Original Article

The Discriminatory Ability of Ganglion Cell Inner Plexiform Layer Complex Thickness in Patients with Preperimetric Glaucoma

Bhavya Mehta[1], Somesh Ranjan[2], Vinod Sharma[3], Neha Singh[1], Nidhi Raghav[2], Acid Dholakia[2], Rahul Bhargava[1], P. Laxmi Sireesha Reddy[1], Pooja Bargujar[1]

[1]Department of Ophthalmology, GS Medical College and Hospital, Hapur, Uttar Pradesh, India, [2]Department of Ophthalmology, Santosh Medical College, Ghaziabad, Uttar Pradesh, India, [3]Department of Ophthalmology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

Abstract

Purpose: To evaluate diagnostic performance of ganglion cell inner plexiform layer (GCIPL) and retinal nerve fiber layer (RNFL) parameters measured with Cirrus high-definition optical coherence tomography (OCT) in patients with preperimetric glaucoma.

Methods: In this multicenter cross-sectional study, 150 eyes of 83 patients with preperimetric glaucoma were compared with 200 eyes of age and sex matched healthy subjects. All patients had visual field testing and OCT scanning of GCIPL and RNFL in all quadrants. The independent Samples *t*-test was used to determine if a difference exists between the means of two independent groups on a continuous dependent variable. The area under the receiver operating characteristic (ROC) curve (AUC) of each parameter was calculated for discriminatory ability between normal controls and preperimetric glaucoma. The sensitivity and specificity were estimated by point coordinates on ROC curve.

Results: The best parameters for distinguishing preperimetric glaucoma from healthy eyes were the combined average GCIPL + average RNFL, followed by average RNFL + GCIPL (inferotemporal), and average RNFL + GCIPL (minimum). The GCIPL parameters with the highest to lowest AUC (in decreasing order) were inferotemporal, followed by average, minimum, superior, inferior, superonasal, inferonasal, superotemporal, and quadrants. The RNFL parameters with the highest to lowest AUC (in decreasing order) were average, followed by nasal, temporal, superior, and inferior quadrants. The sensitivity of combined GCIPL + RNFL parameters ranged 85%–88% and the specificity ranged 76%–88%. The sensitivity for RNFL parameters ranged 80%–90% and the specificity ranged 64%–88%.

Conclusion: GCIPL and RNFL have good discriminatory ability; the sensitivity and specificity increase when both parameters are combined for early detection of glaucoma.

Keywords: Ganglion cell inner plexiform layer, Preperimetric glaucoma, Retinal nerve fiber layer

Address for correspondence: Rahul Bhargava, Department of Ophthalmology, GS Medical College and Hospital, Pilkhuwa, Hapur, Uttar Pradesh, India.
E-mail: brahul2371@gmail.com
Submitted: 28-Jun-2023; **Revised:** 12-Oct-2023; **Accepted:** 13-Oct-2023; **Published:** 29-Mar-2024

Introduction

Glaucoma is the leading cause of irreversible blindness in the world. Loss of retinal ganglion cells (RGCs) is the common denominator in all types of glaucoma.[1,2] Despite recent advances in diagnostic tools measuring structural damage in RGCs, early diagnosis of glaucoma remains a challenging task. In the past, the detection of structural glaucomatous damages was mostly confined to retinal nerve fiber layer (RNFL) and the optic nerve head (ONH) parameters.[3]

The circumpapillary RNFL is the most quantified optical coherence tomography (OCT) parameter assessing the structural loss of RGCs in glaucoma.[4,5] However, this parameter measures the axonal portion of the RGCs without

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joco

DOI: 10.4103/joco.joco_124_23

How to cite this article: Mehta B, Ranjan S, Sharma V, Singh N, Raghav N, Dholakia A, *et al*. The discriminatory ability of ganglion cell inner plexiform layer complex thickness in patients with preperimetric glaucoma. J Curr Ophthalmol 2023;35:231-7.

considering the cell bodies and dendrites, which are also affected in glaucoma; these are mainly located in the ganglion cell layer (GCL) and inner plexiform layer (IPL).

The macular ganglion cell complex (GCC) includes all three innermost retinal layers that are potentially involved in the glaucomatous damage (RNFL, GCL, and IPL). Approximately 50% of the RGCs are located within 4.5 mm of the foveal center.[6,7]

The introduction of spectral domain (SD)-OCT has led to better insight into glaucoma diagnosis as segmentation of inner retinal layers has now become possible. Cirrus OCT (Carl Zeiss Meditec, Dublin, CA, USA) has an inbuilt ganglion cell analysis (GCA) algorithm that allows for segmentation of these layers (GCL and the IPL). A comprehensive review by Mohammadzadeh *et al*. highlighted that macular SD-OCT imaging has emerged as an essential diagnostic tool in glaucoma.[8-11]

A study by Hwang *et al*. found that although Cirrus high-definition (HD)-OCT GCA maps had a good ability to detect early glaucoma, these maps did not show abnormal findings in glaucomatous eyes when the angular distance between fovea and RNFL defect was higher.[11]

The structural changes in GCC precede functional visual field loss; therefore, it is important to identify these changes as early as possible. Recent studies have reported that the diagnostic abilities of GCC was comparable to RNFL parameters; one school of thought believes that early detection of the subtle changes in GCC and RNFL layers may the critical factor in preventing blindness (earlier the detection, less is the damage). Having said this, differentiating preperimetric glaucoma from normal controls becomes easier once visual field changes develop.

Only a few studies from the subcontinent have evaluated GCC parameters in glaucoma patients prior to developing changes in visual fields (preperimetric).[12-14] However, conflicting results have been reported when GCC measurements were compared to RNFL measurements, and the ONH measurements in other studies. The present study aimed to determine the discriminatory ability of macular ganglion cell IPL (GCIPL) parameters between preperimetric glaucoma patients and healthy controls and to compare it with the discriminating ability of the peripapillary RNFL parameters in north Indian population.

Methods

In this multicenter cross-sectional study conducted between December 2017 and January 2020, at 4 tertiary care teaching institutions, 150 eyes of 83 patients with preperimetric glaucoma were compared with 200 eyes of age and sex matched healthy controls. One eye was randomly selected when both the eyes were in preperimetric stage. Approval of institutional ethics committee was obtained, and informed consent obtained from all patients based on the tenets of the Declaration of Helsinki.

All the patients underwent a detailed ocular examination including recording of best-corrected visual acuity (BCVA), indirect ophthalmoscopy, intraocular pressure (IOP) measurement by Goldmann's applanation tonometer, gonioscopy, and stereoscopic optic disc evaluation with +90D lens. Visual field testing was done with Humphrey Visual Field Analyzer (Carl Zeiss Meditec, CA, USA) and SD-OCT examinations were performed with Cirrus SD-OCT (Carl Zeiss Meditec, CA, USA). In the GCA printout, it provides the GCIPL parameter that includes the combined thickness measurements of GCL and IPL. GCA printout displays global average GCIPL, minimum GCIPL, and sectoral GCIPL measurements. In addition to these parameters, GCA also provides a color-coded deviation map of GCIPL measurements over the elliptical area that compares localized thickness measurements to age-adjusted normative database of the built-in software.[15]

Inclusion criteria were patients above 40 years of age having a quiet anterior chamber on slit-lamp examination, open angles on indentation gonioscopy with normal structures, and reliable indices on standard automated perimetry. A reliable visual field was one in which fixation losses were <20%, a false-positivity <15%, and false-negativity <15%.

Preperimetric glaucoma patient was one with normal visual fields and one or more localized RNFL defects (on red-free fundus photographs) that were associated with a glaucomatous disc change (notching or neuroretinal rim thinning) and IOP more than 21 mmHg. Patients with at least two consecutive reliable visual fields were enrolled in the study.

Normal subjects were selected from a cohort of nonglaucomatous individuals who were age and sex matched, without any history of ocular disease, an IOP of <21 mmHg, a normal optic disc, visual fields within normal limits, and a normal OCT.

Patients with media opacity, history of trauma, retinal pathology affecting macula, neurological diseases affecting the visual fields, and functional glaucomatous damage in visual fields were excluded. Patients with pathological myopia were also excluded from the study.

OCT was done using the macular cube 200 × 200 protocol for GCA and the optic disc cube 200 × 200 protocol for peripapillary RNFL. The images were acquired through dilated pupils by a single operator, and images with signal strength >6 were included in this study.

The analyzed macular GCIPL thickness measurements were mean, minimum, superior, superonasal, inferonasal, inferior, inferotemporal, and superotemporal thicknesses; the peripapillary RNFL parameters were average, superior, inferior, temporal, and nasal thicknesses.

The combined parameters refer to GCIPL + RNFL thickness (which was the mean of average GCIPL + average RNFL thickness).

An acceptable OCT scan was one in which the scan was properly centered on disc and macula and the signal strength

was >6, color saturation was even and dense across the entire scan. Appropriate care was taken to ensure that there were no missing areas in the scan due to blinks or eye motion.

Statistical analysis

Statistical analysis was performed using IBM statistical software, SPSS Statistics version 29 (IBM Inc. Armonk, New York, United States). Data were checked for normality using Shapiro–Wilk test. Outliers were identified by visual inspection of boxplots. Descriptive measures, such as mean with standard deviation, were calculated for all continuous variables, whereas frequencies and percentages were calculated for all categorical variables. Association between two categorical variables was evaluated using Chi-square tests. The independent Samples *t*-test was used to determine if a difference existed between the means of two independent groups on a continuous dependent variable. A receiver operating characteristic (ROC) curve analysis was done to evaluate the discriminatory ability of the GCC in elucidating RNFL thinning and subtle preperimetric changes. The sensitivity, specificity, and cut-off values were calculated from the coordinate points of the ROC curve. To lower the risk of type I errors, the statistical significance level was set at $P < 0.05$.

Results

A total of 350 eyes (150 preperimetric glaucoma and 200 healthy controls) were included in the study. The baseline demographic characteristics are mentioned in Table 1.

There was no statistically significant difference in age and gender between healthy eyes and preperimetric glaucoma patients (independent *t*-test, $P = 0.144$ and Chi-square tests, $P = 0.760$). The BCVA of the participants was comparable between the two groups. The mean deviation (MD) and the pattern standard deviation (PSD) of visual fields were not significantly different between the two groups ($P = 0.051$, for MD; $P = 0.076$, for PSD).

Table 2 shows the GCIPL and RNFL parameters of the subjects obtained by Cirrus HD-OCT. The average GCIPL thickness was 84.6 ± 5.9 µm in the healthy eyes, and it decreased to 77.4 ± 4.9 µm in preperimetric glaucoma patients along with other GCIPL parameters. There were statistically significant differences in all GCIPL parameters between healthy eyes and preperimetric glaucoma patients.

The average RNFL thickness was 104.7 ± 8.4 µm in the healthy eyes, and it decreased to 91.7 ± 11.2u in preperimetric glaucoma patients. Statistically significant differences between healthy eyes and preperimetric glaucoma patients were detected for all RNFL parameters.

The areas under the curve (AUCs) of discriminating abilities of GCIPL and RNFL parameters between preperimetric glaucoma and healthy controls are shown in Table 3.

The best parameters for distinguishing preperimetric glaucoma from healthy eyes in descending order were the combined average (GCIPL + average RNFL), followed by (average RNFL + GCIPL inferotemporal), and (average RNFL + GCIPL minimum) [Figure 1]. The sensitivity of combined parameters ranged 85%–88% and specificity ranged 78%–80% [Table 4].

The GCIPL parameters with the highest to lowest AUC (in decreasing order) were inferotemporal, followed by average, minimum, superior, inferior, superonasal, inferonasal, superotemporal, and quadrants [Table 3].

Table 1: Demographic and clinical characteristics of study subjects

Parameter	Preperimetric glaucoma ($n=150$)	Healthy controls ($n=200$)	*P**
Age (years)	54.7±8.6	55.6±8.7	0.144
Gender, *n* (%)			
Male	72 (48)	98 (49)	0.746
Female	78 (52)	102 (51)	
BCVA (logMAR)	0.1±0.04	0.09±0.08	0.945
Refractive error (diopter)	−1.78±1	−0.68±0.8	0.001
Axial length (mm)	24.68±1.4	23.06±1.8	0.056
IOP (mmHg)	20.3±4.1	16.8±2.5	0.001
CCT (u)	544±8.8	551.4±30	0.002
Rim area (mm^2)	1.24±0.4	1.74±0.52	0.001
Vertical CDR	0.61±0.2	0.32±0.18	0.001
MD (dB)	−0.52±0.06	−0.44±0.29	0.051
PSD (dB)	1.8±0.1	1.7±0.1	0.076

*Independent *t*-test. BCVA: Best-corrected visual acuity, IOP: Intraocular pressure, MD: Mean deviation, PSD: Pattern standard deviation, CCT: Central corneal thickness, CDR: Cup-disk ratio

Table 2: Macular ganglion cell inner plexiform layer and peripapillary retinal nerve fiber layer parameters obtained by Cirrus high-definition optical coherence tomography

Parameter	Healthy eyes	Preperimetric glaucoma	*P**
GCIPL			
Minimum	84.6±5.9	77.4±4.9	<0.001
Average	89.1±6.1	80.6±4.4	<0.001
Superior	85.4±6.3	77.6±4.4	<0.001
Inferior	85±5.5	79.6±4.6	<0.001
Superonasal	87.7±5.4	82.3±4.4	<0.001
Superotemporal	83.1±5.6	77.3±4.4	<0.001
Inferonasal	89.6±5.3	84.6±4.9	<0.001
Inferotemporal	88.6±5.5	80.6±4.5	<0.001
RNFL			
Average	104.7±8.4	91.7±11.2	<0.001
Superior	112.1±17.9	92±12.6	<0.001
Inferior	105±8.4	92.1±11.4	<0.001
Nasal	92±12.8	70±21.5	<0.001
Temporal	84.8±12	68.7±13.9	0.023

*Independent *t*-test. GCIPL: Ganglion cell inner plexiform layer, RNFL: Retinal nerve fiber layer

Table 3: Area under the receiver operating characteristic curve values of ganglion cell inner plexiform layer and retinal nerve fiber layer parameters for preperimetric glaucoma and healthy controls

Parameter	AUC 95% CI	*P**
Combined parameters		
Average RNFL + average GCIPL	0.950 (0.930–0970)	<0.001
Average RNFL + GCIPL (IT)	0.938 (0.915–0.962)	0.001
Average RNFL + GCIPL (minimum)	0.925 (0.899–0.952)	0.001
GCIPL		
Inferotemporal	0.887 (0.852–0.921)	<0.001
Average	0.878 (0.840–0.916)	<0.001
Minimum	0.822 (0.777–0.866)	<0.001
Superior	0.819 (0.749–0.844)	<0.001
Inferior	0.799 (0.752–0.847)	<0.001
Superonasal	0.798 (0.752–0.847)	<0.001
Inferonasal	0.794 (0.748–0.844)	<0.001
Superotemporal	0.790 (0.740–0.830)	<0.001
RNFL		
Average	0.885 (0.846–0.924)	0.001
Temporal	0.816 (0.768–0.863)	0.001
Nasal	0.810 (0.764–0.856)	0.001
Inferior	0.808 (0.759–0.857)	0.001
Superior	0.804 (0.760–0.849)	0.001

*Independent *t*-test. AUC: Area under the receiver operating characteristic curve, CI: Confidence interval, GCIPL: Ganglion cell inner plexiform layer, RNFL: Retinal nerve fiber layer, IT: Inferotemporal

Table 4: The sensitivity and specificity of ganglion cell inner plexiform layer and retinal nerve fiber layer parameters in the diagnosis of preperimetric glaucoma

Parameter	Sensitivity (%)	Specificity (%)	Cut-off
Combined parameters			
Average RNFL + average GCIPL	88	86	87
Average RNFL + GCIPL (IT)	85	82	90
Average RNFL + GCIPL (minimum)	82	80	91
GCIPL			
Inferotemporal	82	80	79.85
Average	82	80	83.50
Superior	88	66	80.00
Minimum	76	74	80.50
Inferior	80	70	82
Nasal	78	74	84.2
Superotemporal	74	70	80
RNFL			
Average	90	66	91.6
Temporal	80	64	78.5
Nasal	78	68	86.5
Inferior	78	76	98
Superior	76	74	96.5

The 'cut-off' refers to the highest point on the receiver operating characteristic curve. The value corresponding to this point on the y-coordinate (y-axis) was the sensitivity. The value corresponding to this point on the x-coordinate was the false positive rate (1-specificity). GCIPL: Ganglion cell inner plexiform layer, RNFL: Retinal nerve fiber layer, IT: Inferotemporal

The sensitivity of average GCIPL was 82% and specificity was 80%. For GCIPL (inferotemporal quadrant), sensitivity was 82% and specificity was 80%.

The RNFL parameters [Figure 1] with the highest to lowest AUC (in decreasing order) were average, nasal, temporal, superior, and inferior quadrants.

A total of 24 scans were excluded due to improper centration, uncooperative patients, and poor signal strength.

The box plots of GCCIPL and RNFL parameters based on diagnosis (preperimetric glaucoma and healthy controls) and their respective cut-off values are shown in Figures 2 and 3.

Discussion

The present study evaluated the diagnostic ability of GCIPL and RNFL parameters in differentiating preperimetric glaucoma from healthy eyes. Age, gender, and baseline clinical characteristics did not significantly differ between both groups [Table 1]. The results of our study suggest that the combined average GCIPL + average RNFL thickness (the mean of average GCIPL + average RNFL thickness) had the best diagnostic performance in distinguishing preperimetric glaucoma from age and sex matched healthy eyes as evidenced by AUC values; the AUC assesses the overall accuracy of a diagnostic test by plotting the rate of true positive against that of false positive rate. In general, these parameters were more sensitive but less specific in preperimetric glaucoma. Second, GCIPL parameters were more sensitive and RNFL parameters more specific for glaucoma diagnosis.

Glaucoma leads to RGC death and RGCs are most concentrated at the macula; this observation has led researchers to explore the potential of macular thickness for being the critical factor for discriminating glaucomatous eyes from normal eyes.[16]

Glaucoma progresses through several stages and the diagnosis of glaucoma can often be difficult in early stages as subtle structural and functional damage is not clinically apparent. Delayed or inappropriate diagnosis may be consequential: any delay may potentially lead to progression of disease and inappropriate diagnosis may end up treating a person who does not have glaucoma. This has led to exploration of newer modalities for a more reliable diagnosis of glaucoma.

Measuring OCT-based macular GCL has slowly become the standard approach to assess ganglion cell death.[17] However, there is paucity of data in literature on the diagnostic performance of GCIPL parameters in distinguishing different stages of glaucoma.[18-20] A study by Kim *et al*. evaluated the diagnostic performance of macular GCIPL thickness in discriminating preperimetric glaucoma ($n = 92$) from healthy controls ($n = 92$). The authors found that the AUC for macular GCIPL was 0.823 (inferotemporal) and peripapillary RNFL was

0.764 (7 o'clock quadrant). The diagnostic accuracy of macular GCIPL parameters was comparable to that of peripapillary RNFL and ONH parameters in preperimetric glaucoma.[20] Our study was comparable to this study with slightly better performance of GCIPL (average and inferotemporal quadrant; AUC = 0.856 and 0.878, respectively).

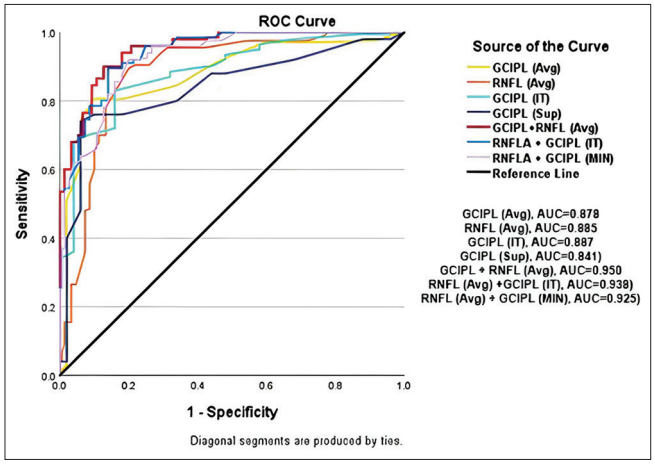

Figure 1: Receiver operating curve showing area under curve for average ganglion cell inner plexiform layer (GCIPL), average retinal nerve fiber layer (RNFL), GCIPL (IT) and GCIPL (superior), and combined GCIPL and RNFL parameters. ROC: Receiver operating characteristic, GCIPL: Ganglion cell inner plexiform layer, RNFL: Retinal nerve fiber layer, IT: Inferotemporal

It is debatable whether the AUCs of RNFL parameters have more diagnostic ability or GCIPL parameters. Inuzuka evaluated preperimetric glaucoma patients (n = 77) and reported that GCIPL thicknesses (inferior and inferotemporal quadrants) may be useful parameters to monitor glaucoma progression in eyes of patients with preperimetric glaucoma.[21] A study by Begum *et al*. reported that the GCIPL parameters did not statistically differ between eyes with preperimetric glaucoma and healthy eyes; the diagnostic performance of GCIPL parameters was significantly lower than that of RNFL and ONH parameters for preperimetric patients and comparable for patients with functional visual field damage (perimetric).[22]

Our study differs in reporting that the GCIPL inferotemporal quadrant to have better diagnostic ability. However, the study by Deshpande *et al*. observed that the GCIPL inferotemporal sector to be the best performer in differentiation preperimetric glaucoma from healthy eyes.[12]

A prospective, cross-sectional study by Kaushik *et al*. found that GCA (SD-OCT based), do not appear to score over RNFL measurements in the diagnosis of preperimetric glaucoma. However, in this study, ocular hypertensives and glaucoma suspects were included. Different criteria of preperimetric glaucoma in both studies could probably account for the difference in observations.[13]

In our study, sensitivity of GCIPL parameters ranged 84%–90% and specificity ranged 52%–58%. The sensitivity for

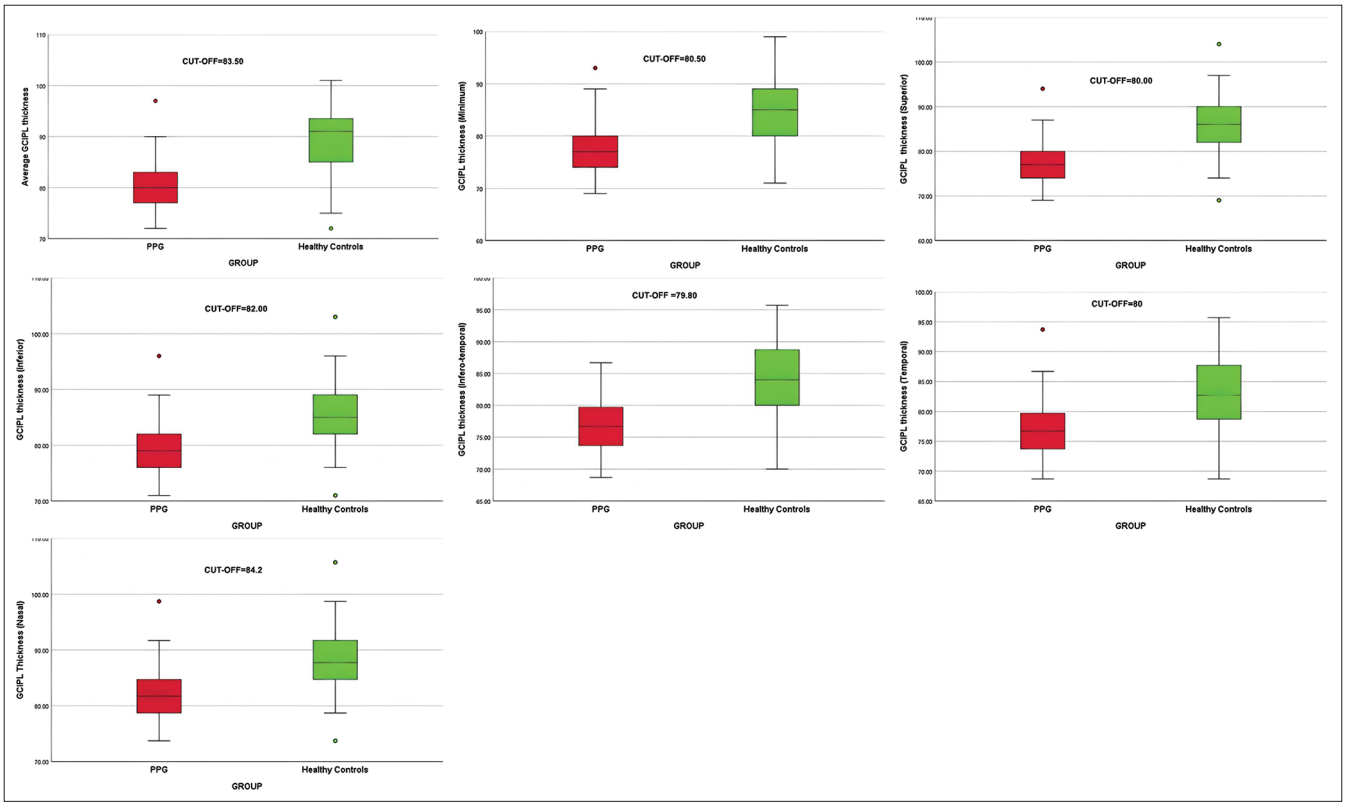

Figure 2: Box plots of ganglion cell inner plexiform layers based on diagnosis; preperimetric glaucoma (red color) and controls (green color) with cut-off values. GCIPL: Ganglion cell inner plexiform layer, PPG: Preperimetric glaucoma

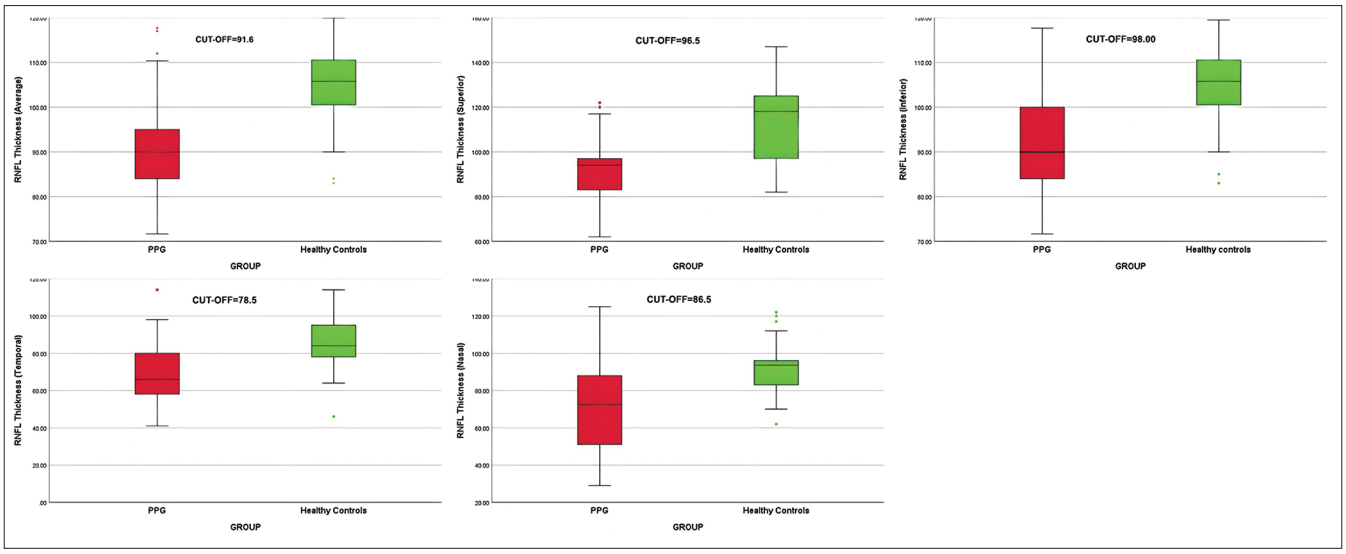

Figure 3: Box plots of retinal nerve fiber layers based on diagnosis; preperimetric glaucoma (red color) and controls (green color) with cut-off values. RNFL: Retinal nerve fiber layer, PPG: Preperimetric glaucoma

RNFL parameters ranged 80%–85% and specificity ranged 64%–70%. A recent Ethiopian study evaluating glaucoma diagnostic performance of GCIPL and RNFL parameters had comparable observations to our study. These parameters had a good diagnostic performance with excellent sensitivity but poor specificity. However, the combination of GCIPL and RNFL parameters had specificity of 62.2% and a sensitivity of 93.5%.[21] In our study, the combined average GCIPL and RNFL had an AUC of 0.950 (95% confidence interval, 0.930–0.970), $P < 0.001$. The sensitivity and specificity of the combined parameters were ranged from 80% to 88% and 70% to 80%, respectively.

Sung *et al*. compared GCIPL and RNFL thickness deviation maps for discriminating preperimetric glaucoma from healthy controls by quantifying the area of abnormal color code. The authors found that GCIPL and RNFL thickness deviation maps have good and comparable discrimination ability. Second, they found GCIPL measurement had a similar diagnostic ability to peripapillary RNFL preperimetric glaucoma patients. In our study, GCIPL thickness deviation maps were comparable to RNFL thickness deviation maps [Figure 1]; however, the AUC for GCIPL thickness was slightly higher than RNFL thickness. The probable explanation for this could be that quantification in peripapillary RNFL thickness deviation map showed a superior capability for detection of a focal glaucomatous visual field defects when compared with traditional peripapillary RNFL thickness measurement in Cirrus HD-OCT. Possibly, calculating the average thickness underestimates a focal RNFL thinning.[23]

Our study had several limitations and strengths. The controls ($n = 200$) could not be matched for refractive error. Second, the study was not a randomized one potentially leading to selection bias. Subjects were evaluated at a single time point. The ability of GCIPL parameters for discriminating other stages of glaucoma was not evaluated in our study. Having a significantly higher number of controls as compared to cases ($n = 200$ vs. 150) which were matched for age and gender was one of the strengths of this study.

In conclusion, both GCIPL and RNFL parameters have good discriminatory ability in preperimetric glaucoma patients but inferotemporal GCIPL has a slight edge. These parameters have good sensitivity but poor specificity. However, sensitivity and specificity increase when both parameters are combined for early detection of glaucoma. This indicates that these tests are complimentary to each other, and both are of paramount importance for early detection of glaucoma. Future studies need to explore new paradigms to improve glaucoma progression detection by analyzing the combined RNFL and GCIPL thickness in different stages of glaucoma.

Acknowledgment

We are thankful to www.indianmedicalstats.com for statistical analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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