

# Retinal Nerve Fiber Layer and Ganglion Cell Complex Thickness Analysis in Treatment – Naive Glaucoma Patients

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## SUMMARY

**Aim:** To evaluate RNFL (Retinal Nerve Fiber Layer) and GCC (Ganglion Cell Complex) thickness, using SD-OCT in treatment-naive patients of primary open-angle glaucoma (POAG), primary angle-closure glaucoma (PACG) and normal-tension glaucoma (NTG) and to compare these findings with healthy controls.

**Material and Methods:** The study included 150 eyes of 75 glaucoma patients (25 each of POAG, PACG, NTG) and 200 eyes of 100 controls. In this cross-sectional observational study, patients meeting the inclusion criteria underwent comprehensive ophthalmic examinations, including best-corrected visual acuity, intraocular pressure (IOP) by Goldmann applanation tonometry (GAT), gonioscopy to differentiate between open and closed angle and visual field analysis (VFA). GCC-IPL and RNFL thickness were measured using SD-OCT.

**Results:** Significant thinning of RNFL was noted in all glaucoma subtypes, especially in inferior and superior quadrants ( $p < 0.0001$ ). GCC also showed thinning, notably in inferior and superior sectors, although the average GCC reduction was not statistically significant overall ( $p = 0.0611$ ). Visual field mean deviation (MD) was worse in glaucoma eyes ( $-2.69$  dB) compared to controls ( $-0.89$  dB,  $p = 0.041$ ), reflecting functional loss. POAG and NTG showed more prominent GCC, RNFL, VF correlations than PACG.

**Conclusion:** The study highlights that RNFL remains a robust early biomarker of glaucomatous damage, while inferior and superior GCC thickness may enhance sensitivity in detecting early structural changes, especially in treatment-naive patients. Combining RNFL and GCC analysis with VFA strengthens early diagnosis and subtype differentiation in treatment-naive primary glaucoma.

**Key words:** glaucoma, optical coherence tomography, retinal nerve fiber layer, ganglion cell complex, visual field analysis

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## INTRODUCTION

Glaucoma is a multifactorial optic neuropathy, characterized by loss of the retinal ganglion cell complex with subsequent loss of nerve fibers, resulting in functional visual impairment. Globally, it is the second-most common cause of blindness after cataract [1]. Primary Glaucoma can manifest as either primary open-angle glaucoma (POAG), primary angle closure glaucoma (PACG) or normal tension glaucoma (NTG). Loss of retinal ganglion cells results in characteristic changes to the optic nerve – optic neuropathy and corresponding visual field (VF) defects.

Nevertheless, significant visual field loss is detected only after 40% structural damage has occurred [2].

Optical Coherence Tomography (OCT) is a non-invasive imaging method that has been widely used for the evaluation of structural abnormalities affecting the optic nerve head, retinal nerve fiber layer (RNFL) of the peripapillary region and the macular area including the ganglion cell complex (GCC) [3]. Peripapillary RNFL (pRNFL) has long been used as an OCT parameter for the evaluation of glaucoma and other ocular diseases affecting the optic nerve. With the introduction of newer OCT technology [4], evaluation of the macular GCC is now possible by using automatized segmentation of the retinal layers. GCC is one of the parameters used for the early-stage diagnosis of glaucomatous disease, evaluation of disease progression and monitoring of the advanced stages.

Given the fact that the first segments affected are the ganglion cells, followed by the inner plexiform layer (IPL), and the GCL, GCC may prove to be a better diagnostic tool for early glaucomatous lesions. The process of mitochondrial splitting is one of the initial changes observed that demonstrates damage on the dendritic layer of the GCC-IPL [5–8]. In addition, it has been found that GCC is a superior parameter in cases of ocular hypertension associated with structural changes such as tilted disc or atrophy surrounding the optic nerve, in which the pRNFL could not be properly determined on OCT.

Despite significant advancements in diagnostic tools, such as Spectral-Domain Optical Coherence Tomography (SD-OCT), understanding the structural-functional changes in treatment-naive glaucoma remains under-explored. For this reason, we evaluated the retinal nerve fiber layer and ganglion cell complex thickness in treatment-naive glaucoma patients. We also drew a structural-functional relationship between GCC thickness and visual field loss, as well as RNFL thickness and visual field loss in patients in the entire spectrum of treatment-naive primary glaucoma patients i.e. POAG, PACG & NTG.

## MATERIAL AND METHODS

This cross-sectional observational study was conducted in a tertiary care hospital in Western India over 18 months, to include newly diagnosed patients with primary glaucoma (POAG, PACG, NTG). A total of 150 eyes of 75 treatment-naive glaucoma patients and 200 eyes of 100 control subjects were examined. Informed written consent was taken from all study subjects and institutional Ethics Committee approval was obtained.

Patients newly diagnosed as cases of glaucoma (POAG, PACG, NTG) with characteristic glaucomatous visual field loss and fulfilling Anderson criteria i.e. three or more congruous points in the typical arcuate area depressed at  $< 0.05$ , and at least one at  $P < 0.01$  in the pattern standard deviation (PSD) plot,  $PSD < 5\%$ , GHT outside normal limits, confirmed on two consecutive tests/visits with a reliable HFA test with false positive  $< 15\%$ , false negative  $< 15\%$  and fixation loss  $< 20\%$ , were included in this study. Exclusion criteria included patients with a history suggestive of, or diagnosed cases of secondary glaucoma, ophthalmic or neurological conditions other than glaucoma that can affect retinal parameters, including AION, optic neuritis and diabetic or hypertensive retinopathy, or any other retinal disease affecting retinal parameters, all diagnosed patients of primary glaucoma already on therapy, OCT scan signal strength  $< 5/10$ .

All patients who met the inclusion criteria underwent basic ophthalmic examination at their visit to the Center. Standard diagnostic protocols, including best-corrected visual acuity, intraocular pressure (IOP) by Goldmann applanation tonometry (GAT), fundus examination with 90D slit-lamp bio-microscopy, were performed to diagnose cases of glaucoma with cup-to-disc ratio  $> 0.7$ , cup asym-

metry  $> 0.2$  or neuro-retinal rim notching, focal thinning, disc hemorrhage, or vertical elongation of the optic cup. Gonioscopy to differentiate between open and closed angle, and visual field analysis (VFA) were employed. GCC-IPL and RNFL thickness were measured using SD-OCT.

Patients were categorized into 4 subgroups according to the IOP level and gonioscopic findings. The NTG group was defined as those with untreated peak IOP lower than 21 mmHg on repeated 3 measurements, taken at different times on separate visits during clinical follow-up. The POAG group included those with IOP before treatment exceeding 21 mmHg, based on 3 measurements on different days. The PACG group included those with raised IOP and features suggestive of primary angle-closure glaucoma on gonioscopic findings and IOP before treatment exceeding 21 mmHg, based on 3 measurements on different days. Patients with normal IOP and no disc or macular findings were included to serve as controls.

All patients underwent Spectral-Domain Optical Coherence Tomography (SD-OCT) by Cirrus HD-OCT (Carl Zeiss Meditec, Model – 5000) after pupil dilatation. Scans were obtained in the macular cube mode and RNFL mode (200X200). Scans were analyzed under analyzing the protocols 'ONH and RNFL OU analysis' and 'GC-IPL OU analysis'.

ONH and RNFL parameters scan 6mm retina around the optic disc. Disc area, cup area, rim area, horizontal and vertical CDR and average, superior and inferior RNFL thickness were generated automatically by the machine. The GCC scan was centered on the fovea and covered a square grid on the central macula. GCC thickness was measured from the internal limiting membrane to the outer inner plexiform layer. Average superior, inferior nasal, and temporal GCC thicknesses were calculated.

Data analysis was done utilizing SPSS v23 (IBM Corp.). For continuous variables, descriptive statistics were developed as means/standard deviations and medians/IQR; for categorical variables, they were developed as frequencies and percentages. The independent sample t-test was used to contrast 2 groups of continuously distributed data; the One-Way ANOVA was used to compare more than 2 groups. The chi-square test was employed to compare groups of categorical data. Statistical significance was determined at  $p < 0.05$ .

## RESULTS

The study population exhibited a well-distributed age range, with participants spanning from younger than 30 years to 71 years or older. The majority (60%) were within the 31- to 60-year age bracket, which is the common age range for glaucoma diagnosis. The mean age of the cohort was 50 years, further reflecting the typical demographic of glaucoma patients.

In the control group, the majority of patients were aged  $< 40$  years (46%), while in the glaucoma subtypes, most patients were older, with a higher proportion in the 51- to 70-year range for NTG (53.3%), PACG (66.7%), and

POAG (53.3%). These findings suggest that older age may be a risk factor for certain glaucoma subtypes. The age distribution was statistically significant ( $p = 0.0306$ ) across the diagnostic groups, suggesting potential age-related differences in disease presentation or risk factors. While there was a slight predominance of male patients (54.7%) over females (45.3%), the sex distribution was relatively balanced overall.

The study analyzed data from 149 eyes of the total of 75 patients. There was an approximately equal distribution between right eyes (75 eyes) and left eyes (74 eyes). One patient with normal-tension glaucoma (NTG) was excluded from the analysis due to perception of light (PL) negative vision in the left eye, indicating advanced visual impairment in that eye.

The mean Log MAR BCVA did not differ significantly between the control group (0.904) and total glaucoma cases (0.111) ( $p = 0.1639$ ). Similarly, there were no statistically significant differences in mean BCVA between the control group and the individual glaucoma subtypes: NTG (0.112,  $p = 0.8753$ ), POAG (0.109,  $p = 0.1085$ ), and PACG (0.112,  $p = 0.1115$ ). These findings suggest that visual acuity was relatively preserved in the glaucoma patients included in this study, as they had been recently diagnosed.

The mean IOP was significantly higher in the total glaucoma cases (18.3 mmHg) compared to the control group (16.65 mmHg) ( $p < 0.0001$ ). This difference was also observed in each glaucoma subtype: NTG (17.8 mmHg,  $p = 0.0176$ ), POAG (17.9 mmHg,  $p = 0.0228$ ), and PACG (19.2 mmHg,  $p < 0.0001$ ). The baseline IOP in different groups of glaucoma patients was different. These results align with the known pathophysiology of glaucoma, where elevated IOP is a significant risk factor for the development and progression of disease.

The mean CCT was slightly lower in the total glaucoma cases (511.2  $\mu\text{m}$ ) compared to the control group (512.7  $\mu\text{m}$ ), and this difference was statistically significant ( $p = 0.04$ ). However, when examining the individual glaucoma subtypes, only the POAG group exhibited a significantly lower CCT (505.23  $\mu\text{m}$ ,  $p = 0.023$ ) relative to the control group. The differences in CCT were not statistically significant for the NTG (513.4  $\mu\text{m}$ ,  $p = 0.05$ ) and PACG (506.2  $\mu\text{m}$ ,  $p = 0.15$ ) subtypes.

### 1. Retinal Nerve Fiber Layer (RNFL) Thickness in Glaucoma

#### a) Average RNFL:

Mean RNFL thickness was significantly reduced in glaucoma (92.62  $\mu\text{m}$ ) vs controls (95.5  $\mu\text{m}$ ,  $p = 0.011$ ), with consistent thinning across subtypes: NTG (91.27  $\mu\text{m}$ ,  $p = 0.046$ ), POAG (92.20  $\mu\text{m}$ ,  $p = 0.044$ ), PACG (95.8  $\mu\text{m}$ ,  $p = 0.040$ ), indicating diffuse structural loss. (Table 1).

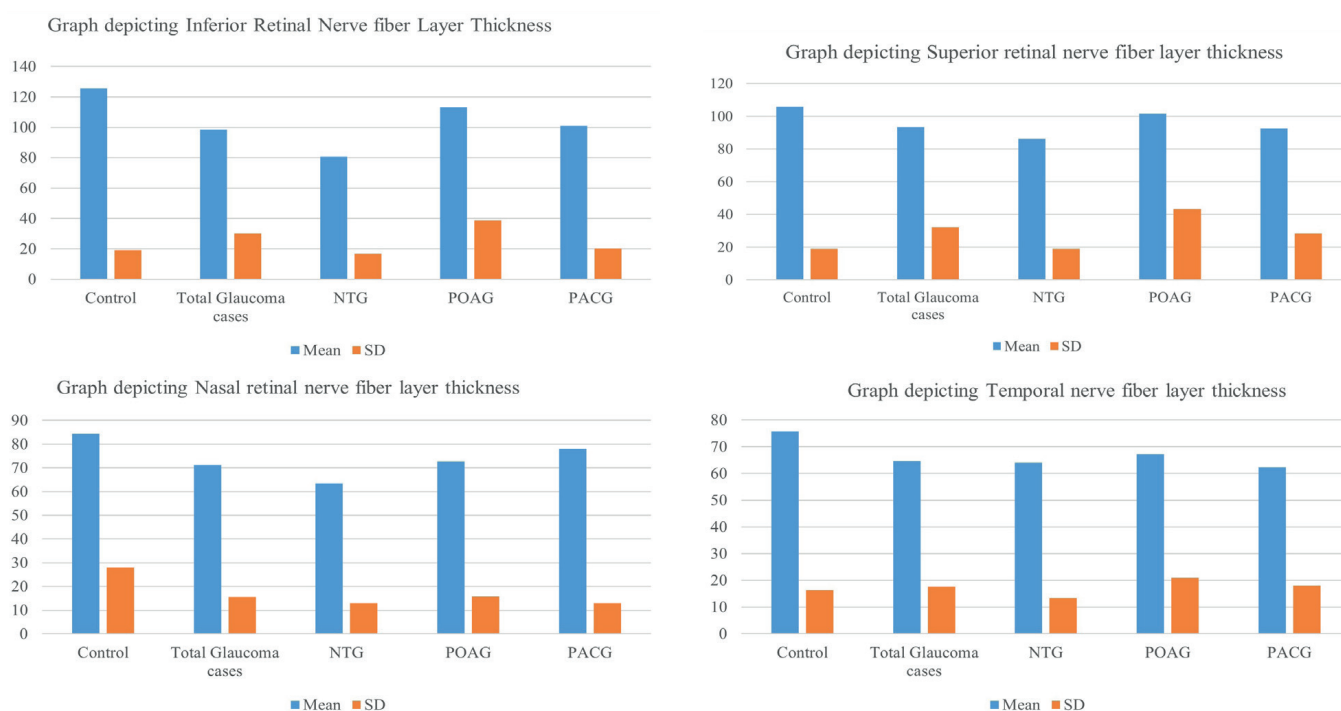
#### b) Inferior RNFL:

Inferior RNFL showed marked thinning in glaucoma (98.48  $\mu\text{m}$ ) compared to controls (125.61  $\mu\text{m}$ ,  $p < 0.0001$ ), notably in NTG (80.65  $\mu\text{m}$ ), POAG (113.20  $\mu\text{m}$ ), and PACG (101.00  $\mu\text{m}$ ), highlighting its vulnerability in disease. (Figure 1).

**Table 1.** Distribution of mean Average RNFL thickness in patients & controls

Average RNFL	Number	Mean	SD	p-value
Control	200	95.05	9.585	
Total Glaucoma cases	149	92.62	10.36	<b>0.0110</b>
NTG	49	91.27	11.31	<b>0.0457</b>
POAG	50	92.20	10.31	<b>0.0438</b>
PACG	50	95.8	9.266	<b>0.0397</b>

RNFL – retinal nerve fiber layer, NTG – normal tension glaucoma, POAG – primary open angle glaucoma, PACG – primary angle closure glaucoma



**Figure 1.** Distribution of RNFL thickness in different quadrants among patients and controls

RNFL – retinal nerve fiber layer, NTG – normal tension glaucoma, POAG – primary open angle glaucoma, PACG – primary angle closure glaucoma

**c) Superior RNFL:**

Superior RNFL was significantly reduced in glaucoma (93.52 μm) vs controls (105.91 μm, **p = 0.001**), with subtype values: NTG (86.10 μm), POAG (101.53 μm), PACG (92.57 μm), suggesting upper quadrant involvement. (Figure 1).

**d) Nasal RNFL:**

Nasal RNFL was thinner in glaucoma (71.28 μm) than controls (84.41 μm, **p < 0.0001**), significant in NTG (63.37 μm) and POAG (72.7 μm), but not PACG (78.13 μm, **p = 0.236**), indicating relatively preserved nasal fibers in PACG. (Figure 1).

**e) Temporal RNFL:**

Temporal RNFL was significantly reduced in glaucoma (64.60 μm) vs controls (75.71 μm, **p < 0.0001**) across all subtypes: NTG (64.10 μm), POAG (67.30 μm), PACG (62.37 μm), confirming its involvement in glaucomatous damage. (Figure 1).

**2. Ganglion Cell Complex Thickness in Glaucoma**

**a) Average GCC:**

Mean GCC thickness showed no statistically significant difference between glaucoma patients (74.42 μm) and controls (76.49 μm; **p = 0.0611**). Subgroup analysis revealed non-significant reductions in NTG (76.19 μm; **p = 0.0765**), POAG (73.70 μm; **p = 0.2071**), and PACG (72.23 μm; **p = 0.3131**), suggesting limited sensitivity of average GCC as a biomarker for glaucomatous damage in recently diagnosed treatment-naive patients (Table 2).

**b) Inferior GCC:**

Inferior GCC thickness was significantly reduced in glaucoma eyes (98.48 μm) compared to controls (125.61 μm;

**Table 2.** Distribution of mean Average (GCC) thickness in patients & controls

Average RNFL	Number	Mean	SD	p-value
Control	200	76.49	17.41	
Total Glaucoma cases	149	74.42	22.38	0.0511
NTG	49	76.19	22.15	0.0765
POAG	50	73.70	15.93	0.2071
PACG	50	72.23	27.65	0.3131

*GCC – ganglion cell complex, NTG – normal tension glaucoma, POAG – primary open angle, glaucoma, PACG – primary angle closure glaucoma*

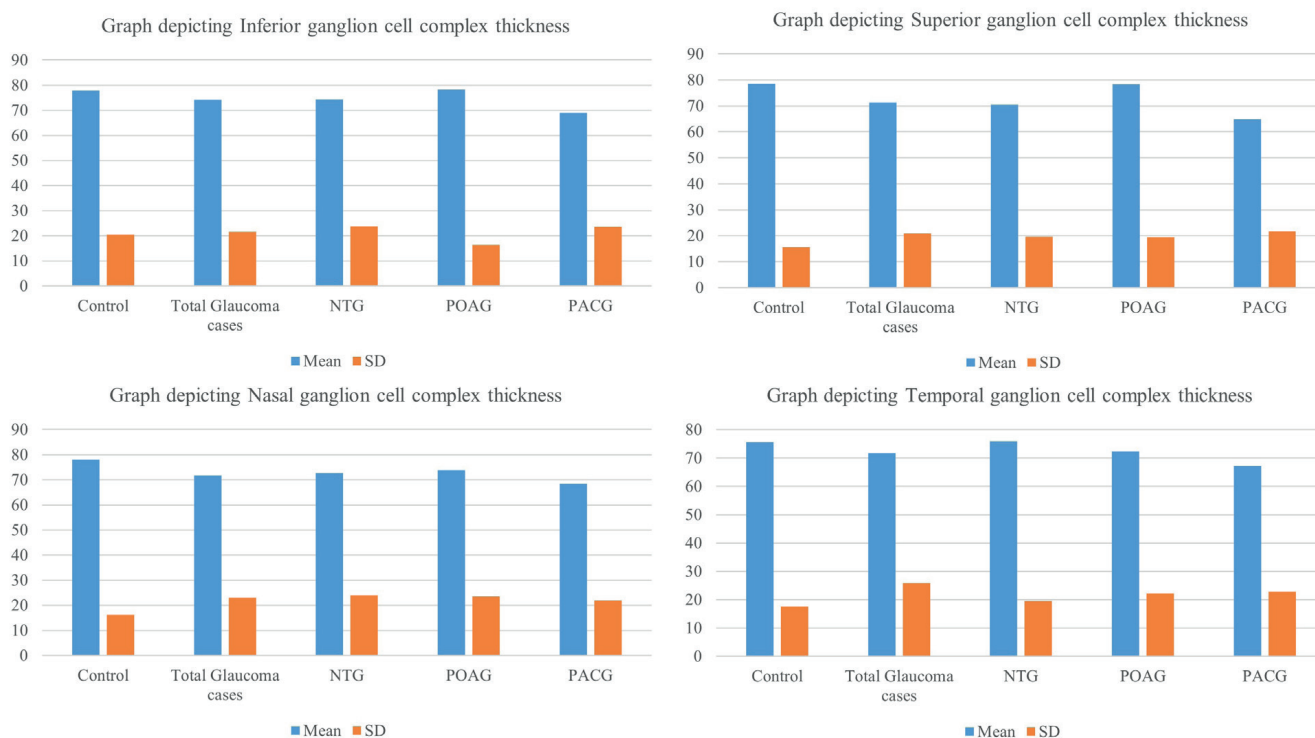
**p < 0.0001**), with consistent thinning across NTG (80.65 μm; **p < 0.0001**), POAG (113.20 μm; **p = 0.0182**), and PACG (101.00 μm; **p < 0.0001**). This highlights the inferior GCC region as particularly susceptible to glaucomatous neurodegeneration. (Figure 2).

**c) Superior GCC:**

A significant reduction in superior GCC was observed in glaucoma cases (93.52 μm) versus controls (105.91 μm; **p = 0.0013**), with subtype-specific reductions in NTG (86.10 μm; **p < 0.0001**), POAG (101.53 μm; **p = 0.0440**), and PACG (92.57 μm; **p = 0.0032**), confirming its diagnostic relevance alongside the inferior region. (Figure 2).

**d) Nasal GCC:**

Glaucoma patients exhibited a significant reduction in nasal GCC (71.68 μm) compared to controls (78.16 μm; **p = 0.025**). This was evident in NTG (72.65 μm; **p = 0.015**) and POAG (73.93 μm; **p = 0.026**), but not in PACG patients (68.50 μm; **p = 0.219**), suggesting relative preservation in the latter. (Figure 2).



**Figure 2.** Distribution of GCC thickness in different quadrants among patients and controls

*GCC – ganglion cell complex, NTG – normal tension glaucoma, POAG – primary open angle, glaucoma, PACG – primary angle closure glaucoma*

### e) Temporal GCC:

Temporal GCC thickness did not differ significantly between glaucoma and control groups (71.75  $\mu\text{m}$  vs. 75.7  $\mu\text{m}$ ;  $p = 0.21$ ). While NTG (75.96  $\mu\text{m}$ ;  $p = 0.440$ ) and PACG (67.20  $\mu\text{m}$ ;  $p = 0.06$ ) showed no significant change, POAG demonstrated a modest but significant reduction (72.33  $\mu\text{m}$ ;  $p = 0.039$ ), indicating selective vulnerability. (Figure 2).

### 3. VFA (db)

The mean deviation on VFA was significantly more negative (worse) in the total glaucoma cases (-0.89 dB) compared to the control group (-2.69 dB) ( $p = 0.041$ ), indicating functional visual field defects in glaucoma patients. This pattern was observed across all glaucoma subtypes. (Table 3).

## DISCUSSION

Early detection and monitoring of glaucoma are crucial for timely intervention and the prevention of irreversible vision loss. OCT has emerged as a valuable tool for assessing structural changes in the retina and optic nerve head associated with glaucoma [5–7]. The measurement of RNFL and GCC thickness using SD-OCT has shown promise in detecting early glaucomatous damage in established patients on treatment [12–14].

This study aimed to comprehensively evaluate the RNFL and GCC thickness in treatment-naïve POAG, PACG, and NTG patients using SD-OCT and to compare these findings with healthy controls. By including treatment-naïve patients, we sought to minimize the confounding effects of antiglaucoma medications on the study parameters. In addition, we investigated the spatial patterns of RNFL and GCC thinning across glaucoma subtypes to gain insights into the potential differences in the pathophysiology of glaucomatous damage. The integration of structural and functional assessments, including visual VFA, allowed for a more comprehensive understanding of the complex interplay between anatomical changes and visual function in glaucoma.

In our study, the average RNFL thickness was significantly lower in all glaucoma subtypes compared to controls. The RNFL, which is composed of RGC axons, is a sensitive indicator of glaucomatous damage [15–17]. Thinning of the RNFL in glaucoma is thought to result from the loss of RGCs and their axons – a hallmark of the disease [18]. The significantly lower average RNFL thickness in all glaucoma subtypes in our study supports the use of this parameter in the detection and monitoring of glaucomatous damage. Our findings are consistent with numerous previous studies that have demonstrated significant RNFL thinning in glaucoma patients, compared to healthy controls [18–22]. The inclusion of treatment-naïve patients in our study strengthens the evidence for the use of average RNFL thickness as a biomarker for early glaucoma detection.

**Table 3.** Distribution of VFA mean deviation (db) in patients & controls

VFA	Number	Mean	SD	p-value
Control	200	-2.69	1.10	
Total Glaucoma cases	149	-0.89	0.87	<b>0.041</b>
NTG	49	-1.66	0.789	<b>&lt; 0.0001</b>
POAG	50	11	0.106	<b>0.01</b>
PACG	0	-1.87	1.58	<b>0.0017</b>

VFA – visual field analysis, NTG – normal tension glaucoma, POAG – primary open angle, glaucoma, PACG – primary angle closure glaucoma

In our study, the inferior and superior RNFL thicknesses were significantly lower in all glaucoma subtypes, compared to controls. The inferior and superior RNFL are particularly susceptible to glaucomatous damage, as these regions contain the highest density of RGC axons [23,24]. The significant thinning of the inferior and superior RNFL in all glaucoma subtypes in our study is consistent with the typical pattern of glaucomatous damage, which often manifests as early defects in these regions [25]. Previous studies have consistently reported significant thinning of the inferior and superior RNFL in glaucoma patients compared to healthy controls [19–25]. Our findings corroborate these reports and highlight the importance of assessing regional RNFL thickness in the detection and monitoring of glaucoma.

In our study, the nasal and temporal RNFL thicknesses were significantly lower in POAG and NTG compared to controls. However, the nasal RNFL thickness was not significantly different between PACG and controls. The nasal and temporal RNFL are generally less affected in early glaucoma, compared to the inferior and superior regions [26]. However, as the disease progresses, these regions may also exhibit significant thinning [27]. The relative sparing of the nasal RNFL in PACG compared to POAG and NTG in our study suggests potential differences in the spatial pattern of RNFL damage among glaucoma subtypes. Previous studies have reported variable results regarding the significance of nasal and temporal RNFL thinning in glaucoma [28–30]. Our findings suggest that the nasal and temporal RNFL may be affected differently across glaucoma subtypes, with POAG and NTG exhibiting more pronounced thinning in these regions, compared to PACG.

The average GCC thickness was not significantly different between the total glaucoma cases and controls or among the individual glaucoma subtypes. The GCC has been proposed as a sensitive marker for early glaucomatous damage. However, the lack of significant differences in average GCC thickness between glaucoma cases and controls in our study suggests that this parameter may not be as sensitive as RNFL thickness in detecting early glaucomatous changes.

Previous studies have reported conflicting results regarding the diagnostic performance of average GCC thickness in glaucoma [31]. Some studies have found

significant thinning of the average GCC in glaucoma patients compared to controls, while others have not found any significant differences [31–33]. Our findings suggest that the sensitivity of average GCC thickness in detecting early glaucoma may be limited, and that regional GCC measurements may be more informative.

However, the inferior and superior GCC thicknesses were significantly lower in all glaucoma subtypes compared to controls. The significant thinning of the inferior and superior GCC in all glaucoma subtypes in our study is consistent with the pattern of RGC loss in glaucoma, which typically begins in these regions [32,33]. The inferior and superior GCC may be more sensitive to early glaucomatous damage compared to the average GCC thickness, as localized defects may be masked when analyzing the entire GCC<sup>33</sup>. Previous studies have demonstrated significant thinning of the inferior and superior GCC in glaucoma patients compared to controls [28–33]. Our findings support the use of regional GCC measurements, particularly in the inferior and superior regions for the detection and monitoring of glaucoma.

Noticeably, the nasal GCC thickness was significantly lower in POAG and NTG compared to controls, while the temporal GCC thickness was significantly lower only in POAG. The nasal and temporal GCC are generally less affected in early glaucoma, compared to the inferior and superior regions [32]. However, as the disease progresses, these regions may also exhibit significant thinning [33]. The selective involvement of the nasal and temporal GCC in POAG and NTG in our study suggests potential differences in the spatial pattern of GCC damage among glaucoma subtypes. Previous studies have reported variable results regarding the significance of nasal and temporal GCC thinning in glaucoma [32–36]. Our findings suggest that the nasal and temporal GCC may be affected differ-

ently across glaucoma subtypes, with POAG exhibiting more pronounced thinning in these regions, compared to PACG and NTG.

We also found that the mean deviation on VFA was significantly worse in all glaucoma subtypes, compared to controls. Visual field defects are a hallmark of glaucomatous damage and are often used to monitor disease progression [35]. Previous studies have consistently demonstrated more negative VFA mean deviation in glaucoma patients compared to healthy controls [30–36]. Our findings corroborate these reports and highlight the importance of functional assessment in the diagnosis and management of glaucoma.

However, this study has limitations that should be considered. The sample size was relatively small, potentially limiting the generalizability of our findings. The cross-sectional design precludes the assessment of longitudinal changes in RNFL and GCC thickness. Lastly, the study was conducted at a single tertiary care center, which may introduce selection bias.

## CONCLUSION

Consequently, the present study demonstrates the value of comprehensive structural and functional assessments in the early detection and characterization of glaucomatous damage in treatment-naïve POAG, PACG, and NTG patients. It also highlights that RNFL remains a robust early biomarker of glaucomatous damage, while inferior and superior GCC thickness may enhance sensitivity in detecting early structural changes, especially in treatment-naïve patients. Combining RNFL and GCC analyses with VFA strengthens early diagnosis and subtype differentiation in treatment-naïve primary glaucoma.

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