

Structural evaluation of perimetrically normal and affected hemifields in open angle glaucoma

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Purpose: To study macular ganglion cell layer--inner plexiform layer complex (GCL + IPL) in relation to peripapillary retinal nerve fiber layer (RNFL) in glaucomatous eyes with superior or inferior hemifield defects (HD) and to study structural configuration in normal hemifield. **Methods:** This was an observational cross-sectional study. Data from consecutive 45 superior HD (SHD) and 50 inferior HD (IHD) eyes were analyzed. Each patient underwent detailed ocular examination, standard automated perimetry, and spectral domain optical coherence tomography (SD-OCT). After adjusting for age, gender, and signal strength, area under receiver operating characteristic curve (AUC) was calculated to determine diagnostic ability of GCL + IPL and peripapillary RNFL. Apparently normal hemifield was compared with true normal hemifield. Data were analyzed with SPSS, analysis of variance, *t*-test, Chi-square test, and receiver operating curve. **Results:** In the SHD glaucoma group, best parameters for discriminating normal eyes from glaucomatous eyes were inferotemporal GCL + IPL thickness (0.935) and inferior quadrant RNFL thickness (0.971). For IHD glaucoma, average GCL + IPL thickness (0.877) and average RNFL thickness (0.950) had best AUC values. When evaluating apparently normal hemifield in both groups, statistically significant difference was found in inferior GCL + IPL sector (0.865) and inferior quadrant RNFL (0.883) in IHD and superonasal GCL + IPL (0.725) and superior quadrant RNFL (0.842) in SHD groups. **Conclusion:** SD-OCT may be a useful ancillary diagnostic tool for evaluation of early macular and circumpapillary structural changes in glaucomatous eyes with localized visual field defects. Apparently normal hemifields show structural damage and should be considered in management of glaucoma.

Key words: Ganglion cell layer--inner plexiform layer, inferior hemifield, retinal nerve fiber layer, superior hemifield

Glaucoma is a progressive optic neuropathy characterized by optic nerve head (ONH) damage, retinal nerve fiber layer (RNFL) loss, and corresponding visual field (VF) defects. More than two decades ago, Quigley *et al* demonstrated that 40% axonal loss may occur before any detectable change in visual function with perimetry.^[1] Studies have shown that both macular ganglion cell complex (GCC) and RNFL can be used for the diagnosis of early and preperimetric glaucoma.^[2]

Significant advances in imaging have led to quantitative measurements of these structures. OCT is a noninvasive, noncontact, transpupillary imaging technology that can image retinal structures *in vivo* with a resolution of 8--10 micron. Recent data have shown that macular thickness changes are detectable in glaucomatous eyes using OCT and are well correlated with changes in visual function and peripapillary RNFL atrophy.^[3]

Glaucoma hemifield defect is an interesting entity in which one half of the hemifield is damaged on perimetry and the other half appears apparently unaffected. Several studies have shown the presence of diffuse glaucomatous RNFL atrophy in eyes with localized visual field abnormalities.^[4] Such studies

have led to speculation that the GCC of glaucomatous eyes also exhibit diffuse atrophy in normal visual hemifields with localized visual field loss.^[4] There are a handful of studies analyzing the structural parameters in such patients and even lesser in examination of the perimetrically normal hemifield.

We designed this study to evaluate the RNFL and GCL + IPL structural parameters in eyes (1) with localized glaucomatous damage limited to either hemifield and (2) the other perimetrically normal hemifield.

Methods

Participants

This was a hospital-based cross-sectional study performed at a tertiary care center from central India and included patients who presented between December 2015 and May 2017. All the patients underwent a detailed ocular examination comprising visual acuity, cycloplegic refraction, slit-lamp examination, indirect ophthalmoscopy, intraocular pressure

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with Goldmann's Applanation Tonometer, 4 mirror indentation gonioscopy with 4 mirror Sussman's Gonioscope, optic nerve head evaluation with slit-lamp biomicroscopy using 78D non-contact lens. Visual fields were mapped using Humphrey Visual Field 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.

Inclusion and exclusion criteria

The inclusion criteria were: age more than 18 years, best corrected visual acuity of Snellens >6/12 (logMAR < 0.3), refractive error (under cycloplegia) between -6 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 artifacts 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 visual field, medications known to affect visual field sensitivity, or with problems that affect color vision. Controls were eyes with no history of ocular disease, an intraocular pressure (IOP) of ≤ 21 mmHg, a normal-appearing optic disc, and normal SAP (reliable indices, no points in pattern classic for glaucoma in pattern deviation plot and GHT within normal limits) and OCT (signal strength of 4 or more, no RNFL defects and normal TSNIT curve) test results.

Definition of hemifield defect

A glaucoma hemifield defect (HD) was defined as follows: (1) 3 adjacent points with $P < 5\%$ and at least 1 with $P < 1\%$ or smaller on the pattern deviation probability map of a superior or inferior hemifield; (2) no point with $P < 1\%$ or smaller on the pattern deviation probability map of the opposite hemifield; and (3) a glaucoma hemifield test result that was outside of the normal limits. VF results were considered reliable if fixation loss were <15%, a false-positive <15%, and false-negative <15%.

OCT 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 artifact, or incorrect segmentation were excluded. The Optic Disc Cube 200 \times 200 consisted of 40,000 axial scans (in a 6 \times 6 \times 2 mm cube) centered 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 color-coded scheme. RNFL pseudocolor thickness maps and deviation maps for the 6 \times 6 mm area were also provided. The RNFL parameters identified were average RNFL thickness, superior, inferior, temporal, and nasal RNFL quadrant thicknesses.

The GCL + IPL analysis available on the Cirrus software version 6.0 (or higher) measured the combined thickness of GCL and IPL in a 4.8 \times 4.0 mm oval with a longer horizontal axis. It provided measurements in 6 wedge-shaped sectors after excluding the central foveolar region (1 mm in diameter) along with a pseudocolor 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 GCL + IPL, minimum GCL + IPL, and sector measurements (superonasal, superior, superotemporal, inferonasal, inferior, and inferotemporal).

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

Statistical methods

Patient characteristics were compared across normal, inferior hemifield defect (IHD), and superior hemifield defect (SHD) groups statistically according to scales of measurement. Further, sector-wise thickness on GCL + IPL and RNFL were compared between these groups after adjusting for signal strength, gender, age, and mean deviation using analysis of covariance. Receiver operating characteristic curve analysis was performed on each thickness parameter to differentiate normal and IHD as well as normal and SHD glaucoma eyes. The statistical comparison between two AUCs was also performed. All the analyses were performed using R-3.4.3 (R Core team 2017, Vienna, Austria).

Results

The study involved 34 subjects with normal eyes and 95 with glaucomatous eyes. Among 95, IHD was present in 50 (52.6%) patients, while SHD was present in 45 (47.4%) patients. The descriptive statistics for demographic features are given in Table 1. The mean age of patients showed statistically significant difference between normal group and each glaucomatous group ($P = 0.0118$, $P = 0.0013$); however, the difference in the mean age between IHD and the SHD was statistically insignificant. The gender distribution was

Table 1: Characteristics of subjects in normal and glaucomatous groups

Patient characteristics	Groups					
	Normal (n=34)	Inferior Hemifield (n=50)	P^*	Superior Hemifield (n=45)	P^i	P^j
Age (yr) [Mean \pm SD]	54.06 \pm 12.43	60.46 \pm 8.60	0.0118 (S)	62.22 \pm 9.25	0.0013 (S)	0.3379 (NS)
Gender [Male: No. (%)]	18 (52.94)	29 (58.00)	0.8146 (NS)	21 (46.67)	0.7451 (NS)	0.3687 (NS)
MD (HVF)	-2.35 \pm 1.75 ^a	-4.57 \pm 2.49 ^b	<0.0001 (HS)	-6.10 \pm 4.27 ^c	<0.0001 (HS)	0.0190 (S)
PSD (HVF)	2.88 \pm 1.49 ^a	5.64 \pm 3.50 ^b	<0.0001 (HS)	6.68 \pm 4.17 ^c	<0.0001 (HS)	0.1377 (NS)

*Comparison between normal group and inferior hemifield defect glaucoma group, ⁱComparison between normal group and superior hemifield defect glaucoma group, ^jComparison between inferior hemifield defect glaucoma group and superior hemifield defect glaucoma group, S=Significant; NS=Non-Significant, ^aBased on 65 eyes of 34 normal subjects; ^bBased on 55 eyes with inferior defect; ^cBased on 60 eyes with superior defect

insignificantly different across three groups. A total of 65 eyes of 34 normal subjects, 55 eyes of 50 patients with IHD, and 60 eyes of 45 patients with SHD were considered in the study. The parameters MD and PSD were significantly different between normal and each defect group ($P < 0.0001$). Also, the MD differed significantly between IHD and SHD ($P = 0.019$), while PSD was insignificantly different between two groups.

The comparison of signal strength and sector-wise thickness across three groups is shown in Table 2. The mean signal strength (SS) for GCL + IPL was significantly lower in IHD and SHD groups as compared with normal group ($P < 0.0001$). The sector-wise mean thickness after adjusting with signal strength, age, and MD showed statistically significant difference between normal and each glaucomatous group ($P < 0.0001$). The inferior quadrant (inferior, inferior temporal) and minimum GCL + IPL parameter were also significantly different between the IHD and SHD groups ($P < 0.0001$).

On analyses, the average RNFL thickness was significantly smaller in IHD and SHD groups as compared with normal group. Similar were the observations for four quadrants (superior, nasal, inferior, and temporal). The mean thickness of all the sectors of macula showed statistically significant difference between normal and IHD group. The inferior quadrant of SHD group was significantly thinner than those of the normal group.

The AUCs for thickness measurements at different sites obtained for GCL + IPL and RNFL to differentiate each

glaucoma group from normal eyes are shown in Table 3. When studying IHD, for GCL + IPL, the parameter average GCL + IPL had the maximum AUC of 0.877 [95% CI: 0.808–0.945]. For RNFL, the average RNFL thickness was the best discriminator with AUC of 0.950 [95% CI: 0.913–0.987].

On similar lines, the diagnostic strength of parameters was determined for SHD. On GCL + IPL, the best parameters were inferotemporal (0.935 [95% CI: 0.889–0.982]) and inferior quadrant for RNFL (0.971 [95% CI: 0.944–0.998]). Fig. 1a and b shows the ROC curves for the best discriminating parameters for both IHD and SHD groups in comparison with normal group.

Fig. 2 shows the box-plot representation of thickness of inferior and superior parameters for normal and unaffected

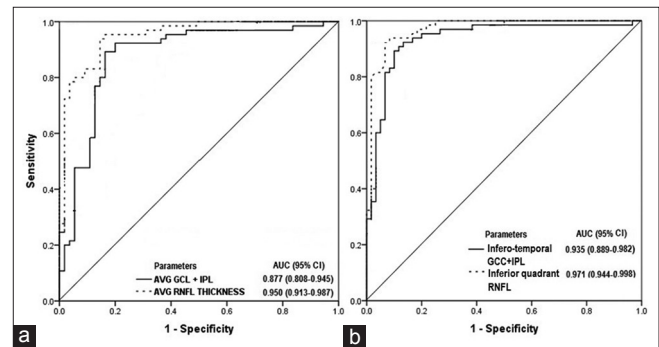


Figure 1: (a and b) Shows the ROC curves for the best discriminating parameters for both IHD and SHD groups in comparison with normal group

Table 2: Comparison of GCL + IPL and RNFL thickness for normal and glaucomatous eyes

	Groups								
	Normal (n=65)		Inferior hemifield (n=55)		P*	Superior hemifield (n=60)		P†	P‡
	Mean	Standard deviation	Mean	Standard deviation		Mean	Standard deviation		
Ganglion Cell Layer - Inner Plexiform Layer (GCL-IPL)									
Signal Strength	6.06	0.46	5.05	1.02	<0.0001 (HS)	5.40	0.98	<0.0001 (HS)	0.0606 (NS)
Superior Nasal	83.56	5.77	73.22	9.16	<0.0001 (HS)	73.76	16.01	<0.0001 (HS)	0.8242 (NS)
Superior	80.60	7.13	69.53	8.28	<0.0001 (HS)	72.24	15.56	<0.0001 (HS)	0.2517 (NS)
Superior Temporal	76.25	6.83	69.32	9.19	<0.0001 (HS)	69.21	13.96	<0.0001 (HS)	0.9595 (NS)
Inferior Nasal	81.03	7.39	69.80	9.39	<0.0001 (HS)	66.14	16.73	<0.0001 (HS)	0.1560 (NS)
Inferior	78.46	9.21	65.81	7.93	<0.0001 (HS)	57.31	15.73	<0.0001 (HS)	<0.0001 (HS)
Inferior Temporal	78.87	8.70	68.45	8.00	<0.0001 (HS)	56.06	14.29	<0.0001 (HS)	<0.0001 (HS)
AVG GCL + IPL	80.26	6.65	69.09	7.68	<0.0001 (HS)	65.50	14.11	<0.0001 (HS)	0.0969 (NS)
MIN GCL + IPL	74.63	11.05	60.82	9.80	<0.0001 (HS)	50.16	17.29	<0.0001 (HS)	<0.0001 (HS)
Retinal Nerve Fiber Layer (RNFL)									
AVG RNFL THICKNESS	87.41	7.53	67.71	10.38	<0.0001 (HS)	67.54	9.96	<0.0001 (HS)	0.9279 (NS)
Superior	110.93	12.07	79.75	16.71	<0.0001 (HS)	90.24	17.28	<0.0001 (HS)	0.0013 (S)
Nasal	68.65	8.87	57.28	9.38	<0.0001 (HS)	58.25	9.42	<0.0001 (HS)	0.5798 (NS)
Inferior	112.32	13.13	87.72	17.86	<0.0001 (HS)	68.09	17.53	<0.0001 (HS)	<0.0001 (HS)
Temporal	57.76	8.19	47.86	8.13	<0.0001 (HS)	53.74	9.28	0.0112 (S)	<0.0001 (HS)

*Means obtained after adjusting with signal strength and age and MD; †Comparison between the normal group and inferior hemifield defect glaucoma group.

‡Comparison between the normal group and superior hemifield defect glaucoma group.

§Comparison between the inferior hemifield defect glaucoma group and superior hemifield defect glaucoma group. HS=Highly Significant; S=Significant; NS=Non-Significant

hemifields of IHD and SHD on GCL + IPL and RNFL. Statistically significant difference of structural parameters was observed ($P < 0.0001$).

Discussion

We designed this study to analyze the performance of GCL + IPL and RNFL in eyes with either superior or inferior hemifield defects. And to further evaluate the above structural parameters in the apparently normal hemifield when compared with normal population.

It has been shown recently that the GCL + IPL thickness has greater diagnostic ability in eyes with parafoveal scotoma because RNFL defects are located closer to the fovea in eyes with a parafoveal visual field defect than in eyes with peripheral scotoma.^[2-11]

In our study, we found that when analyzing the IHD group, the performance of GCL + IPL fared secondary when compared with RNFL parameters. However, the difference was small. The AUROCs of all the superior sectors (superonasal, superior and superotemporal) on GCA were lower than the AUROC of superior RNFL, as seen with previous similar study by Kim *et al.*^[2] It is noteworthy that the best discriminating ability was found with the average thicknesses in both GCA and RNFL. The

reason the authors give is in the location of the macula, which is slightly lower than the ONH, which causes asymmetry in the distribution of the RNFL between the superior and inferior retinal halves.^[12,13] Some ganglion cell damage at the superior macula, particularly in IHD glaucoma, may have been outside the measurement annulus of Cirrus OCT. Therefore, it would not be detected by the retinal GCA algorithm. The superior sector GCL + IPL thicknesses measured by Cirrus OCT, such as the superotemporal, superior, and superonasal GCL + IPL thicknesses, would not thoroughly reflect the glaucomatous damage of the superotemporal optic disc, one of the areas that is most vulnerable to glaucomatous damage [Fig. 3]. It is notable that a recent study by Hwang *et al.* found that, if most RGCs of the peripheral retina, those farther than 4.5 mm from the fovea, have died, detection of RGC loss by GCIPL measurement will be somewhat difficult relative to pRNFL measurement.^[14]

In the SHD group, the AUC analysis showed that the performance of RNFL was comparable to the GCL + IPL. As can be expected, the inferotemporal on GCA and corresponding inferior quadrant on the RNFL analysis had the best discriminating ability. The difference was however small. The inferior quadrant on RNFL was closely followed by average RNFL thickness, which has been cited by previous similar studies.^[13-19]

We also studied the structural parameters in the apparently normal hemifield in both the groups. We found that in the IHD group, the inferior temporal sector on GCA showed statistically significant difference when compared with normal. Similarly, inferior quadrant thickness on RNFL also differed significantly. Correspondingly, in the SHD group, the superonasal and superior sectors on GCA differed significantly from normal and so did superior quadrant thickness in RNFL. This indicates towards an on-going glaucomatous damage, which is not visible on perimetry (the unaffected hemifield) and must be taken into consideration when managing a glaucomatous eye with hemifield defect [Fig. 4]. This structural

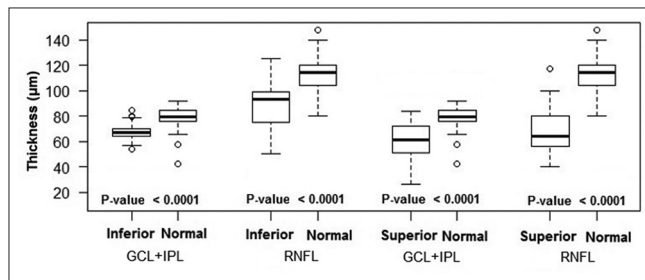


Figure 2: Shows the box-plot representation of thickness of inferior and superior parameters for normal and unaffected hemifields of IHD and SHD on GCL + IPL and RNFL

Table 3: Area under the Receiver Operating Characteristic Curve values for normal and glaucomatous eyes

	Inferior Hemifield Defect (n=55)	Superior Hemifield Defect (n=60)	P
Ganglion Cell Layer-Inner Plexiform Layer (GCL + IPL)			
Superior Nasal	0.848 (0.774-0.922)	0.725 (0.635-0.815)	0.0315 (S)
Superior	0.863 (0.793-0.933)	0.652 (0.553-0.751)	0.0007 (S)
Superior Temporal	0.730 (0.640-0.819)	0.651 (0.553-0.749)	0.2446 (NS)
Inferior Nasal	0.841 (0.763-0.918)	0.797 (0.717-0.878)	0.4505 (NS)
Inferior	0.865 (0.795-0.935)	0.907 (0.852-0.963)	0.3547 (NS)
Inferior Temporal	0.840 (0.768-0.912)	0.935 (0.889-0.982)	0.0291 (S)
Average GCL-IPL	0.877 (0.808-0.945)	0.875 (0.814-0.936)	0.9697 (NS)
Minimum GCL-IPL	0.865 (0.796-0.934)	0.910 (0.858-0.962)	0.3005 (NS)
Retinal Nerve Fiber Layer (RNFL)			
Average RNFL Thickness	0.950 (0.913-0.987)	0.941 (0.904-0.978)	0.7325 (NS)
Superior	0.933 (0.886-0.979)	0.842 (0.774-0.911)	0.0320 (S)
Nasal	0.785 (0.706-0.865)	0.778 (0.698-0.857)	0.8984 (NS)
Inferior	0.883 (0.821-0.945)	0.971 (0.944-0.998)	0.0106 (S)
Temporal	0.842 (0.767-0.917)	0.626 (0.528-0.724)	0.0006 (S)

HS=Highly Significant; S=Significant; NS=Non-Significant

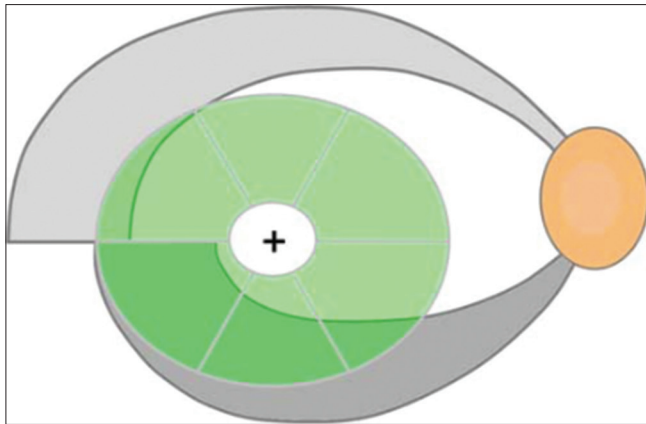


Figure 3: Retinal nerve fiber distribution

alteration may be easily missed if the treating physician relies only on perimetry. A similar study by Takagi *et al.* recently reported that the macular ganglion cell complex thickness corresponding to the normal hemifield of the glaucomatous eye was significantly decreased compared with that of normal eyes of controls matched for age, sex, and refractive errors.^[9] Inuzuka *et al.* found that macular retinal thickness decreases with a corresponding visual hemifield defect and that retinal structural changes precede the loss of the visual field in the apparently normal side.^[20]

The statistically significant difference between both the affected groups when studying the temporal quadrant on RNFL could not be explained.

There are potential limitations to our study. The sample size is small and large population-based studies are required for generalization of results. The MD shows statistically significant variation between the two affected groups and may be explained by the fact that we included all the stages of glaucoma: mild, moderate, and severe and hence the chances of possible skewing of data cannot be ruled out. Only eyes with high IOP were included and hence our results may not be applicable to normal tension glaucoma. 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 -6DS and +4DS. Our results may not be applicable to eyes falling beyond our criterion, especially glaucomatous eyes in high myopia.^[21] In our study, we included OCT scans with SS more than 4 which may not be the case in clinical practice. All these limitations must be taken into account before interpreting OCT results for individual cases.

Conclusion

In conclusion, in our study, we found that the RNFL structural analysis holds better ground than GCL + IPL, in eyes with either kind of hemifield defect. The unaffected hemifield also shows structural damage and hence should be considered when treating a similar patient.

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Nil.

Conflicts of interest

There are no conflicts of interest.

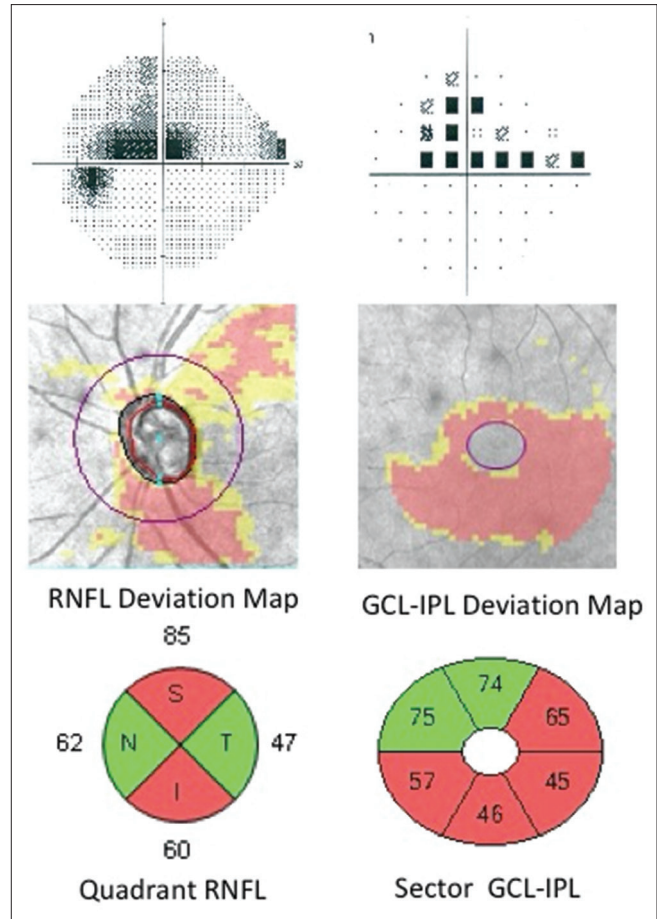


Figure 4: Eye with superior hemifield defect showing both superior and inferior RNFL and GCL + IPL loss

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