

Associations of Ganglion Cell-Inner Plexiform Layer and Optic Nerve Head Parameters with Visual Field Sensitivity in Advanced Glaucoma

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ABSTRACT

Purpose: To evaluate the associations of optical coherence tomography (OCT)-derived macular ganglion cell-inner plexiform layer thickness (mGCIPLT) ; circumpapillary retinal nerve fiber layer thickness (cpRNFLT) ; optic nerve head (ONH) parameters with visual field (VF) sensitivity in advanced glaucoma

Methods: In this hospital based cross-sectional observational study , 43 eyes from 43 patients with advanced glaucoma were subjected to assess mGCIPLT, cpRNFLT, and ONH parameters (including the rim area, average cup-to-disc [C:D] ratio, and vertical C:D ratio) using Cirrus high-definition OCT, 24-2 and 10-2 VF sensitivity visual field tests using The Humphrey field analyzer (HFA) . Pearson correlation coefficients were used to analyze relationships between OCT-derived parameters and VF parameters .

Results: The mGCIPLT and rim area were significantly positively correlated with the 24-2 VF MD , while the average and vertical C:D ratios were significantly negatively correlated with the 24-2 VF MD . Moderate correlations were observed between the mGCIPLT and ONH parameters and the 24-2 VF PSD. The correlations between the mGCIPLT and ONH parameters and the 24-2 VF VFI were also moderate . Moderate or strong correlations were observed between the mGCIPLT and ONH parameters and the 10-2 VF MD. The mGCIPLT and rim area were significantly positively correlated with the 10-2 VF MD , while the average and vertical C:D ratios were significantly negatively correlated with the 10-2 VF MD.

Conclusion: In conclusion, we found that mGCIPLT and ONH parameters were associated with the severity of VF damage and reflected functional damage better than cpRNFLT in advanced glaucoma. These results suggested that structural measurements of mGCIPLT and ONH parameters and functional measurement of the 10-2 VF may be useful for monitoring progression in advanced glaucoma.

INTRODUCTION

Glaucoma has become the most frequent cause of irreversible blindness worldwide and is associated with characteristic structural changes in the optic nerve head (ONH) and retinal nerve fiber layer (RNFL), which are accompanied by functional visual field (VF) loss . Glaucomatous optic neuropathy is characterized by progressive loss of retinal ganglion cells (RGCs) and their axons, thinning of retinal nerve fiber layer (RNFL), increased optic disc cup or notching of optic nerve head (ONH), and characteristic visual field (VF) defects. The structural changes are evaluated by ONH changes and peripapillary retinal nerve fiber layer (pRNFL) defects .

Loss of RGCs was commonly seen in early glaucoma, so segmentation of IML for Isolated retinal layer can help for early diagnosis of glaucoma^[1]. Combining GCA thickness with

macular VF sensitivity may provide a better understanding of the amount of glaucomatous damage that occurs in the macula region.^[2] Structural changes in the macula, such as reductions in mGCIPLT, may be indicators of defects in the central VF, which have a greater impact than peripheral VF defects on vision related quality of life (QOL) ^[3].

OCT is a reliable method for detecting glaucoma and assessing structural parameters like circumpapillary retinal nerve fiber layer thickness (cpRNFLT) and macular ganglion cell-inner plexiform layer thickness (mGCIPLT). Serial OCT measurements of cpRNFLT can objectively identify progressive changes and are a strong indicator of visual field (VF) progression. However, in advanced glaucoma, cpRNFLT may reach a "floor effect," limiting its ability to detect further progression. In contrast, mGCIPLT is less likely to reach this threshold, making it a more effective marker for progression in advanced glaucoma. Studies have shown that the rate of change in mGCIPLT is significant in advanced glaucoma, while changes in cpRNFLT are less pronounced. For instance, Lavinsky et al. found a significant decline in mGCIPLT ($-0.57 \mu\text{m}/\text{year}$) in patients with advanced glaucoma, whereas changes in rim area were minimal. Similarly, Shin et al. reported that mGCIPLT changes were more pronounced in VF progressors compared to non-progressors, while cpRNFLT changes were not significant.^[4]

The Humphrey Field Analyzer (HFA) is a widely used device for standard automated perimetry (SAP). The 24-2 program tests 54 points 6° apart, while the 10-2 program tests 68 points 2° apart. The 24-2 program only includes 12 points within the central 10 degrees of fixation, limiting its ability to assess the macular region. Studies have shown that the rate of mean deviation (MD) changes is significantly greater with the 10-2 program, making it a more effective tool for tracking glaucoma progression, particularly in advanced and severe cases.^[4] We hypothesized that mGCIPL and the optic nerve head (ONH) are more reliable markers for monitoring glaucoma progression than cpRNFLT, and that the 10-2 VF test is better suited for assessing function in advanced glaucoma. In this study, we examined the structure-function relationships between mGCIPLT, cpRNFLT, and ONH parameters, measured with Cirrus HD-OCT, and the results of 24-2 and 10-2 VF tests in patients with advanced glaucoma.^[4]

MATERIALS & METHODS

This prospective study was conducted at Ophthalmology Department, R L Jalappa Hospital, Kolar, Karnataka, India, from June 2023 to August 2024 and was analysed in November 2024. All consecutive patients visiting Ophthalmology Out patient department of either sex and >18 years of age, diagnosed with Advanced glaucoma are included in the study. Criteria for advanced glaucoma was severe stage glaucoma which is defined as optic nerve abnormalities consistent with glaucoma, retinal nerve fiber layer changes, glaucomatous visual field abnormalities in both hemifields and/or vision loss within 5 degrees of fixation in at least one hemifield.

The inclusion criteria for all subjects were a diagnosis of advanced primary open angle glaucoma (POAG) or chronic primary angle closure glaucoma (CPACG) based on a 24-2 VF MD of ≤ -12 dB with age ≥ 18 years whose BCVA is of at least 20/50 and a spherical refraction of -6.0 to $+3.0$ diopters and cylinder correction within ± 3.0 diopters. Advanced glaucoma was defined by a baseline 24-2 VF MD of -12 dB or less. If both eyes of a patient satisfied the eligibility criteria, then 1 eye was selected randomly for inclusion.

Exclusion criterias for the following study were patients with a history of intraocular surgery (except for uncomplicated cataract or glaucoma surgery), coexisting retinal pathology, non-glaucomatous optic neuropathy, uveitis, ocular trauma, or other factors leading to secondary glaucoma. Patients with diagnosis of Parkinson's disease, Alzheimer's disease, or dementia or a history of stroke, diabetic or hypertensive retinopathy were also excluded. This study also reduced patients with problems other than glaucoma that could affect color vision or a life-

threatening disease . Lastly, patients with unreliable VF measurements and poor quality OCT scans were not included .

After taking an informed consent from the patient , in- depth ocular examination of all the patients was performed , which included Visual acuity recording by Snellen's chart ; Slit lamp biomicroscopy for evaluation of anterior segment ; Fundus examination by + 90D lens assisted slit lamp biomicroscopy and direct ophthalmoscopy; Intraocular Pressure measurement by Goldmann Applanation Tonometer ; Fundus evaluation through direct, indirect ophthalmoscopy and slit lamp 90D Examination ; mGCIPLT, cpRNFLT, and ONH parameters (including the rim area, average cup-to-disc [C:D] ratio, and vertical C:D ratio) were measured using SD-OCT ; 24-2 and 10-2 Visual field sensitivity tests were performed using The Humphrey field analyzer (HFA) .

Visual fields (VFs) were measured using the Swedish Interactive Thresholding Algorithm (SITA) with 24-2 and 10-2 perimetry after refractive correction, employing a Goldmann size III target and a background luminance of 31.5 asb. The 24-2 test was done first, followed by the 10-2 test if the Mean Deviation (MD) of the 24-2 was ≤ -12 dB, with a minimum 20-minute interval between tests. Reliable VFs had $<33\%$ fixation loss and false responses. The analysis included Mean Deviation (MD), Pattern Standard Deviation (PSD), and Visual Field Index (VFI). ^[4]

All subjects underwent imaging with Cirrus HD-OCT, including one optic disc scan (Optic Disc Cube 200×200) and one macular scan (Macular Cube 512×128), both performed by the same operator on the same day. The optic disc scan measured the circumpapillary retinal nerve fiber layer thickness (cpRNFLT) and optic nerve head (ONH) parameters, while the macular scan assessed the ganglion cell-inner plexiform layer thickness (mGCIPLT) using the ganglion cell analysis (GCA) algorithm. Scans were excluded if signal strength was <7 , or if they had segmentation errors or motion artifacts (defined as a blood vessel discontinuity exceeding 1 major vessel diameter). The analysis included cpRNFLT (global and quadrants), mGCIPLT (global and sectorial), and ONH parameters (rim area, average C:D ratio, and vertical C:D ratio). ^[4]

STATISTICAL ANALYSIS

Data will be entered into Microsoft excel data sheet and will be analyzed using SPSS 22 version software. Categorical data will be represented in the form of Frequencies and proportions. Chi-square test or Fischer's exact test (for 2x2 tables only) will be used as test of significance for qualitative data. Yates correction will be applied were ever chi-square rules were not fulfilled (for 2x2 tables only).

Continuous data will be represented as mean and standard deviation. Independent t test or Mann Whitney U test will be used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively.

Graphical representation of data: MS Excel and MS word will be used to obtain various types of graphs such as bar diagram, Pie diagram and Scatter plots.

Pearson correlation or Spearman's correlation will be done to find the correlation between two quantitative variables and qualitative variables respectively.

Correlation coefficient (r)	Interpretation
0 - 0.3	Positive Weak correlation
0.3-0.6	Positive Moderate correlation
0.6-1.0	Positive Strong correlation
0 to (-0.3)	Negative Weak correlation
(-0.3) to (-0.6)	Negative Moderate Correlation
(-0.6) to – (1)	Negative Strong Correlation

p value (Probability that the result is true) of <0.05 will be considered as statistically significant

Parameter	Value
Advanced Glaucoma	
Age (years)	52.3 ± 9.5
Gender (Male, Female)	60, 40
IOP (mm Hg)	25.1 ± 10.3
CCT (μm)	541.2 ± 31.7
Spherical Equivalent (diopters)	0.46 ± 1.4
BCVA (logMAR)	0.59 ± 0.19
Type of Glaucoma (POAG, CPACG)	45, 55
VF Parameters	
24-2 VF MD (dB)	-24.6 ± 6.3
24-2 VF PSD (dB)	7.2 ± 3.5
24-2 VF VFI (%)	23.2 ± 20.8
10-2 VF MD (dB)	-21.59 ± 8.29
10-2 VF PSD (dB)	8.92 ± 3.37
cpRNFLT (μm)	
Average	61.48 ± 10.3
Superior	71.5 ± 16.1
Inferior	69.9 ± 14.4
Nasal	62.5 ± 10.4
Temporal	52.3 ± 12.8
mGCIPLT (μm)	
Average	58.2 ± 7.52
Minimum	47.3 ± 9.18
Superior	56.2 ± 9.87
Inferior	58.06 ± 9.43
Superonasal	61.21 ± 10.29
Inferonasal	58.63 ± 11.37
Superotemporal	55.42 ± 9.58
Inferotemporal	54.58 ± 9.32
ONH Parameters	
Rim Area (mm^2)	0.52 ± 0.24
Average C:D Ratio	0.41 ± 0.01

after assuming all the rules of statistical tests ^[5]

RESULTS

A total of 50 eyes from 50 participants were initially evaluated for inclusion in the study. However, 7 subjects with unreliable visual field (VF) tests or optical coherence tomography (OCT) images were excluded. As a result, 43 eyes from 43 patients with advanced glaucoma were included in this cross-sectional study. Among these, 18 patients had primary open-angle glaucoma (POAG), and 18 had chronic primary angle-closure glaucoma (CPACG). The demographics and clinical characteristics of the study population are summarized in Table 1. The mean age of the participants was 59.25 ± 13.58 years, with a mean baseline intraocular pressure (IOP) of 27.85 ± 11.62 mm Hg. The mean mean deviation (MD) for the 24-2 and 10-2 visual field tests were -26.68 ± 6.22 dB and -22.59 ± 9.29 dB, respectively. The average values for central retinal nerve fiber layer thickness (cpRNFLT), macular ganglion cell-inner plexiform layer thickness (mGCIPLT), and cup-to-disc (C:D) ratio were 63.48 ± 9.94 μm , 57.26 ± 8.52 μm , and 0.86 ± 0.06 , respectively.

TABLE-1 : Demographics and clinical characteristics of the study population

	24-2 MD		24-2 PSD		24-2 VFI		10-2 MD		10-2 PSD	
	r	p value	r	p value	r	p value	r	p value	r	p value
mGCIPLT (μm)										
Average	0.528	<0.001	0.52	<0.001	0.52	<0.001	0.631	<0.001	0.216	0.041
Minimum	0.538	<0.001	0.54	<0.001	0.558	<0.001	0.616	<0.001	0.192	0.074
Superior	0.528	<0.001	0.521	<0.001	0.532	<0.001	0.541	<0.001	0.24	0.025
Inferior	0.424	<0.001	0.449	<0.001	0.456	<0.001	0.553	<0.001	0.084	0.5
Superonasal	0.463	<0.001	0.548	<0.001	0.467	<0.001	0.574	<0.001	0.289	0.001
Inferonasal	0.425	<0.001	0.498	<0.001	0.442	<0.001	0.616	<0.001	0.191	0.055
Superotemporal	0.564	<0.001	0.537	<0.001	0.561	<0.001	0.542	<0.001	0.224	0.014
Inferotemporal	0.541	<0.001	0.462	<0.001	0.549	<0.001	0.604	<0.001	0.072	0.465
ONH parameters										
Rim area (mm²)	0.548	<0.001	0.48	<0.001	0.545	<0.001	0.613	<0.001	0.184	0.061
Average C/D	-0.590	<0.001	-0.536	<0.001	-0.586	<0.001	-0.537	<0.001	-0.172	0.073
Vertical C/D	-0.473	<0.001	-0.432	<0.001	-0.481	<0.001	-0.428	<0.001	-0.077	0.422
cpRNFLT(μm)										
Average	0.082	0.432	0.164	0.126	0.079	0.474	0.1	0.315	0.133	0.132
Superior	0.176	0.114	0.163	0.114	0.158	0.145	0.086	0.397	0.172	0.074
Inferior	0.047	0.681	0.042	0.709	0.047	0.674	0.153	0.124	0.047	0.618
Nasal	-0.040	0.712	0.102	0.356	-0.044	0.661	0.11	0.271	0.148	0.149
Temporal	0.013	0.918	0.049	0.669	0.003	0.941	0.029	0.775	0.017	0.845

The Pearson correlation coefficients of the mGCIPLT, cpRNFLT, and ONH parameters with VF parameters are shown in Table 2.

TABLE 2 : Pearson correlation coefficients of the mGCIPLT, cpRNFLT, and ONH parameters with VF parameters in advanced glaucoma

In advanced glaucomatous eyes, significant correlations were found between mGCIPLT and ONH parameters with various visual field (VF) measures. Specifically, mGCIPLT and rim area showed positive correlations with both 24-2 VF MD ($r = 0.415\text{--}0.574$, $p < 0.001$) and 10-2 VF MD ($r = 0.542\text{--}0.621$, $p < 0.001$), while average and vertical C:D ratios were negatively correlated with these measures ($r = -0.580$ to -0.428 , $p < 0.001$). Moderate correlations were also observed between mGCIPLT and ONH parameters with 24-2 VF PSD ($r = 0.431\text{--}0.550$, $p < 0.001$) and 24-2 VF VFI ($r = 0.443\text{--}0.585$, $p < 0.001$). Additionally, moderate to strong correlations were found with the 10-2 VF MD^[1]. However, only mild positive correlations were observed between mGCIPLT subfields and 10-2 VF PSD ($r = 0.206\text{--}0.289$, $p < 0.05$), and none of the cpRNFLT parameters showed significant correlations with any VF measures. Scatter plots illustrated the linear relationships between mGCIPLT, ONH parameters, and the 10-2 VF MD (Fig. 1).

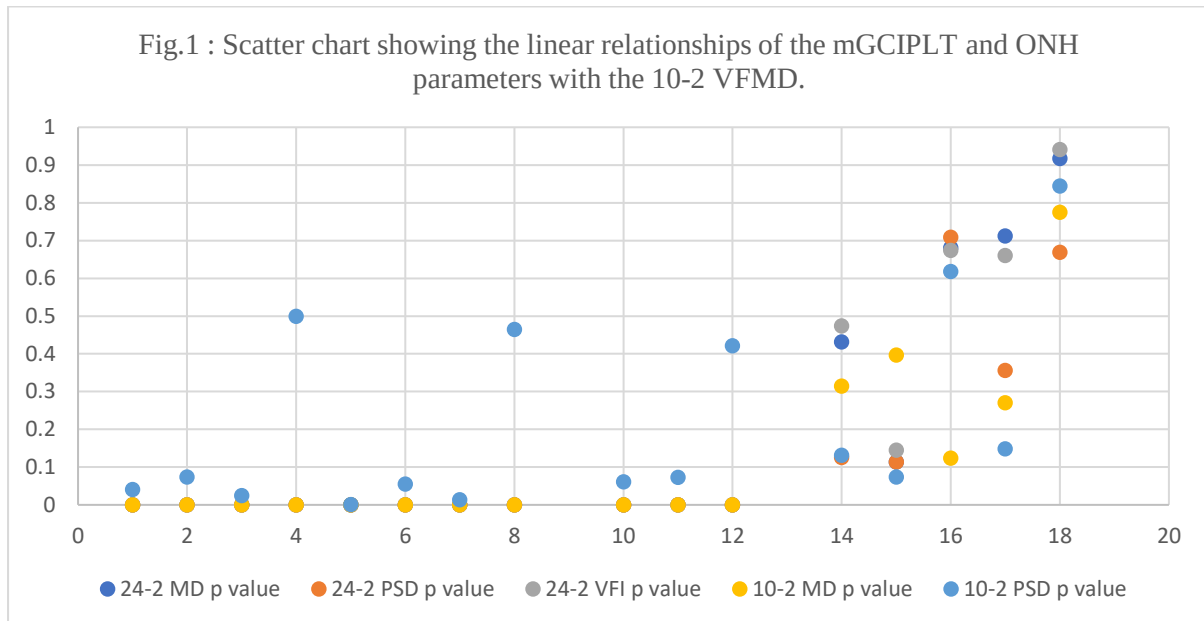


Table 3 presents the results of multivariable linear regressions, adjusted for age and scan quality index, between mGCIPLT, ONH parameters, and 24-2 VF MD and 10-2 VF MD. The regression coefficients (β) for these parameters remained significant after controlling for potential confounders. Specifically, each 1- μ m increase in the average mGCIPLT was associated with a 0.355-dB change in the 24-2 VF MD ($p < 0.001$) and a 0.642-dB change in the 10-2 VF MD ($p < 0.001$) in advanced glaucoma^[1]. Additionally, each 0.1 change in the average C:D ratio corresponded to a 5.414-dB change in the 24-2 VF MD ($p < 0.001$) and a 7.567-dB change in the 10-2 VF MD ($p < 0.001$).

	24-2 MD		10-2 MD	
	β (95% CI)	P value	β (95% CI)	P value
mGCIPLT				
Average	0.356 (0.217–0.492)	<0.001	0.643 (0.467–0.817)	<0.001
Minimum	0.398 (0.250–0.547)	<0.001	0.688 (0.507–0.867)	<0.001
Superior	0.341 (0.210–0.469)	<0.001	0.521 (0.341–0.703)	<0.001
Inferior	0.306 (0.151–0.459)	<0.001	0.585 (0.395–0.773)	<0.001
Superonasal	0.229 (0.124–0.333)	<0.001	0.439 (0.300–0.577)	<0.001
Inferonasal	0.227 (0.107–0.349)	<0.001	0.520 (0.377–0.665)	<0.001
Superotemporal	0.384 (0.258–0.513)	<0.001	0.545 (0.359–0.724)	<0.001
Inferotemporal	0.392 (0.254–0.533)	<0.001	0.654 (0.479–0.831)	<0.001
ONH parameters				
Rim area (mm ²)	19.159(12.989–25.331)	<0.001	32.798 (24.858–40.735)	<0.001
Average C/D	–54.141(–70.959 to –37.321)	<0.001	–75.667 (–100.367 to –50.965)	<0.001
Vertical C/D	–41.788 (–59.348 to –24.229)	<0.001	–55.622 (–80.696 to –30.541)	<0.001

TABLE 3 : Multivariable (adjusted for age and the scan quality index) linear regression results describing the relationships of the mGCIPLT and ONH parameters with VF parameters in advanced glaucoma.

DISCUSSION

Glaucoma is typically characterized by the preservation of central visual acuity until the later stages of the disease. Monitoring disease progression is critical in patients with advanced glaucoma, as they are at heightened risk for complications that can significantly impair vision. However, tracking progression in these patients is challenging, as conventional structural and functional tests become less effective in the advanced stages of the disease.

In our study, we found that the 10-2 VF MD had a significantly stronger association with inferonasal mGCIPLT than did the 24-2 VF MD in eyes with advanced glaucoma and that each 1 μ m change in the average mGCIPLT was associated with an approximately 0.368 dB change in the 24-2 VF MD and 0.677dB change in the 10-2 VF MD suggesting that the 10-2 VF test may be more suitable than the 24-2 VF test for assessing functional damage in advanced glaucoma.

mGCIPLT showed a stronger association with VF MD than cpRNFLT, likely for many reasons. First, the macula, particularly the papillomacular bundle, is more resistant to glaucomatous damage and remains intact until the later stages of the disease. Second, the macula contains about 30% of retinal ganglion cells (RGCs), which contribute to 55-60% of the primary visual cortex, making mGCIPLT less likely to reach measurement limits in advanced glaucoma compared to cpRNFLT. Third, mGCIPLT is measured within the central 24-2 and 10-2 VF regions, while cpRNFLT includes retinal areas outside the VF testing zone, potentially reducing its correlation with VF results. Finally, VF sensitivity changes significantly in advanced glaucoma, making it easier to detect with VF tests. Studies by Kim et al. and Shin et al. have shown significant correlations between mGCIPLT and macular or central VF sensitivity in advanced glaucoma, aligning with our findings on the structure-function relationship in this stage of the disease ^[6].

In advanced glaucoma, changes in ONH parameters, such as rim area and C:D ratio (both average and vertical), were small but statistically significant. Previous studies have shown similar findings, with Kostianeva et al. reporting significant correlations between rim area, C:D ratio, and VF MD in advanced open-angle glaucoma. Lee et al. found that a reduced rim area correlated with worse VF MD and sensitivity in moderate to advanced glaucoma. Our study also confirmed significant associations between rim area, C:D ratio, and VF loss in advanced glaucoma, suggesting continued optic nerve damage and tissue loss at this stage.

The lack of correlation between cpRNFLT and VF sensitivity in advanced glaucoma may be due to the "floor effect," where further thinning of the RNFL no longer results in measurable changes. Additionally, differences in the composition of residual mGCIPLT and cpRNFLT may explain why these structures show varying degrees of sensitivity to damage. Another challenge is the difficulty in comparing precise local measurements of structural and functional changes, as retinal axons originate from multiple regions. Our findings align with earlier studies showing weak structure-function relationships between cpRNFLT and VF parameters in advanced glaucoma, indicating that cpRNFLT may not be ideal for tracking disease progression in these patients ^[1,7].

In eyes with advanced glaucoma, the 10-2 VF MD showed a stronger correlation with inferonasal mGCIPLT compared to the 24-2 VF MD. Specifically, each 1- μ m change in the average mGCIPLT was linked to a 0.368-dB change in the 24-2 VF MD and a 0.677-dB change in the 10-2 VF MD ($R^2 = 0.268$, $p < 0.001$ and $R^2 = 0.385$, $p < 0.001$, respectively). This stronger association with the 10-2 VF may be because, in advanced glaucoma, peripheral VF points often reach a "floor," meaning no further changes can be detected. As a result, changes in central vision are more apparent when measured with the higher resolution of the 10-2 test. Additionally, the 24-2 VF may not sample the macular region sufficiently, leading to underrepresentation of macular sensitivity. Tomairek et al. also noted that the 10-2 VF is valuable for assessing central vision in severe glaucoma cases, especially when there are central defects in the 24-2 VF ^[2,6].

The significant structure-function relationships between mGCIPLT, ONH parameters, and the 24-2 VF VFI are likely because the VFI is less affected by cataracts and gives more weight to

central points, which are crucial for visual function. Regression analysis often uses VFI to predict future VF loss. In our study, moderate and significant correlations were found between mGCIPLT and the central vision thresholds (4 central points) as well as the VFI on the 24-2 VF test, across early to severe stages of glaucoma.

In advanced glaucoma, mGCIPLT and ONH parameters showed moderate, significant positive correlations with the 24-2 VF PSD. This is likely because the PSD, a global measure of VF loss, is less affected by media opacities and may better reflect VF changes in eyes with MD worse than -20 dB. However, the 24-2 VF PSD can be lower or even normal in advanced glaucoma due to the diffuse sensitivity loss, making it less effective at detecting local defects. Mild positive correlations were found between mGCIPLT and the 10-2 VF PSD, but these correlations were less consistent, likely due to irregularities in the 10-2 PSD caused by fluctuations in local VF defects. Overall, neither the 24-2 nor 10-2 VF PSD is ideal for assessing progression in advanced glaucoma^[8].

Several studies have evaluated the structure-function relationship between mGCIPLT and VF sensitivity^[9,10] and we added structural parameters such as ONH parameters, which rendered the structure-function studies more complete and systematic. Studies have re-reported a good correlation between mGCIPLT and central 24--2 VF sensitivity^[9,11], while other studies have reported a good correlation between mGCIPLT and 10--2 VF sensitivity in the relatively early stage of glaucoma^[12].

However, we systematically evaluated and compared the relationships between mGCIPLT, cpRNFLT, and ONH parameters and 24--2 and 10--2 VF parameters in advanced glaucomatous eyes in this study.

LIMITATIONS

The limitations of our study included that this study had a cross-sectional design which instead longitudinal studies had to be used to confirm our findings. Secondly, potential misclassification of the study groups and inaccurate assessment of disease severity based on the MD of perimetry were possible due to the high test-retest variability of the VF test. Thirdly, although the regression model best fit our data, structural parameters did not completely account for the variation observed in functional loss associated with glaucoma. Lastly, statistical indices (the MD and PSD) can sometimes be misleading in advanced glaucoma due to low reliability and low reproducibility in the 24-2 VF test.

CONCLUSION

In conclusion, we found that mGCIPLT and ONH parameters were associated with the severity of VF damage and reflected functional damage better than cpRNFLT in advanced glaucoma. These results suggested that structural measurements of mGCIPLT and ONH parameters and functional measurement of the 10-2 VF may be useful for monitoring progression in advanced glaucoma.

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