Classification Algorithms Enhance the Discrimination of Glaucoma from Normal Eyes Using High-Definition Optical Coherence Tomography

Mani Baskaran,1 Ee-Lin Ong,2 Jia-Liang Li,3 Carol Y. Cheung,1 David Chen,4 Shamira A. Perera,1 Ching Lin Ho,1 Ying-Feng Zheng,1 and Tin Aung1,4,5

PURPOSE. To evaluate the diagnostic performance of classification algorithms based on Linear Discriminant Analysis (LDA) and Classification And Regression Tree (CART) methods, compared with optic nerve head (ONH) and retinal nerve fiber layer (RNFL) parameters measured by high-definition optical coherence tomography (Cirrus HD-OCT) for discriminating glaucoma subjects.

METHODS. Consecutive glaucoma subjects (Training data = 184; Validation data = 102) were recruited from an eye center and normal subjects (n = 508) from an ongoing Singaporean Chinese population-based study. ONH and RNFL parameters were measured using a 200 × 200 scan protocol. LDA and CART were computed and areas under the receiver operating characteristic curve (AUC) compared.

RESULTS. Average RNFL thickness (AUC 0.92, 95% confidence interval [CI] 0.91, 0.93), inferior RNFL thickness (AUC 0.92, 95% CI 0.91, 0.93), vertical cup-disc ratio (AUC 0.91, 95% CI 0.90, 0.92) and rim area/disc area ratio (AUC 0.90, 95% CI 0.86, 0.93) discriminated glaucoma better than other parameters (P ≤ 0.053). LDA (AUC 0.96, 95% CI 0.95, 0.96) and CART (0.98, 95% CI 0.98, 0.99) outperformed all parameters for diagnostic accuracy (P ≤ 0.005). Misclassification rates in LDA (8%) and CART (5.6%) were found to be low. The AUC of LDA for the validation data was 0.98 (0.95, 0.99) and CART was 0.99 (0.99, 0.994). CART discriminated mild glaucoma from normal better than LDA (AUC 0.94 vs. 0.99, P < 0.0001).

CONCLUSIONS. Classification algorithms based on LDA and CART can be used in HD-OCT analysis for glaucoma discrimination. The CART method was found to be superior to individual ONH and RNFL parameters for early glaucoma discrimination.

From the 1Singapore National Eye Center and Singapore Eye Research Institute, Singapore; the 2University of Melbourne, Melbourne, Australia; the 3Department of Statistics and Applied Probability, National University of Singapore, Singapore; the 4Johns Hopkins University, Baltimore, Maryland; and the 5Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

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Corresponding author: Tin Aung, Singapore National Eye Centre, 11 Third Hospital Avenue, Singapore 168751; tin11@pacific.net.sg.

Assessment of the retinal nerve fiber layer (RNFL) by optical coherence tomography (OCT) is widely used in the management of glaucoma patients. High-definition optical coherence tomography (HD-OCT) has recently been introduced,1–4 and has advantages of increased resolution, accuracy, and repeatability of RNFL measurement over time-domain OCT.5,6 The ability of time-domain OCT to discriminate glaucomatous discs from normals using optic nerve head (ONH) parameters has been found to be variable, and is affected by optic disc size, ethnicity,7–13 stage of disease,14 and artifacts in imaging.9 Recently, Mwanza et al.15 evaluated the diagnostic performance of HD-OCT (Cirrus software version 5.0, Carl Zeiss Meditec, Dublin, CA), which included both ONH and RNFL analysis. They reported that individual ONH and RNFL parameters showed similar diagnostic ability (area under the receiver operator characteristic [ROC] curves [AUCs] ranging from 0.89 to 0.96) in discriminating glaucomatous from normal eyes.

Classifiers use algorithms and statistical methods that allow “learning” to use multiple variables in decision-making. Researchers have utilized methods such as Linear Discriminant Analysis (LDA),16 Artificial Neural Networks (ANN),17 and Classification And Regression Tree (CART)17 to enhance the performance of Heidelberg Retinal Tomography (HRT) and time-domain OCT for glaucoma detection, which were found to have consistently better performances with such algorithms compared with individual ONH and RNFL parameters for glaucoma prediction.

The purpose of this study was to evaluate the diagnostic performance of individual ONH and RNFL parameters derived from Cirrus HD-OCT for discriminating glaucomatous from normal eyes, and to compare these with classification algorithms using LDA and CART methods.

METHODS

This was a diagnostic study of consecutive glaucoma subjects who underwent Cirrus HD-OCT (Version 4.5.1.1, Carl Zeiss Meditec Inc.) at a Singapore eye hospital between August and September 2010. Normal subjects were consecutively recruited from an ongoing Singaporean Chinese population-based study during this period. The study had the approval of the institutional review board of the hospital and the study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Glaucoma subjects were those identified with glaucomatous optic neuropathy (having typical rim notching or thinning, retinal nerve fiber layer defects or disc hemorrhage, and/or disc asymmetry between eyes) with corresponding visual field changes on reliable threshold visual field examination (SITA Standard central 24-2 algorithm, Humphrey; Carl Zeiss Meditec Inc.). The latter was defined as glaucoma hemifield test (GHT) results outside normal limits, and
with three or more nonedge contiguous points (except the horizontal nasal meridian) depressed to $P < 5\%$. Reliable visual fields were defined as fixation losses less than 20\% and false positive and false negative errors less than 33\%. Glaucoma subjects were further classified as mild (mean deviation [MD] $\geq -6$ decibels [dB]), moderate ($-6 \text{ dB} \geq \text{MD} \geq -12 \text{ dB}$) and severe ($<-12 \text{ dB}$) according to visual field MD. Clinical data such as intraocular pressure (IOP) measured by Goldmann applanation tonometry, gonioscopy, type of glaucoma, vertical cup-to-disc ratio (CDR), and central corneal thickness (CCT) values were obtained from the charts. Subjects with high myopia ($\leq -6 \text{ D}$), unreliable visual fields, poor image quality for Cirrus HD-OCT scans (defined as signal strength <6, or image acquisition artifacts such as discontinuity, or blink artifacts seen as breaks in the OCT scans), as well as those with retinal diseases such as moderate to severe diabetic retinopathy and age-related macular degeneration were excluded. Optic disc abnormalities due to other causes such as myelinated nerve fibers, anterior ischemic optic neuropathy, grossly tilted discs, or optic disc drusen were also excluded. Type of glaucoma was further classified as primary open angle glaucoma (with IOP $> 21 \text{ mm Hg}$), normal tension glaucoma (with IOP never recorded above $21 \text{ mm Hg}$), primary angle closure glaucoma (with established angle closure signs such as previous laser peripheral iridotomy or peripheral anterior synechiae), and secondary glaucoma (based on signs of pseudoexfoliation or pigment dispersion) apart from the above definition of glaucoma.

The control group of normal subjects were recruited from an ongoing population-based study of ethnic Chinese aged 40–80+ years, the Singapore Chinese Eye Study (SCES). Normal subjects had IOP $< 21 \text{ mm Hg}$ with open angles, healthy optic discs on stereomicroscopic disc examination and normal visual fields (defined as MD and pattern standard deviation [PSD] within 95\% confidence limits, and GHT within normal limits), no previous ocular surgery, and with no family history of glaucoma. The inclusion and exclusion criteria for visual field tests and Cirrus HD-OCT scans followed protocols similar to those in the glaucoma group and consecutive normal subjects were included for analysis in this study. Two age, sex, ethnicity, and severity-matched glaucoma data sets were collected separately, one for training the classification-based algorithms and one for validation.

Cirrus HD-OCT Imaging

ONH and RNFL parameters were measured with the optical disc cube 200 × 200 scan protocol using Cirrus HD-OCT (software version 5.0.0). The method of scan acquisition adhered to standard protocol described in the manufacturer’s manual. In brief, the subjects were scanned after dilation with 1\% tropicamide solution. After positioning the subject, the line scan was focused onto the optic nerve head by adjusting for the refractive error using the mouse alignment. The Z-offset and polarization optimization were performed using mouse-alignment protocols. The laser scanned a 6 × 6 mm cube centered on ONH acquiring the data required. Care was taken to obtain good signal strength for the scans and the best image stored. The RNFL parameters were measured from a circle with diameter 3.46 mm, which is centered on the optic disc. The output from the version 5.0.0 included average RNFL thickness, RNFL thickness for the four quadrants (superior, inferior, temporal, and nasal), and individual clock hour thicknesses (clock hours 1–12). The clock hours 11 for the right eye and 1 for the left eye were grouped as supertemporal thickness (clock hour 11/1) and 7 for the right eye and 5 for the left eye were grouped as inferotemporal thickness (clock hour 7/5) for analysis. Similar grouping was done for all clock hour RNFL thickness data to represent nasal and temporal clock hours for the purpose of analysis. The symmetry readout was another parameter included as a measure of RNFL symmetry between the two eyes of each subject in the analysis. The ONH parameters selected for analysis included rim area, disc area, vertical CDR, and average CDR. The ratio of rim area/disc area was manually computed for all subjects and included in the analysis as a measure adjusting for variation in disc area. Signal strength was included to evaluate the quality of the image acquired.

Statistical Analysis

If both eyes were eligible, one eye was randomly selected for analysis in the study. Statistical analysis was performed using R software (version 2.4.0, provided in the public domain by R Foundation for Statistical Computing, Vienna, Austria; available at http://www.r-project.org/) and a commercial software package (PASW version 18.0; SPSS Inc., Chicago, IL). Categorical variables between groups were compared using a chi-square test for proportions and numeric variables were compared using Student’s t-test for independent samples. One-way ANOVA with Bonferroni correction was performed to compare variables between various glaucoma diagnoses. The areas under the ROC curves (AUCs) for individual ONH and RNFL parameters were computed on their ability to discriminate glaucoma from normal eyes.

Linear Discriminant Analysis (LDA) and Classification And Regression Tree (CART) methods were used for automated classification of glaucoma using all the ONH and RNFL parameters tested. The LDA assumes a Gaussian distribution and defines linear discrimination boundaries between the categories, where it maximizes the variance between classes while minimizing the variance within classes, giving the best fit Linear Discriminant Function (LDF). The CART method is a decision tree learning technique that produces either classification or regression trees. The CART makes no assumption on the distribution of the data and applies a set of rules to split each node of a tree, decide when a tree is complete, assign each terminal node a class outcome, and select the “right-sized tree.” It leads to the best classification based on a minimum set of variables. The CART method has inherent training and testing methods for the given sample. For LDA and CART, we had conducted 10-fold cross-validation to examine the out-sample performance of these classifiers. Specifically, we split the whole data into 10 subsets at random and formed separate training samples and test samples. We then evaluated the accuracy of the test samples by using

### Table 1. Comparison of Demographic and Clinical Characteristics between Normal and Glaucoma Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal (n = 508)*, Mean (SD)</th>
<th>Glaucoma (training) (n = 184), Mean (SD)</th>
<th>Glaucoma (validation) (n = 102), Mean (SD)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.7 (6.2)</td>
<td>65 (11.6)</td>
<td>67.5 (11.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex (Male:Female)</td>
<td>279:232</td>
<td>157:149:9:4</td>
<td>90.5:3.5:3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ethnicity (Chinese:Malay:Indian:Others)</td>
<td>508:0:0</td>
<td>100:84</td>
<td>48.54</td>
<td>0.19</td>
</tr>
<tr>
<td>Laterality of Eye (Right:Left Eye)</td>
<td>295:259</td>
<td>106:79</td>
<td>62.40</td>
<td>0.49</td>
</tr>
<tr>
<td>Central Corneal Thickness (CCT) (μm)</td>
<td>556 (33.4)</td>
<td>528.3 (33.1)</td>
<td>530.3 (35.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Vertical cup-disc ratio (Clinical)</td>
<td>0.39 (0.11)</td>
<td>0.78 (0.14)</td>
<td>0.77 (0.14)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean Deviation (dB)</td>
<td>−0.7 (1.2)</td>
<td>−8.1 (13.67)</td>
<td>−9.04 (7.33)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pattern Standard Deviation (dB)</td>
<td>1.59 (0.38)</td>
<td>6.95 (10.43)</td>
<td>6.29 (4.22)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* CCT done in 507 subjects; SD, standard deviation; dB, decibels.
† Normal versus glaucoma (training data); P value for glaucoma groups was >0.05 for all parameters.
Table 2. Comparison of Optic Nerve Head and Retinal Nerve Fiber Layer Parameters between Normal and Glaucoma Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal (n = 508), Mean (SD)</th>
<th>Glaucoma (n = 184), Mean (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal strength</td>
<td>8.6 (0.99)</td>
<td>6.02 (1.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average RNFL thickness (µm)</td>
<td>97.99 (9.1)</td>
<td>73.98 (15.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Superior RNFL thickness (µm)</td>
<td>123.39 (16.02)</td>
<td>88.78 (23.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inferior RNFL thickness (µm)</td>
<td>127.37 (15.98)</td>
<td>83.77 (26.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symmetry</td>
<td>0.72 (0.34)</td>
<td>0.49 (0.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rim area (mm²)</td>
<td>1.3 (0.25)</td>
<td>0.84 (0.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disc area (mm²)</td>
<td>1.97 (0.37)</td>
<td>2.12 (0.45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vertical cup-disc ratio</td>
<td>0.49 (0.12)</td>
<td>0.75 (0.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average cup-disc ratio</td>
<td>0.55 (0.12)</td>
<td>0.75 (0.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cup volume (mm³)</td>
<td>0.17 (0.13)</td>
<td>0.49 (0.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rim area/disc area ratio</td>
<td>0.68 (0.13)</td>
<td>0.17 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SD, standard deviation; RNFL, retinal nerve fiber layer.

The classification rule constructed from the training samples. Finally, we took the sample average of the AUC values from the test samples. The cross-validated AUC provides a reasonable estimate for the classification accuracy for future analysis.

For comparing the AUC values, we considered the bootstrap resampling method. Specifically, we took random samples with replacement from the original data and formed bootstrap samples. The AUC values for various parameters based on the bootstrap samples were computed and used in the bootstrap tests. Similar methods were used for the validation data set.

Comparison of independent ROC curves was performed between individual parameters and algorithm-derived functions. Misclassification rates were reported as the proportion of total number of false positives and false negatives among the total number of eyes used.

Results

Out of the 196 glaucoma subjects selected for the training data set, 12 subjects were excluded for the following reasons: missing visual field data (1 eye), image artifacts (6 eyes), and high myopia (5 eyes), leaving 184 glaucoma subjects (93.9%) in the final analysis. Of 104 eyes selected for the validation data set, 2 eyes were excluded due to high myopia.

The majority of the subjects in the glaucoma group of the training data were Chinese (157/184, 85.3%). Comparing the glaucoma subjects with normal controls, those with glaucoma were older, had thinner CCT, larger vertical CDR, and a smaller MD and greater PSD ($P < 0.0001$, Table 1). The baseline clinical parameters of the validation data were comparable for age, sex, ethnicity, vertical CDR, and visual field indices ($P > 0.05$, Table 1).

The majority of the glaucoma subjects were diagnosed to have primary open angle glaucoma (POAG, 126, 68.5%) followed by primary angle closure glaucoma (PACG, 48, 26.1%) and secondary glaucoma (10, 5.4%). POAG included 56 normal tension glaucoma (NTG) subjects. NTG subjects did not differ in terms of disc area or symmetry, whereas they had higher average RNFL thickness, larger vertical CDR, and a higher MD compared with POAG ($P < 0.0001$, one-way ANOVA with Bonferroni correction). Based on visual field MD, there were 108 subjects with mild glaucoma, 58 with moderate glaucoma, and 18 with severe glaucoma. The signal strength of scans in the normal group was higher than that of the glaucoma group. All the parameters including average RNFL thickness, rim area, vertical CDR, and cup volume were significantly different between normal and glaucomatous eyes (Table 2). Disc area was found to be significantly larger in glaucomatous eyes ($1.97 \text{ vs. } 2.12 \text{ mm}^2; P < 0.0001$) compared with controls.

Table 3 shows the comparison of AUCs for various ONH and RNFL parameters in discriminating glaucoma from normal.

Table 3. Area under the Curve for Spectral-Domain Optical Coherence Tomography (OCT) Parameters (Optic Disc and RNFL Thickness), Linear Discriminant Function and CART in Detecting Glaucoma (n = 184)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC for Glaucoma Diagnosis (95% CI)</th>
<th>Clock Hour</th>
<th>AUC for Glaucoma Diagnosis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average RNFL thickness (µm)</td>
<td>0.92 (0.91, 0.93)</td>
<td>Clock hour 1a</td>
<td>0.62 (0.60, 0.64)</td>
</tr>
<tr>
<td>Superior RNFL thickness (µm)</td>
<td>0.89 (0.88, 0.90)</td>
<td>Clock hour 2</td>
<td>0.77 (0.76, 0.78)</td>
</tr>
<tr>
<td>Inferior RNFL thickness (µm)</td>
<td>0.92 (0.91, 0.93)</td>
<td>Clock hour 3</td>
<td>0.86 (0.85, 0.87)</td>
</tr>
<tr>
<td>Symmetry</td>
<td>0.76 (0.72, 0.79)</td>
<td>Clock hour 4</td>
<td>0.79 (0.78, 0.80)</td>
</tr>
<tr>
<td>Rim area (mm²)</td>
<td>0.88 (0.87, 0.89)</td>
<td>Clock hour 5</td>
<td>0.81 (0.80, 0.82)</td>
</tr>
<tr>
<td>Disc area (mm²)</td>
<td>0.60 (0.58, 0.62)</td>
<td>Clock hour 6</td>
<td>0.70 (0.68, 0.72)</td>
</tr>
<tr>
<td>Vertical cup-disc ratio</td>
<td>0.91 (0.90, 0.92)</td>
<td>Clock hour 7</td>
<td>0.52 (0.50, 0.54)</td>
</tr>
<tr>
<td>Average cup-disc ratio</td>
<td>0.89 (0.88, 0.90)</td>
<td>Clock hour 8</td>
<td>0.61 (0.59, 0.63)</td>
</tr>
<tr>
<td>Cup volume (mm³)</td>
<td>0.84 (0.80, 0.88)</td>
<td>Clock hour 9</td>
<td>0.83 (0.82, 0.84)</td>
</tr>
<tr>
<td>Rim area/disc area ratio</td>
<td>0.90 (0.86, 0.93)</td>
<td>Clock hour 10</td>
<td>0.88 (0.87, 0.89)</td>
</tr>
<tr>
<td>LDF†</td>
<td>0.955 (0.947, 0.963)</td>
<td>Clock hour 11</td>
<td>0.87 (0.86, 0.88)</td>
</tr>
<tr>
<td>CART†</td>
<td>0.982 (0.975, 0.991)</td>
<td>Clock hour 12</td>
<td>0.70 (0.68, 0.72)</td>
</tr>
</tbody>
</table>

AUC, area under the receiver operating characteristic curve; CI, confidence interval; RNFL, retinal nerve fiber layer; LDF, Linear Discriminant Function; CART, Classification And Regression Tree.

a Clock hours 1 to 6 represent temporal quadrants, whereas 7 to 12 represent nasal quadrants.

† Misclassification rate for LDF 8%; CART, 5.6%.

Group 1a parameters were found to have higher AUC compared with other individual OCT parameters ($P \leq 0.033$) except group 1b, whereas group 2 (LDA and CART) had the highest AUC overall ($P \leq 0.0005$).
whereas Table 4 shows the comparison between mild and moderate glaucomas. Average RNFL thickness (AUC 0.92), inferior RNFL thickness (0.92), vertical CDR (0.91), and rim area/disc area ratio (0.90) showed excellent AUCs compared with other parameters \((P < 0.0001)\). Disc area showed poor discrimination between normal and glaucomatous eyes. Supero- temporal (clock hour 1) thickness (AUC 0.62) and inferotemporal (clock hour 5) thickness (AUC 0.81) were not found to be robust parameters for discrimination. All the parameters performed less well \((AUC < 0.90)\) for mild glaucoma discrimination, whereas almost all except disc area performed excellently \((AUC > 0.90)\) for moderate glaucomas. Similar results were obtained for discrimination of mild versus moderate glaucomas except for inferior RNFL thickness and vertical CDR, which showed AUC > 0.90. We had not included the diagnostic performance for severe glaucomas separately due to small sample size. Figure 1 depicts the comparison of AUC among the ONH and RNFL parameters in discriminating glaucomatous eyes from normal eyes, suggesting that both performed equally well in our study.

The equation derived from LDA is provided here:

\[
\begin{align*}
1 & = 5.63 \times \text{Disc Area} - 1.83 \times \text{Rim Area} - 6.21 \times \text{Average CDR} + 5.12 \times \text{Vertical CDR} - 0.022 \times \text{Superior RNFL thickness} - 0.031 \times \text{Inferior RNFL thickness} + 0.016 \times \text{Average RNFL thickness}
\end{align*}
\]

When this equation was used to derive the LDF, it showed an AUC of 0.96 (95% CI, 0.95, 0.96) for diagnosing glaucoma and had a misclassification rate of 8% (54/692). The LDF misclassified 47 subjects as having mild glaucoma (Normal, 7; other stages of glaucoma, 40), 6 as having moderate glaucoma (other stages of glaucoma, 6), and 1 as having severe glaucoma (other stage of glaucoma, 1). The CART analysis showed an AUC of 0.98 (95% CI, 0.98, 0.99) and a misclassification rate of 5.6% (39/692). The CART was the best method among all the parameters (and LDF) for discrimination of normal versus overall glaucoma diagnosis \((P < 0.0001; \text{Table 3, Fig. 2})\). Figure 1A depicts the comparison of AUC among the ONH and RNFL parameters in discriminating glaucomatous eyes from normal eyes, suggesting that both performed equally well in our study.

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When this equation was used to derive the LDF, it showed an AUC of 0.96 (95% CI, 0.95, 0.96) for diagnosing glaucoma and had a misclassification rate of 8% (54/692). The LDF misclassified 47 subjects as having mild glaucoma (Normal, 7; other stages of glaucoma, 40), 6 as having moderate glaucoma (other stages of glaucoma, 6), and 1 as having severe glaucoma (other stage of glaucoma, 1). The CART analysis showed an AUC of 0.98 (95% CI, 0.98, 0.99) and a misclassification rate of 5.6% (39/692). The CART was the best method among all the parameters (and LDF) for discrimination of normal versus overall glaucoma diagnosis \((P < 0.0001; \text{Table 3, Fig. 2})\). Figure 1A depicts the comparison of AUC among the ONH and RNFL parameters in discriminating glaucomatous eyes from normal eyes, suggesting that both performed equally well in our study.

\[
\begin{align*}
1 & = 5.63 \times \text{Disc Area} - 1.83 \times \text{Rim Area} - 6.21 \times \text{Average CDR} + 5.12 \times \text{Vertical CDR} - 0.022 \times \text{Superior RNFL thickness} - 0.031 \times \text{Inferior RNFL thickness} + 0.016 \times \text{Average RNFL thickness}
\end{align*}
\]

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Figure 3 shows the flow chart depicting the CART cutoff values used for discrimination between normal and glaucomatous eyes.

The CART method used inferior RNFL thickness, vertical CDR, average RNFL thickness, superior RNFL thickness, disc area, cup volume, symmetry, and nasal RNFL thickness for the classification. The CART method was also uniformly excellent in performance for both mild and moderate forms of glaucoma discrimination, compared with the diagnostic accuracy of the individual ONH and RNFL parameters ($P < 0.007$; Table 4). The CART misclassified 35 subjects as having mild glaucoma (Normal, 15; other stages of glaucoma, 20), 3 as having moderate glaucoma (other stages of glaucoma, 3), and 1 as having severe glaucoma (other stage of glaucoma, 1). The LDF performed less well in the discrimination of normal versus mild glaucoma compared with CART ($P < 0.0001$, Table 4).

The AUC of LDA for the validation data set was 0.98 (0.95, 0.99) and CART was 0.99 (0.99, 0.99).

**DISCUSSION**

To the best of our knowledge, this is the first study highlighting the superiority of classification algorithms derived from LDA and CART analysis methods for discriminating glaucomatous from normal eyes with Cirrus HD-OCT, using both ONH and RNFL parameters. The CART method also consistently performed better for mild and moderate glaucomas, compared with LDF and the individual OCT parameters.

We demonstrated that the diagnostic performance of ONH and RNFL parameters measured by HD-OCT in discriminating glaucoma from normals was comparable, and is in agreement with an earlier publication by Mwanza et al. The latter demonstrated slightly higher but insignificant difference in AUCs for ONH parameters, such as vertical rim thickness (0.96) and rim area (0.96) compared with inferior RNFL thickness, RNFL thickness at 7 clock hour position, and average RNFL thickness (0.95), among 73 glaucoma and 146 age-matched normal subjects. We demonstrated slightly lower AUCs for both ONH and RNFL parameters in our study. Our study did not have strict age matching between groups and the distribution of disease severity was different from their study (Mild: 58.7% vs. 42.5%; Moderate: 31.5% vs. 19.1%; Severe: 9.8% vs. 38.4%). The high AUC levels seen with superotemporal and inferotemporal clock hour RNFL thicknesses were also not demonstrated, which might be attributed to the lower prevalence of focal glaucomatous defects in our cohort.

Previous studies have shown that optic disc size and glaucoma severity influence the diagnostic performance of OCT. It has been reported that the optic disc size in Asian eyes is larger than that in white Americans. Similarly, the disc area (1.93 vs. 1.85 mm$^2$) was larger for normal subjects in our study compared with normal subjects in the article by Mwanza et al., whereas the rim area was similar (1.3 vs. 1.27 mm$^2$). Rao et al. found that optic disc size did not influence any of the scanning protocols in spectral-domain OCT (RTVue; Optovue, Inc., Fremont, CA) but the sensitivity of the rim area increased and the specificity decreased with larger optic discs. They also noted that disease severity affected AUCs for various parameters. Similarly, Leite and colleagues observed that subjects with severe visual field loss, represented by lower visual field index, had better AUC for RNFL parameters in detecting glaucoma. We had a greater number of patients with mild glaucoma in our study sample compared with that in the article by Mwanza et al. Thus, differences in optic disc topography due to ethnic differences as well as varying disease severity may have influenced the differences in diagnostic performance of individual parameters in our study. We also found a larger disc area in glaucomatous eyes compared with normals (1.97 vs. 2.12 mm$^2$, $P < 0.0001$). Xiao et al. noted similar findings in 52 consecutive unilateral glaucomatous eyes compared with the normal fellow eyes in a clinic-based Chinese population.

Few studies have evaluated ONH parameters measured by spectral domain/high-definition OCT compared with RNFL parameters for the diagnosis of glaucoma. Classification algorithms have used both these parameters in the diagnosis of glaucoma, using OCT and HRT with a view to improve diagnostic accuracy. Medeiros et al. reported better diagnostic performance for LDA compared with inferior RNFL thickness, which had the best AUC in isolated parameter analysis (0.97 vs. 0.91; $P = 0.012$). Pablo et al. used only ONH parameters and included disc area and horizontal rim width in...
their LDA, which performed slightly better than vertical rim area (AUC 0.92 vs. 0.9, P > 0.05). Naithani et al.\textsuperscript{17} reported the performance of both LDF and CART derived from time-domain OCT parameters to be similar (0.98) and found them to do better than Heidelberg retina tomography–derived discriminant functions. Manassakorn et al.\textsuperscript{27} found that in a group of 65 patients with glaucoma, the CART method used inferior RNFL thickness and vertical CDR and achieved the best misclassification rate of 6.2%. In our study, we found that vertical CDR, average RNFL thickness, and inferior RNFL thickness had the best AUC and the classifying algorithms performed better than the isolated parameters in diagnosis of glaucoma.

Our study has several limitations. There were age, CCT, and ethnic group differences between normal and glaucoma subjects. However, when subanalysis of Chinese glaucoma subjects alone was performed, we found no difference in the AUCs for the various parameters tested (data not shown). The clinical diagnosis of glaucoma was based on optic disc findings and this might be one of the reasons for the higher AUCs observed. However, this need not affect our aim of comparison between methods used in our study. The severity of glaucoma was based on arbitrary nonlinear divisions of the Humphrey visual field data. There were relatively few subjects with severe glaucoma, limiting our ability to compare AUCs for this group. Most studies have found higher AUCs for discriminating severe glaucoma from normals using isolated OCT parameters.\textsuperscript{14,15,23,24}

In conclusion, we have used the Cirrus HD-OCT to evaluate classification algorithms against individual RNFL and ONH parameters for glaucoma detection. We found that the LDA and CART methods performed better than any single parameter, although CART performed better than all other parameters for mild or early glaucoma discrimination. The inclusion of such classifiers may enhance the diagnostic performance of HD-OCT for glaucoma discrimination.

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