Diagnostic accuracy of posterior pole asymmetry analysis parameters of spectralis optical coherence tomography in detecting early unilateral glaucoma

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Purpose: To report the diagnostic ability of posterior pole asymmetry analysis (PPAA) parameters of spectralis optical coherence tomography (OCT) in detecting early unilateral glaucoma. **Methods:** A prospective, cross-sectional study which included 80 eyes of 80 normal subjects and 76 eyes of 76 patients with unilateral early primary open-angle glaucoma by Hodapp-Anderson-Parrish classification. All subjects were of age more than 18 years, best-corrected visual acuity 20/40 or better, and a refractive error within ± 5 diopter (D) sphere and ± 3 D cylinder. Control subjects had a normal ocular examination, intraocular pressure (IOP) <22 mmHg, no past history of high IOP, no family history of glaucoma, normal optic disc morphology, and visual field in both eyes. One eye of the control subject was randomly included. All eyes underwent OCT for retinal nerve fiber layer (RNFL) analysis and PPAA. The number of continuous black squares was noted in the asymmetry analysis (right-left + hemisphere asymmetry). The area under curve (AUC) was calculated for all OCT parameters. **Results:** The best value for AUC for RNFL analysis was 0.858 for the inferotemporal quadrant thickness. This was similar to the best value for AUC for PPAA which was 0.833 for the inferior macular thickness parameter ($P = 0.5$). The AUC for the right-left and the hemisphere asymmetry part of PPAA was 0.427 and 0.499, respectively. **Conclusion:** The macular thickness PPAA parameters were equally good as the RNFL parameters. However, the asymmetry analysis parameters performed poorly and need further refinement before its use in early unilateral glaucoma diagnosis.

Key words: Early, glaucoma, posterior pole asymmetry analysis, spectral domain optical coherence tomography

Glaucoma is characterized by a progressive degeneration of the retinal ganglion cells (RGCs) and their axons leading to a reduction in the thickness of the retinal nerve fiber layer (RNFL).[1] Reductions in the thickness of the RNFL is an early sign of glaucoma, and there may be a significant loss of RGCs before the appearance of visual field defects.[1,2] The region of the macula is of special importance in detecting early glaucoma as more than 50% of the RGCs are located here. Furthermore, the ganglion cell layer is more than one layer thick.[3,4]

Optical coherence tomography (OCT) has been widely used for glaucoma diagnosis as it allows objective measurement of the optic nerve head, RNFL, and macular thickness parameters.[5-9] Spectral-domain OCT (SD-OCT) is a further refinement of this technique which allows imaging with a faster scan rate and at a higher resolution.[10-11] The spectralis OCT (Heidelberg Engineering, Carlsbad, CA, USA) in addition to measuring the RNFL has introduced a posterior pole asymmetry analysis (PPAA) test.[12] This includes the right-left asymmetry, hemisphere asymmetry, average superior macular thickness, average inferior macular thickness, and the total average macular thickness. There is very limited literature on the applicability of the PPAA parameters in detecting early glaucoma based on the visual field (VF) defects. Since asymmetry is the basic premise of PPAA, we decided to test it in only unilateral glaucoma patients to give it the best possibility

for accurate early glaucoma diagnosis. The purpose of the present study was to investigate the ability of SD-OCT PPAA parameters to detect early unilateral glaucoma.

Methods

This was a prospective, cross-sectional study conducted at a tertiary care ophthalmic institute between August 2013 and March 2014. An informed consent was obtained from each participant. The study protocol was prospectively approved by the Institutional Review Board and Health Research Ethics Committee.

The subjects underwent a full ophthalmic examination including best-corrected visual acuity, manifest refraction, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, slit-lamp biomicroscopy, anterior chamber angle examination by 4-mirror gonioscopy, optic disc, and nerve fiber layer with a stereoscopic examination and photograph. The VF examination was done on a Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) by using Swedish interactive threshold algorithm Standard 24-2 program. The OCT scanning for RNFL and PPAA was

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Cite this article as: Dave P, Shah J. Diagnostic accuracy of posterior pole asymmetry analysis parameters of spectralis optical coherence tomography in detecting early unilateral glaucoma. Indian J Ophthalmol 2015;63:837-42.

done using spectralis OCT. All patient examination was performed by an experienced glaucoma specialist (PD). OCT scanning and VF examinations were performed by one of the authors (JS). All OCT examinations were performed within 1 month of the last VF test.

The study group consisted of consecutive unilateral primary open-angle glaucoma patients categorized as early stage by Hodapp-Anderson-Parrish classification.[13] Age-matched normal subjects were recruited from among those who came for a routine eye examination in the outpatient department. The other inclusion criteria were age more than 18 years, best-corrected visual acuity 20/40 or better, refractive error within ± 5 diopter (D) sphere and ± 3 D cylinder, and a willingness to participate in the study. Exclusion criteria included media opacities preventing imaging, any intraocular surgery within the last 6 months, and any retinal or neurological disease other than glaucoma that could confound the results of VF examination and SD-OCT. Control subjects had normal ocular examination, open-angle on gonioscopy, IOP < 22 mmHg, no past history of high IOP, no family history of glaucoma, normal optic disc morphology, and VF in both eyes. One eye of control subject was randomly selected by using a random number table. Glaucomatous damage was suspected on the basis of neuroretinal rim thinning or nerve fiber layer defects. All patients in the glaucoma group had these characteristic disc changes which correlated with the VF changes in the absence of other abnormalities that could explain the VF defect. The VF changes were confirmed on two separate examinations and were considered reliable only when the reliability parameters (fixation losses and false-positive or false-negative errors) were ≤ 20%. Glaucomatous VF defects were defined by the presence of two of the following three criteria: Cluster of three points on pattern deviation probability plot with a $P < 5\%$, one of which had a $P < 1\%$ or a pattern standard deviation (PSD) with a $P < 5\%$ or a glaucoma hemifield test outside normal limits.

Optical coherence tomography measurements

All images were acquired with the spectralis SD-OCT (version 5.6.1 Heidelberg Engineering, Carlsbad, California, USA.) after pupillary dilation. The instrument has a scan speed of 40,000 A-scans per second, with a 12° diameter scan circle around the optic nerve. The scan circle diameter (mm) depends on the axial eye length of the eye and is typically 3.5–3.6 mm. TruTrack (Heidelberg Engineering, Carlsbad, California, USA) image alignment software tracks for eye movement and provides the ability to obtain multiple images from the exact same location. All scans had a quality score of >25. The average measurement values for all the six sectors were noted. The retinal thickness measurement and asymmetry analysis has been described in detail elsewhere.[12] Retinal thickness measurements were compared between eyes (right-left asymmetry) and between the hemispheres (hemisphere asymmetry) of each eye. The average superior, inferior, and the total macular thickness were noted. The asymmetry map was displayed as a gray scale. The total number of continuous black squares (denoting a difference in thickness of >30 µm) in the right-left and the hemisphere asymmetry analysis was also noted. The VF, RNFL, and PPAA printouts for early glaucoma patients and controls are as shown [Fig. 1 and 2]. We also tested out the diagnostic ability of the number of continuous black squares on the PPAA (right-left + hemisphere) in differentiating early

glaucoma from normal. All OCT scans were done bilaterally as the right-left asymmetry analysis requires data from the other eye. This data are then incorporated into the analyzed printout of each eye. Hence, the fellow eye printout could be ignored according to our inclusion criteria.

Statistical analysis

Descriptive and inferential statistics were performed using STATA version 12 for Windows (StataCorp LP, College Station, Texas, USA). A $P < 0.05$ was considered statistically significant. Normality for all variables was tested using the Shapiro–Wilk test. The demographics, RNFL, and PPAA parameters were compared using the independent sample t-test for normally distributed variables and Mann–Whitney test for nonnormally distributed variables. Chi-square test was used to find significant differences in the gender distribution between the two groups. Receiver operating characteristic (ROC) curves were used to describe the ability to discriminate early glaucomatous from healthy eyes for each spectralis OCT software parameter. Sensitivities at fixed specificities of 80% and 95% were also determined for all the parameters.

Results

In all, 80 eyes of 80 normal subjects and 76 eyes of 76 patients with early glaucoma were included for the study analysis. Patient demographics and VF parameters are presented in Table 1. The differences in characteristics were not significantly different between the two groups except for mean deviation ($P < 0.01$) and PSD ($P < 0.01$).
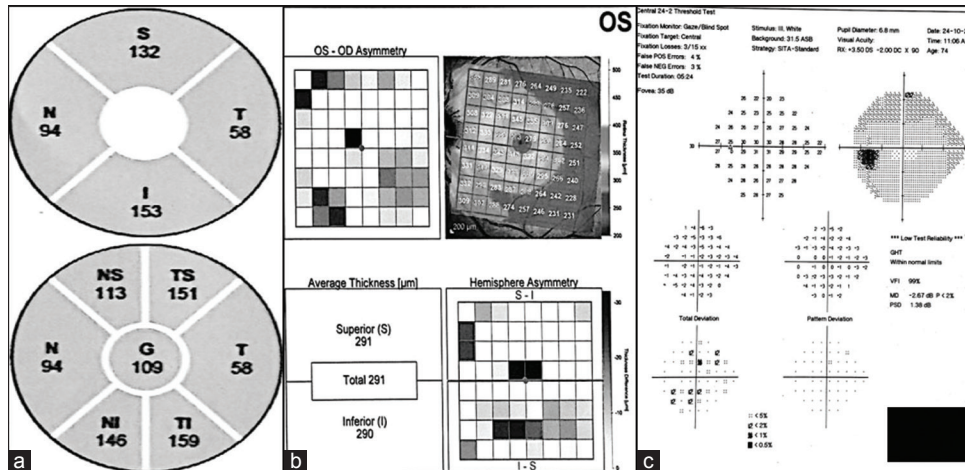
Retinal nerve fiber layer parameters

The mean values of the RNFL parameters in the two groups of participants are given in Table 2. There were significant differences between the groups for all RNFL parameters ($P < 0.01$) except for the temporal quadrant RNFL thickness ($P = 0.2$). The area under curve (AUC) and sensitivities at fixed specificities for all the RNFL parameters are also shown in Table 2. The values ranged from 0.563 for the temporal quadrant thickness to 0.858 for the inferotemporal quadrant RNFL thickness. The inferotemporal quadrant thickness had the highest sensitivity of 60% at 95% specificity. Table 3 shows the predictive values and the likelihood ratios (LRs) based on the SD-OCT normative data classification.

Macular posterior pole asymmetry analysis parameters

The mean values of the macular PPAA measurements in the two groups of participants are given in Table 4. Significant differences between the two groups were seen for all PPAA parameters ($P < 0.01$) except for the right-left asymmetry ($P = 0.1$) and the hemispheric asymmetry analysis ($P = 1$). The AUC and sensitivities at fixed specificities for all the macular PPAA parameters are also shown in Table 3. The AUC ranged from 0.427 for the right-left asymmetry to 0.833 for the average inferior macular thickness value. The average inferior macular thickness had the highest sensitivity of 65% at a specificity of 95%. Table 5 shows the sensitivity, specificity, predictive values, and LRs for different diagnostic criteria depending on the number of continuous black cells on asymmetry analysis. Criteria A (two black cells) had the highest sensitivity at 73.7% with a specificity of only 30%. Criteria D (five black cells) had the highest specificity of 90% with a sensitivity of only 42.1%.
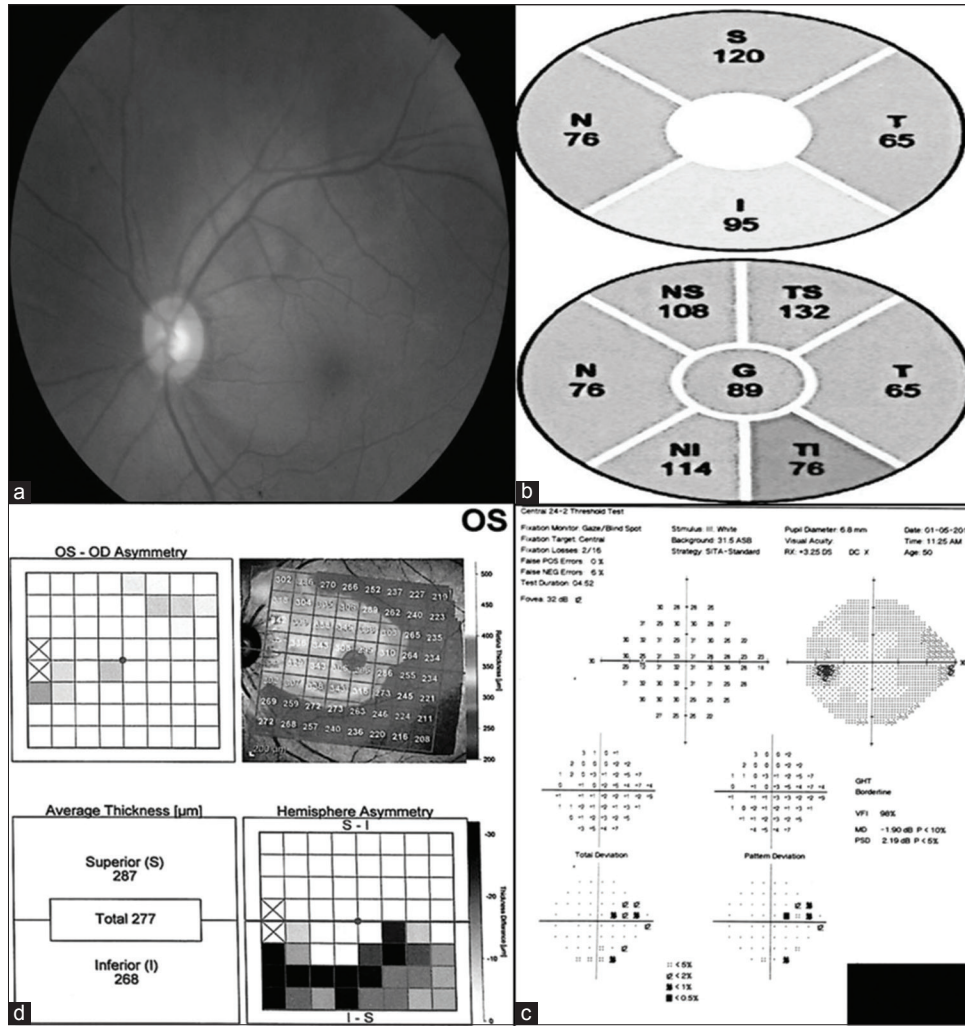
Figure 1: The study group patient with early glaucoma. (Clockwise from top-left) (a) Fundus photograph with an inferior nerve fiber layer defect. (b) Retinal nerve fiber layer thickness printout with thinning in the inferotemporal quadrant. (c) Visual field printout of the patient showing an early superior nasal step. (d) Posterior pole asymmetry analysis report with nine continuous black squares in the inferior quadrant on hemispheric asymmetry analysis

Figure 2: The control group subject without glaucoma. (From left to right) (a) Normal retinal nerve fiber layer thickness printout. (b) Posterior pole asymmetry analysis report with two continuous black squares each in the right-left asymmetry and the hemisphere asymmetry (total 4). (c) Visual field printout showing a normal visual field

The ROC curves for the best RNFL and macular PPAA parameter are as shown in Fig. 3. There was no significant

difference ($P = 0.5$) between the AUCs of the best RNFL parameter (inferotemporal RNFL thickness) and the best macular PPAA parameter (inferior macular thickness). The sensitivities of these parameters at 95% specificity were comparable (60% vs. 65%, respectively).

Discussion

Our study demonstrates that the macular thickness PPAA parameters were as good as the RNFL parameters for diagnosis of early glaucoma. There was no significant difference ($P = 0.5$) between the AUCs of the best RNFL parameter (inferotemporal RNFL thickness) and the best macular PPAA parameter (average inferior macular thickness). The sensitivities of these parameters

Table 1: Patient demographics and visual field parameters

	Glaucoma (*n*=76)	Normal (*n*=80)	*P*
Age (years)	61.6±11.1	59.9±5.5	0.9
Sex (male: female)	52:24	50:30	0.8
SE (D)	−0.6±1.4	−0.8±1.6	0.7
MD (dB)	−5.0±1	−2.6±0.6	<0.001
PSD (dB)	3.1±1.6	2±1	<0.001

n: Number of subjects, SE: Spherical equivalent, D: Diopter, dB: Decibel, MD: Mean deviation, PSD: Pattern standard deviation

Table 2: Retinal nerve fiber layer thickness parameters in glaucoma and healthy eyes with area under curve and sensitivities at fixed specificities

RNFL thickness (in µm)	Mean±SD		*P*	AUC	95% CI	Sensitivity at 95% specificity (%)	Sensitivity at 80% specificity (%)
	Early glaucoma	Normal					
Superior quadrant	103.4±32.5	122.4±10.6	<0.001	0.788	0.713-0.863	25	50
Inferior quadrant	94.3±25.7	126.8±14.5	<0.001	0.855	0.795-0.915	30	80
Supratemporal quadrant	114.2±34.1	138.3±11.5	<0.001	0.810	0.739-0.882	25	60
Supranasal quadrant	92.8±32.9	106.9±14.1	<0.001	0.729	0.642-0.816	5	50
Infratemporal quadrant	102.8±29.9	141.1±17.4	<0.001	0.858	0.800-0.915	60	75
Infranasal quadrant	85.7±25	113.4±19.2	<0.001	0.799	0.715-0.906	25	65
Temporal quadrant	65.5±17	70.6±18.3	0.2	0.563	0.472-0.654	5	20
Nasal quadrant	68.1±12.7	78.9±13.8	<0.001	0.746	0.665-0.827	20	75

RNFL: Retinal nerve fiber layer, AUC: Area under curve, SD: Standard deviation, CI: Confidence interval

Table 3: Predictive values and likelihood ratios of the eye classification based on the normative database of spectral domain optical coherence tomography retinal nerve fiber layer parameters

RNFL thickness	95% CI					
	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR−
Within normal limits	90 (81.2-95.6)	73.7 (62.3-83.1)	78.3 (68.4-86.2)	87.5 (76.8-94.5)	3.42 (2.3-5)	0.2 (0.1-0.3)
Borderline	15.8 (8.4-26)	90 (81.2-95.6)	60 (36-81)	53 (44.2-61.5)	1.6 (0.7-3.6)	0.9 (0.8-1)
Outside normal limits	57.9 (46-69.1)	98.7 (93.2-99.9)	97.8 (88.2-99.9)	71.2 (61.8-79.3)	46.32 (6.5-327.8)	0.4 (0.3-0.6)

CI: Confidence interval, RNFL: Retinal nerve fiber layer, PPV: Positive predictive values, NPV: Negative predictive values, LR+: Positive likelihood ratio, LR−: Negative likelihood ratio

Table 4: Posterior pole asymmetry analysis parameters in glaucoma and healthy eyes with area under curve and sensitivities at fixed specificities

PPAA parameters	Mean±SD		*P*	AUC	95% CI	Sensitivity at 95% specificity (%)	Sensitivity at 80% specificity (%)
	Early glaucoma	Normal					
Superior macular thickness (µm)	277.6±19.1	293.4±8.2	<0.001	0.825	0.752-0.898	5	80
Inferior macular thickness (µm)	273.8±19.4	290.5±11	<0.001	0.833	0.765-0.901	65	80
Total macular thickness (µm)	275.8±16.6	292±9.4	<0.001	0.832	0.766-0.900	40	80
Right-left asymmetry (nbs)	4.1±7.5	2.2±1.8	0.1	0.427	0.340-0.515	5	10
Hemispheric asymmetry (nbs)	3.5±4.3	1.2±1.8	1	0.499	0.404-0.593	5	10

PPAA: Posterior pole asymmetry analysis, AUC: Area under curve, SD: Standard deviation, nbs: Number of continuous black squares, CI: Confidence interval

Table 5: Sensitivity, specificity, predictive values, and likelihood ratios for glaucoma diagnosis based on the number of black cells (difference >30 μm)

Criteria	Number of black squares	95% CI					
		Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR−
A	2	73.7 (62.8-82.3)	30 (21-41)	50 (40.0-59.6)	54.5 (38.8-59.6)	1 (0.9-1.3)	0.9 (0.5-1.5)
B	3	52.6 (41.6-63.5)	50 (39.3-60.7)	50 (38.6-61.4)	52.6 (40.8-64.2)	1 (0.8-1.4)	0.9 (0.7-1.3)
C	4	47.4 (36.5-58.5)	80 (70-87.3)	69.2 (54.9-81.3)	61.5 (51.5-70.9)	2.4 (1.4-3.9)	0.7 (0.5-0.8)
D	5	42.1 (31.7-53.3)	90 (81.5-94.9)	80 (64.4-91)	62 (52.6-70.9)	4.2 (2-8.6)	0.6 (0.5-0.8)

CI: Confidence interval, PPV: Positive predictive values, NPV: Negative predictive values, LR+: Positive likelihood ratio, LR−: Negative likelihood ratio
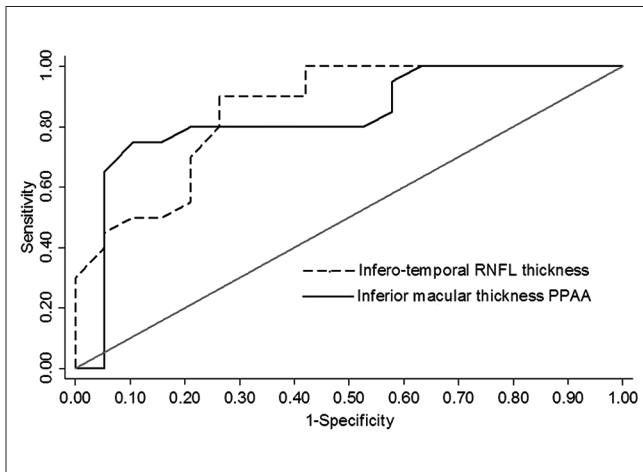
Figure 3: Receiver operating characteristic curves of the best retinal nerve fiber layer (inferotemporal quadrant retinal nerve fiber layer thickness) and posterior pole asymmetry analysis (inferior quadrant macular thickness) parameters

at 95% specificity were comparable (60% vs. 65%, respectively). This is similar to other reports in the literature stating equal diagnostic abilities of both RNFL and macular parameters.[14-17] In contrast, the right-left asymmetry and the hemispheric asymmetry did not perform as well. The AUC for the right-left and the hemispheric asymmetry was 0.427 and 0.499, respectively. The total number of black cells in right-left and hemispheric asymmetry was similar in early glaucoma as well as the control group ($P = 0.1$ and $P = 1$, respectively). Both of them had 5% sensitivity at 95% specificity and 10% sensitivity at 80% specificity for early glaucoma diagnosis. Comparing the diagnostic criteria based on the number of black cells, criteria A (two black cells) had the highest sensitivity at 73.7% with a specificity of only 30%, while criteria D (five black cells) had the highest specificity of 90% with a sensitivity of only 42.1%. A tradeoff between the sensitivity and specificity was seen with criteria C. These results are poorer compared to those reported by Seo *et al.*[18] This was probably because they included patients with localized defects confined to one hemisphere only which could have improved the hemisphere asymmetry analysis. We did not do so in this study as our inclusion criteria allowed for RNFL defects in both hemispheres simultaneously as long as they fell under the early glaucoma category. The positive predictive value of a test is defined as the proportion of people with a positive test result who actually have the disease. Similarly, the negative predictive value is defined as the

proportion of people with a negative test result who do not have the disease. Predictive values are limited by the fact that they vary with the disease prevalence and therefore cannot be used interchangeably with different populations.[19] The predictive values for the classification of the eye based on the normative data for SD-OCT RNFL parameters were better than the PPAA diagnostic criteria based on the number of black cells. Positive LR is defined as the probability of an individual with disease having a positive test divided by the probability of an individual without disease having a positive test. Similarly, negative LR is defined as the probability of an individual with disease having a negative test divided by the probability of an individual without disease having a negative test. A LR of more than 10 is considered significant. A LR close to 1 means that it fails to provide any additional information about the posttest probability of the disease.[20] The highest positive LR was seen for the "outside normal limits" classification of the eye based on the SD-OCT RNFL parameters (46.32), while the highest negative LR (0.9) was similar between the PPAA criteria based on the number of black cells and the classification of the eye based on the RNFL parameters. Early diagnosis of glaucoma can be achieved by population-based screening or case detection (also known as opportunistic screening). The requirement for population-based screening is a high specificity of 90% with a reasonable sensitivity of preferably higher than 80% for which none of the parameters in this study qualified. The objective for case detection, on the other hand, is to provide definitive care for which a high sensitivity is most important.[21] The strength of our study is its relatively large sample size. We included patients with unilateral glaucoma only. Despite this, the diagnostic ability of the right-left asymmetry analysis was poor. We can only speculate that the ability would have been poorer if we had included bilateral early glaucoma patients. Nevertheless, the results of our study may not be applicable to bilateral early glaucoma patients. The SD-OCT scans in our study were done once and not repeated. However, Kochendörfer *et al.*[22] have demonstrated a good reproducibility of PPAA parameters and so this would not have affected our study results in any way. A limitation of our study was that it involved the analysis of Indian eyes only. Further studies with different ethnic groups are warranted. Another limitation is the case–control design with a clear distinction between glaucoma patients and normal subjects recruited from the general population. Such a design may inflate the actual diagnostic ability of a test.[23,24] The effect of this "spectrum bias" has recently been shown wherein the diagnostic abilities were significantly higher when clear cut normal cases were taken as controls compared to when suspicious-looking discs were taken as the control group which may be clinically more relevant.[25]

Conclusion

The macular thickness PPAA parameters were equally good as the RNFL parameters. However, the right-left and the hemisphere asymmetry components of the PPAA performed poorly and probably needed further refinement before they can be effectively used for diagnosing early unilateral glaucoma patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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