Original Article

Evaluation of spectral domain optical coherence tomography parameters in ocular hypertension, preperimetric, and early glaucoma

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Purpose: The objective of this study is to evaluate the diagnostic ability of retinal nerve fiber layer (RNFL), macular, optic nerve head (ONH) parameters in healthy subjects, ocular hypertension (OHT), preperimetric glaucoma (PPG), and early glaucoma (EG) patients, to reveal factors affecting the diagnostic ability of spectral domain-optical coherence tomography (SD-OCT) parameters and risk factors for glaucoma. **Methods:** Three hundred and twenty-six eyes (89 healthy, 77 OHT, 94 PPG, and 66 EG eyes) were analyzed. RNFL, macular, and ONH parameters were measured with SD-OCT. The area under the receiver operating characteristic curve (AUC) and sensitivity at 95% specificity was calculated. Logistic regression analysis was used to determine the glaucoma risk factors. Receiver operating characteristic regression analysis was used to evaluate the influence of covariates on the diagnostic ability of parameters. **Results:** In PPG patients, parameters that had the largest AUC value were average RNFL thickness (0.83) and rim volume (0.83). In EG patients, parameter that had the largest AUC value was average RNFL thickness (0.98). The logistic regression analysis showed average RNFL thickness was a risk factor for both PPG and EG. Diagnostic ability of average RNFL and average ganglion cell complex thickness increased as disease severity increased. Signal strength index did not affect diagnostic abilities. Diagnostic ability of average RNFL and rim area increased as disc area increased. **Conclusion:** When evaluating patients with glaucoma, patients at risk for glaucoma, and healthy controls RNFL parameters deserve more attention in clinical practice. Further studies are needed to fully understand the influence of covariates on the diagnostic ability of OCT parameters.

Key words: Area under receiver operating characteristic curve, ganglion cell complex, optic nerve head, retinal nerve fiber layer, spectral domain-optical coherence tomography

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_157_17

Quick Response Code:

Glaucoma is an optic neuropathy characterized by progressive loss of retinal ganglion cells (RGCs) and their axons, eventually resulting in visual field loss.[1,2] Spectral domain optical coherence tomography (SD-OCT) is an important diagnostic tool for glaucoma, which enables measurement of retinal nerve fiber layer (RNFL), optic nerve head (ONH) and macular parameters.

Standard automated perimetry, which is the gold standard diagnostic test for glaucomatous optic neuropathy, detects visual-field defects by the time 30%–50% of RGCs were lost.[3] Identifying RGC loss as early as possible is of paramount importance to prevent the development of irreversible visual-field defects. At this point, SD-OCT comes forward with its ability to detect early RGC loss with quantitative assessment of several parameters linked to glaucoma.[4,5]

This is a comprehensive study evaluating both diagnostic ability of OCT parameters and covariates affecting diagnostic ability of OCT parameters, in addition to determining risk factors for glaucoma. Several studies have been carried out to evaluate the diagnostic ability of different OCT parameters for glaucoma.[6-21] We aimed to conduct a study with four study groups to investigate every aspect of OCT parameters in glaucoma diagnosis and elicit the more important parameters in clinical practice.

Methods

Patients

This study included 237 eyes of 122 patients that have been followed at Glaucoma Unit of Umraniye Training and Research Hospital at least for 2 years and 89 eyes of 45 healthy controls that were selected randomly from general ophthalmology clinic. Of the 237 eyes, 77 were followed with ocular hypertension (OHT) diagnosis, 94 were followed with preperimetric glaucoma (PPG) diagnosis, and 66 were followed with early glaucoma (EG) diagnosis. All patients had been followed by one particular glaucoma expert. Informed consent was obtained from all study subjects. This study adhered to the tenets of the Declaration of Helsinki and the research protocol was approved from Local Ethic Committee.

All patients underwent full ophthalmic examination including review of medical history, measurement of

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Manuscript received: 02.03.17; Revision accepted: 26.09.17

Cite this article as: Aydoğan T, Akçay Bİ, Kardeş E, Ergin A. Evaluation of spectral domain optical coherence tomography parameters in ocular hypertension, preperimetric, and early glaucoma. Indian J Ophthalmol 2017;65:1143-50.

best-corrected visual acuity (BCVA), and intraocular pressure (IOP) using Goldmann applanation tonometry, gonioscopy, dilated fundus examination with 90 D lens, ultrasound pachymetry, visual-field examination with the Humphrey Field Analyzer (HFA) (Carl Zeiss Meditec, Jena, Germany) Swedish Interactive Threshold Algorithm (SITA) 24-2 test and measurement of RNFL, macular, and ONH parameters with SD-OCT (RTVue-100; Optovue, Fremont, CA, USA).

Inclusion criteria were BCVA of at least 20/40, spherical refraction <±6.0 D, cylinder correction <3.0 D, open angle with gonioscopy, at least two reliable HFA SITA test results with a fixation loss of <20%, false-negative error of <15%, and false-positive error of <15%. Patients with coexisting retinal disease, uveitis, nonglaucomatous optic disc neuropathy, and any other disease resulting in visual field defects were excluded from the study.

Four groups of eyes were included (healthy, OHT, PPG and EG eyes). Healthy eyes were defined as those who had no history of intraocular surgery, no first-degree relative with glaucoma, IOP <21 mmHg, normal optic disc appearance and normal visual-field test with mean deviation (MD) >−2 dB. OHT eyes were defined as those who had IOP of >21 mmHg, normal optic disc appearance, and normal visual-field test with MD >−2 dB. PPG eyes were defined as those who had glaucomatous changes (focal/diffuse neuroretinal rim loss, notching, nerve fiber layer defects) during follow-up and normal visual field test with MD >−2 dB. EG eyes were defined as those who had glaucomatous changes (focal/diffuse neuroretinal rim loss, notching, nerve fiber layer defects) during follow-up and visual-field defects classified according to Hodapp-Parrish-Andersons criteria[22] in which EG defects described as having one of these with a MD >−6 dB: a cluster of 3 or more nonedge points with $P < 5\%$ and at least 1 point with $P < 1\%$ in the pattern deviation probability plot; pattern standard deviation (PSD) of <5%; or glaucoma hemifield test results outside normal limits.

Optical coherence tomography

OCT measurements were performed using RTVue-100 (software version 6.1.0.4; Optovue Inc., Fremont, CA, USA). The RTVue-100 is one of the SD-OCT devices with a scan rate of 26 000 A scans per second and an axial resolution of 5 μm, allowing fast imaging of the retinal microstructure at high resolution. ONH protocol and ganglion cell complex (GCC) protocol were used. Good quality images with a signal strength index (SSI) ≥50 were included.

Optic nerve head scan

The ONH protocol was used to obtain RNFL and ONH measurements. In the measurement of RNFL parameters, ONH protocol generates a polar RNFL thickness map from which RNFL thickness is measured along a circle 3.45 mm in diameter centered on the optic disc. Parameters including overall average, superior hemisphere, inferior hemisphere, temporal quadrant, superior quadrant, inferior quadrant, and nasal quadrant are provided. In the measurement of ONH parameters, ONH protocol consists of 12 radial scans 3.4 mm in length and 13 concentric ring scans ranging from 1.3 to 4.9 mm in diameter all centered on the optic disc. Retinal pigment epithelium (RPE) tips are detected by the software, and the optic disc margins are delinated automatically by joining the RPE tips. The optic cup is also automatically defined by the software by intersecting the nerve head inner boundary and a parallel line that is 150 μm above the joining line of the RPE tips. Parameters including disc area, rim area, rim volume, vertical cup-to-disc (C/D) ratio, horizontal C/D ratio, cup area, cup volume, C/D area ratio, and nerve head volume are provided.

Ganglion cell complex scan

The GCC protocol was used to obtain macular measurements. In the measurement of macular parameters, GCC protocol scans a 7 mm square region with 15 vertical lines at 0.55 mm intervals and 1 horizontal line. A 6 mm diameter circle inside the scanned region is centered 1 mm temporal to the fovea which provides analysis of the nasal visual field where glaucomatous damage is most likely to occur. This macular B-scan evaluates macular total retinal (TR) measurement in two layers: GCC and OR layers. GCC is composed of ganglion cell layer, nevre fiber layer, and inner plexiform layer. GCC parameters including overall average thickness, superior thickness, inferior thickness, superior minus inferior thickness, global loss volume (GLV), and focal loss volume (FLV) are provided. GLV shows the average GCC loss over the entire GCC map. FLV shows local GCC loss using a pattern deviation map to correct for overall absolute changes. TR and OR parameters including overall average thickness, superior thickness, inferior thickness, and superior minus inferior thickness are also provided.

Statistical analyses

Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) software was used for the statistical analyses. Shapiro–Wilk test was used to test the distribution of numerical data. Linear-mixed model was used in the comparison of normally distributed data. Generalized linear mixed model was used in the comparison of nonnormally distributed data. The ability of the each parameter to differentiate between patient groups and healthy subjects defined as diagnostic ability and it is evaluated by area under the receiver operating characteristic curve (AUC). Sensitivity at fixed specificity of 95% was calculated for each parameter. A bootstrap resampling procedure ($n = 1000$ samples) was used to determine confidence intervals. As measurements from both eyes from the same subject are likely to be correlated, the cluster of the data for the study subject is considered as the unit of resampling when calculating standard errors. This method has been used when multiple correlated measurements of the same unit are present.[23] AUC of each parameter was compared using the Delong test. Sensitivity at 95% specificity of each parameter was compared using the *Z*-test. To determine which parameters were associated with glaucoma, we used a backward selection method to find which parameters reached a significance level of <0.25. Then, logistic regression analysis was used to determine the factors that were significantly associated with PPG and EG. Receiver operating characteristic (ROC) regression analysis was used to evaluate the influence of covariates on the diagnostic ability of certain OCT parameters. This method was previously described by Medeiros *et al*.[24] for the evaluation of the influence of covariates on the performance of diagnostic tests in glaucoma. ROC curves for specific values of covariates can be obtained with this model. $P < 0.05$ was considered to be significant in all statistical analysis.

Results

Patients

Demographics and clinical characteristics of the study subjects are shown in Table 1. Age of the study subjects was significantly

Table 1: Demographics and clinical characteristics of the study participants

	Healthy (89 eyes)	OHT (77 eyes)	PPG (94 eyes)	EG (66 eyes)	*P*					
					Healthy versus OHT	Healthy versus PPG	Healthy versus EG	OHT versus PPG	OHT versus EG	PPG versus EG
Age (years)	33.1±10.1	52.8±8.2	53.2±11.1	59.4±9.5	<0.001	<0.001	<0.001	0.999	<0.001	<0.001
Male/female (*n*/*n*)	32/57	15/62	37/57	30/36	0.021*	0.594*	0.212*	0.005*	0.001*	0.442*
MD (dB)	−0.91±0.90	−1.12±0.80	−1.27±0.85	−3.83±1.28	0.999	0.026	<0.001	0.658	<0.001	<0.001
PSD (dB)	1.51±0.37	1.65±0.45	1.82±0.44	3.62±1.37	0.999	0.057	<0.001	0.767	<0.001	<0.001

Data are expressed as means±SDs. *Pearson's Chi square test. *P*: Linear-mixed model, OHT: Ocular hypertension, PPG: Preperimetric glaucoma, EG: Early glaucoma, MD: Median deviation; dB: Decibels; PSD: Pattern standard deviation, SDs: Standard deviations

different in all comparisons except when comparing OHT patients with PPG patients. MD and PSD values were significantly lower in EG patients than every other study group.

Optical coherence tomography parameters

Comparison of the OCT parameters among the study groups is shown in Table 2. Almost all parameters decreased from healthy subjects to EG patients. FLV, GLV, cup area, cup volume, horizontal, and vertical C/D ratio values increased from healthy subjects to EG patients. Almost all comparisons were statistically significant among the study groups except for comparisons between healthy subjects and OHT patients and comparisons involving OR parameters and disc area. In addition, comparisons of PPG patients with OHT and EG patients for the ONH parameters were not statistically significant.

Area under the receiver operating characteristic curves and sensitivities at 95% specificity

The AUC and sensitivity at 95% specificity of the OCT parameters to diagnose PPG and EG are shown in Table 3. When discriminating between healthy controls and PPG patients, OCT parameters that had the largest AUC value in their groups were average RNFL thickness (0.83), superior GCC thickness (0.79), superior TR thickness (0.76), superior OR thickness (0.64), and rim volume (0.83) [Fig. 1]. Pairwise comparisons did not show statistically significant differences between the AUC values of these parameters except for superior OR thickness [Table 4]. When discriminating between healthy controls and EG patients, OCT parameters that had the largest AUC value in their groups were average RNFL thickness (0.98), superior GCC thickness (0.94), superior TR thickness (0.90), superior OR thickness (0.75), and rim volume (0.90) [Fig. 2]. Average RNFL thickness performed significantly better in pairwise comparisons [Table 4].

When discriminating between healthy subjects and PPG patients, OCT parameters that had the largest sensitivity at 95% specificity in their groups were average RNFL thickness (32.5%), superior GCC thickness (34.0%), superior TR thickness (28.7%), superior OR thickness (20.2%) and rim volume (51.4%). In pairwise comparisons, rim volume had significantly the highest sensitivity at 95% specificity [Table 5]. When discriminating between healthy subjects and EG patients, OCT parameters that had the largest sensitivity at 95% specificity in their groups were average RNFL thickness (87.4%), superior GCC thickness (75.8%), average TR thickness (62.1%), superior OR thickness (34.9%), and rim volume (65.2%). In pairwise comparisons, average RNFL thickness had significantly the highest sensitivity at 95% specificity except for superior GCC thickness [Table 5].

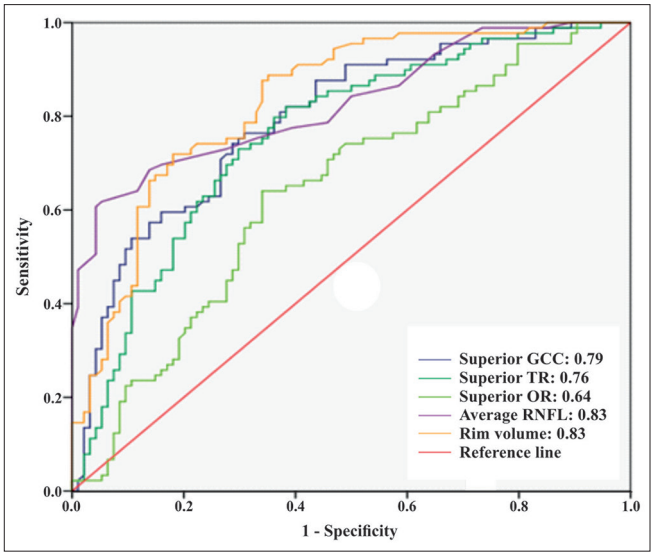

Figure 1: The area under the receiver operating characteristic curves of the best optical coherence tomography parameters in their groups for discriminating between healthy subjects and preperimetric glaucoma patients

Logistic regression analysis

The logistic regression analysis showed that average RNFL thickness was a risk factor for both PPG (odds ratio = 0.79, $P < 0.001$) and EG (odds ratio = 0.49, $P = 0.001$) [Table 6].

Receiver operating characteristic regression analysis

The influence of disease severity, disk area, and SSI as covariates on the diagnostic ability of certain OCT parameters is shown in Table 7. Diagnostic ability of average RNFL and average GCC thickness increased as MD decreased (disease severity increased) (−1.8; $P = 0.003$ and − 2.0; $P = 0.044$, respectively). SSI did not have any influence on diagnostic ability. Diagnostic ability of average RNFL and rim area increased as disk area increased (4.08; $P = 0.014$ and 0.33; $P = 0.023$, respectively).

Discussion

Glaucoma is a multifactorial disease that must be treated before irreversible damage to the RGCs occurs. In this study, we investigated several OCT parameters with different patient

Table 2: Comparison of the optical coherence tomography parameters among the study groups

	Healthy (89 eyes)	OHT (77 eyes)	PPG (94 eyes)	EG (66 eyes)	*P*					
					Healthy versus OHT	Healthy versus PPG	Healthy versus EG	OHT versus PPG	OHT versus EG	PPG versus EG
RNFL parameters										
Average thickness (μm)	112.8±8.7	112.2±6.3	102.5±5.8	90.94±7.8	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
Temporal quadrant (μm)	82.3±9.6	82.6±11.4	75.96±10.1	68±11.1	0.999	0.005	<0.001	0.003	<0.001	<0.001
Superior quadrant (μm)	139.9±18	137.7±11.2	124.3±11.2	110.9±13.4	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
Nazal quadrant (μm)	83±10.6	82.2±10.6	76.3±8	67.6±9.5	0.999	<0.001	<0.001	0.006	<0.001	<0.001
Inferior quadrant (μm)	145.9±14.6	146.4±12.1	133.1±13.4	117.1±14.2	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
SSI	85±12	83±12	78±14	74±14	0.999	0.022	<0.001	0.239	0.008	0.822
GCC parameters										
Average thickness (μm)	100.7±6.4	100.5±4.9	99.9±6.6	87±6.7	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
Superior thickness (μm)	101.2±6.6	99.9±5.2	93.6±7	86.6±7	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
Inferior thickness (μm)	100.2±6.5	101±5.1	94.2±6.6	87.4±8.4	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
FLV (%)	0.3±0.5	0.4±0.4	0.8±1	2.3±2.6	0.999	0.382	<0.001	0.704	<0.001	<0.001
GLV (%)	2±2.2	1.8±1.5	5.3±4.4	10.7±5.9	0.999	<0.001	<0.001	<0.001	<0.001	<0.001
TR parameters										
Average thickness (μm)	274.7±12.1	270.1±10.5	263.7±12.7	253.3±13.2	0.196	<0.001	<0.001	0.004	<0.001	<0.001
Superior thickness (μm)	277.4±12.4	271.7±11	265.31±12.8	254.34±13.6	0.236	<0.001	<0.001	0.001	<0.001	<0.001
Inferior thickness (μm)	272.1±12.1	268.5±10.4	262.2±13	252.2±14.1	0.259	<0.001	<0.001	0.058	<0.001	<0.001
OR parameters										
Average thickness (μm)	174.1±8.1	169.7±8.2	169.9±9.3	166.3±9.1	0.069	0.003	0.002	0.999	0.999	0.999
Superior thickness (μm)	176.3±8.3	171.8±8.5	171.8±9.4	167.8±9.6	0.069	0.004	<0.001	0.999	0.745	0.999
Inferior thickness (μm)	172±8.2	167.6±8.1	168±9.3	164.8±8.8	0.074	0.003	0.005	0.999	0.999	0.999
SSI	79±7	76±9	72±10	70±11	0.598	<0.001	<0.001	0.084	0.016	0.999
ONH parameters										
Disc area (mm^2)	2.22±0.38	2.17±0.34	2.23±0.42	2.16±0.42	0.999	0.999	0.999	0.999	0.999	0.999
Cup area (mm^2)	0.55±0.37	0.76±0.37	0.97±0.47	1.02±0.46	0.081	<0.001	<0.001	0.203	<0.001	0.009
Rim area (mm^2)	1.66±0.41	1.41±0.36	1.26±0.38	1.14±0.36	0.004	<0.001	<0.001	0.477	<0.001	0.011
Rim volume (mm^3)	0.24±0.14	0.16±0.07	0.12±0.07	0.10±0.06	<0.001	<0.001	<0.001	0.080	<0.001	0.318
Nerve head volume (mm^3)	0.44±0.21	0.32±0.16	0.25±0.14	0.21±0.12	0.005	<0.001	<0.001	0.023	<0.001	0.349
Cup volume (mm^3)	0.11±0.14	0.20±0.19	0.30±0.27	0.28±0.21	0.083	<0.001	<0.001	0.780	0.074	0.999
Horizontal C/D ratio	0.51±0.20	0.64±0.17	0.69±0.20	0.72±0.17	0.010	<0.001	<0.001	0.817	0.008	0.106
Vertical C/D ratio	0.44±0.18	0.55±0.14	0.61±0.17	0.67±0.14	0.009	<0.001	<0.001	0.160	<0.001	0.011
SSI	77±10	72±11	69±14	65±14	0.184	<0.001	<0.001	0.513	0.034	0.999

Data are expressed as means±SDs. *P*: Linear-mixed model, OHT: Ocular hypertension, PPG: Preperimetric glaucoma, EG: Early glaucoma, RNFL: Retinal nerve fiber layer, SSI: Signal strength index, GCC: Ganglion cell complex, FLV: Focal loss volume, GLV: Global loss volume, TR parameters: Macular total retinal parameters, OR parameters: Macular outer retinal parameters, ONH: Optic nerve head, C/D ratio: Cup-to-disk ratio, SDs: Standard deviations

groups and healthy subjects to reveal the parameter that is the most crucial in the early diagnosis of glaucoma.

This study included OHT, PPG, and EG patient groups to investigate the change in OCT parameters at patients who are at risk for glaucoma, who have early signs of glaucoma and who have glaucoma. OCT parameters decreased/increased accordingly from healthy subjects to EG patients as expected. Comparison of healthy subjects with OHT patients was not statistically significant as reported in earlier studies.[6-8] Comparisons for OR parameters were significant only when comparing healthy controls with PPG and EG patients. This finding agrees with other studies suggesting that OR parameters are affected less during the course of glaucoma.[4,25,26]

In the comparison of PPG patients with EG patients for the ONH parameters, the difference was not significant unlike RNFL, GCC, and TR parameters. Diagnosis of PPG was based on glaucomatous changes in the optic disk before development of visual-field defects. This finding shows observation of glaucomatous changes and measurement of ONH parameters has similar courses that there was not significant difference in the ONH parameters.

In the comparison of ONH parameters between OHT parameters and healthy controls, there was a significant difference between two groups, but the difference was not significant when comparing OHT patients with PPG patients. This finding puts OHT patients in a closer position to PPG patients unlike other OCT parameters and is needed to be explored in ONH parameters for OHT patients basis.

Table 3: The area under receiver operating characteristic curve and sensitivity at 95% specificity of the optical coherence tomography parameters to diagnose preperimetric glaucoma and early glaucoma

	Healthy versus PPG		Healthy versus EG	
	AUC	Sensitivity at 95% specificity (%)	AUC	Sensitivity at 95% specificity (%)
RNFL parameters				
Average thickness	0.83 (0.77-0.88)	32.5 (21.4-43.3)	0.98 (0.94-0.99)	87.4 (77.5-94.3)
Temporal quadrant	0.67 (0.60-0.74)	26.2 (16.6-35.4)	0.85 (0.78-0.90)	59.4 (46.3-71.3)
Superior quadrant	0.77 (0.70-0.83)	15.1 (5.6-30.7)	0.91 (0.85-0.95)	59.4 (42.8-76.3)
Nazal quadrant	0.70 (0.63-0.77)	6.1 (0.0-17.5)	0.86 (0.80-0.91)	44.3 (20.4-62.8)
Inferior quadrant	0.73 (0.66-0.79)	24.8 (13.5-38.7)	0.93 (0.88-0.97)	64.9 (48.1-81.8)
GCC parameters				
Average thickness	0.77 (0.70-0.83)	27.7 (8.5-41.5)	0.93 (0.88-0.97)	71.2 (45.5-83.3)
Superior thickness	0.79 (0.73-0.85)	34.0 (14.9-59.7)	0.94 (0.89-0.97)	75.8 (51.5-89.4)
Inferior thickness	0.73 (0.66-0.80)	21.3 (10.0-29.8)	0.89 (0.83-0.94)	60.6 (43.9-71.2)
FLV	0.70 (0.63-0.76)	11.7 (3.2-28.7)	0.86 (0.80-0.91)	39.4 (22.7-60.6)
GLV	0.78 (0.71-0.84)	27.7 (12.8-42.6)	0.94 (0.89-0.97)	73.4 (53.0-84.9)
TR parameters				
Average thickness	0.74 (0.67-0.80)	24.5 (11.7-45.7)	0.88 (0.82-0.93)	62.1 (42.4-81.8)
Superior thickness	0.76 (0.69-0.82)	28.7 (11.7-44.7)	0.90 (0.84-0.94)	59.8 (40.9-77.3)
Inferior thickness	0.71 (0.64-0.78)	22.3 (9.6-40.4)	0.86 (0.79-0.91)	57.6 (37.9-72.7)
OR parameters				
Average thickness	0.64 (0.56-0.71)	13.8 (5.3-26.6)	0.74 (0.67-0.81)	28.8 (13.6-40.9)
Superior thickness	0.64 (0.57-0.71)	20.2 (8.5-31.9)	0.75 (0.67-0.82)	34.9 (22.7-51.5)
Inferior thickness	0.63 (0.55-0.70)	11.7 (3.2-23.4)	0.73 (0.66-0.80)	24.2 (6.1-40.9)
ONH parameters				
Disc area	0.50 (0.43-0.58)	6.4 (0.00-10.4)	0.54 (0.46-0.62)	9.8 (0.00-19.7)
Cup area	0.76 (0.69-0.82)	26.5 (12.3-51.5)	0.79 (0.72-0.85)	29.3 (13.6-50.0)
Rim area	0.79 (0.72-0.84)	38.2 (21.7-56.7)	0.86 (0.79-0.91)	52.9 (34.9-73.5)
Rim volume	0.83 (0.77-0.88)	51.4 (22.2-69.2)	0.90 (0.40-0.94)	65.2 (38.2-78.8)
Nerve head volume	0.82 (0.75-0.87)	48.9 (18.0-62.8)	0.87 (0.81-0.92)	60.6 (27.3-72.9)
Cup volume	0.75 (0.68-0.81)	29.8 (13.5-42.6)	0.78 (0.71-0.84)	21.2 (6.1-39.4)
Horizontal C/D ratio	0.77 (0.70-0.83)	34.9 (20.2-49.8)	0.80 (0.73-0.86)	35.4 (19.5-51.5)
Vertical C/D ratio	0.79 (0.73-0.85)	36.5 (7.5-53.1)	0.87 (0.80-0.92)	50.5 (15.0-72.6)

95% CIs are shown in parentheses. ROC: Receiver operating characteristic, AUC: Area under ROC curve, PPG: Preperimetric glaucoma, EG: Early glaucoma, RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, FLV: Focal loss volume, GLV: Global loss volume, TR parameters: Macular total retinal parameters, OR parameters: Macular outer retinal parameters, ONH: Optic nerve head, C/D ratio: Cup-to-disk ratio, CIs: Confidence intervals

AUCs to differentiate EG patients from healthy controls was larger than AUCs to differentiate PPG patients from healthy controls as shown earlier in a study that calculates AUCs to differentiate both groups.[9] The diagnostic ability of GCC, TR, and ONH parameters were good and comparable to RNFL parameters in PPG patients. Lisboa *et al*.[10] reported similar AUC values in PPG patients for all parameter groups but showed that RNFL parameters performed significantly better than ONH parameters. In their study, the control group consisted of glaucoma suspects with suspicious optic disc appearance that resulted in the poorer diagnostic performance of ONH parameters. In our study, the control group consisted of subjects with healthy optic disk appearance that resulted in ONH parameters to have similar diagnostic performance to RNFL parameters in PPG patients.

Diagnostic ability of both RNFL and ONH parameters increased in EG patients as mentioned earlier. However, RNFL parameters outrun other parameters and performed significantly better in all comparisons in EG patients. On the contrary, Sung *et al*.[11] reported that diagnostic performance of ONH parameters was inferior to average RNFL thickness, especially in early glaucomatous eyes but became similar in advanced glaucomatous eyes. In our study, moderate/advanced glaucomatous eyes were not included. In the diagnosis of PPG, we followed patients with glaucoma suspicion at least for 2 years for the optic disk changes. This resulted in higher diagnostic ability of ONH parameters when differentiating PPG patients from healthy controls. However, with the increasing disease severity, RNFL parameters performed better than ONH parameters. Sensitivity at 95% and specificity of ONH parameters were higher than other parameters in the diagnosis of PPG patients for the reasons mentioned above.

The diagnostic ability of RNFL, GCC, TR, and ONH parameters were good in EG patients. Rao *et al*.[12] reported similar AUC values for RNFL, GCC, and ONH parameters in EG patients. In some studies, GCC parameters showed similar diagnostic ability with RNFL parameters.[8,13-19] Moreno *et al*.[20] reported that GCC parameters have slightly superior ability to

discriminate between eyes with EG and controls. Schulze *et al*.[7] reported that GCC parameters were slightly inferior to RNFL parameters in EG patients. In the diagnosis of PPG patients, Lisboa *et al*.[10] showed that RNFL parameters performed significantly better than macular measurements. In our study, RNFL parameters performed better than other parameters in EG patients. In that aspect, though GCC parameters can be evaluated in the diagnosis of glaucoma RNFL parameters are observed to be more valuable. Sensitivity at 95% specificity of RNFL parameters was higher than other parameters in the diagnosis of EG patients.

The highest AUC values in the EG patients for RNFL parameters were average, inferior, and superior RNFL thicknesses, which is consistent with the typical pattern of RNFL damage in glaucoma patients. Similar results have been

Table 4: The difference between area under receiver operating characteristic curve value of retinal nerve fiber layer, ganglion cell complex, total retinal, outer retinal, and optic nerve head parameters that had the largest area under receiver operating characteristic curve value in their groups

	Healthy versus PPG		Healthy versus EG	
	AUC	*P*	AUC	*P*
Average RNFL versus superior GCC	0.034	0.327	0.041	0.017
Average RNFL versus superior TR	0.068	0.099	0.084	0.001
Average RNFL versus superior OR	0.186	<0.001	0.230	<0.001
Average RNFL versus rim volume	0.005	0.887	0.083	0.001
Superior GCC versus superior TR	0.034	0.201	0.033	0.037
Superior GCC versus superior OR	0.152	<0.001	0.189	<0.001
Superior GCC versus rim volume	0.039	0.353	0.041	0.155
Superior TR versus superior OR	0.118	<0.001	0.146	<0.001
Superior TR versus rim volume	0.073	0.082	0.001	0.974
Superior OR versus rim volume	0.191	<0.001	0.148	0.001

P: De long test. ROC: Receiver operating characteristic, AUC: Area under ROC curve, RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, TR parameters: Macular total retinal parameters, OR parameters: Macular outer retinal parameters, PPG: Preperimetric glaucoma, EG: Early glaucoma

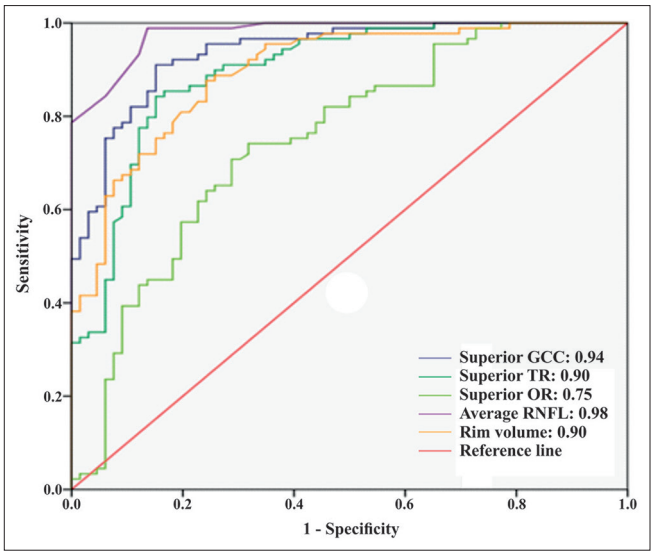

Figure 2: The area under the receiver operating characteristic curves of the best optical coherence tomography parameters in their groups for discriminating between healthy controls and early glaucoma patients

Table 5: The difference between sensitivity at 95% specificity value of retinal nerve fiber layer, ganglion cell complex, total retinal, outer retinal, and optic nerve head parameters that had the largest sensitivity at 95% specificity value in their groups

	Healthy versus PPG		Healthy versus EG	
	Sensitivity at 95% specificity, (%)	*P*	Sensitivity at 95% specificity (%)	*P*
Average RNFL versus superior GCC	1.5	0.817	11.6	0.072
Average RNFL versus average TR	-	-	25.3	0.001
Average RNFL versus superior TR	3.8	0.580	-	-
Average RNFL versus superior OR	12.3	0.058	52.5	<0.001
Average RNFL versus rim volume	18.9	0.009	22.2	0.002
Superior GCC versus average TR	-	-	13.7	0.092
Superior GCC versus superior TR	5.3	0.433	-	-
Superior GCC versus superior OR	13.8	0.033	40.9	<0.001
Superior GCC versus rim volume	17.4	0.019	10.6	0.183
Average TR versus superior TR	-	-	-	-
Average TR versus superior OR	-	-	27.2	0.002
Average TR versus rim volume	-	-	3.1	0.718
Superior TR versus superior OR	8.5	0.176	-	-
Superior TR versus rim volume	22.7	0.002	-	-
Superior OR versus rim volume	31.2	<0.001	30.3	<0.001

P: *Z*-test. RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, TR parameters: Macular total retinal parameters, OR parameters: Macular outer retinal parameters, PPG: Preperimetric glaucoma, EG: Early glaucoma

Table 6: The logistic regression analysis for the optical coherence tomography parameters as glaucoma risk factors in preperimetric glaucoma and early glaucoma patients

Healthy versus PPG			Healthy versus EG		
Parameters	OR	*P*	Parameters	OR	*P*
Average RNFL	0.79 (0.72-0.87)	<0.001	Average RNFL	0.49 (0.33-0.74)	0.001
Average GCC	1.23 (1.02-1.47)	0.030	FLV	15.47 (1.24-193.44)	0.034
Superior GCC	1.69 (1.16-2.47)	0.006	Inferior TR	0.90 (0.82-0.98)	0.019
Cup area	23.19 (6.41-83.88)	<0.001			

The variables are selected by backward selection method. 95% CIs are shown in parentheses. PPG: Preperimetric glaucoma, EG: Early glaucoma, RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, FLV: Focal loss volume, TR parameters: Macular total retinal parameters, CIs: Confidence intervals, OR: Odds ratio

Table 7: The influence of disease severity (based on median deviation), disk area, and signal strength index as covariates on the diagnostic ability of certain optic coherence tomography parameters in early glaucoma patients

	Average RNFL		Average GCC		FLV		GLV		Rim area	
	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*
Intercept	−22.58 (−32.19-−12.96)	0.001	−9.90 (−21.28-1.47)	0.088	0.9 (−0.72-2.51)	0.276	5.37 (−1.37-12.11)	0.118	−0,72 (−1.41-−0.03)	0.042
MD	−1.8 (−3.0-−0.59)	0.003	−2.0 (−3.94-−0.05)	0.044	−0.01 (−0.29-0.27)	0.946	1.17 (−0.2-2.55)	0.095	−0.01 (−0.11-0.09)	0.879
SSI	0.01 (−0.09-0.11)	0.829	0.05 (−0.1-0.19)	0.525	−0.01 (−0.03-0.02)	0.627	−0.01 (−0.10-0.08)	0.777	−0.01 (−0.01-0.001)	0.065
Disk area	4.08 (0.82-7.33)	0.014	−1.25 (−5.33-2.84)	0.550	−0.03 (−0.71-0.66)	0.936	0.16 (−2.72-3.03)	0.915	0.33 (0.05-0.62)	0.023

95% CIs are shown in parentheses. *P*: ROC regression model, MD: Median deviation, SSI: Signal strength index, RNFL: Retinal nerve fiber layer, GCC: Ganglion cell complex, FLV: Focal loss volume, GLV: Global loss volume, ROC: Receiver operating characteristic, CIs: Confidence intervals

reported by Bertuzzi *et al*.[8] and Rao *et al*.[13]. OR parameters were found inferior to other parameters in both PPG and EG patients. As mentioned above this finding shows that OR parameters are affected less during glaucoma.[4,25,26]

Logistic regression analysis for OCT parameters revealed average RNFL thickness as a glaucoma risk factor for both PPG and EG. This finding further emphasizes the importance of RNFL parameters when evaluating glaucoma. In a study Arintawati *et al*.[16] conducted GLV was found to be a risk factor for both PPG and EG; however, in their study, overall GCC parameters had larger AUC values than RNFL parameters in PPG and EG patients.

The influence of disease severity (based on MD), disk area, and SSI as covariates on the diagnostic ability of average RNFL thickness, average GCC thickness, FLV, GLV, and rim area were investigated. SSI value was found to have no effect on the diagnostic ability of the parameters in our study. However, Rao *et al*.[27] reported that diagnostic ability of average RNFL thickness and rim area got better with better SSI values. The reason for this can be the limit for SSI, which was 30 in their study and 50 in our study. In our study, SSI values were higher which led to narrower range of SSI values and minimalized the effect of different SSI values.

In our study, diagnostic ability of average RNFL and GCC thicknesses increased as severity of the disease increased. FLV, GLV, and rim area were not affected by disease severity. Rao *et al*.[27] reported the significant influence of disease severity on the diagnostic ability of average RNFL thickness, average GCC thickness, and rim area. The difference can be explained by MD values (disease severity), which was −3.83 in EG patients in our study and −7.31 in their study, suggesting that the increased disease severity affects more parameters.

In a study that Rao *et al*.[28] reported optic disk size did not influence the diagnostic ability of OCT parameters but increased the sensitivity of rim area at the expense of a decrease in specificity. Sung *et al*.[11] reported that increased disc area resulted in lower diagnostic ability of average RNFL thickness and rim area. In our study, diagnostic ability of both rim area and average RNFL thickness were increased in large optic discs. Since RNFL thickness decreases with increasing distance from the disc margin,[29] smaller discs have lower RNFL thickness values leading to smaller changes throughout glaucoma which results in lower diagnostic ability of RNFL thickness.

One of the limitations of our study was healthy subjects having lower age, but there are other studies with different age groups with this context. In a study Begum *et al*.[9] conducted control group and perimetric glaucoma group had a significant age difference.

Conclusion

When evaluating patients with glaucoma, patients at risk for glaucoma and healthy subjects in terms of diagnostic ability RNFL parameters come forward among other OCT parameters. This study is important, especially for those ophthalmologists that use OCT for routine clinical practice but are not glaucoma specialists. Influence of covariates on the diagnostic ability of OCT parameters can be researched with larger patient groups and more sophisticated statistical analysis for more precise results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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