Original Article

Linear discriminant score for differentiating early primary open angle glaucoma from glaucoma suspects

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Purpose: To determine the diagnostic accuracy of a linear discriminant function (LDF) based on macular ganglion cell complex (GCC), optic nerve head (ONH) and retinal nerve fibre layer (RNFL) for differentiating early primary open-angle glaucoma (POAG) from glaucoma suspects. **Methods:** In this cross-sectional study, data from consecutive 127 glaucoma suspects and 74 early POAG eyes were analysed. Each patient underwent detailed ocular examination, standard automated perimetry, GCC and ONH and RNFL analysis. After adjusting for age, gender and signal strength using the analysis of covariance; Benjamin–Hochberg multiple testing correction was performed to detect truly significant parameters to calculate the LDF. Subsequently, diagnostic accuracy of GCC and ONH and RNFL were determined. The obtained LDF score was evaluated for diagnostic accuracy in another test set of 32 suspect and 19 glaucomatous eyes. Data were analysed with the R-3.2.1 (R Core Team 2015), analysis of variance, *t*-test, Chi-square test and receiver operating curve. **Results:** Among all GCC parameters, *infero temporal* had the best discriminating power and *average RNFL thickness* and *vertical CDR* among ONH and RNFL parameters. LDF scores for GCC had AUROC of 0.809 for a cut-off value 0.07, while scores for ONH and RNFL had AUROC of 0.903 for a cut-off value − 0.24. Analysis on combined parametric space resulted in *avg RNFL thickness, vertical CDR, min GCC + IPL* and *superior GCC + IPL* as key parameters. LDF scores obtained had AUROC of 0.924 for a cut-off value 0.1. The LDF was applied to a test set with an accuracy of 84.31%. **Conclusion:** The LDF had a better accuracy than individual GCC and ONH and RNFL parameters and can be used for diagnosis of glaucoma.

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Glaucoma is a form of progressive optic neuropathy and is one of the leading causes of preventable blindness worldwide. The average life span is increasing leading to more individuals developing glaucoma as well as having the disease longer, which makes early detection and management vital.[1] Glaucoma is characterised by loss of retinal ganglion cells (RGCs) recognised as optic nerve head (ONH) changes, corresponding visual field (VF) defects and retinal nerve fibre layer (RNFL) loss. Atleast 40% of RGCs are lost before the VFs show a defect, hence the emphasis is on early diagnosis.[2]

With advances in glaucoma imaging in the form of spectral domain optical coherence tomography (SD-OCT), structural evaluation can be performed before functional loss becomes evident on perimetry. As > 50% of all RGCs are concentrated and multilayered in the macular area, macular thickness parameters such as total macular thickness, macular inner retinal layer thickness and macular ganglion cell complex (GCC) thickness can be used as complementary methods.[3–18]

Recent articles have analysed combinations of structural parameters to improve the diagnostic ability; some analysed the RNFL thickness and ONH parameters and others the peripapillary RNFL and macular ganglion cell-inner plexiform layer (GCIPL) parameters.[11,18,19] To the best of our knowledge, this is the first study to combine information from GCC, ONH and RNFL to formulate a linear discriminant function (LDF) in Indian population. The primary aim of the study was to determine the diagnostic ability of this LDF, in discriminating suspects and early glaucoma. The strength of this study further lies in validation using an independent sample.

Methods

Participants

This was a hospital-based cross-sectional study performed at a tertiary care centre from central India and included patients who presented between December 2015 to May 2017. All patients underwent a detailed ocular examination comprising visual acuity, cycloplegic refraction, slit-lamp examination, indirect ophthalmoscopy, intraocular pressure (IOP) with the Goldmann's Applanation Tonometer, 4 mirror indentation gonioscopy with 4 mirror Sussman's Gonioscope, ONH evaluation with slit-lamp biomicroscopy using 78D non-contact lens. VFs were mapped using the Humphrey Visual Field

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Analyzer, Carl Zeiss Meditec with the 24-2 Swedish Interactive Threshold Algorithm (SITA) standard program, and spectral domain OCT (SD-OCT) examinations were performed with Cirrus SD-OCT, Carl Zeiss Meditec.

The inclusion criteria were: age >18 years, best-corrected visual acuity of the Snellens >6/12 (logMAR <0.3), refractive error (under cycloplegia) between − 6 dioptre sphere (DS) myopia and +4 DS hyperopia, normal and quiet anterior chamber on slit-lamp examination, open anterior chamber angles on indentation gonioscopy with normal structures, phakic and uncomplicated pseudophakic eyes, standard automated perimetry (SAP) test with reliable indices, SD-OCT with signal strength ≥4 and absence of artefacts in the examination circle. Excluded were the patients with media opacity, history of trauma, history of any intraocular surgery including complicated pseudophakia, retinal pathology affecting macula, previous laser therapy, neurologic disease that could affect the VF and moderate or severe glaucomatous damage based on the Anderson's and Patella classification.

Controls were eyes with no history of ocular disease, an IOP of ≤21 mmHg, a glaucomatous-appearing optic disc (discs with cup asymmetry >0.2, CDR of 0.6:1 or more, suspicious RNFL defects, baring of circumlinear blood vessels), normal SAP (reliable indices, no points in pattern classic for glaucoma in pattern deviation plot and GHT within normal limits) and normal OCT (signal strength of 4 or more, no RNFL defects and normal TSNIT curve) results. Early glaucoma was defined according to the Anderson and Patella's criteria, which included glaucoma hemi-field test outside normal limits; a pattern standard deviation (PSD) probability of <5%; or a cluster of 3 or more adjacent non-edge points in typical glaucomatous locations that did not cross the horizontal meridian, all of which were depressed on the pattern deviation (PD) plot at $P < 5\%$, and 1 of which was depressed at $P < 1\%$, on at least two consecutive examinations. Mean deviation <−6 dB. VF results were considered reliable if fixation loss were <15%, a false-positive <15% and a false-negative <15%.

Optical coherence tomography procedure

OCT image acquisition was carried out after pupillary dilation by a single operator. Images with signal strength <5, lost data on the peripapillary ring, motion artefact or incorrect segmentation were excluded. The optic disc cube 200 × 200 consisted of 40,000 axial scans (in a 6 × 6 × 2 mm cube) centred on the optic disc. Average RNFL thickness and RNFL thickness in quadrants on a measurement circle 3.46 mm in diameter were calculated, and their deviation from a normative database was provided in a colour-coded scheme. RNFL pseudocolour thickness maps and deviation maps for the 6 × 6 mm area were also provided. The ONH and RNFL parameters identified were average RNFL thickness, rim area, disc area, average C/D ratio, vertical C/D ratio, cup volume and superior, inferior, temporal and nasal RNFL quadrant thicknesses.

The GCC analysis available on the Cirrus software version 6.0 (or higher) measured the combined thickness of RNFL, GCL and IPL in a 4.8 × 4.0 mm oval with a longer horizontal axis. It provided measurements in six wedge-shaped sectors after excluding the central foveolar region (1 mm in diameter) along with a pseudocolour scheme for the GCL-IPL thickness. A deviation map also flagged abnormally thin areas within the oval area as yellow ($P < 5\%$) or red ($P < 1\%$) superpixels. The parameters found were average GCC, minimum GCC and sector measurements (superonasal, superior, superotemporal, inferonasal, inferior and inferotemporal).

Images with a signal strength <4, eye movements, blinking artefacts and segmentation failure were excluded from the study.

Statistical analysis

Demographic characteristics of individuals with suspect eyes and early glaucoma were compared using the Student's *t*-test for continuous variables and Chi-square test for categorical variables. The signal strength for GCC and ONH and RNFL, and the respective parameters were compared between the two groups using the Student's *t*-test. The parameters were adjusted for signal strength and age using the analysis of covariance (ANCOVA) to obtain the adjusted parametric means. Multiple testing was performed using the Benjamin–Hochberg correction to account for type I error. The parameters showing significant difference between glaucoma suspect and early POAG groups, after correction, were considered for linear discriminant analysis (LDA). Stepwise variable selection was performed to obtain ocular parameters having major contribution in discriminating two groups. LDA scores were obtained for each individual as a weighted sum of variables. The ability of LDA scores to distinguish suspect and early glaucoma cases was evaluated using the AUROC curves. The cut-off point for scores was obtained using the Youden index. Sensitivity, specificity, positive- and negative-predicted values for the cut-off score were obtained as indicators of diagnostic validity of the score. This analysis was performed independently for GCC, ONH and RNFL and GCC + ONH and RNFL parameters. A comparative assessment of cut-offs for these three parametric sets was performed on the basis of diagnostic indicators. Validation of the best cut-off was performed on a test data set. LDA scores were obtained for the individuals from test set using the derived weights of respective parameters. The best cut-off was referred to obtain the diagnostic indicators for test set.

All the analyses were performed using the R-3.2.1 (R Core Team 2015) programming tool and statistical significance was tested at 5% level.

Results

Participants

The demographics and structural parameters of paramacular and peripapillary areas were obtained for 201 eyes of individuals [Table 1]. Among these, 127 eyes were suspect, while 74 had early POAG. The mean age of patients with suspect eyes was 54.25 ± 9.36 years, while those with early POAG was 61.20 ± 10.50 years. The difference in the mean age was statistically significant between the groups as indicated by P value < 0.001. The gender distribution was similar in two groups (~50%) and the difference of distribution was statistically insignificant as revealed by P value of 0.926.

Ganglion cell complex and optic nerve head and retinal nerve fibre layer measurements

For GCC, the mean signal strength for suspect eyes (6.02 ± 0.53) was significantly higher than those with early POAG eyes (5.85 ± 0.54) with P value of 0.029. Similarly, for ONH and

Table 1: Description of suspect and early primary open-angle glaucoma eyes

Parameters	Diagnosis		Statistic	*P*
	Suspect (*n*=127)	Early POAG (*n*=74)		
Age (years), mean±SD	54.26±9.37	61.2±10.5	−4.70	<0.001*
Gender, *n* (%)				
Male	63 (49.61)	38 (51.35)	0.01	0.926†
Female	64 (50.39)	36 (48.65)		
GCC, mean±SD				
Signal strength	6.02±0.53	5.85±0.54	2.20	0.029*
ONH and RNFL, mean±SD				
Signal strength	5.87±0.39	5.62±0.66	2.93	0.004*

*Obtained using Student *t*-test; †Obtained using Chi-squared test. GCC: Ganglion complex cell, ONH: Optic nerve head, RNFL: Retinal nerve fibre layer, POAG: Primary open-angle glaucoma, SD: Standard deviation

RNFL, the mean signal strength for suspect eyes (5.87 ± 0.39) was statistically significantly higher than those with early POAG eyes (5.62 ± 0.66) as indicated by *P* value of 0.004.

The comparison of crude mean values of GCC and ONH and RNFL parameters between suspect and early POAG eyes was performed using the Student's *t*-test as shown in Table 2. However, since the signal strength showed statistically significant difference between the two groups for both GCC and ONH and RNFL; and moreover, as the mean age was also significantly different in two categories, adjustment of parameter values with signal strength and age as covariates, was performed using the ANCOVA. The adjusted means were obtained for each parameter and compared between suspect and early POAG eyes [Table 2]. After applying the Benjamin–Hochberg correction to account for type I error, on GCC, except mean thickness (MT), the difference of means between the two groups were statistically significant with $P < 0.001$. The mean for all the parameters for suspect eyes was significantly higher than that of early POAG eyes, except average superior versus inferior. On ONH and RNFL, the means of all the parameters, except disc area, were statistically significant ($P < 0.001$) between two groups. The means for all parameters for suspect eyes was significantly higher than that of early POAG eyes, except average CDR, vertical CDR, cup volume and superior-to-inferior ratio.

Diagnostic ability of parameters

The ability of GCC and ONH and RNFL parameters in discriminating suspect and early POAG eyes was further explored through LDA. The analysis was performed independently for GCC and ONH and RNFL parameters, as well as the combined set of parameters. For GCC, the stepwise algorithm showed that *inferior temporal (IT)* had the best discriminating ability with a LDF = −6.609 + 0.090 × IT. The discriminant scores obtained using this expression were subjected to ROC analysis [Figure 1], which resulted into AUROC of 0.81 [95% confidence interval (CI): 0.748–0.871], and cut-off value of 0.07 with associated sensitivity of 77.03% (95% CI: 65.79%–86.01%) and specificity of 75.59% (95% CI: 67.18%–82.77%).

Similar analysis was performed for ONH and RNFL parameters. The stepwise algorithm provided *average RNFL thickness* and *vertical CDR* as the key parameters in discriminating suspect and early POAG eyes. The resulting expression was LDF = −4.924 + 0.102 × avg. RNFL thickness − 5.260 × vertical CDR. The ROC analysis on discriminant scores using this expression showed an AUROC of 0.903 (95% CI: 0.858–0.947) and a cut-off value of − 0.24 with associated sensitivity of 85.14% (95% CI: 74.96%–92.30%) and specificity of 84.25% (95% CI: 76.73%–90.11%).

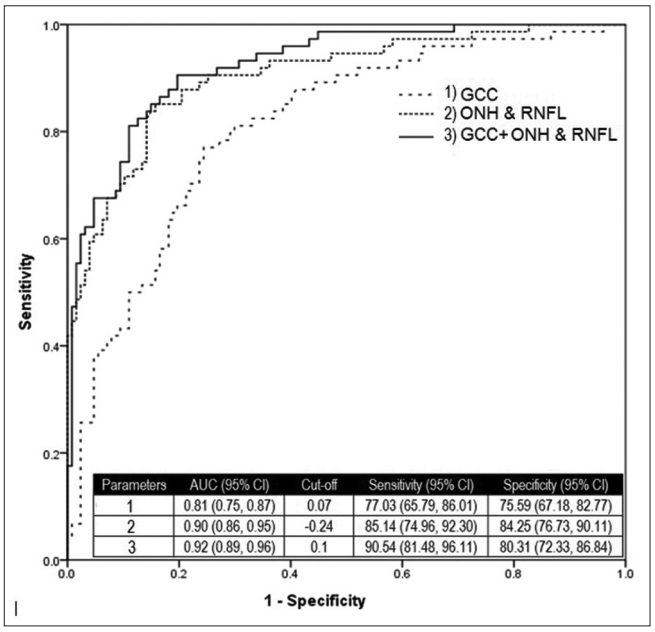

Figure 1: AUROC values of ganglion cell complex, retinal nerve fibre layer and combined ganglion cell complex and retinal nerve fibre layer

For the combined parameter set, stepwise analysis revealed that *average RNFL thickness (ONH and RNFL), vertical CDR (ONH and RNFL), min GCL + IPL (GCC) and superior (GCC)* were the most discriminating parameters between the two groups. The resulting expression was: LDF = −3.793 − 0.035 × superior_GCC + 0.042 × min GCL + IPL_GCC + 0.097 × avg. RNFL thickness − 4.779 × vertical CDR. The discriminant scores obtained for the combined set resulted into AUROC of 0.924 (95% CI: 0.887–0.960) and a cut-off value of 0.10 with associated sensitivity of 90.54% (95% CI: 81.48%–96.11%) and specificity of 80.31% (95% CI: 72.33%–86.84%). Thus, the combination of GCC and ONH and RNFL parameters provided the best diagnostic ability to distinguish between suspect and early POAG eyes.

Table 2: Comparison of ganglion complex cell and optic nerve head and retinal nerve fibre layer parameters between suspect and early primary open angle glaucoma eyes

Parameters	Diagnosis (crude), mean±SD		*t*	*P**	Diagnosis (adjusted)†		*t*	*P**
	Suspect (*n*=127)	Early POAG (*n*=74)			Suspect (*n*=127)	Early POAG (*n*=74)		
GCC								
Mean thickness (MT)	254.39±11.51	255.38±14.25	−0.51	0.6138 (NS)	254.1±11.39	255.88±14.28	−0.91	0.3625 (NS)
Superior nasal (SN)	81.94±8.21	74.77±14.66	3.87	<0.001 (S)	81.49±8.33	75.54±14.28	3.27	<0.001 (S)
Superior (S)	79.25±8.59	71.96±15.42	3.74	<0.001 (S)	78.99±8.64	72.41±15.27	3.40	<0.001 (S)
Superior temporal (ST)	76.64±8.3	68.32±12.85	4.99	<0.001 (S)	76.47±8.34	68.6±12.76	4.75	<0.001 (S)
Inferior nasal (IN)	79.65±9.53	70.23±15.61	4.71	<0.001 (S)	79.09±9.48	71.19±15.26	4.02	<0.001 (S)
Inferior (I)	77.4±10.53	65.5±15.62	5.83	<0.001 (S)	76.88±10.46	66.4±15.35	5.21	<0.001 (S)
Inferior temporal (IT)	77.97±9.06	65.65±13.99	6.79	<0.001 (S)	77.82±9.05	65.91±13.97	6.57	<0.001 (S)
Avg GCL+IPL	78.85±8.12	69.59±13.68	5.30	<0.001 (S)	78.51±8.13	70.19±13.5	4.81	<0.001 (S)
Min GCL+IPL	60.36±17.37	73.42±11.21	5.80	<0.001 (S)	72.91±11.16	61.23±17.13	5.25	<0.001 (S)
Average GCC	0.27±0.05	0.31±0.03	5.35	<0.001 (S)	0.31±0.03	0.27±0.05	5.35	<0.001 (S)
Average superior	0.31±0.03	0.28±0.06	4.31	<0.001 (S)	0.31±0.03	0.28±0.06	4.29	<0.001 (S)
Average inferior	0.31±0.04	0.26±0.06	6.17	<0.001 (S)	0.31±0.04	0.27±0.05	5.31	<0.001 (S)
Average superior versus inferior	1.02±0.09	1.08±0.13	−3.59	<0.001 (S)	1.02±0.09	1.08±0.13	−3.31	<0.001 (S)
ONH and RNFL								
Avg RNFL thickness	87.83±7.88	73.45±9.01	11.43	<0.001(S)	87.53±7.74	73.96±8.95	10.89	<0.001 (S)
Rim area	1.20±0.19	0.99±0.25	6.16	<0.001 (S)	1.21±0.19	0.99±0.25	6.21	<0.001 (S)
Disc area	2.42±1.83	2.31±0.55	0.69	0.491 (NS)	2.41±1.83	2.32±0.54	0.52	0.6071 (NS)
Avg CDR	0.66±0.09	0.74±0.09	−5.76	<0.001 (S)	0.66±0.09	0.74±0.08	−6.13	<0.001 (S)
Vertical CDR	0.63±0.1	0.72±0.09	−7.00	<0.001 (S)	0.63±0.11	0.72±0.09	−7.41	<0.001 (S)
Cup volume	0.43±0.26	0.55±0.33	−2.81	0.006 (S)	0.41±0.26	0.57±0.32	−3.64	<0.001 (S)
Superior (S)	111.2±13.38	90.72±15.38	9.54	<0.001 (S)	110.26±12.58	92.33±15.31	8.53	<0.001 (S)
Nasal (N)	68.5±9.52	59.46±8.64	6.89	<0.001 (S)	68.51±9.63	59.44±8.38	7.00	<0.001 (S)
Inferior (I)	113.55±13.09	89.15±17.65	10.35	<0.001 (S)	113.14±12.84	89.85±17.78	9.87	<0.001 (S)
Superior by inferior (S/I)	0.98±0.11	1.05±0.23	−2.20	0.031 (S)	0.98±0.10	1.06±0.23	−2.97	<0.001 (S)
Temporal (T)	58.09±7.8	54.31±8.8	3.06	0.003 (S)	58.19±7.84	54.13±8.70	3.31	<0.001 (S)

†Means obtained after adjusting with signal strength and age; *Obtained using Student's *t*-test and significance decided after applying the Benjamin and Hochberg correction for multiple testing. GCC: Ganglion complex cell, ONH: Optic nerve head, RNFL: Retinal nerve fibre layer, POAG: Primary open-angle glaucoma, SD: Standard deviation, S: Significant, NS: Not significant

Test set

To validate this, a test set of 51 eyes with 32 suspect and 19 with early POAG were considered. Their demographic details along with signal strengths are shown in Table 3. The mean age in early POAG group was significantly higher than suspect group (*P*-value < 0.001), which was consistent with the original data set. Using the LDF expression for the combined parameter set, the scores were obtained for the test set. A cut-off value of 0.1 was referred, which showed that out of 19 cases, 17 could be correctly diagnosed giving a sensitivity of 89.47% (95% CI: 66.86%–98.70%) and specificity of 81.25% (95% CI: 77.62%–97.99%). The accuracy for test data set was 84.31%.

Discussion

Macular and ONH and peripapillary analysis have been increasingly used for detection of early glaucomatous damage. Because these parameters are numerous and correlated, it is often difficult for ophthalmologists to interpret this data, especially when many parameters show conflicting results.[1] Considering the previous studies, although SD-OCT has refined macular retinal thickness measurement from full thickness to the inner retinal layer thickness, the diagnostic capability of RNFL parameters was found superior to GCC parameters in our study. Only about 50% of the RGCs were assessed in the GCC scan, as against nearly 100% of the RGCs were assessed in the RNFL scan. The ability to measure the diffuse RGC damage done by glaucoma in the entire eye may give the RNFL scan an advantage over the GCC scan in detecting glaucoma.[11,20] ONH and RNFL and GCC assessments target different neuroretinal areas and they may be potentially complementary to overcome the incidence of false positive results of some OCT RNFL parameters.[20]

A multivariable model proposed in this study integrates multiple parameters into a single entity that accounts for the variability in the original data. The advantage of using a single versus a combination of parameters for diagnosis has been achieved in earlier studies. LDF is an established consideration which uses input data and helps in classification of patients.[1] A few studies combined ONH, RNFL and macular GCIPL complex parameters, which accumulate information about different retinal anatomic areas. However, those studies[11,18,21] did not show the mathematical functions

Table 3: Description of suspect and early primary open-angle glaucoma eyes from test data

Parameters	Diagnosis		Statistic	*P*
	Suspect (*n*=32)	Early POAG (*n*=19)		
Age (years), mean±SD	53.38±9.94	61.63±8.23	−3.20	<0.001*
Gender, *n* (%)				
Male	18 (56.25)	6 (31.58)	2.01	0.156†
Female	14 (43.75)	13 (68.42)		
GCC, mean±SD				
Signal strength	5.84±0.37	5.58±0.77	1.41	0.172*
ONH and RNFL, mean±SD				
Signal strength	5.78±0.42	5.53±0.61	1.61	0.120*

*Obtained using Student's *t*-test; †Obtained using Chi-squared test. GCC: Ganglion complex cell, ONH: Optic nerve head, RNFL: Retinal nerve fibre layer, POAG: Primary open-angle glaucoma, SD: Standard deviation

in their reports or provide an external validation or simple implementation of the proposed function in a given patient. In our study, after adjusting for age and signal strength in both the GCC and ONH and RNFL groups, all parameters were found to have statistically significant difference except mean thickness on GCC and disc area in the ONH and RNFL. Like earlier similar studies with the TD-OCT, average RNFL thickness showed a better diagnostic ability in comparison with RNFL parameters, which focused on a small section.[11] Ratio between superior and inferior GCC and RNFL thickness may reflect the localised thickness variation and the asymmetry common to glaucomatous atrophy;[11] hence, in our study we included ratios between superior and inferior hemispheres on GCC, superior and inferior quadrants on ONH and RNFL maps. They were found to differ significantly from suspect eyes.

There are studies that have shown that RNFL and GCC reduce with increased axial length and negative spherical equivalent; hence, we excluded eyes with refractive errors outside −6 DS and +4 DS.[22,23] Our results may not be applicable to eyes falling beyond our criterion, especially glaucomatous eyes in high myopia.

The parameters that provided the best discrimination were *IT* (AUROC 0.809) in GCC group, and *average RNFL thickness* and *vertical CDR* (AUROC 0.903) in ONH and RNFL group. A combined equation of selected parameters from both the groups presented still better discrimination between the two groups (AUROC 0.924). The same calculation when applied to a test set gave an AUROC of 0.92 with a sensitivity of 84.31%.

Recently, Larrosa *et al*.,[20] used both the qualitative and quantitative data and found that the best AUC parameters were: inferior RNFL, average RNFL, vertical cup/disc ratio, minimal GCC and inferior-temporal GCC. They utilised commercially available colour codes, which were qualitative and had no cut-off value, which in turn depended on the version of the Cirrus OCT used. Their normative databases may be updated and modified in the future, and the results cannot be extrapolated directly to other OCT devices. Our study uses quantified data and hence is easier to evaluate as compared to quantifying colour for every eye, which may be time consuming. The authors also included mild, moderate and advanced glaucomatous eyes, which can potentially skew the results. Advanced damage can be easily recognised; however, we need provision for detection of early glaucoma, which is provided for by our study.

Huang *et al*.[11] found that the individual OCT parameter with the largest AUROC and partial AUROC in the high specificity (≥80%) range was the cup/disc vertical ratio (AUROC = 0.854 and partial AUROC = 0.142) for the optic disc parameters, and average thickness (AUROC = 0.919 and partial AUROC = 0.147) for peripapillary RNFL parameters, which is similar to our study. However, we formulated an LDF by combining the above mentioned best performing parameters and found the AUROC (0.903) comparable to the authors. Inferior hemisphere thickness (AUROC = 0.871 and partial AUROC = 0.138) had the best discrimination in GCC parameters, while we found the LDF for *IT* to have the best AUROC (0.809). The authors also included superotemporal RNFL, upper nasal RNFL and inferotemporal RNFL as variables in their LDF. Our LDF differed from theirs in the accompanying presence of GCC parameters in our final equation, which was the aim of both the studies. Also, we avoided clock hour RNFL values in our final LDF for ease of calculation in clinical setting. The authors formulated an LDF by including demographic factors like age, sex, races and refractive errors (which were excluded from the final LDF because of lack of significance) and OCT parameters (ONH, RNFL and GCC parameters). However, they did not validate the diagnostic performance of LDF in another independent sample. The strength of our study is the validation of our LDF with a relatively large independent sample. Demographic factors were not included, because a qualitative factor like race does not carry much significance in our setting. In our study, all the eyes were adjusted according to their age and gender and refractive errors outside +4 DS and −6 DS were excluded for potential bias.

Medeiros *et al*.[24] used ONH, RNFL and total macular thickness parameters to calculate an LDF for the detection of perimetric glaucoma. In their study, LDF showed significantly larger AUROC (0.97) than individual parameters. However, their final LDF did not include macular thickness parameters, which have been found in our study. Also, their study was not limited to early damage on VF and hence, carries a potential for skewing of results.

In our study, eyes which were initially thought to be glaucomatous on clinical examination and later found to be

normal on SAP and OCT were included as controls. This may not be considered as limitation when the controls do not represents true normals in population because, as reported by earlier studies, differentiation between normal and perimetric glaucoma is usually clear in clinical practice. However, differentiation between glaucoma suspect and true glaucoma is a greater clinical challenge.[11] It is true that inclusion of glaucoma suspects to the controls reduces the specificity of the OCT examination in diagnosing glaucoma. We also excluded moderate and advanced glaucomatous eyes for avoiding potential bias by inflating the sensitivity of OCT examination in diagnosing glaucoma.

There are potential limitations to our study. The correlation of our LDF results is limited to only the eyes with early damage. The test set also included eyes with early damage and hence, the efficacy in moderate and advanced damage is not known. More severe disease is associated with the increased sensitivity; therefore, in population settings with more advanced VF losses, a better diagnostic accuracy for the LDF and most ONH parameters may be expected. Only glaucoma patients with high IOP were included, and therefore our results may not be applicable to subjects with low-tension glaucoma. The diagnostic ability may be lower for pre-perimetric glaucoma, because it was designed to detect glaucoma patients with VF losses. In our study, we selected only good quality scans (signal strength 5 or more), but in clinical practice this is not always possible. All these limitations must be taken into account when interpreting OCT results.

However, the advantage of using a single parameter versus combining several parameters in the diagnosis of glaucoma remains to be determined.[1]

Conclusion

In conclusion, the GCC and ONH and RNFL parameters had comparable diagnostic value, while the combined function increased the diagnostic value of these single parameters. In our study, the results in the validating set confirmed those obtained in the training set with high sensitivity and specificity.

The availability of an LDF allows external validation in other datasets (from different racial and geographic origins) and its potential use in clinical practice as a potential tool to interpret the OCT data analysis. Further studies with this LDF and other discriminant functions are needed to determine the ability of learning classifiers at early stages of the disease or eyes where it is difficult to decide on the basis of other parameters.

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Conflicts of interest

There are no conflicts of interest.

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