Ability of Different Scanning Protocols of Spectral Domain Optical Coherence Tomography to Diagnose Preperimetric Glaucoma

Harsha L. Rao,[1,2] Uday K. Addepalli,[1] Shashikant Chaudhary,[1] Tukaram Kumbar,[1] Sirisha Senthil,[1] Nikhil S. Choudhari,[1] and Chandra S. Garudadri[1]

[1]Vazir Sultan Tobacco (VST) Glaucoma Center, L V Prasad Eye Institute, Banjara Hills, Hyderabad, India
[2]Center for Clinical Epidemiology and Biostatistics, L V Prasad Eye Institute, Banjara Hills, Hyderabad, India

Correspondence: Harsha L. Rao, Kallam Anji Reddy campus, L V Prasad Eye Institute, Banjara Hills, Hyderabad - 500034, India; harshalaxmanarao@gmail.com.

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Purpose. To evaluate the ability of the optic nerve head (ONH), retinal nerve fiber layer (RNFL), and ganglion cell complex (GCC) parameters of spectral domain optical coherence tomograph (SDOCT) in detecting preperimetric glaucoma.

Methods. In a cross-sectional study, 34 preperimetric glaucoma eyes (34 patients) and 72 control eyes (72 subjects) with large physiologic optic disc cupping underwent ONH, RNFL, and GCC imaging with SDOCT. Preperimetric glaucoma was diagnosed in the presence of glaucomatous optic neuropathy on masked evaluation of optic disc photographs by two glaucoma experts and normal visual fields. The ability of SDOCT parameters to discriminate preperimetric glaucoma eyes from eyes with large physiologic cups was evaluated by areas under the receiver operating characteristic curves (AUC), sensitivities at fixed specificities, and likelihood ratios (LR).

Results. All SDOCT parameters were significantly different ($P < 0.05$) between the two groups. The ONH, RNFL, and GCC parameters with best AUCs to differentiate preperimetric glaucoma from eyes with large physiologic cups were vertical cup to disc ratio (0.76), inferior quadrant RNFL thickness (0.76), and inferior quadrant GCC thickness (0.75), respectively. Sensitivities at 95% specificity of SDOCT parameters ranged between 15% and 29%. Likelihood ratios of outside normal limits category of parameters ranged between 3 and 11, and within normal limits category between 0.5 and 0.8.

Conclusions. Diagnostic abilities of ONH, RNFL, and GCC parameters of SDOCT to differentiate preperimetric glaucoma eyes from control eyes with large physiologic cupping were only moderate.

Keywords: spectral domain optical coherence tomograph, preperimetric glaucoma, ganglion cell complex, retinal nerve fiber layer, diagnostic ability

Spectral domain optical coherence tomography (SDOCT) is a recent technique, which enables imaging the ocular structures with higher resolution and a faster scan rate compared with the previous version of this technology (Stratus OCT; Carl Zeiss Meditec, Inc., Dublin, CA).[1,2] Several studies have reported good diagnostic ability of SDOCT in glaucoma.[3–7] These, as well as most of the studies with imaging technologies in glaucoma, have employed a case-control design including glaucoma patients (cases), defined based on the presence of repeatable characteristic glaucomatous visual field (VF) defects, and healthy subjects (controls), usually recruited from the general population and having normal IOP, healthy appearance of the optic nerve, and normal VFs. However, selection of both cases and controls in this manner defeats the purpose for which glaucoma imaging technologies are used in clinical practice. In clinical practice, imaging tests are used to diagnose glaucoma early, which necessarily has to be before a VF defect develops (preperimetric stage) because studies in primates have shown that half the number of ganglion cells are already lost by the time a VF defect develops.[8] Recently, a few studies have evaluated the diagnostic ability of SDOCT in preperimetric glaucoma.[9–15] However, these studies have evaluated preperimetric glaucoma patients against control subjects, with no suspicious findings of glaucoma. In clinical practice once again, a diagnostic test is used to rule out disease in subjects suspected of having a disease and not in subjects without any suspicious findings of a disease. This bias introduced when a diagnostic accuracy study is not conducted in a clinically relevant population is called spectrum bias.[16] We have previously demonstrated how the selection of the control group affected the diagnostic accuracy of SDOCT in early glaucoma.[17]

The purpose of the current study was to evaluate the ability of optic nerve head (ONH), retinal nerve fiber layer (RNFL), and ganglion cell complex (GCC) parameters of SDOCT in detecting preperimetric glaucoma. The control group, against which the preperimetric glaucoma group was evaluated, consisted of subjects referred to our institute from general ophthalmologists as glaucoma suspects based on the optic disc appearance who were later judged as normals with large physiological cups by glaucoma experts at our institute (detailed below). We also used a traditional control group

consisting of eyes with no suspicious findings of glaucoma to compare our results with previous studies and to emphasize the importance of spectrum bias.

Methods

This was an observational, cross-sectional study of subjects referred by general ophthalmologists for a glaucoma evaluation, to a tertiary eye care facility between January 2010 and December 2012. Informed consent was obtained from all subjects and the ethics committee of L V Prasad Eye Institute approved all methodology. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

Inclusion criteria were 18 years of age or older, best corrected visual acuity of 20/40 or better, and refractive error within ±5 diopter (D) sphere and ±3 D cylinder. Exclusion criteria were presence of any media opacities that prevented good quality optic disc photographs and SDOCT imaging and any retinal (including macular) disease other than glaucoma that could confound the evaluations. All participants underwent a comprehensive ocular examination, which included a detailed medical history, best corrected visual acuity measurement, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, standard automated perimetry (SAP), digital optic disc photography, and SDOCT imaging with RTVue (Optovue, Inc., Fremont, CA).

Standard automated perimetry was performed using a Humphrey Field analyzer, model 750 (Zeiss Humphrey Systems, Dublin, CA), with the Swedish interactive threshold algorithm (SITA) standard 24-2 algorithm. Reliability criteria were fixation losses, false positive and false negative response rates of less than 20%. Visual fields were considered normal if the pattern SD had a *P* value of more than 5% or the glaucoma hemifield test result was within normal limits.[18]

Digital optic disc photographs were obtained by trained technicians (FF 450^{plus} with VISUPAC 4.2.2; Carl Zeiss Meditec Systems GmbH, Pirmasens, Germany). Photographs were two dimensional and consisted of a 50° image centered on the optic disc, a similar image centered on the macula, a 30° image centered on the optic disc and a 20° image centered on the disc. All these images also consisted of one colored and one red-free image each. Optic disc photographs were evaluated independently by two glaucoma experts (with at least 5 years' experience of working as glaucoma specialists), who were masked to the clinical examination results of the subjects and also the results of VF and SDOCT examinations. They classified the optic discs into glaucoma and nonglaucoma (control) groups based on the presence or absence of characteristic glaucomatous optic disc changes (focal or diffuse neuroretinal rim thinning, localized notching or nerve fiber layer defects). Discrepancies between the two experts were resolved by consensus.

Spectral domain optical coherence tomograph examination was performed with the RTVue (software version 5.1.0.90; Optovue, Inc.). The protocols used for imaging with RTVue in this study were ONH and GCC. These protocols and the parameters measured have been explained earlier.[17,19] All patients had both protocols as well as the VF testing performed on the same day. Only well-centered images with a signal strength index (SSI) of greater than or equal to 30 were used for analysis. Eyes in which the segmentation algorithm failed were excluded. A few of the RTVue parameters are compared with the internal normative database within the software and one of the three diagnostic categorizations is provided. "Outside normal result" categorization indicates that the value is lesser than the lower 99% confidence interval (CI) of the healthy, age-matched population. "Borderline" result indicates that the value is between the 95% and 99% CI, and a "within-normal-limits" indicates that the value is within the 95% CI.

Preperimetric glaucoma eyes included in this study had glaucomatous optic neuropathy (neuroretinal rim thinning, notching, and/or RNFL defects), as evaluated by masked experts and normal SAP results. In addition, the other eye of these patients had perimetric glaucoma with glaucomatous optic neuropathy and correlating SAP defects. Subjects for control group consisted of consecutive subjects who were referred to our center by general ophthalmologists, as glaucoma suspects based on the optic disc morphology (control group 1). Though found suspicious by the general ophthalmologists, their optic discs were confirmed on masked evaluation of disc photographs by the glaucoma experts to be nonglaucomatous with large physiologic cupping. In addition, all these subjects had IOP less than 22 mm Hg in both eyes, no past history of increased IOP, no family history of glaucoma, and normal VF. They were also not on any antiglaucoma medications. In addition to this control group, we included a traditional control group consisting of subjects with no suspicious findings for glaucoma (control group 2). Subjects for this control group were recruited from those who came for a routine eye examination and hospital staff. These subjects also had a normal ocular examination, IOP less than 22 mm Hg in both eyes, no past history of increased IOP, no family history of glaucoma, and normal VF. The characteristic features of this group have been detailed earlier.[17,19]

Statistical Analysis

Descriptive statistics included mean and SD for normally distributed variables and median and interquartile range (IQR) for nonnormally distributed variables. The Shapiro Wilk test was used to check for the normality of distribution. Receiver operating characteristic (ROC) curves were used to describe the ability of each RTVue software (Optovue, Inc.) provided parameter to discriminate preperimetric glaucomatous eyes from control eyes. Sensitivities at fixed specificities of 80% and 95% were determined for all the parameters. To obtain CIs for area under the ROC curves (AUC), a bootstrap resampling procedure was used ($n = 1000$ resamples). Z-test was used to compare the AUCs[20,21] and χ^2 test to compare the sensitivities at fixed specificities of SDOCT parameters in diagnosing preperimetric glaucoma. Likelihood ratios were reported for diagnostic categorization (outside normal limits, borderline, or within normal limits) provided after comparison with the instrument's internal normative database. The LR is the probability of a given test result in those with disease divided by the probability of the same test result in those without the disease.[22] The LR for a given test result indicates how much that result will raise or lower the probability of disease. A LR of 1 or close to 1 would mean that the test provides no additional information about the posttest probability of the disease. Likelihood ratios higher than 10 or lower than 0.1 would be associated with large effects on posttest probability, LRs from 5 to 10 or from 0.1 to 0.2 would be associated with moderate effects, and LRs from 2 to 5 or from 0.2 to 0.5 would be associated with small effects.[22] The 95% CIs for LRs were calculated according to the method proposed by Simel et al.[23]

Statistical analyses were performed using commercial software (Stata ver. 11.2; StataCorp, College Station, TX). A *P* value of less than 0.05 was considered statistically significant.

Table 1. Demographic, Visual Field, and Spectral Domain Optical Coherence Tomograph Characteristics of the Participants

	Preperimetric Glaucoma, $n = 34$	Control Group 1, $n = 72$	Control Group 2, $n = 60$	P^1	P^2
Age, y	54 (41–61)	52 (41–62)	50 (38–57)	0.89	0.13
Disc area, mm^{2*}	2.00 ± 0.63	2.23 ± 0.56	2.37 ± 0.39	0.07	0.001
Mean deviation, dB	−2.14 (−4.25 to −0.98)	−1.90 (−3.63 to −0.71)	−1.26 (−2.10 to −0.50)	0.49	<0.001
Pattern standard deviation, dB	1.82 (1.44–2.18)	1.63 (1.45–1.93)	1.52 (1.34–1.77)	0.15	0.01
SSI of ONH scan	52.2 (46.3–61.0)	50.8 (43.7–58.2)	58.0 (52.9–66.2)	0.46	0.01
Rim area, mm^2	0.45 (0.16–0.67)	0.80 (0.46–1.04)	1.60 (1.36–1.92)	<0.001	<0.001
Sup rim area, mm^2	0.18 (0.04–0.21)	0.26 (0.18–0.32)	0.48 (0.39–0.53)	<0.001	<0.001
Inf rim area, mm^2	0.06 (0.01–0.18)	0.20 (0.10–0.28)	0.45 (0.37–0.55)	<0.001	<0.001
Rim volume, mm^3	0.02 (0.01–0.07)	0.06 (0.03–0.11)	0.21 (0.15–0.29)	<0.001	<0.001
Cup-disc area ratio	0.82 (0.66–0.91)	0.68 (0.49–0.79)	0.27 (0.11–0.43)	<0.001	<0.001
Vertical cup-disc ratio	0.92 (0.88–0.99)	0.82 (0.71–0.89)	0.55 (0.36–0.65)	<0.001	<0.001
Sup RNFL, μm*	110.9 ± 20.0	123.2 ± 16.7	131.7 ± 15.5	0.001	0.001
Inf RNFL, μm*	112.8 ± 17.8	130.1 ± 17.7	141.9 ± 15.1	<0.001	<0.001
Avg RNFL, μm*	91.6 ± 12.8	103.1 ± 11.1	108.8 ± 9.8	<0.001	<0.001
SSI of GCC scan	61.3 (55.2–65.6)	60.6 (54.2–67.4)	67.1 (62.3–71.4)	0.85	0.002
Avg GCC, μm	88.0 (81.4–92.4)	94.6 (89.2–100.3)	96.5 (92.4–101.5)	<0.001	<0.001
Sup GCC, μm	87.3 (83.6–95.0)	94.7 (89.1–98.5)	94.8 (91.0–100.1)	0.002	0.002
Inf GCC, μm	86.3 (79.7–92.2)	95.2 (89.1–101.6)	97.6 (93.6–102.8)	<0.001	<0.001
GCC FLV, %	2.7 (1.4–4.7)	1.1 (0.3–2.4)	−0.1 (−0.1–0.3)	<0.001	<0.001
GCC GLV, %	11.2 (6.1–15.8)	5.2 (2.0–9.2)	0.1 (0.0–3.6)	<0.001	<0.001

SSI, signal strength index; Sup, superior; Inf, inferior; Avg, average. All values are median with interquartile range in parentheses unless otherwise specified. P^1 represents the P value (Wilcoxon rank sum test) associated with the comparisons between preperimetric glaucoma group and control group 1 (healthy eyes with large physiologic cup). P^2 represents the P value (Wilcoxon rank sum test) associated with the comparisons between and preperimetric glaucoma group and control group 2 (healthy eyes with no suspicious findings for glaucoma).

* Values are mean ± SD.

Results

We included 34 preperimetric glaucoma eyes of 34 glaucoma patients as cases and 72 eyes of 72 subjects with large physiological optic disc cupping as controls (control group 1). The glaucomatous optic disc changes noted in the preperimetric glaucoma group by the experts consisted of rim thinning in all eyes, notching in eight eyes (23.5%) and localized wedge-shaped RNFL defect in 25 eyes (73.5%). We also included 60 eyes of 60 subjects with no suspicious findings of glaucoma as control group 2. Table 1 shows the age, VF, and SDOCT parameters of the three groups of participants. All SDOCT parameters were significantly different between the preperimetric glaucoma and the control group 1. VF parameters were comparable between the preperimetric glaucoma and the control group 1. All VF and SDOCT parameters were significantly different between the preperimetric glaucoma and the control group 2. Optic disc area was statistically significantly smaller in the preperimetric glaucoma group compared with the control group 2, while the difference in optic disc area between preperimetric glaucoma and control group 1 showed borderline significance.

Table 2 shows the AUC and sensitivities at fixed specificities of SDOCT parameters in differentiating preperimetric glaucoma eyes from control group eyes. Areas under the receiver operating characteristic curve of the SDOCT parameters to differentiate preperimetric glaucoma eyes from control group 1 eyes ranged between 0.69 and 0.76; sensitivities at 95% specificity ranged between 15% and 30%. Areas under the receiver operating characteristic curve and sensitivities at fixed specificities of all SDOCT parameters were better in differentiating preperimetric glaucoma eyes from control group 2 eyes compared with differentiating preperimetric glaucoma eyes from control group 1 eyes. The differences in AUCs were statistically significant for all ONH parameters ($P < 0.001$) and for GCC focal loss volume (FLV) ($P = 0.03$). Differences in the sensitivities at fixed specificities of 95% and 80% were statistically significant for all ONH parameters ($P < 0.001$), inferior quadrant RNFL measurement ($P < 0.05$) and GCC FLV ($P < 0.001$).

Table 3 shows the LRs associated with the normative database classification of SDOCT parameters to discriminate preperimetric glaucoma from control eyes. Outside normal limits category of GCC FLV and global loss volume (GLV) were associated with small effects on the posttest probability of preperimetric glaucoma. Outside normal limits category of all other parameters were associated with large effects on the posttest probability of preperimetric glaucoma when compared with control group 2. When compared against control group 1, outside normal limits category of all other parameters, however, were associated with only moderate effects on the posttest probability of disease. Within normal limits category of all SDOCT parameters were associated with no effect on the posttest probability of preperimetric glaucoma when compared against control group 2 as well as control group 1. Borderline category of some of the parameters were associated with moderate effects on posttest probability of preperimetric glaucoma when compared against control group 2 but were associated with no effects when compared against control group 1.

In clinical practice, glaucoma is suspected when an abnormal test result on imaging is found either in the superior or inferior quadrant and an eye is considered healthy when an abnormal result is not found at any location. Thus, we also evaluated the LRs for the outside normal limit category in either the superior or inferior quadrant and for the within normal limits category in both superior and inferior quadrants. Evaluating the preperimetric glaucoma group against the control group 1, LR associated with the outside normal limits category either in the superior or inferior RNFL quadrant was 4.1 (95% CI: 2.2–7.6) and the LR associated with the within normal limits category in both superior and inferior RNFL quadrants was 0.37 (95% CI: 0.21–0.67). The same, when preperimetric glaucoma group was evaluated against the

Table 2. Diagnostic Ability of SDOCT Parameters in Differentiating Preperimetric Glaucoma From Control Group 1 (Healthy Eyes With Large Physiologic Cups) and Control Group 2 (Healthy Eyes With No Suspicious Findings for Glaucoma)

Optical Coherence Tomograph Parameters	Preperimetric Glaucoma From Control Group 1			Preperimetric Glaucoma From Control Group 2		
	AUC (95% CI)	Sensitivity at 95% Specificity (95% CI)	Sensitivity at 80% Specificity (95% CI)	AUC (95% CI)	Sensitivity at 95% Specificity (95% CI)	Sensitivity at 80% Specificity (95% CI)
Rim area	0.72 (0.62–0.81)	23.5% (3.1–38.2)	47.1% (26.8–77.4)	0.96 (0.90–1.00)	82.4% (60.0–95.9)	94.1% (78.8–100)
Sup rim area	0.71 (0.60–0.81)	26.5% (9.7–45.5)	47.1% (22.9–62.9)	0.95 (0.89–0.99)	79.4% (57.1–94.3)	91.2% (75.8–100)
Inf rim area	0.72 (0.61–0.82)	29.4% (8.3–54.8)	47.1% (22.9–62.9)	0.96 (0.90–0.99)	76.5% (42.1–92.3)	97.1% (86.8–100)
Rim volume	0.72 (0.61–0.81)	17.6% (3.2–36.1)	52.9% (25.0–80.6)	0.91 (0.75–0.99)	64.7% (23.5–90.3)	85.3% (64.9–100)
Cup–disc area ratio	0.70 (0.58–0.80)	23.5% (6.7–44.8)	55.9% (35.5–75.0)	0.98 (0.92–1.00)	85.3% (64.3–96.9)	97.1% (87.9–100)
Vertical cup–disc ratio	0.76 (0.65–0.84)	26.5% (9.7–45.5)	58.8% (25.6–81.6)	0.97 (0.90–1.00)	88.2% (66.7–100)	94.1% (74.3–100)
Sup RNFL	0.69 (0.57–0.80)	23.5% (7.1–47.6)	47.1% (27.6–70.7)	0.77 (0.54–0.89)	32.4% (8.3–54.1)	76.5% (55.0–94.1)
Inf RNFL	0.76 (0.64–0.84)	23.5% (8.6–44.4)	52.9% (26.1–72.7)	0.85 (0.73–0.94)	52.9% (15.2–72.7)	82.4% (62.5–97.0)
Avg RNFL	0.75 (0.64–0.85)	23.5% (3.6–42.9)	55.9% (32.3–80.0)	0.82 (0.69–0.91)	41.2% (19.2–67.6)	79.4% (63.9–94.9)
Avg GCC	0.72 (0.61–0.83)	14.7% (2.8–38.7)	50.0% (31.0–73.5)	0.78 (0.66–0.87)	35.3% (8.8–57.6)	67.6% (44.1–87.0)
Sup GCC	0.69 (0.57–0.80)	20.6% (4.5–46.2)	52.9% (28.1–75.0)	0.73 (0.58–0.84)	35.3% (10.8–59.4)	58.8% (37.5–81.3)
Inf GCC	0.75 (0.64–0.84)	26.5% (3.2–52.8)	52.9% (35.6–76.5)	0.83 (0.72–0.91)	35.3% (11.8–55.0)	76.5% (60.0–96.8)
GCC FLV	0.72 (0.60–0.82)	14.7% (2.7–33.3)	47.1% (25.0–69.4)	0.89 (0.72–0.97)	50.0% (5.6–82.4)	91.2% (63.9–100)
GCC GLV	0.74 (0.62–0.84)	20.6% (3.1–45.0)	52.9% (32.1–72.7)	0.86 (0.74–0.94)	20.6% (2.8–61.1)	73.5% (51.5–96.9)

All comparisons between AUCs of different scanning protocols with control group 1 showed $P > 0.50$.

control group 2, was 13.2 (4.3–40.8) and 0.33 (0.18–0.58), respectively. Similarly, evaluating the preperimetric glaucoma group against the control group 1, LR associated with the outside normal limits category either in the superior or inferior GCC quadrant was 8.1 (95% CI: 2.4–27.0), and the LR associated with the within normal limits category in both superior and inferior GCC quadrants was 0.65 (95% CI: 0.47–0.88). The same, when preperimetric glaucoma group was evaluated against the control group 2, was 11.2 (2.6–47.4) and 0.64 (0.47–0.87), respectively. We also evaluated the LRs for the outside normal limit category in either the superior or inferior quadrant of either the RNFL or the GCC protocol and for the within normal limits category in both superior and inferior quadrants of both the RNFL and the GCC protocols. Evaluating the preperimetric glaucoma group against the control group 1, LR associated with the outside normal limits category either in the superior or inferior quadrant of RNFL or GCC was 3.8 (95% CI: 2.1–6.8), and the LR associated with the within normal limits category in both superior and inferior quadrants of RNFL and GCC was 0.31 (95% CI: 0.15–0.63). The same, when preperimetric glaucoma group was evaluated against the control group 2, was 8.3 (3.5–19.6) and 0.28 (0.14–0.55), respectively.

None of the scanning protocol of SDOCT was better than the other in its ability to differentiate preperimetric glaucomatous eyes from control group 1 eyes in terms of the either AUCs or sensitivities at fixed specificities ($P > 0.5$ for all comparisons between the global ONH, RNFL, and GCC parameters).

Discussion

In this study, to evaluate the ability of ONH, RNFL, and GCC parameters of SDOCT in differentiating preperimetric glaucoma eyes from eyes with large physiologic cups, we found that the AUCs of the best parameters of each of these scanning areas were around 0.7 and sensitivities at a specificity of 95% were around 25%.

The AUCs as well as the sensitivities at fixed specificities found in our study were lower than those reported for SDOCT parameters by other diagnostic accuracy studies in preperimetric glaucoma.[9–15] One of the major reasons for this, as mentioned earlier is the nature of the control group. All these studies have used a control group consisting of eyes with no suspicious findings of glaucoma. When we analyzed the ability of SDOCT to differentiate preperimetric glaucoma from eyes with no suspicious findings of glaucoma (traditional control group), the diagnostic ability parameters were very similar to that reported in earlier studies.[9–15] In contrast to earlier studies, we used subjects with large physiologic cups as the control group. These were the subjects referred by general ophthalmologists as glaucoma suspects based on the optic disc appearance. These subjects underwent a masked evaluation of their optic disc photographs by glaucoma experts in our institute and were judged as normals with large physiological cupping of optic nerves. We have demonstrated earlier how a control group with no suspicious findings of glaucoma can significantly inflate the diagnostic ability of SDOCT in glaucoma compared with a control group that is likely to be misinterpreted as glaucoma.[17]

One of the other reasons for low sensitivities of SDOCT parameters in our study is that the parameters evaluated in our study were quadrant averages, and averaging of thicknesses over quadrants might have masked localized defects. Earlier studies have shown that RNFL defects with narrow angular width are less likely to be detected in sector maps.[9,24] Another possible reason for low diagnostic accuracy is the issue with false positives on SDOCT. There is a possibility that the eyes labeled as "false positives" on SDOCT were actually eyes with early glaucomatous damage that was not possible to be picked up by experts on disc photographs. Follow up of these eyes would help in evaluating this possibility.

In addition to sensitivity, specificity and AUC, diagnostic tests are also summarized in terms of LR, which is higher than the previous measures in hierarchy, as it expresses the magnitude by which the probability of a diagnosis in a given patient is modified by the results of the test.[25,26] In other words, the LR indicates how much a given diagnostic test result will raise or lower the pretest probability of the disease

Table 3. Likelihood Ratios (With 95% CI) of the Normative Database Classification of SDOCT Parameters to Discriminate Preperimetric Glaucoma From Control Group 1 (Healthy Eyes With Large Physiologic Cups) and Control Group 2 (Healthy Eyes With No Suspicious Findings for Glaucoma)

Parameter	Within Normal Limits	Borderline	Outside Normal Limits
Preperimetric glaucoma against control group 1			
Sup RNFL	0.69 (0.50–0.96)	1.9 (0.9–4.1)	3.8 (1.5–9.6)
Inf RNFL	0.54 (0.37–0.79)	1.6 (0.6–4.2)	6.4 (2.6–16.1)
Avg RNFL	0.68 (0.51–0.89)	1.1 (0.3–3.3)	5.9 (2.0–16.9)
Avg GCC	0.76 (0.60–0.96)	1.3 (0.5–3.7)	5.9 (1.7–20.6)
Sup GCC	0.83 (0.69–1.01)	1.5 (0.5–4.4)	4.5 (1.2–16.7)
Inf GCC	0.69 (0.53–0.90)	2.1 (0.8–5.6)	10.8 (2.5–46.9)
FLV	0.63 (0.44–0.90)	1.6 (0.4–6.7)	2.7 (1.5–5.1)
GLV	0.58 (0.41–0.82)	1.1 (0.3–3.9)	4.6 (2.1–10.0)
Preperimetric glaucoma against control group 2			
Sup RNFL	0.65 (0.47–0.89)	5.9 (1.7–19.9)	10.7 (2.5–45.8)
Inf RNFL	0.51 (0.35–0.74)	2.6 (0.8–8.7)	28.0 (3.88–202.0)
Avg RNFL	0.67 (0.51–0.88)	7.1 (0.8–60.6)	7.2 (2.2–23.9)
Avg GCC	0.72 (0.58–0.91)	2.2 (0.6–7.7)	32.3 (1.9–541.0)
Sup GCC	0.81 (0.67–0.98)	8.8 (1.1–72.4)	12.2 (1.5–96.7)
Inf GCC	0.68 (0.52–0.89)	6.2 (1.4–28.1)	19.3 (2.6–145.0)
FLV	0.61 (0.43–0.87)	2.6 (0.5–15.1)	3.1 (1.6–6.3)
GLV	0.57 (0.40–0.80)	2.6 (0.5–15.1)	5.6 (2.3–14.0)

in question. We therefore evaluated the LRs associated with the diagnostic categorization of SDOCT parameters. The magnitude of the LRs associated with the outside normal limits category of most of the ONH, RNFL, and GCC parameters were associated with moderate effects on the posttest probability of preperimetric glaucoma against healthy eyes with large physiologic cups. These effects become very relevant and useful, depending on other clinical information and the pretest probability of disease, in ruling in the disease. Within normal limits and borderline category of SDOCT parameters were associated with small effect on the posttest probability of disease, which would mean that within normal limits results were of little use in ruling out the diagnosis.

The preperimetric glaucoma group of our study was homogeneous. However, a possible limitation of our study is the inclusion of a few preperimetric glaucoma cases into the control group of eyes with large physiologic cups. This is, however, less likely as two glaucoma experts independently identified them as nonglaucomatous. These subjects also had no family history of glaucoma or any history of raised IOP. Optic disc size tended to be larger in the control group indicating that these were nonglaucomatous subjects with large discs and large cups. Therefore, in true sense, optic discs included in the control group 1 were not true disc suspects for glaucoma (optic discs that cause diagnostic uncertainty among glaucoma experts). We excluded such true disc suspects (optic discs that were unable to be classified into glaucoma or nonglaucoma group, by one or both of the experts) from the analysis. Such true disc suspects would require a longitudinal study to look for progressive structural changes and to definitively classify them into glaucoma or nonglaucoma groups.[27] Accordingly, Lisboa et al.[28] recently evaluated the diagnostic ability of SDOCT parameters in 142 eyes of 91 glaucoma suspects (based on optic disc appearance) with normal VFs, followed-up longitudinally for progressive changes in ONH and RNFL structure. Forty-eight eyes that showed progressive optic disc damage (without VF damage) and 94 eyes, which showed no progressive optic disc damage, over a 15 year follow-up period, were considered by them as preperimetric glaucoma and control group, respectively. The diagnostic abilities of ONH and GCC parameters reported in their study were similar to that found in our study, but the diagnostic abilities of RNFL parameters were better than that found in our study. Average RNFL thickness in their study showed an AUC of 0.89 and sensitivity at 95% specificity of 70%. The difference in the results between our study and the study by Lisboa et al.[28] may be related to the differences in the study methodology and the characteristics of the included subjects. It is also important to note that our results, unlike the results of Lisboa et al.[28] are not applicable to a population of such true disc suspects for glaucoma.

In conclusion, we found that the abilities of ONH, RNFL, and GCC parameters of SDOCT in differentiating preperimetric glaucoma eyes from healthy eyes with large physiologic cups were only moderate.

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