Diagnostic Classification of Retinal Nerve Fiber Layer Measurement in Myopic Eyes: A Comparison Between Time-Domain and Spectral-Domain Optical Coherence Tomography

KUN LIANG QIU, MING ZHI ZHANG, CHRISTOPHER KAI-SHUN LEUNG, RI PING ZHANG, XUE HUI LU, GENG WANG, AND DENNIS SHUN CHIU LAM

PURPOSE: To evaluate and compare the diagnostic classification of retinal nerve fiber layer (RNFL) measurement between time-domain and spectral-domain optical coherence tomography (OCT) in myopic eyes.

DESIGN: Prospective, observational study.

METHODS: A total of 97 eyes from 97 healthy myopic subjects were included. The RNFL in each eye was imaged sequentially with the Stratus OCT and the Cirrus HD-OCT (Carl Zeiss Meditec). With reference to the built-in normative database, the number of abnormal diagnostic classifications (borderline or outside normal limits) in each OCT device was analyzed and compared using the likelihood ratio chi-square test. Multiple logistic regression analysis was performed to evaluate factors associated with abnormal diagnostic classification.

RESULTS: The Cirrus HD-OCT classified a significantly higher percentage of eyes as outside normal limits/borderline in at least 1 clock hour (Stratus, 14.4%/24.8%; Cirrus, 21.6%/34.1%; all \( P < .01 \)). RNFL measurement at 1 (23.6%) and 2 o’clock (23.5%) of all eyes was the most frequent location classified as abnormal by the Cirrus HD-OCT and the Stratus OCT, respectively. Eyes with smaller optic disc and longer axial length were more likely to have abnormal diagnostic classification.

CONCLUSIONS: In myopic eyes, Cirrus HD-OCT was more likely to have abnormal diagnostic classification than the Stratus OCT. (Am J Ophthalmol 2011;xx: xxx. © 2011 by Elsevier Inc. All rights reserved.)

MYOPIA IS A COMMON OCULAR CONDITION worldwide that has been shown to be one of the risk factors for primary open-angle glaucoma.1–3 Diagnosing glaucoma in myopic subjects is important in clinical practice. It has been reported that retinal nerve fiber layer (RNFL) thinning may be an early sign of glaucomatous damage and measurement of RNFL thickness is an important diagnostic approach for detection of glaucoma.4 The optical coherence tomography (OCT) has been developed to determine the in vivo RNFL thickness quantitatively,5,6 And the Stratus OCT (Carl Zeiss Meditec, Dublin, California, USA) is the most updated and widely used time-domain OCT that has been reported to be useful for glaucoma detection in clinical practice.7–9 Although the normative database provided by Stratus OCT has been shown to be useful in identifying glaucomatous damage, a significant proportion of normal myopic eyes were reported to be classified as abnormal (outside normal limits or borderline).10 This has limited the use of Stratus OCT for glaucoma diagnosis in myopic subjects.

Recently, the spectral-domain OCT has been developed to provide a higher axial resolution and a much faster scan speed than time-domain OCT.11 These improvements have the potential to improve the diagnostic accuracy for glaucoma detection. And the diagnostic performance of Cirrus OCT has been investigated in normal and glaucoma subjects.12–14 However, no study has been performed to evaluate the diagnostic ability of Cirrus OCT in myopic subjects. The purpose of this study was to evaluate and compare the diagnostic classification of RNFL measurement of Stratus OCT and Cirrus HD-OCT in healthy myopic eyes. We also investigated potential factors associated with abnormal diagnostic classification.

MATERIALS AND METHODS

SUBJECTS: One hundred Chinese myopic subjects were recruited in our study. One eye from each subject was randomly selected. All subjects received complete ophthalmic examinations in Joint Shantou International Eye Center, which included visual acuity, intraocular pressure (IOP) measurement, refraction, axial length measurement...
by IOL master (Carl Zeiss Meditec), and dilated fundus stereoscopic examination. All the included eyes have spherical equivalent of less than −0.5 diopters (D) and no other concurrent diseases. Subjects with best-corrected visual acuity of less than 20/40, IOP over 21 mm Hg, family history of glaucoma, intraocular surgery, myopic macular degeneration, glaucoma, parapapillary atrophy (PPA) extending outside the measurement circle of the OCT, refractive surgery, neurological diseases, or diabetes were excluded. The study was designed following the ethical standards of the Declaration of Helsinki and approved by the local ethical committee with informed consent obtained before the study.

- **VISUAL FIELD TESTING:** All visual field tests were performed with the static automated white-on-white threshold 24-2 SITA standard strategy (Humphrey Field Analyzer II; Carl Zeiss Meditec). A visual field test was considered to be reliable when fixation loss, false positive, and false negative were all less than 20%. All the visual field tests of included eyes were those with pattern standard deviation (PSD) with $P > 5\%$ and within normal limits in glaucoma hemifield test (GHT).

- **CONFOCAL SCANNING LASER OPHTHALMOSCOPY IMAGING:** The optic disc was imaged with confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph II [HRT 2]; Heidelberg Engineering, GmbH, Dossenheim, Germany). A 3-dimensional topographic image consisting of $384 \times 384 \times 16$ up to $384 \times 384 \times 64$ pixels is constructed from multiple focal planes axially along the optic nerve head. An average of 3 consecutive scans is obtained and aligned to compose a single mean topography for analysis. Images obtained in this study were reviewed carefully for image quality and selected for analyses only when an average pixel height standard deviation (PSD) with $P > 5\%$ and within normal limits in glaucoma hemifield test (GHT).

- **OPTICAL COHERENCE TOMOGRAPHY IMAGING:** Time-domain OCT imaging was performed with Stratus OCT (software version 4.0.4, Carl Zeiss Meditec). The acquisition rate of the Stratus OCT is 400 A-scans per second and the axial resolution is 8 to 10 mm. RNFL thickness was measured with the fast RNFL (3.4) scanning protocol consisting of 256 A-scans. Average measurements of 3 sequential circular scans of diameter 3.46 mm centered on the optic disc were recorded. The RNFL 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 included scans had signal strength of at least 7.

### TABLE 1. Comparison of Average and Clock-Hour Retinal Nerve Fiber Layer Thickness Between Cirrus HD-OCT and Stratus OCT in 97 Normal Myopic Eyes (Paired $t$ Test)

<table>
<thead>
<tr>
<th>Clock Hours</th>
<th>Stratus OCT (um)</th>
<th>Cirrus HD-OCT (um)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>135.5 ± 25.56</td>
<td>112.9 ± 30.45</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>1</td>
<td>125.8 ± 22.68</td>
<td>102.1 ± 20.84</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>2</td>
<td>92.1 ± 25.79</td>
<td>74.7 ± 14.43</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>3</td>
<td>68.6 ± 19.05</td>
<td>58.5 ± 10.28</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>4</td>
<td>75.3 ± 20.70</td>
<td>58.9 ± 9.95</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>5</td>
<td>106.4 ± 23.10</td>
<td>91.5 ± 18.60</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>6</td>
<td>134.4 ± 26.40</td>
<td>127.6 ± 26.90</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>7</td>
<td>164.1 ± 22.36</td>
<td>157.7 ± 30.70</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>8</td>
<td>100.2 ± 24.98</td>
<td>89.6 ± 21.85</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>9</td>
<td>75.1 ± 16.5</td>
<td>65.5 ± 11.72</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>10</td>
<td>110.7 ± 23.47</td>
<td>100.8 ± 20.80</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>11</td>
<td>155.9 ± 24.37</td>
<td>144.6 ± 20.96</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Average thickness</td>
<td>111.7 ± 11.34</td>
<td>98.7 ± 9.02</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Spectral-domain OCT imaging was obtained using Cirrus HD-OCT (software version 4.5.1.11; Carl Zeiss Meditec). The scan speed for Cirrus is 27 000 A-scans per second and the axial resolution is 5 µm.15 The parapapillary RNFL thickness was measured by Cirrus HD-OCT using the Optic Disk Cube 200 × 200 protocol. This protocol obtains data through an area of $6 \times 6$ mm at the optic disc region by acquiring a series of 200 horizontal scan lines each composed of 200 A-scans. Eye movements were monitored by real-time fundus images. Images with misaligned vessels within the scanning circle were excluded and retaken. The signal for the included images had a minimum signal strength of 7.

For both OCT measurements, all images were acquired by 2 well-trained technicians during the same visit. Parameters including average and clock-hour RNFL thicknesses were generated automatically in the analysis reports of the Stratus OCT and Cirrus HD-OCT. Based on the internal normative databases, diagnostic classification (within normal limits, borderline, or outside normal limits) of each device was provided in the analysis printout. For both OCTs, there were 4 diagnostic classes. The upper 5th percentile was indicated in white, the 5th to 95th percentiles were indicated in green (within normal limits), the 1st to 5th percentiles were indicated in yellow (borderline), and the lower 1st percentile was indicated in red (outside normal limits).15,16 White and green were regarded as normal while yellow and red were abnormal in our analysis.

### STATISTICAL ANALYSIS:

The statistical analyses were performed with commercially available software (SPSS ver.13.0; SPSS Inc, Chicago, Illinois, USA). The relationship between Cirrus HD-OCT and Stratus OCT measurements was evaluated using Pearson correlation analysis. Based on the internal normative databases, diagnostic classification (within normal limits, borderline, or outside normal limits, abnormal) was evaluated using the $t$-test.
normal limits) provided by each device were compared using the likelihood ratio chi-square test. Logistic regression analysis was performed to investigate the factors associated with the diagnostic classification. A \( P < .05 \) was considered statistically significant.

RESULTS

AFTER EXCLUDING 2 SUBJECTS WITH UNRELIABLE VISUAL field tests and 1 for extensive PPA, 97 eyes from 97 subjects (43 female and 61 right eyes) were analyzed. The mean age, axial length, and spherical equivalent were 22.84 ± 3.92 years (range, 18-40), 25.55 ± 1.11 mm (range, 22.52–28.77 mm), and −4.93 ± 2.17 D (range, −1.00 to −12.75 D), respectively. The visual field mean deviation and pattern standard deviation were −2.13 ± 1.12 dB and 1.49 ± 0.98 dB. The signal strength of Stratus OCT was significantly higher than that of Cirrus HD-OCT (9.1 ± 0.8 vs 8.0 ± 0.7, \( P < .01 \)).

The average and clock-hour RNFL thickness for both OCTs were demonstrated in Table 1. RNFL thickness obtained by Stratus OCT was significantly thicker than that of Cirrus HD-OCT (9.1 ± 0.8 vs 8.0 ± 0.7, \( P < .01 \)).

Logistic regression analysis showed that eyes with smaller optic disc size (Stratus, odds ratio: 0.23, \( P < .01 \); Cirrus, odds ratio: 0.17, \( P < .01 \)) and longer axial length (Stratus, odds ratio: 2.75, \( P < .01 \); Cirrus, odds ratio: 1.80, \( P < .01 \)) were significantly associated with higher percentage of abnormal diagnostic classification (Table 2). Age, visual field mean deviation, and signal strength were not associated with abnormal diagnostic classification in both OCTs (Table 2).

FIGURE 1. Scatterplot showing the relationship of average retinal nerve fiber layer thickness between both OCTs in 97 myopic eyes.

Discussion

IN THIS STUDY, WE FOUND THAT NASAL RNFL MEASUREMENT was frequently classified as borderline or outside normal limits in both OCTs and that the frequency of abnormal classification of RNFL measurement was significantly higher in Cirrus HD-OCT than Stratus OCT. Eyes with smaller optic disc size and longer axial length
were found to be associated with significantly higher percentages of abnormal diagnostic classification in both devices.

The Stratus OCT is a time-domain OCT that has been shown reliable for detecting glaucoma in clinical practice. Jeoung and associates reported that the Stratus OCT diagnostic classification can detect localized RNFL defects with moderate sensitivity and high specificity. Although the normative database provided by Stratus OCT has been shown useful to detect glaucomatous damage, Leung and associates reported that a significant proportion (44.2% at 2 o’clock) of normal myopic eyes were classified as abnormal (outside normal limits or borderline). In agreement with Leung’s study, we found that 23.5% of eyes were classified as abnormal in myopic eyes, with 2 o’clock being the most frequent abnormal clock hour. With a higher scan resolution and a much faster scan speed, the Cirrus HD-OCT has the potential to provide more accurate RNFL measurements and improve the diagnostic accuracy for glaucoma detection. The diagnostic performance of Cirrus HD-OCT has been investigated in normal and glaucoma subjects. However, only a few studies have been performed on myopic subjects. We found that the frequency of having an abnormal classification (borderline or outside normal limits) was significantly higher in Cirrus HD-OCT than Stratus OCT (55.7% vs 39.2% in at least 1 clock hour).

According to the normative database from the manufacturer, 1 out of 20 normal eyes (the thinnest 5%) would be classified as abnormal. Kim and associates reported that the false-positive rates (percentage of abnormal classification in normal eyes) at the 5% level ranged from 0% to 5.1% with the Stratus OCT normative database. In another study, Sung and associates reported that no eyes were classified as abnormal in 60 healthy eyes. In the present study, however, sectorial RNFL measurement was

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**FIGURE 2.** Clock-hour abnormal classification of retinal nerve fiber layer measurement with (Top) Cirrus OCT and (Bottom) Stratus OCT in 97 myopic eyes.
frequently classified as abnormal for both OCTs in normal myopic eyes. These contradictory results may be explained in part by the differences in refractive errors in the study population. Of note, only subjects with myopia (mean spherical equivalent was $-4.93 \pm 2.17$ D) were included in our study and the mean spherical equivalent in the
present study was 3.90 D less than that reported in Kim’s study (mean refraction, −1.03 ± 2.08 D).19 In Leung’s study, the authors also reported that more eyes were classified as abnormal in the high myopia group than in the low-to-moderate myopia group.10 These results indicated that refractive errors may play a significant role on diagnostic classification in both OCTs.

The relationship between myopia and OCT RNFL measurements has been investigated. While some studies found a significant negative relationship between axial length and RNFL thickness, others have reported different results.10,21,22 Hoh and associates22 did not find any significant association between RNFL thickness and axial length or spherical equivalent. By using logistic regression analysis, we found that eyes with longer axial length were associated with a higher percentage of abnormal diagnostic classification in both OCTs. Our findings demonstrated a significant association between axial length and abnormal diagnostic classification in both OCTs. According to the manufacturer, the RNFL normative database is adjusted only by age but not by axial length or refractive error.15 Due to high abnormal classification rates observed in the present study, the authors also reported that more eyes were subsequently classified as borderline or outside normal limits in both devices.

Controversies exist regarding the association between optic disc size and RNFL measurements. Some histologic studies have reported a positive correlation between disk size and the number of nerve fibers, while other studies have reported different results.23–25 Most studies demonstrated a positive correlation between disk area and RNFL measurement. Budenz and associates26 and Savini and associates27 demonstrated a positive correlation between average RNFL thickness and the disc area using Stratus OCT. Medeiros and associates28 found that the diagnostic performance of Stratus OCT was significantly influenced by the optic disc size. As both Stratus OCT and Cirrus HD-OCT measure RNFL at a fixed-diameter circle of 1.73-mm radius around the optic disc, the optic disc size is negatively correlated to distance between disc margin and the measurement circle. On the other hand, it has been shown that RNFL thickness decreases when the measurement distance increases from the disc.29 Therefore, it is not surprising that eyes with smaller optic disc size were associated with a higher percentage of abnormal diagnostic classification in both OCTs. Thus, disc size should be taken into consideration when interpreting the results of Stratus OCT and Cirrus HD-OCT in clinical practice.

Previous investigations reported that Cirrus HD-OCT measured a significantly thinner RNFL than the Stratus OCT. We also found that Stratus OCT measured significantly thicker RNFL than the Cirrus in myopic eyes. Different technologies and segmentation algorithms of the 2 OCT systems may be accountable for the thinner RNFL measurement observed in Cirrus HD-OCT. Signal strength has been shown to affect RNFL measurement in Stratus OCT. Cheung and associates30 reported that the signal strength was positively correlated with RNFL thickness in Stratus OCT. At the time of this writing, no study has been performed to evaluate the effect of signal strength on RNFL thickness in Cirrus HD-OCT. To reduce the potential effect of signal strength, only images with signal strength ≥7 were included in the present analysis and we did not find a significant association between signal strength and the diagnostic classification in both OCTs.

One limitation in this study is that we did not have any gold standard for preperimetric glaucoma. Abnormal diagnostic classification observed in the present study may indicate early glaucomatous damage not detected by perimetry or clinical optic disc examination. It has been shown that the RNFL thickness of a normal eye is thickest in the superior and inferior sectors, and thinnest in the nasal and temporal sectors (ISNT rule). Early glaucomatous defects are frequently observed in the inferotemporal and superotemporal sectors. Abnormal diagnostic classification at the nasal sector may not be suggestive of glaucomatous damage. Longitudinal follow-up would be useful to address this issue. Another limitation is that both Stratus OCT and Cirrus HD-OCT did not consider the effect of ocular magnification on RNFL measurement. The diameter of the measurement circle could be greater than 3.4 mm in myopic eyes and resulted in higher percentages of eyes having an abnormal classification.

In conclusion, the nasal RNFL measurement was frequently classified as borderline or outside normal limits in myopic eyes and the frequency of such abnormal classification was significantly higher in Cirrus HD-OCT than that in Stratus OCT. Eyes with smaller optic disc size and longer axial length were associated with higher percentages of abnormal diagnostic classification in both devices. Caution should be exercised in interpreting the results of Stratus OCT and Cirrus HD-OCT in highly myopic eyes with small optic disc.

### TABLE 2. Factors Associated With the Diagnostic Classification of Stratus OCT and Cirrus HD-OCT in 97 Normal Myopic Eyes (Multiple Logistic Regression Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Stratus OCT</th>
<th>Cirrus HD-OCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Odds Ratios</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CI</strong></td>
<td>P</td>
<td><strong>CI</strong></td>
</tr>
<tr>
<td>Age</td>
<td>1.07 (0.95–1.20)</td>
<td>.25</td>
</tr>
<tr>
<td>Signal strength</td>
<td>2.04 (0.97–4.27)</td>
<td>.06</td>
</tr>
<tr>
<td>Axial length</td>
<td>2.75 (1.61–4.69)</td>
<td>.01</td>
</tr>
<tr>
<td>Disc area</td>
<td>0.23 (0.07–0.70)</td>
<td>.01</td>
</tr>
<tr>
<td>Visual field MD</td>
<td>1.01 (0.66–1.54)</td>
<td>.95</td>
</tr>
</tbody>
</table>

CI = confidence interval; MD = mean deviation.
REFERENCES


Mingzhi Zhang, is a Professor of Glaucoma at Joint Shantou International Eye Center of Shantou University and The Chinese University of Hong Kong. She is experienced in glaucoma surgery and cataract and refractive surgery. Dr. Zhang’s primary research focus is ocular imaging and neuroprotection in glaucoma.
Kunliang Qiu, is currently a resident at Department of Glaucoma, Joint Shantou International Eye Center of Shantou University and The Chinese University of Hong Kong. Dr. Qiu is interested in ocular imaging with hopes of becoming a proliferative clinician-scientist.