Original Article, Special Focus - Glaucoma

Comparison of peripapillary capillary plexus using optical coherence tomography angiography and retinal nerve fibre layer analysis using spectral domain optical coherence tomography in glaucoma patients, glaucoma suspects, and healthy subjects

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Purpose: To assess the association between radial peripapillary capillary (RPC) plexus using optical coherence tomography angiography (OCTA) and retinal nerve fibre layer (RNFL) thickness using spectral domain OCT (SD-OCT) in primary open-angle glaucoma (POAG) patients, glaucoma suspects, and healthy subjects. **Methods:** In this single-centre cross-sectional observational study, POAG, glaucoma suspects, and healthy patients underwent OCT-RNFL and optic nerve head angiography scans. The RNFL thickness and the vascular parameters obtained from RPC plexus, including perfusion density (PD), flux index (FI), and vessel density (VD), were analysed. **Results:** In all, 120 eyes of 120 patients, including 40 POAG patients, 40 glaucoma suspects, and 40 healthy subjects, were included. The pairwise comparison of mean RNFL thickness, FI, and VD showed significant difference ($P < 0.001$) in all sectors between POAG, glaucoma suspects, and healthy eyes. However, PD showed no significant difference between glaucoma suspects and healthy eyes. The average RNFL thickness was found to have a better diagnostic ability than VD to distinguish POAG eyes from healthy eyes and glaucoma suspects based on receiver operating characteristics curve and area under the curve. VD had better diagnostic accuracy than RNFL when glaucoma suspects and healthy were compared. **Conclusion:** OCT-RNFL has better diagnostic capability in differentiating glaucoma from healthy eyes compared to OCTA. However, OCTA was found to be better in screening out glaucoma suspects from healthy eyes. The VD is a better OCTA parameter than FI and PD to differentiate POAG and glaucoma suspects from healthy eyes.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1456_22

Quick Response Code:

Key words: Glaucoma, OCTA, OCT RNFL, Optical coherence tomography angiography, SD-OCT

Glaucoma is the leading cause of irreversible blindness in the world characterized by permanent loss of retinal ganglion cells (RGC), optic nerve head (ONH), and retinal nerve fibre layer (RNFL) changes.[1] The proposed pathophysiology of glaucoma is described in two theories – mechanical and vascular. The mechanical theory suggests that elevated intraocular pressure (IOP) causes stress on RGC by production of substances, such as tumour necrosis factor α, leading to RGC axons damage at the lamina cribrosa level, followed by cell death through apoptosis resulting in RNFL thinning.[2] The vascular theory suggests that glaucomatous optic neuropathy results from insufficient blood supply because of the increased IOP and other risk factors reducing ocular blood flow. Reduced blood flow causes elevated oxidative stress because of the increased reactive oxygen species and activation of pro-inflammatory mediators.[3]

Radial peripapillary capillaries (RPC) form a network of capillary beds within the RNFL that supply the RGC axons whose loss is implicated in visual field defects.[4,5] A reliable and reproducible clinical method for evaluating the ONH perfusion will, thus, help us in early detection and monitoring.[6] Optical coherence tomography angiography (OCTA) is a new method of analysis based on high-resolution, non-invasive imaging techniques whereby retinal, choroidal, and ONH circulation can be visualised without the need to inject any contrast. It distinguishes blood vessels from the static neurosensory retina by assessing the change in the OCT signal caused by the motion of the red blood cells.[7]

Various types of OCTA devices using different techniques are available in the market.[8] AngioPlex™ (Cirrus HD-OCT 5000, Carl ZeissMeditec., Inc. Dublin, CA, USA) based on microangiography, and AngioVue™ (OptovueRTVue XR Avanti, Optovue Inc., Fremont, CA, USA) based on split-spectrum amplitude-decorrelation are the most commonly used devices in clinical practice. AngioPlex™ requires a short execution time and provide a higher number of images for analysis with few motion artefacts.[9]

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Received: 17-Jun-2022 Revision: 03-Aug-2022
Accepted: 17-Aug-2022 Published: 30-Nov-2022

Cite this article as: Dutta A, Thulasidas M, Sasidharan A, Pradeep B, Rajesh Prabu V. Comparison of peripapillary capillary plexus using optical coherence tomography angiography and retinal nerve fibre layer analysis using spectral domain optical coherence tomography in glaucoma patients, glaucoma suspects, and healthy subjects. Indian J Ophthalmol 2022;70:4146-51.

The primary purpose of the present study was to evaluate the association between peripapillary capillary plexus using OCTA and RNFL thickness using spectral domain OCT (SD-OCT) in primary open-angle glaucoma (POAG) patients, glaucoma suspects, and healthy subjects. The secondary purpose was to find out the diagnostic ability of the OCTA parameters and normative data for OCTA RPC vascular parameters in Indian population.

Methods

A cross-sectional observational study was conducted at our eye hospital between September 1, 2020 and August 31, 2021 to compare peripapillary vessel density using OCTA and RNFL analysis using SD-OCT in glaucoma patients, glaucoma suspects, and healthy subjects. The institutional ethical committee approval was obtained before beginning the study and informed consent was obtained from each patient according to the tenets of the Declaration of Helsinki. The study was registered in the Clinical Trials Registry, India (CTRI/2020/11/028912).

Inclusion criteria were as follows: subjects aged more than 18 years of age newly diagnosed as POAG, or being followed as glaucoma suspects, or with healthy eyes, visual acuity ≥6/24, a spherical equivalent refractive error between −3 dioptres (D) and +3D and astigmatism ≤2.5 D. POAG diagnosis was on the basis of the presence of repeatable visual field defects with corresponding structural defects in the ONH or RNFL, elevated IOP, and open iridocorneal angle on gonioscopy. Glaucoma suspects were patients being followed because of elevated IOP, suspect ONH or RNFL changes, or a positive family history of glaucoma, but without manifest glaucoma. Healthy subjects were individuals with normal IOP, normal ONH (cup-disc ratio ≤0.5) and RNFL with healthy neuroretinal rim, and normal visual field. Patients already on ocular hypotensive medications and those with a history of intraocular surgery other than glaucoma surgery or uncomplicated cataract surgery, secondary glaucoma, neurological disease, or other ocular diseases were excluded. Eyes with OCTA and OCT images of inadequate signal strength <8, containing lines or gaps, or motion artefacts were also excluded.

All study participants underwent a complete ophthalmologic examination, including refractive status, slit-lampbiomicroscopy, IOP measurement with Goldmann applanation tonometry, gonioscopy, ultrasound pachymetry, standard automated perimetry (24-2 Swedish Interactive Threshold Algorithm; Humphrey Field Analyzer 3 840; Carl Zeiss Meditec, Inc., Dublin, CA, USA), and dilated fundus examination.

The peripapillary RNFL thickness and ONH cube scans for all subjects were taken using Cirrus HD-OCT 500 (Carl Zeiss Meditech, Inc., Dublin, CA, USA). The scan used for viewing the ONH is the optic disc cube 200x200 scan that generates a cube of data in a 6-mm square grid by acquiring a series of 200 horizontal scan lines, each composed of 200 A-scans. The fixation target is offset to one side to allow for the centre of the ONH to move to the centre of the scan pattern. In addition, the scan pattern overlay consists of concentric rings to assist in the alignment of the ONH. The RNFL thickness map is calculated based on all the data of the scanned cube. A colour scale is used to demonstrate the normal and defective areas in the RNFL thickness ranging from zero (blue) to 350 μm (white). Cold colours represent thinned areas, whereas hot colours represent thick areas. The RNFL thickness across the temporal, superior, nasal, inferior, and temporal calculation ring is also displayed in a numerical chart format. In this chart, the average thickness of each point across the calculation is demonstrated. In addition, the average thickness for each quadrant is also demonstrated separately and in time zones. The values of the patient are compared to normative data in the chart. To demonstrate the normal distribution percentages of the individuals in the same age group, the RNFL normative database uses the colours as below:

Red: The lowest portion of 1% with regard to all measurements is in the red zone and these indicators must be considered as abnormal.

Yellow: In case the measurements are within the lowest portion of 5%, they are displayed in yellow and should be interpreted as doubtful.

Green: About 90% of all measurements are in this section and should be considered as normal.[10]

The RNFL thickness in inferior, superior, nasal, and temporal sectors and the average thickness were recorded for the study.

The participants then underwent Angioplex™ OCTA using Cirrus HD-OCT 5000 and the images were stored and documented. ONH angiography scans labs can be acquired in 4.5 × 4.5 mm. The RPC plexus characteristics were analysed in this study. The vascular parameters obtained from RPC plexus are perfusion density (PD), flux index (FI), and vessel density (VD). The PD is the total area of perfused vasculature per unit area in a region of interest, expressed in percentage. The PD values are directly available from the OCTA system. The FI is the total area of perfused vasculature per unit area in a region of interest, weighted by the brightness (intensity) of the flow signal. It has no unit, ranging from 0 (no perfusion) to 1(maximum perfusion). The FI values are directly available from the OCTA system. The VD is the total length of perfused vasculature per unit area in a region of interest, measured in units of inverse millimetre. It can be described as untangled vasculature in a region of interest measured with a ruler, then divided by the area it originally occupied.[10] The VD values are not directly available. The images with good quality were outsourced and VD was estimated. Using MATLABS software, the black pixel portion in the given OCTA image was segmented and the given OCTA image was converted to fractal dimension image by estimating local fractal dimension at each pixel using box counting method. On the fractal dimension image, the smallest circle covering the black pixel portion was drawn to identify the pixels to exclude in VD calculation. With centre as reference point, another circle of diameter 2.5 mm was drawn on the fractal dimension image and peripapillary area (between smaller and bigger circle) was bisected into four sectors – inferior, superior, nasal, and temporal. VD was calculated as the ratio of total number of pixels with normalized ratio of local fractal dimension between 0.7 and 1.0 to the total number of pixels in the image.

Sample size calculation

Considering the previous hospital data with regard to prevalence of glaucoma patients, and published articles in

literature, the sample size was taken as 120 subjects. The sample size formula was the following:

$n = z^2 \times p(1-p)/E^2$

n = required sample size, z = 95% confidence level (standard value of 1.96), P = expected frequency of the factor under study (8.1%), E = margin of error of 5% (standard value of 0.05).

The sample size was further increased by 5% to account for contingencies, such as non-response or recording error.

Statistical analysis

Data were entered in Microsoft Excel v. 2017 and analysed using a trial version of Statistical Package for the Social Sciences (SPSS) v. 23. Categorical variables were summarised using frequency and percentage. Chi-square test was used to determine the association between categorical variables. Continuous variables were summarised with measures of central tendency (mean, standard deviation, standard error, and 95% confidence interval). Unpaired *t*-test was used for comparison of same variable between two groups and one-way ANOVA was applied for comparison between three groups. Post-hoc test with Bonferroni's correction was used for pairwise comparisons. Pearson's correlation technique was adopted to determine the correlation between two continuous variables. Receiver operating characteristics (ROC) curve was used to determine the diagnostic capacity of the test, including the sensitivity and specificity, and area under the curve (AUROC) was also computed to comment on superiority of one test over another. $P < 0.05$ was considered as significant at a 95% confidence level.

Results

A total of 120 eyes of 120 patients were included in the study. The study subjects were divided into three groups: 40 POAG patients, 40 glaucoma suspects, and 40 healthy subjects.

The age-adjusted mean OCT RNFL thickness for POAG eyes, glaucoma suspects, and healthy eyes is given in Table 1, which was statistically significant in all sectors between the groups. The pairwise comparison of mean RNFL thickness showed significant difference in all sectors between POAG and healthy eyes. However, RNFL thickness showed statistically significant difference only in inferior sector and average values between glaucoma suspects and healthy eyes.

The mean PD, FI, and VD values from OCTA for POAG eyes, glaucoma suspects, and healthy eyes are given in Table 2. The FI and VD showed statistically significant difference in all sectors between the groups. However, PD showed significant difference only in average values, superior, and inferior sectors between the groups. The pairwise comparison of mean FI and VD showed significant difference in all sectors between POAG, glaucoma suspects, and healthy eyes. In contrast, PD showed no significant difference between glaucoma suspects and healthy eyes.

The strongest correlation was found between RNFL and FI compared to VD and PI. Fig. 1 shows the correlation between FI and RNFL thickness in glaucoma patients, glaucoma suspects, and healthy subjects. The ROC curve and AUROC for RNFL thickness and VD to differentiate between the three groups are given in Fig. 2. The average RNFL thickness was found to have a better diagnostic ability than VD to distinguish POAG eyes from healthy eyes and glaucoma suspects. However, VD is a better parameter to distinguish glaucoma suspects from healthy eyes.

Table 3 shows the cutoff points and sensitivity and specificity values of the VD derived from ROC curve analysis used to discriminate healthy eyes from glaucoma suspects and POAG eyes. Based on the ROC curve and AUROC, VD with a cutoff value of 44 having a sensitivity of 88.2% and specificity of 70.2% can be used to differentiate healthy eyes from POAG eyes.

Table 4 shows the cutoff points and sensitivity and specificity values of the FI derived from ROC curve analysis used to discriminate healthy eyes from glaucoma suspects and POAG eyes. Based on the ROC curve and AUROC, FI with a cutoff value of 0.26 having a sensitivity of 100% and specificity of 97% can be used to differentiate healthy eyes from POAG eyes.

Discussion

In the present study, we compared structural OCT-derived RNFL thickness and OCTA-derived peripapillary vascular parameters (PD, FI, and VD) across patients with POAG, glaucoma suspects, and healthy subjects. In addition, the correlation between structural and vascular variables and their diagnostic abilities was also assessed. In literature, no study has assessed the utility of the parameters, FI and PD, in Indian population, which are inherently provided by the machine, unlike the VD that had to be extracted separately using software, causing some inconvenience and loss of data during transfer. To the best of our knowledge, this is the first study to compare all the available OCTA vascular parameters with RNFL thickness, obtain their normative data with diagnostic cutoff values to differentiate healthy eyes from glaucoma suspects and POAG eyes in Indian population.

Table 1: Age-adjusted mean values for OCT-RNFL thickness measurements among the study participants

Diagnostic parameters: OCT-RNFL thickness (in µm)	Age adjusted mean (95% Confidence interval)			*P**
	POAG patients (*n*=40)	Glaucoma suspects (*n*=40)	Healthy individuals (*n*=40)	
Superior	92.53±4.74 (87.79-97.26)	112.03±4.36 (107.67-116.40)	118.87±4.29 (114.58-123.16)	<0.001†
Nasal	65.00±2.94 (62.06-67.95)	71.91±2.72 (69.19-74.63)	73.33±2.67 (70.66-76.00)	<0.001†
Inferior	92.45±4.61 (87.84-97.06)	111.28±4.25 (107.03-115.53)	123.89±4.18 (119.71-128.07)	<0.001†
Temporal	57.68±3.1 (54.58-60.77)	58.73±2.86 (55.87-61.58)	62.89±2.81 (60.08-65.69)	0.03‡
Average	76.94±2.73 (74.21-79.69)	88.76±2.52 (86.24-91.28)	94.76±2.48 (92.28-97.23)	<0.001†

OCTA=optical coherence tomography angiography, RNFL=retinal nerve fibre layer, POAG=primary open-angle glaucoma. *Age-adjusted ANOVA test, †*P*<0.001 highly significant, ‡*P*<0.05 significant

Table 2: The mean PD, FI, and VD values from OCTA for POAG eyes, glaucoma suspects, and healthy eyes

OCTA Diagnostic Parameters	POAG Eyes (*n*=40)	Glaucoma Suspects (*n*=40)	Healthy Eyes (*n*=40)	*P**	Difference Between the Means (*P* value) with post hoc test	
					POAG vs Healthy Ryes	Glaucoma Suspects versus Healthy Eyes
Perfusion density	43.59 (42.93-44.25)	45.06 (44.45-45.67)	45.53 (44.94-46.14)	<0.001†	<0.001†	0.8
Flux index	0.367 (0.357-0.378)	0.411 (0.402-0.421)	0.429 (0.420-0.439)	<0.001†	<0.001†	0.02‡
Vessel density	38.32 (36.85-39.78)	39.35 (37.99-40.69)	47.99 (46.67-49.32)	<0.001†	<0.001†	<0.001†

OCTA=optical coherence tomography angiography, PD=perfusion density, FI=flux index, VD=vessel density, POAG=primary open-angle glaucoma.
*Age-adjusted ANOVA test, †*P*<0.001 highly significant, ‡*P*<0.05 significant

Table 3: Sensitivity and specificity of VD derived from ROC curve at various cutoffs to discriminate healthy eyes from glaucoma suspects and POAG eyes

Purpose of the Cutoff	Average VD Cutoff	Sensitivity (%)	Specificity (%)
To differentiate healthy individuals from glaucoma suspects	22.3	100	0
	35.7	100	24.0
	39.2	97.5	45.0
	40.1	95.0	50.0
	42.1	92.5	70.0
	43.9	88.0	80.0
	44.2	87.5	83.8
	44.4	85.0	86.3
	45.4	77.5	90.0
	46.5	78.0	95.0
To differentiate healthy individuals from POAG patients	9.03	100	0
	33.1`	100	25.2
	35.6	100	32.4
	36.4	98.2	38.1
	39.1	97.1	46.3
	44.0	88.2	70.2
	46.4	75.5	86.4
	48.3	48.3	94.6
	48.5	45.4	95.2
	51.87	15.0	97.3

VD=vessel density, POAG=primary open-angle glaucoma, ROC=receiver operating characteristics curve

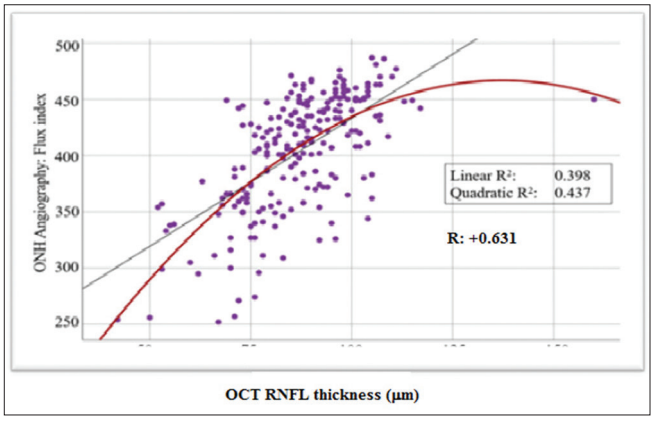

Figure 1: Correlation of optical coherence tomography-retinal nerve fibre layer and optical coherence tomography angiography flux index in primary open-angle glaucoma, glaucoma suspects, and healthy subjects. *R* = Pearson's correlation coefficient, R^2 = coefficient of determination, *P* < 0.001 highly significant

The RNFL thickness showed significant thinning in all retinal quadrants in POAG eyes when compared to healthy eyes. However, a statistically significant decrease in RNFL thickness was observed only in inferior quadrant and average values in glaucoma suspects compared to healthy eyes. These findings are consistent with the studies by Khanal *et al*.[11] and Subbiah *et al*.,[12] where RNFL thickness was significantly less in POAG eyes compared to suspects and healthy eyes.

For better understanding of the pathogenesis of glaucoma and exploring the hypothesis of the vascular component, the ocular blood flow to the ONH has been investigated using various instruments, including fluorescein and indocyanine green angiography, laser speckle flowgraphy, colour Doppler imaging, Doppler OCT, confocal scanning laser Doppler flowmetry, and retinal functional imager.[13-19] However, none of these eventually made space in clinical practice because of their limitations, such as reliability, invasiveness, accuracy, and the need for expert technicians. OCTA was introduced in the market, and it has multiple merits over previous devices as it is non-invasive, reliable, depth-resolved, and a user-friendly technique that enables evaluation of retinal and choroidal circulation both in the macula and the ONH.[20] Since the first description by Jia *et al*.[7] in 2012, there have been multiple studies on the role of OCTA in glaucoma providing evidence that VD is diminished in glaucomatous eyes.[21-29]

In our study, we evaluated the OCTA RPC plexus parameters (PD, FI, and VD) and found that glaucomatous eyes exhibited a marked reduction in FI and VD on average and in all quadrants compared to glaucoma suspects and healthy eyes. The present finding is in accordance with previous studies.[26-28] In contrast, a study by Triolo *et al*.[29] observed no significant difference in VD between the control and glaucoma suspect group. They explained this by putting forward a hypothesis that neurodegeneration may occur before vascular damage, and therefore, capillary dropouts may be secondary to loss of RNFL. Another explanation given by the authors was that OCTA could not be as sensitive as structural OCT to detect early changes and, thus, could miss subtle vascular capillary rarefaction. Nevertheless, we believe that the difference in findings between the studies could be because of different instruments, algorithms, and post-processing techniques used. With regard to the correlation analysis between structural and vascular variables, we found a significant association between RNFL thickness and FI compared to VD and PI. The

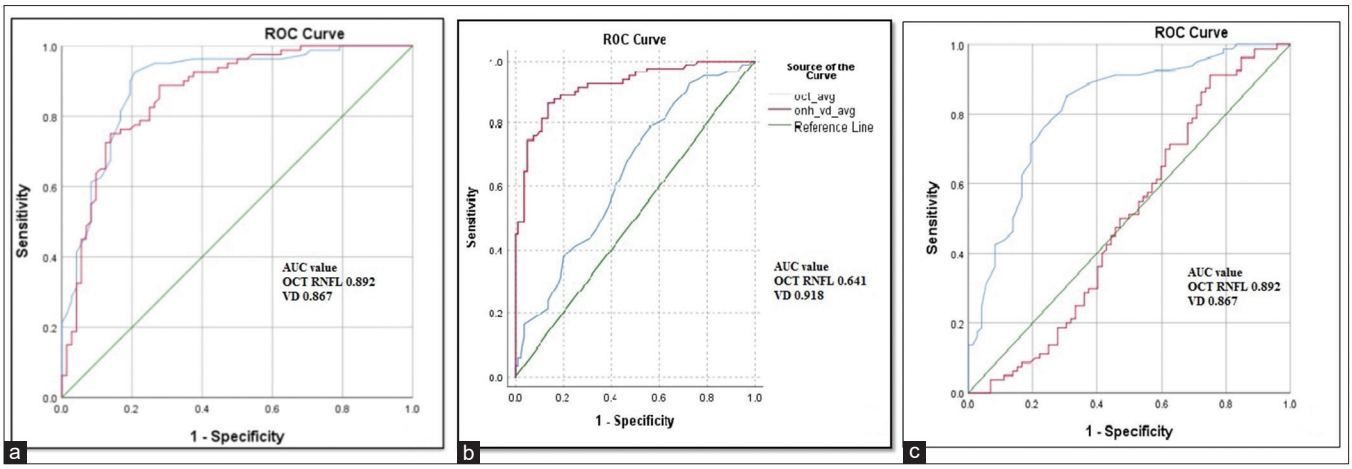

Figure 2: Receiver operating characteristics curve for average optical coherence tomography-retinal nerve fibre layer thickness and vessel density for differentiating between (a) primary open-angle glaucoma (POAG) and healthy subjects (b) glaucoma suspects and healthy subjects (c) POAG and glaucoma suspects

weak correlation of VD with RNFL thickness in the present study is in contrast with the findings by Toshev *et al*.[30] and Rao *et al*.,[31] where they observed a strong positive correlation in glaucomatous eyes. Cennamo *et al*.,[32] however, found no correlation between OCT RNFL and VD in pre-perimetric open-angle glaucoma, which was more consistent with our finding. This variation in the findings between the studies could be because of the difference in the study population, and devices and softwares used to estimate VD.

Based on the ROC curve and AUROC, we found that the average RNFL thickness was found to have a better diagnostic ability than VD to distinguish POAG eyes from healthy eyes and glaucoma suspects. However, VD is a better parameter to distinguish glaucoma suspects from healthy eyes. This may be explained by the hypothesis that changes in blood flow are detectable in glaucoma suspects with no structural changes.[33] Triolo *et al*.,[29] in their study, showed that RNFL had a better diagnostic accuracy compared to RPC VD between POAG versus control, glaucoma suspect versus control, and POAG versus suspect. They put forward the hypothesis that neurodegeration in POAG may be more significant than microvascular changes. Liu *et al*.[22] and Yarmohammadi *et al*.[26] found that the average VD and RNFL thickness have similar diagnostic accuracy for differentiating healthy eyes from glaucoma suspects and POAG eyes. We have derived a normative data from the healthy participants and OCTA VD with a cutoff value of 44 can be used to differentiate healthy eyes from POAG eyes in Indian population.

The strengths of our study include the comparison of all the available OCTA vascular parameters (PD, FI, and VD) with OCT-derived RNFL thickness, exclusion of patients on ocular hypotensive medications thereby ruling out their confounding effects, and the exclusive study population of Indian origin. Our study has limitations. We have relied on the medical history of study participants and not subjected them to any medical examination to exclude patients with underlying disease that may affect the vascular system. Also, during the process of extraction of VD, data may be lost during transfer and we have included both macro- and micro-vessel measurements for calculation as the device does not have default software for VD estimation. The current study is cross-sectional and needs longitudinal follow-up to check for repeatability. Further longitudinal studies with a larger sample size and longer follow-up are needed so that a standardized normative database can be generated for the parameters of OCTA similar to the normative data available for OCT-RNFL thickness. An inbuilt plug in for VD calculation should be made available with the device to obtain more meaningful results without confounding factors, and help the clinical practitioners.

Table 4: Sensitivity and specificity of FI derived from ROC curve analysis at various cutoffs to discriminate healthy eyes from glaucoma suspects and POAG eyes

Purpose of the Cutoff	Average FI Cutoff	Sensitivity (%)	Specificity (%)
To differentiate healthy individuals from glaucoma suspects	0.31	100	99
	0.32	100	97
	0.33	99	97
	0.33	98	97
	0.34	96	97
	0.34	96	96
	0.35	96	95
	0.35	96	94
	0.35	96	92
	0.35	96	91
To differentiate healthy individuals from POAG patients	0.26	100	97
	0.27	100	95
	0.28	100	92
	0.30	100	90
	0.30	100	87
	0.30	100	85
	0.31	100	82
	0.32	100	79
	0.33	99	79
	0.33	98	79

FI=flux index, POAG=primary open-angle glaucoma, ROC=receiver operating characteristics curve

Conclusion

OCT-RNFL has better diagnostic capability in differentiating glaucoma from healthy eyes compared to OCTA. However, OCTA was found to be better in screening out glaucoma suspects from healthy eyes. Among OCTA parameters, VD is better at differentiating POAG and glaucoma suspects from healthy eyes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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