressive glaucomatous damage had to be present before the imaging test date. The use of this composite reference standard for glaucoma diagnosis allowed us to evaluate the accuracy of diagnostic tests in a broad spectrum of patients with the disease, in that both those with visual field loss and those with normal visual fields, but confirmed progressive glaucomatous optic nerve damage, were included.

For evaluation of progressive optic disc damage, stereoscopic sets of slides were obtained using a simultaneous stereo camera (TRC-SS; Topcon Instrument Corp. of America, Paramus, NJ) and examined with a stereoscopic viewer (Pentax; Asahi Optical Co., Tokyo, Japan). The photographs were evaluated by two experienced graders, each of whom was masked to the subject's identity and to the other test results. For inclusion, photographs had to be of adequate quality or better. To identify a subgroup of patients with progressive glaucomatous optic disc change for this study, the research database in the DIGS was reviewed for all patients who had been imaged with the three instruments and who had been observed for at least 1 year before the imaging test date. For each patient, the most recent stereophotograph was compared to the oldest available one, to maximize the chance of detecting progressive optic disc change. Each observer was masked to the temporal sequence of the photographs. The definition of change was based on focal or diffuse thinning of the neuroretinal rim, increased excavation, or enlargement of RNFL defects. Changes in rim color, presence of disc hemorrhage, or progressive parapapillary atrophy were not sufficient for characterization of progression. Discrepancies between the two graders were either resolved by consensus or by adjudication of a third experienced grader. Initial agreement between graders was obtained in 83% of the cases.

OCT Imaging

Optical coherence tomography was performed with the StratusOCT version 3 (Carl Zeiss Meditec Inc.). RNFL thickness was measured with the fast RNFL (3.4; 256 A-scans) scanning protocol. Average measurements of three sequential circular scans of 3.4-mm diameter centered at the optic disc were recorded. Thickness is determined by the difference in distance between the vitreoretinal interface and a posterior border based on a predefined reflectivity signal level. All the scans had signal strength of at least 7.

Confocal Scanning Laser Ophthalmoscopy Imaging

Confocal scanning laser ophthalmoscopy (CSLO) was performed with the Heidelberg Retinal Tomograph (HRT 2; Heidelberg Engineering, GmbH, Dossenheim, Germany). In brief, a three-dimensional topographic image consisting of from 384 × 384 × 16 up to 384 × 384 × 64 pixels is constructed from multiple focal planes axially along the optic nerve head. An average of three consecutive scans is obtained and aligned to compose a single mean topography for analysis. An experienced examiner outlined the optic disc margin on the mean topographic image while viewing stereoscopic photographs of the optic disc. Images with an SD greater than 50 μm were excluded. Once the contour line is drawn, the software automatically calculates all the optic disc measurements. In this study, we focused only on the neuroretinal rim measures including the rim area, rim/disc area, and rim volume. The reference plane is defined at 50 μm posterior to the mean retinal height between 350° and 356° along the contour line. The area above the reference is defined as the rim and the area below as the cup.

In CUHK, two patients were excluded because of poor-quality images, one with OCT, and one with CSLO. In DIGS, 19 were excluded due to poor OCT images and 12 due to poor CSLO images.

Statistical Analysis

Differences in visual field, OCT, and HRT measurements between the normal and the glaucoma groups were evaluated with the independent *t*-test. In all statistical analyses, $P < 0.05$ was considered statistically significant.

Evaluation of Diagnostic Sensitivity for Glaucoma Detection. The area under the receiver operating characteristic curve (AUC) was used to assess the ability to differentiate suspected glaucomatous or glaucomatous eyes from normal eyes with each testing parameter. An AUC of 1.0 represents perfect discrimination, whereas an AUC of 0.5 represents chance discrimination. The method described by Hanley and McNeil[8] was used to compare the AUCs.

Analysis of Structure–Function Relationship. The relationships between the RNFL and neuroretinal rim measurements and visual sensitivity were evaluated with linear and nonlinear regression analyses. The linear model ($y = ax + b$) was compared with two common nonlinear models: (1) the second-order polynomial ($y = ax^2 + bx + c$) and (2) the logarithmic regression ($y = a \ln(x) + b$). To facilitate the comparison of the regression equations derived from each of the structural measures, the measurements of the RNFL and neuroretinal rim were standardized and expressed in fractions (defined as "structural integrity" in Figs. 4–6), which was obtained by dividing the individual measurement by the mean value derived from the normal group. The first derivative plots of the derived regression equation were constructed to provide a graphic representation of the degree of change in visual sensitivity in reference to different levels of structural damage. The details of the statistical methods of the regression analyses have been described.[6,9]

Table 1. Comparisons of RNFL Thickness and Topographic ON Head Parameters in Normal and Glaucomatous Eyes

	Normal (n = 101)	Glaucoma (n = 156)	P
Age (y)	56.0 ± 16.5	61.7 ± 14.9	0.004
Refraction (D)	−0.87 ± 2.46	−1.35 ± 1.56	0.137
RNFL thickness (μm)	102.10 ± 12.37	73.63 ± 15.98	<0.001
Rim area (mm^2)	1.48 ± 0.33	1.14 ± 0.37	<0.001
Rim-disc area ratio	0.78 ± 0.13	0.54 ± 0.18	<0.001
Rim volume (mm^3)	0.44 ± 0.16	0.27 ± 0.16	<0.001
Visual field MD (dB)	−0.81 ± 1.15	−6.74 ± 7.20	<0.001
Visual field PSD (dB)	1.60 ± 0.34	6.00 ± 4.26	<0.001

Data are the mean ± SD. *P,* independent *t*-test.

Results

A total of 101 normal (59 from DIGS, 42 from CUHK) and 156 glaucomatous (105 from DIGS, 51 from CUHK) eyes of 257 subjects were analyzed. Significant differences were found in the RNFL thickness, rim area, rim/disc area, rim volume, and visual field MD and PSD between the normal and the glaucoma groups (all with $P < 0.001$; Table 1). The average visual field MD (±SD) of the glaucoma group was −6.74 ± 7.20 dB (range, 1.08 to −30.63 dB). The distribution of patients with glaucoma with reference to visual field MD is illustrated in Figure 1. Table 2 compares the demographic data between the study populations from CUHK and DIGS. Subjects with glaucoma in CUHK had worse visual field results, as indicated by the lower MD and higher PSD.

Diagnostic Sensitivity for Detecting Glaucomatous Damage

The AUC was used to compare the discriminating power of RNFL thickness and the neuroretinal rim measures (Fig. 2). The AUC for the RNFL (0.923) was significantly larger than those for the rim area (0.773, $P < 0.001$), rim/disc area (0.858, P = 0.030), and rim volume (0.791, $P < 0.001$). At 90% specificity, the diagnostic sensitivities for glaucoma detection were 82.7%, 67.3%, 67.3%, and 52.6%, whereas at 80% specificity, they were 87.2%, 75.0%, 76.3%, and 63.5% for the RNFL, rim area, rim/disc area, and rim volume, respectively.

Regression Analyses of the Structure–Function Relationships of the RNFL and Neuroretinal Rim

The structure–function relationship profiles between visual field MD and each of the structural measures are shown in Figure 3. Only patients with glaucoma (n = 156) were analyzed. Quadratic regression models fit significantly better than the linear models when describing the relationship between visual sensitivity and the RNFL (R^2 = 0.383), rim area (R^2 = 0.303), and rim/disc area (R^2 = 0.265), whereas logarithmic function attained the best fit in the plot of visual sensitivity against rim volume (R^2 = 0.175). The RNFL showed the highest association with visual sensitivity in linear and nonlinear regression models fits compared with the respective regression analyses of neuroretinal rim measures. Figure 4 shows the composite view of the four best-fit regression profiles of the RNFL, rim area, rim/disc area, and rim volume. At the same proportional loss in structural integrity, the RNFL was associated with a poorer visual sensitivity compared with the neuroretinal rim measures. The first derivative plots of the derived regression equation were constructed to provide a graphic representation of the degree of change in visual sensitivity in reference to different levels of structural damage (Fig. 5). The change in visual sensitivity per unit change in structural integrity was found to be higher in the RNFL compared with the neuroretinal rim measures. Analyses of the respective subset of patients with glaucoma from DIGS and CUHK showed similar trends and patterns of regression fitting in each of the struc-

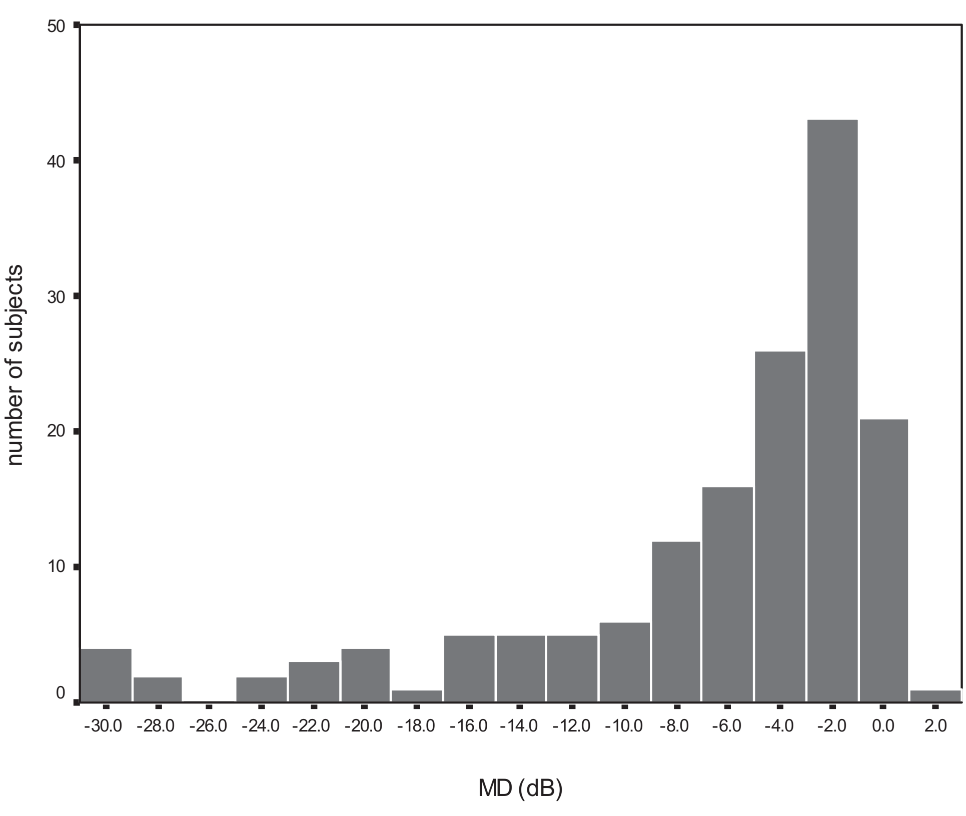


Figure 1. Distribution of glaucoma patients by the degree of visual field loss.

TABLE 2. Comparisons of Demographic Data of Normal and Glaucoma Groups from the Two Studies

	CUHK Normal (*n* = 42)	DIGS Normal (*n* = 59)	*P*	CUHK Glaucoma (*n* = 51)	DIGS Glaucoma (*n* = 105)	*P*
Age (y)	41.0 ± 13.3	66.6 ± 8.4	<0.001	50.7 ± 13.6	67.5 ± 12.1	<0.001
Refraction (D)	−2.20 ± 2.85	0.09 ± 1.85	<0.001	−1.50 ± 3.15	−1.24 ± 2.18	0.539
Visual field MD (dB)	−0.93 ± 1.20	−0.74 ± 1.12	0.406	−11.51 ± 9.37	−4.74 ± 5.09	<0.001
Visual field PSD (dB)	1.58 ± 0.30	1.62 ± 0.36	0.624	8.45 ± 4.29	4.85 ± 3.71	<0.001

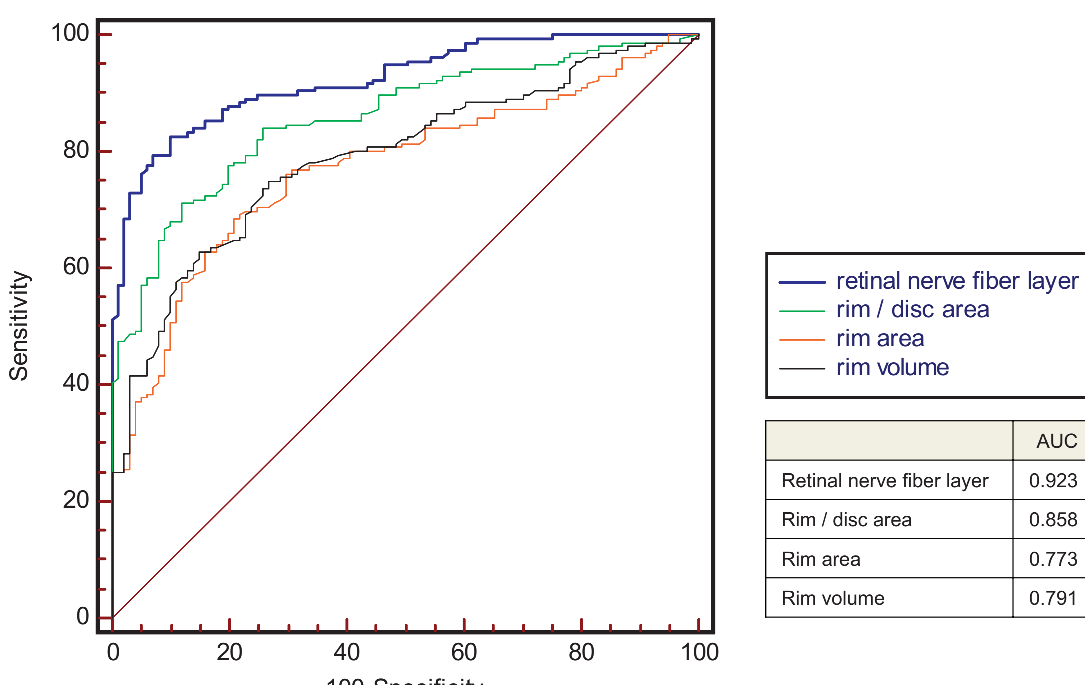
Data are the mean ± SD. *P,* independent *t*-test.

tural measures compared with those in Figure 3 (Fig. 6). In Figures 4 to 6, we show only the most representative portion of the curves (structural integrity, 0.4–0.8) for comparison among the regression equations.

DISCUSSION

Assessment of the RNFL and neuroretinal rim is fundamental for the evaluation of glaucomatous optic neuropathy. Nevertheless, attention has been focused more on the optic disc than on the RNFL in the diagnosis and monitoring of glaucoma. Outcome measures of glaucoma progression in major clinical trials, such as the Ocular Hypertension Treatment Study and the Early Manifest Glaucoma trial, have been essentially based on the changes in the optic disc, but not in the RNFL.[10,11] Evaluation of the RNFL is not widely used, because it is difficult, if not impossible, to quantify the loss of RNFL in fundus photographs. Generalized reduction of the RNFL also is difficult to detect. However, with the availability of modern imaging instrumentation, reliable and reproducible RNFL measurements are possible.[12–15] In this study, we showed that changes in the RNFL had a stronger structure–function association and a higher diagnostic sensitivity for glaucoma detection and, therefore, may provide a better surrogate measure to monitor glaucoma progression compared with the neuroretinal rim. We selected the rim area, rim/disc area, and rim volume for analyses because they directly reflect the structural integrity of the neuroretinal rim.

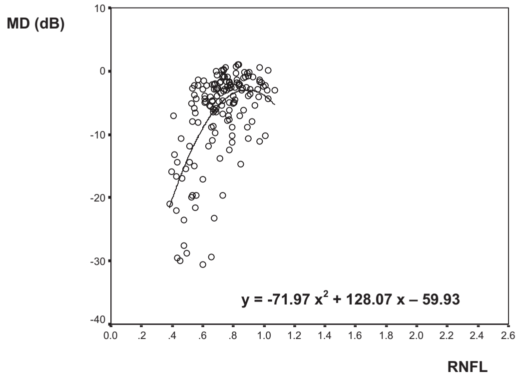
Few studies have been performed to compare the diagnostic sensitivities of RNFL and rim area with the latest versions of imaging instruments.[4,16] Medeiros et al.[4] found that the AUCs were similar among the best parameters measured by the StratusOCT (Carl-Zeiss Meditec, Inc.), the HRT2 (Heidelberg Engineering, GmbH), and the GDx VCC (Carl-Zeiss Meditec, Inc.). In a recent study by DeLéon-Ortega et al.,[16] rim/disc area ratio and cup-disc area ratio were found to have the best diagnostic performance among all the HRT2 measurements with the same AUC (0.861) and diagnostic sensitivity (75.95%) at 80% specificity. A similar AUC was also found in the average RNFL thickness measured by the StratusOCT (0.826) with diagnostic sensitivity of 70.89% at 80% specificity. In contrast, in this study population, the diagnostic sensitivity of global RNFL thickness (AUC = 0.923, sensitivity 87.2% at 80% specificity) was in fact higher than that of the neuroretinal rim measures, suggesting that RNFL is a more sensitive parameter for detection of glaucomatous damage. It should be noted that the average age in the glaucoma group was older than that in the normal group (Table 1). Nevertheless, it is unlikely that this would affect the comparison of the ROC curves. In those studies reporting a significant correlation between age and RNFL, the strength of association was weak.[17–20] In the cross-sectional study by Kanamori et al.[18] evaluating the effect of



	AUC	SE	95% CI
Retinal nerve fiber layer	0.923	0.019	0.884 to 0.953
Rim / disc area	0.858	0.026	0.810 to 0.899
Rim area	0.773	0.031	0.717 to 0.822
Rim volume	0.791	0.030	0.736 to 0.839

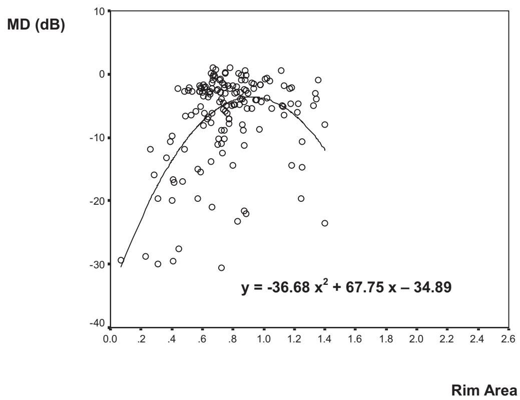
FIGURE 2. AUCs of RNFL, rim area, rim/disc area, and rim volume.

A



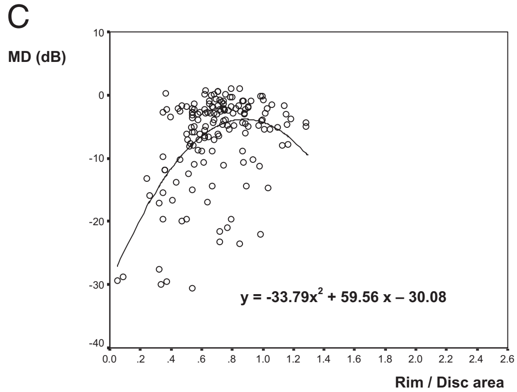
Regression Model	R^2	Probability of Correct Fitting Linear / Nonlinear Models	Evidence Ratio	Absolute Difference in AICc	F test (P value)
Linear	0.297	-		-	-
2^{nd} order polynomial	**0.383**	**0.01% / 99.99%**	**9179.55**	**18.25**	**<0.001**
Logarithmic	0.335	1.19% / 98.81%	83.09	8.84	-

B



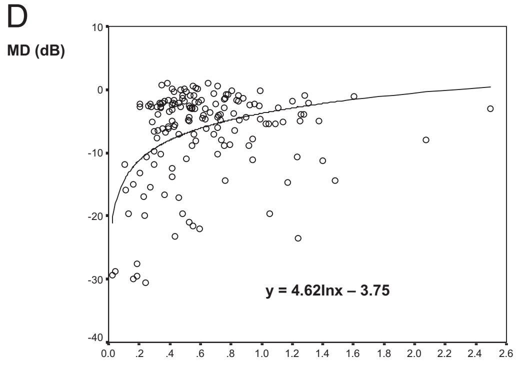
Regression Model	R^2	Probability of Correct Fitting Linear / Nonlinear Models	Evidence Ratio	Absolute Difference in AICc	F test (P value)
Linear	0.085	-		-	-
2^{nd} order polynomial	**0.303**	**<0.01% / >99.99%**	**>9999.00**	**40.46**	**<0.001**
Logarithmic	0.178	0.02% / 99.98%	4254.84	16.71	-

C



Regression Model	R^2	Probability of Correct Fitting Linear / Nonlinear Models	Evidence Ratio	Absolute Difference in AICc	F test (P value)
Linear	0.142	-		-	-
2^{nd} order polynomial	**0.265**	**<0.01% / >99.99%**	**>9999.00**	**22.12**	**<0.001**
Logarithmic	0.229	0.02% / 99.98%	4390.84	16.77	-

D



Regression Model	R^2	Probability of Correct Fitting Linear / Nonlinear Models	Evidence Ratio	Absolute Difference in AICc	F test (P value)
Linear	0.047	-		-	-
2^{nd} order polynomial	0.124	0.41% / 99.59%	245.35	11.01	<0.001
Logarithmic	**0.175**	**<0.01% / >99.99%**	**>9999.00**	**22.40**	-

FIGURE 3. Scatterplots of the relationship between visual field MD and each of the structural measures (expressed in fractions). Linear and nonlinear regression models are compared with F-test and corrected Akaike's Information Criterion (AICc).[9] The best-fit models are highlighted, with corresponding regression profiles and equations indicated in the scatterplots. (**A**) RNFL measured by OCT; (**B**) rim area, by CLSO; (**C**) rim/disc area, by CLSO; and (**D**) rim volume, by CLSO.

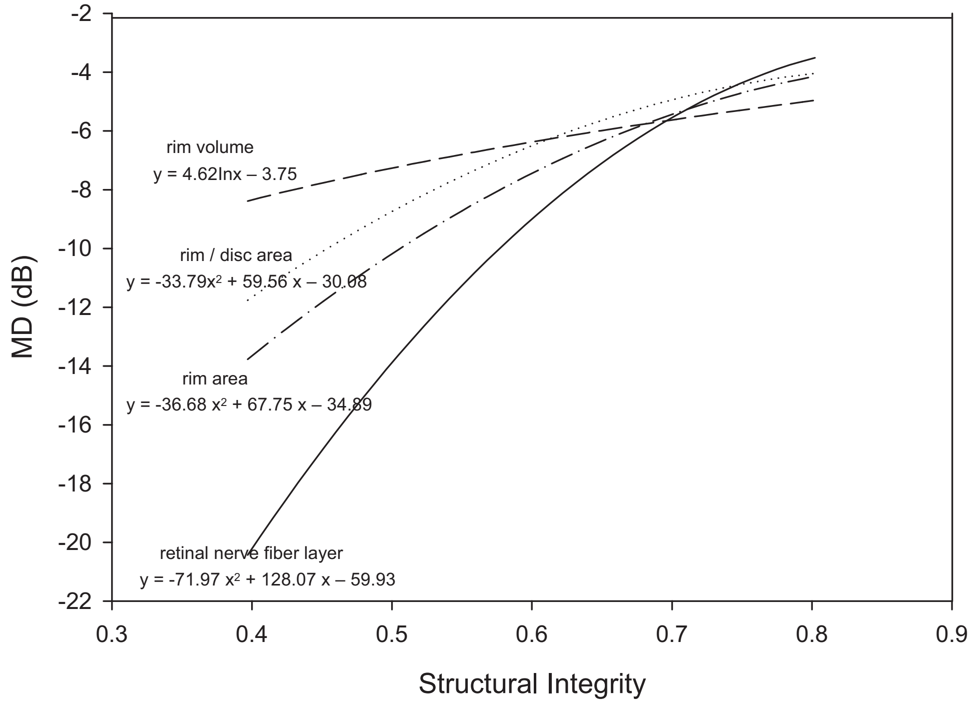


FIGURE 4. A composite view of the structure–function regression profiles of rim volume, rim area, rim/disc area, and RNFL thickness in 156 patients with glaucoma. Structural integrity from 0.4 to 0.8 is the most representative portion of the combined regression plots.

aging on RNFL thickness measured by OCT, the R^2 between average RNFL thickness and age was only 0.12, and the authors reported that RNFL thickness was estimated to decrease by 0.17% per year. For rim area, it was reported that it declined at a rate of 0.003 mm^2 per year.[20] We believe that, even if the age-related change in RNFL or rim area exists, this small difference would be unlikely to affect the comparison of discriminatory performance between these structural measures. The discriminatory performance, represented as AUC, represents the probability that a random pair of normal and abnormal parameters will be correctly ranked as to their "disease state." Therefore, the performance of AUC of any particular testing parameter is dependent on the diagnostic criteria of the disease state. A higher AUC is derived when one compares a normal group to a glaucoma group with more severe mean visual field defect. Since the objective of the present study was to compare the diagnostic performance of RNFL thickness and rim measurements in the selected samples, emphasis was placed on the

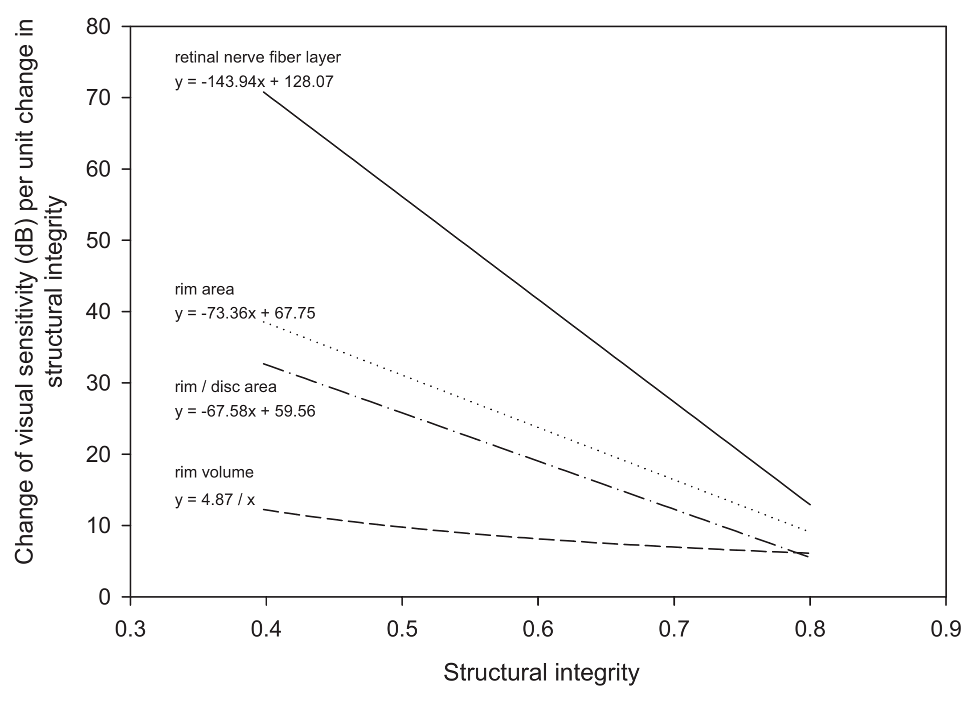


FIGURE 5. The first derivative plots of the regression equations of RNFL, rim area, rim/disc area, and rim volume (see Fig. 4).

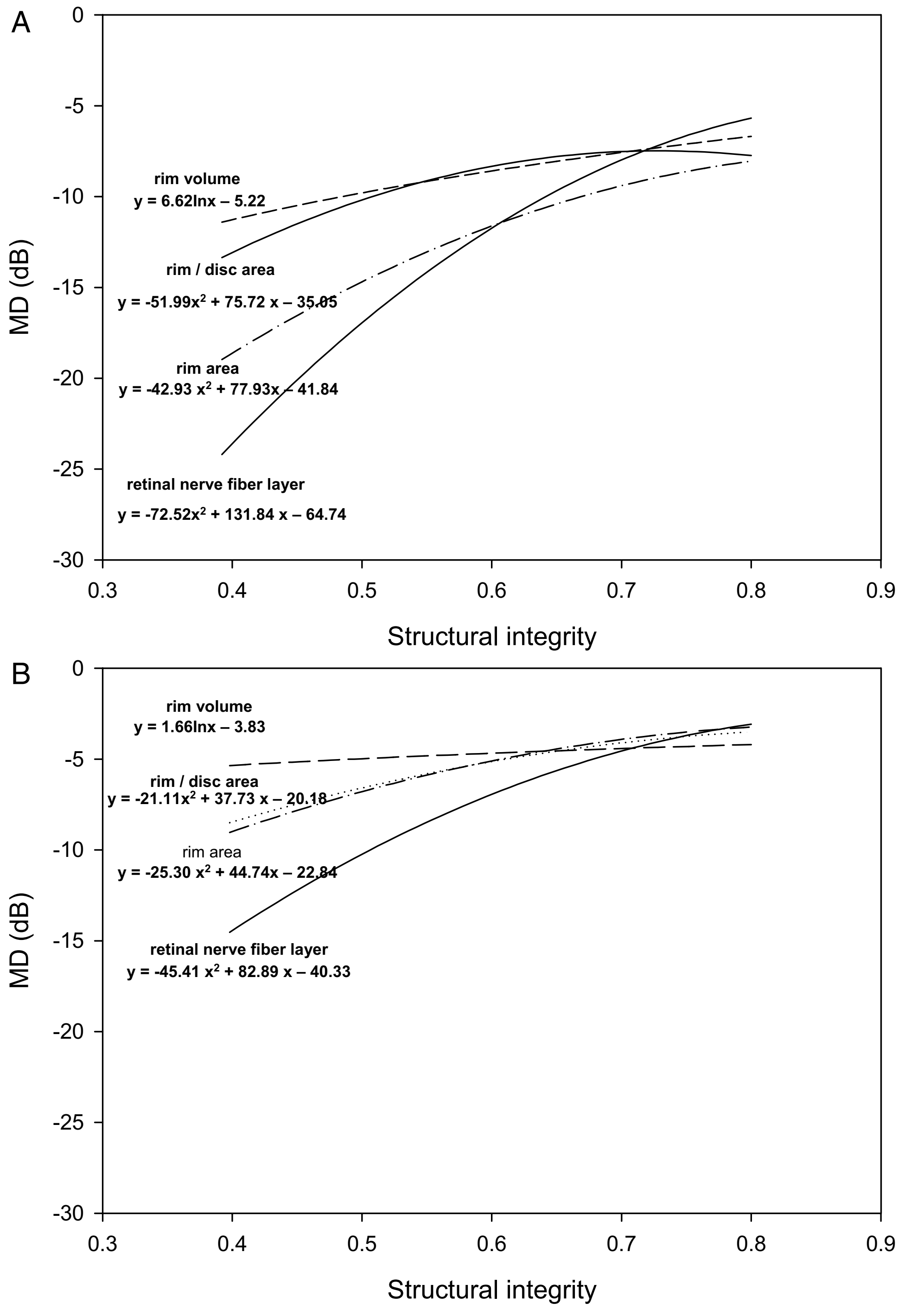


FIGURE 6. Composite plots of structure–function regression profiles of rim volume, rim area, rim/disc area, and RNFL thickness from (**A**) CUHK (n = 51) and (**B**) DIGS (n = 105) patients with glaucoma.

comparison of the relative values of AUCs rather than on the absolute data. AUCs obtained in individual parameters should be extrapolated to other population samples with caution.

The structure–function relationships of glaucoma have been investigated by OCT, CSLO, and SLP. Because OCT and SLP were designed to examine the RNFL, whereas CSLO was designed to assess optic nerve head topography, most of the previous studies on structure–function relationship were isolated to evaluate either the RNFL or the neuroretinal rim.[6,7,21] These studies demonstrated that a curvilinear function provided the best fit in the relationship between visual field sensitivity (in dB) and RNFL/neuroretinal rim. However, the flatter portion of the curves may represent the wide variations of RNFL-neuroretinal rim in normal individuals, giving a false impression of the curvilinear fit. In addition, the number of subjects with glaucoma in these studies may be too small to represent the genuine structure–function profile. In a recent study by Bowd et al.,[22] the structure–function relationship was compared among OCT, HRT, and SLP in 40 normal, 46 suspect, and 41 glaucomatous eyes. They found that there was no difference in the structure–function relationship between curvilinear and linear fits and that the OCT RNFL measurement had the strongest association with visual sensitivity. However, it should be noted that only glaucomatous eyes with mild visual field defect were analyzed (mean MD = −0.7dB, range, −4.1 to −1.8dB) and the structure–function relationship profile essentially described normal and suspect eyes.

The strength of the present study is that it included only patients with glaucoma and yet comprised the full spectrum of glaucomatous damage, from preperimetric glaucoma confirmed with optic disc progression to advanced glaucoma with extensive visual field loss. The large sample size ($n = 156$) has provided a representative capture of the structure–function relationship, and the influence of outliers should be minimal. Although analyses of regression profiles in previous structure–function relationship studies have been essentially focused on comparing the strength of association, by standardizing the units of the structural measures, we were able to compare directly the trend and pattern of regression profiles in this study. Our finding of curvilinear regression profiles in all the structural measures is in agreement with most of the previous investigations. The composite plot (Fig. 4) revealed that for the same proportion of structural loss, the corresponding loss of visual sensitivity is more dramatic in the RNFL compared with other neuroretinal rim measures. These findings were echoed in the first derivative plots showing that change in visual sensitivity increases with an increasing degree of structural damage. Comparisons on the first derivative plots demonstrated that RNFL attained a higher value in the change of visual sensitivity with respect to different levels of structural damage compared with neuroretinal rim measures. Collectively, our results suggest that at different stages of the disease, RNFL could be a more sensitive surrogate to capture the corresponding loss in visual function. These findings could be explained by the fact that the RNFL is a more direct measure of the integrity of retinal ganglion cells. It is conceivable that axon loss is more directly correlated to functional loss. This finding is in contrast to the neuroretinal rim, which is composed of nerve fiber bundles, glial cells, and connective tissues. The fact that the HRT invariably measures the central retinal vessels also contributes to the lowered structure function association and the reduced diagnostic sensitivity.

Our cross-sectional results are consistent with the longitudinal study by Quigley et al.[23] performed more than 10 years ago, before the advent of all the imaging instruments. In their 5-year prospective study comparing optic disc and optic nerve photographs in the detection of progressive glaucomatous damage in 813 ocular hypertensive eyes, 18 (49%) of 37 visual field converters were found to have progressive nerve fiber damage, whereas only 7 (19%) of 37 converters had disc changes. It was suggested that serial nerve fiber examination was more sensitive to detect glaucoma progression. Our cross-sectional data with modern imaging instruments agree with this conclusion.

It should be noted that the strength of the structure–function relationship depends critically on the selection of parameters representing the structural and functional surrogates. Unless we could count the number of retinal ganglion cells and examine their functions directly, the use of the surrogates would never be accurate in capturing this relationship in full. The noise and variability of the surrogate measurements could weaken the association. We limited our RNFL measurement by using only OCT, because we have shown previously that the structure function association is stronger in OCT RNFL measurement than the RNFL measurement obtained from the SLP GDx VCC.[6,22] For optic disc measurement, the design of the HRT may provide a more comprehensive assessment than the that of the OCT, because a significant portion of the disc cannot be captured by the standard OCT optic disc scanning protocol. By using only two different imaging modalities, it may be difficult to distinguish the differences caused by instrumentation from the genuine differences found in the structural measures. Another limitation is that different races of patients with glaucoma (Chinese and white) were analyzed in this study. It is unknown whether race could have a role in determining the structure–function relationship, although we did not find any dissimilarity in the trend and patterns of the regression fittings in each of the structural measures between the two study populations.

In summary, our results provide evidence suggesting that the RNFL is more sensitive for detecting glaucomatous damage and has a stronger structure–function relationship than does the neuroretinal rim. Although the RNFL may more suitable for monitoring glaucoma progression, a prospective analysis comparing the RNFL and optic disc measurements is essential to confirm and cross-validate the proposed regression models.

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