• Clinical Research •

Values of macular ganglion cell-inner plexiform layer and 10-2 visual field measurements in detecting and evaluating glaucoma

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Abstract

● **AIM:** To assess the performance of macular ganglion cell-inner plexiform layer thickness (mGCIPLT) and 10-2 visual field (VF) parameters in detecting early glaucoma and evaluating the severity of advanced glaucoma.

● **METHODS:** Totally 127 eyes from 89 participants (36 eyes of 19 healthy participants, 45 eyes of 31 early glaucoma patients and 46 eyes of 39 advanced glaucoma patients) were included. The relationships between the optical coherence tomography (OCT)-derived parameters and VF sensitivity were determined. Patients with early glaucoma were divided into eyes with or without central 10° of the VF damages (CVFDs), and the diagnostic performances of OCT-derived parameters were assessed.

● **RESULTS:** In early glaucoma, the mGCIPLT was significantly correlated with 10-2 VF pattern standard deviation (PSD; with average mGCIPLT: β=-0.046, 95%CI, -0.067 to -0.024, P<0.001). In advanced glaucoma, the mGCIPLT was related to the 24-2 VF mean deviation (MD; with average mGCIPLT: β=0.397, 95%CI, 0.199 to 0.595, P<0.001), 10-2 VF MD (with average mGCIPLT: β=0.762, 95%CI, 0.485 to 1.038, P<0.001) and 24-2 VF PSD (with average mGCIPLT: β=0.244, 95%CI, 0.124 to 0.364, P<0.001). Except for the minimum and superotemporal mGCIPLT, the decrease of mGCIPLT in early glaucomatous eyes with CVFDs was more severe than that of early glaucomatous eyes without CVFDs. The area under the curve (AUC) of the average mGCIPLT (AUC=0.949, 95%CI, 0.868 to 0.982) was greater than that of the average circumpapillary retinal nerve fiber layer thickness (cpRNFLT; AUC=0.827, 95%CI, 0.674 to 0.918) and rim area (AUC=0.799, 95%CI, 0.610 to 0.907) in early glaucomatous eyes with CVFDs versus normal eyes.

● **CONCLUSION:** The 10-2 VF and mGCIPLT parameters are complementary to 24-2 VF, cpRNFLT and ONH parameters, especially in detecting early glaucoma with CVFDs and evaluating the severity of advanced glaucoma in group level.

● **KEYWORDS:** 10-2 visual field; ganglion cell-inner plexiform layer; retinal nerve fiber layer thickness; glaucoma
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INTRODUCTION

Glaucoma is a group of diseases characterized by the progressive death of retinal ganglion cells and characteristic visual field (VF) defects[1]. There were convincing evidences that macular damage of glaucoma occurs even in the early stages and continues to the late stages[2-4].

In clinical practice, 24-2 VF test has been widely used to evaluate visual function of glaucoma patients[5]. It was shown that VF damage within the center 10° missed by 24-2 VF test could be found by 10-2 VF test[3]. The reason could be that 24-2 VF test are spaced every 6° and only 12 points located in the central 10° of the VF[6-7]. However, the abnormalities that exist outside the central 10° of the VF could not be detected by 10-2 VF test[3]. The mean deviation (MD) change of 10-2

VF was significantly larger than that of 24-2 VF in advanced glaucoma[8]. Considering that central vision usually remains in the late stage of glaucoma, the 10-2 VF test was helpful for evaluating the remaining vision of patients with severe central VF damage on the 24-2 VF test[9].

Optical coherence tomography (OCT) is a common objective tool to detect structural changes in glaucoma. Many studies confirmed that the diagnosis abilities of macular ganglion cell-inner plexiform layer thickness (mGCIPLT) were similar to the optic nerve head (ONH) parameters and circumpapillary retinal nerve fiber layer thickness (cpRNFLT) in glaucoma with varying degrees of severity[2,10-11]. The mGCIPLT was more valuable for detecting early glaucoma with parafoveal scotoma, while the cpRNFLT was better for detecting early glaucoma with peripheral nasal step[12]. However, cpRNFLT has the smallest actual measured value in advanced glaucoma, which limits its effectiveness in detecting the progression of glaucoma[13]. The change rate of cpRNFLT was not significant, but that of ONH parameters and mGCIPLT was significant in advanced glaucoma[14]. Our previous study demonstrated that the ONH parameters and mGCIPLT were significantly correlated with VF parameters in advanced glaucoma, while cpRNFLT was not[15].

Since glaucoma affects retinal ganglion cells and their axons, mGCIPLT and 10-2 VF measurement would be helpful for estimating macular damage of glaucoma. However, evaluating all patients using both the 24-2 and 10-2 VF test or optic disc and macular scanning is time-consuming and costly. Therefore, determining whether 10-2 VF test and macular scanning with OCT are required for a particular glaucoma patient is important. Therefore, we assessed the associations between OCT-derived parameters and VF sensitivity in early and advanced glaucoma in our study. Patients with early glaucoma were divided into eyes with or without central 10° of the VF damages (CVFDs), and the diagnostic performances of OCT-derived parameters were evaluated in early glaucomatous eyes with CVFDs versus normal eyes.

SUBJECTS AND METHODS

Ethical Approval The retrospective study was conducted at the Affiliated Eye Hospital of Nanchang University (Jiangxi Province, China) from November 2017 to December 2022. The study was approved by the Ethics Committee of our hospital (IRB number: YLP201710011) and carried out according to the Declaration of Helsinki. All participants obtained informed consent.

Subjects All participants underwent a comprehensive eye examination, including a detailed medical history evaluation, best-corrected visual acuity measurement, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement by Goldmann applanation tonometry, fundoscopy examination, 24-2 and 10-2 VF testing, and OCT imaging for the measurement of ONH parameters, mGCIPLT and cpRNFLT. The IOP of all participants was measured at our hospital for the first visit. All glaucoma patients had their IOP controlled within the normal range before VF testing and OCT imaging.

Inclusion criteria were age ≥18y, refractive error of -6.0 to +3.0 diopters sphere and ±3 diopters cylinder and best-corrected visual acuity of at least 20/50. Exclusion criteria included non-glaucomatous optic neuropathy; neurologic diseases (*i.e.*, Alzheimer's disease, Parkinson's disease), retinal diseases (*i.e.*, diabetic retinopathy, hypertensive retinopathy), and other diseases that could affect the OCT and VF.

Healthy subjects were required to include normal optic disc morphology, reliable normal VF testing, and IOP≤21 mm Hg[2]. Glaucomatous patients have glaucomatous optic neuropathy (*i.e.*, notching of the neuroretinal rim, focal thinning, retinal nerve fiber layer defect or optic disc hemorrhage), accompanied by glaucomatous VF defects[12]. Based on the Hodapp-Parrish-Anderson criteria, glaucoma can be divided into three different degrees of severity: advanced glaucoma (MD<-12.00 dB), moderate glaucoma (-12.00≤MD<-6.00 dB) and early glaucoma (MD≥-6.00 dB)[16]. Considering the relatively difficult diagnosis of early glaucoma and follow-up of advanced glaucoma, early and advanced glaucoma were included in our study.

Visual Field Testing All participants were examined with the Humphrey Field Analyzer (720i, Carl Zeiss Meditec, Dublin, CA, USA). Before the formal test, all participants were trained in VF test to obtain reliable results. After refractive correction, the Swedish interactive thresholding algorithm strategy with a Goldmann size III target was used for 24-2 and 10-2 VF testing. 24-2 and 10-2 VF testing were randomly assigned, and the interval between the two examinations on the same day was at least 20min. Reliable VF examinations of early glaucoma were considered to be a false negative error <15%, a false-positive error <15%, and a fixation loss <20%[12], while the reliable VF examinations of advanced glaucoma were considered to be a false negative error, a false-positive error, and a fixation loss <33%[15]. VF testing with signs of evidence of inattention or fatigue effects or eyelid artifacts was excluded.

Visual Field Criteria for Early Glaucomatous Eyes with or Without CVFDs The classification method for early glaucoma was similar to previous studies[17-18]. Patients with early glaucoma were divided into eyes with or without CVFDs. The early glaucomatous eyes with CVFDs group were defined as a cluster consisting of at least three adjacent points (P<5%, 2%, and 2%; P<5%, 5%, and 1%; or worse) within a hemifield of the central 10°, regardless of whether glaucomatous VF damage exists outside the central 10° on 24-2 VF pattern

deviation probability map. The early glaucomatous eyes without CVFDs group were defined as glaucomatous VF defects located outside the central 10°, and there was no abnormality within the central 10°.

OCT Imaging All participants were examined with Cirrus HD-OCT (5000, Carl Zeiss Meditec, Dublin, CA, USA). Macular (macular cube 512×128 protocol) scan and optic disc (optic disc cube 200×200 protocol) scan were obtained on the same day. The ONH parameters and cpRNFLT were derived from the optic disc scan, while the mGCIPLT was derived from the macular scan. Scans were excluded if the signal strength was <7, motion and blinking artifacts or segmentation failure.

Statistical Analysis SPSS version 24.0 (SPSS, Chicago, IL, USA) and MedCalc version 20.0.22 (MedCalc Software bvba, Mariakerke, Belgium) were applied to the analyses. Mean±standard deviation (SD) was used for normally distributed variables. The one-way analysis of variance followed by Tukey's post hoc test was used for the comparison of the variables among three or more groups, while independent Student's *t*-test was used for the comparison of the variables between two groups. The differences in gender distribution were assessed by the Chi-square test. To compare the ocular parameters among the groups, generalized estimating equation (GEE) models were applied to adjust within-patient and intereye correlations[19]. Univariable linear regression models with GEE method were applied to assess the associations of the OCT-derived parameters with VF sensitivity.

The area under the curve (AUC) values of the receiver operating characteristic (ROC) were measured to assess the discriminating ability of OCT-derived parameters. The ophthalmic parameters of both eyes of the same participant may be related, and standard statistical methods may contribute to narrow confidence intervals (CI) and underestimation of standard error. The cluster of data for the participant was regarded as the unit of resampling, and bias-corrected standard error was assessed[20]. DeLong *et al*[21] methods were applied to compare the AUC values of different groups. Sensitivities at fixed specificities of 90% and 95% were calculated. $P<0.05$ was regarded as statistically significant.

RESULTS

Participants' Characteristics Totally 127 eyes from 89 participants (36 eyes of 19 healthy participants, 45 eyes of 31 early glaucoma patients and 46 eyes of 39 advanced glaucoma patients) were included in our study. The participants' characteristics were displayed in Table 1. The differences in age, spherical equivalent (SE) and gender among the groups were not significant. However, the IOP of early and advanced glaucoma patients was significantly higher than that of the healthy participants (all $P<0.001$). There were significant differences in all ONH parameters, mGCIPLT and cpRNFLT except for the nasal cpRNFLT among the groups. The optic disc area of the advanced glaucoma group was larger than that of the early glaucoma and healthy participants group. However, there was no significant difference in optic disc area between the early glaucoma and healthy participants groups. The cpRNFLT and mGCIPLT significantly decreased as the severity of glaucoma increased. Advanced glaucoma eyes had a significantly thinner average mGCIPLT and cpRNFLT when compared with early glaucoma eyes (58.50 *vs* 78.24 μm, $P<0.001$, and 64.96 *vs* 91.44 μm, $P<0.001$, respectively).

Associations of the OCT-derived Parameters with VF Sensitivity in Early Glaucoma Table 2 showed the associations of OCT-derived parameters with VF sensitivity in early glaucoma using univariable linear regression analysis with GEE method. The mGCIPLT was significantly related to 10-2 VF pattern standard deviation (PSD), while the superior, inferior and average cpRNFLT, and superotemporal mGCIPLT were significantly related to 24-2 VF PSD. In early glaucoma, a thinning of 1 μm in average mGCIPLT was related to a reduction of 0.046 dB change in the 10-2 VF PSD ($P<0.001$), a thinning of 1 μm in average cpRNFLT was related to a reduction of 0.035 dB change in the 24-2 VF PSD ($P=0.006$). The ONH parameters were not significantly related to VF sensitivity in early glaucoma.

Associations of the OCT-derived Parameters with VF Sensitivity in Advanced Glaucoma Table 3 showed the associations of OCT-derived parameters with VF sensitivity in advanced glaucoma using univariable linear regression analysis with GEE method. The ONH parameters and mGCIPLT were significantly associated with the 24-2 VF MD, 24-2 VF PSD and 10-2 VF MD ($P<0.001$), while the cpRNFLT were not. In advanced glaucoma, a thinning of 1 μm in average mGCIPLT was related to a reduction of 0.397 dB in 24-2 VF MD ($P<0.001$) and a reduction of 0.762 dB in 10-2 VF MD ($P<0.001$).

Comparison of OCT-derived Parameters and VF Sensitivity Between the Early Glaucomatous Eyes with CVFDs and Without CVFDs Patients with early glaucoma were divided into eyes with or without CVFDs, and the OCT-derived parameters and VF sensitivity between the two groups were compared. There were no significant differences in age, SE, gender and IOP between the early glaucomatous eyes with CVFDs and without CVFDs (Table 4). However, except for the minimum and superotemporal mGCIPLT, the decrease of global and sector mGCIPLT in early glaucomatous eyes with CVFDs was more severe than those of early glaucomatous eyes without CVFDs, while VF damage and cpRNFLT defect were similar between the early glaucomatous eyes with CVFDs and without CVFDs.

Table 1 Characteristics of participants included in the study

Parameters	Healthy participants (*n*=36 eyes)	Early glaucoma (*n*=45 eyes)	Advanced glaucoma (*n*=46 eyes)	P^1	P^2	P^3	P^4
Age (y)	42.32±15.38	47.52±16.37	49.41±9.70	0.180[a]	0.391[a]	0.155[a]	0.831[a]
Gender (M/F)	12/7	19/12	21/18	0.735[b]	0.895[b]	0.502[b]	0.532[b]
IOP (mm Hg)	14.98±2.69	20.04±5.34	28.98±12.49	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
SE (D)	-1.34±1.77	-1.69±1.76	-1.68±1.28	0.736[c]	0.487[c]	0.450[c]	0.978[c]
VF parameters (dB)							
24-2 VF MD	-2.42±1.34	-3.12±1.46	-26.46±6.34	<0.001[c]	0.046[c]	<0.001[c]	<0.001[c]
24-2 VF PSD	1.60±0.77	2.21±1.18	6.96±3.86	<0.001[c]	0.009[c]	<0.001[c]	<0.001[c]
10-2 VF MD	-2.17±0.99	-2.67±1.26	-21.63±9.87	<0.001[c]	0.080[c]	<0.001[c]	<0.001[c]
10-2 VF PSD	1.16±0.18	1.41±0.63	8.32±4.69	<0.001[c]	0.049[c]	<0.001[c]	<0.001[c]
mGCIPLT (μm)							
Average	86.17±3.76	78.24±7.50	58.50±8.31	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Minimum	83.47±4.04	73.27±10.87	48.59±6.78	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Superior	87.86±4.17	79.02±9.08	60.09±9.67	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Inferior	84.11±4.97	75.87±7.77	58.37±7.47	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Superonasal	89.31±3.88	81.98±9.21	61.89±12.30	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Inferonasal	86.83±4.02	78.84±7.51	60.33±10.30	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Superotemporal	84.64±4.06	77.07±8.20	55.78±8.77	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Inferotemporal	84.78±4.81	76.96±8.32	54.46±6.73	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
ONH parameters							
Rim area (mm^2)	1.32±0.15	1.12±0.23	0.56±0.18	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Optic disc area (mm^2)	1.89±0.51	1.97±0.44	2.16±0.37	0.033[c]	0.537[c]	0.029[c]	0.049[c]
Average C/D ratio	0.45±0.22	0.63±0.12	0.85±0.07	<0.001[c]	0.001[c]	<0.001[c]	<0.001[c]
Vertical C/D ratio	0.43±0.22	0.59±0.12	0.84±0.08	<0.001[c]	0.002[c]	<0.001[c]	<0.001[c]
cpRNFLT (μm)							
Average	102.28±8.30	91.44±13.70	64.96±9.19	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Superior	129.14±13.08	112.22±23.01	74.24±12.82	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Inferior	129.92±15.26	113.82±21.63	68.02±12.90	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Nasal	67.42±9.35	66.42±10.49	65.13±8.59	0.613[c]	0.707[c]	0.341[c]	0.559[c]
Temporal	82.69±17.55	73.04±19.28	52.78±11.73	<0.001[c]	0.060[c]	<0.001[c]	<0.001[c]

P^1: Comparison among early glaucoma, advanced glaucoma and healthy participants groups; P^2: Comparing early glaucoma and healthy participants groups; P^3: Comparing advanced glaucoma and healthy participants groups; P^4: Comparing early glaucoma and advanced glaucoma groups. M: Male; F: Female; IOP: Intraocular pressure; SE: Spherical equivalent; VF: Visual field; MD: Mean deviation; PSD: Pattern standard deviation; dB: Decibels; mGCIPLT: Macular ganglion cell-inner plexiform layer thickness; ONH: Optic nerve head; C/D ratio: Cup-to-disc ratio; cpRNFLT: Circumpapillary retinal nerve fiber layer thickness. [a]Comparison by one-way analysis of variance analysis; [b]Comparison by Chi-square test; [c]Comparison by GEE method.

Diagnostic Ability of OCT-derived Parameters in Early Glaucomatous Eyes with CVFDs Versus Normal Eyes The AUC and sensitivity at fixed specificity of the mGCIPLT, cpRNFLT and ONH parameters to distinguish early glaucomatous eyes with CVFDs from normal eyes were shown in Table 5. Among the mGCIPLT, the average mGCIPLT had the largest AUC (0.949, P<0.001). Among the ONH parameters and cpRNFLT, the average cpRNFLT and rim area had the largest AUC (0.827, P<0.001; 0.799, P<0.001, respectively). In early glaucomatous eyes with CVFDs, the AUC of the average mGCIPLT was greater than that of the average cpRNFLT and rim area (P=0.032 and 0.026, respectively). At 90% specificity, average and inferior mGCIPLT had the highest sensitivity (all 81.36%) among the mGCIPLT, and inferior cpRNFLT and rim area had the highest sensitivity (67.27% and 57.27%, respectively) among the cpRNFLT and ONH parameters. Figure 1 shows the ROC curves for the best discriminating ability of mGCIPLT, cpRNFLT and ONH parameters in early glaucomatous eyes with CVFDs versus normal eyes.

Representative Cases As shown in Figure 2, a representative case of an early glaucomatous eye (Figure 2A-2H) showed that the abnormality in the central 10° on the 24-2 VF test (Figure 2B) received a more detailed evaluation by the 10-2 VF test (Figure 2F). The superior and inferior cpRNFLT were outside

Table 2 Univariable linear regression analysis with GEE method describing the relationships of the OCT-derived parameters with VF sensitivity in early glaucoma

OCT-derived parameters	24-2 MD glaucoma		24-2 PSD glaucoma		10-2 MD glaucoma		10-2 PSD glaucoma	
	β (95%CI)	*P*	β (95%CI)	*P*	β (95%CI)	*P*	β (95%CI)	*P*
mGCIPLT (μm)								
Average	0.024 (-0.036 to 0.083)	0.426	-0.036 (-0.083 to 0.011)	0.126	0.031 (-0.020 to 0.082)	0.230	-0.046 (-0.067 to -0.024)	<0.001
Minimum	0.035 (-0.005 to 0.075)	0.087	-0.028 (-0.060 to 0.004)	0.089	0.030 (-0.004 to 0.065)	0.086	-0.028 (-0.044 to -0.013)	0.001
Superior	0.012 (-0.037 to 0.061)	0.630	-0.033 (-0.072 to 0.005)	0.088	0.009 (-0.034 to 0.052)	0.676	-0.039 (-0.057 to -0.022)	<0.001
Inferior	0.028 (-0.030 to 0.085)	0.336	-0.023 (-0.069 to 0.024)	0.330	0.040 (-0.009 to 0.088)	0.105	-0.027 (-0.051 to -0.003)	0.027
Superonasal	0.002 (-0.047 to 0.051)	0.936	-0.025 (-0.063 to 0.014)	0.201	0.013 (-0.029 to 0.054)	0.551	-0.036 (-0.054 to -0.019)	<0.001
Inferonasal	0.018 (-0.042 to 0.077)	0.546	-0.014 (-0.062 to 0.034)	0.564	0.039 (-0.012 to 0.089)	0.128	-0.039 (-0.062 to -0.016)	0.001
Superotemporal	0.034 (-0.019 to 0.088)	0.205	-0.048 (-0.089 to -0.006)	0.026	0.018 (-0.029 to 0.065)	0.433	-0.047 (-0.066 to -0.028)	<0.001
Inferotemporal	0.037 (-0.016 to 0.090)	0.162	-0.039 (-0.081 to 0.003)	0.066	0.045 (0.000 to 0.089)	0.050	-0.029 (-0.051 to -0.007)	0.010
ONH parameters								
Rim area (mm^2)	0.272 (-1.714 to 2.259)	0.783	-0.914 (-2.494 to 0.666)	0.250	-0.790 (-2.491 to 0.912)	0.355	0.124 (-0.738 to 0.987)	0.773
Average C/D ratio	0.254 (-3.569 to 4.077)	0.894	-0.670 (-3.750 to 2.410)	0.663	-0.305 (-3.610 to 3.000)	0.853	-1.113 (-2.739 to 0.512)	0.174
Vertical C/D ratio	-0.392 (-4.027 to 3.243)	0.829	-0.135 (-3.071 to 2.800)	0.926	-0.292 (-3.435 to 2.851)	0.852	-0.732 (-2.296 to 0.831)	0.350
cpRNFLT (μm)								
Average	0.011 (-0.021 to 0.044)	0.492	-0.035 (-0.059 to -0.010)	0.006	-0.007 (-0.035 to 0.021)	0.625	-0.006 (-0.020 to 0.008)	0.372
Superior	0.009 (-0.010 to 0.028)	0.355	-0.018 (-0.032 to -0.003)	0.020	-0.007 (-0.023 to 0.010)	0.419	-0.003 (-0.012 to 0.005)	0.408
Inferior	0.010 (-0.010 to 0.031)	0.317	-0.027 (-0.041 to -0.012)	0.001	-0.007 (-0.025 to 0.011)	0.446	-0.002 (-0.011 to 0.007)	0.676
Nasal	0.009 (-0.034 to 0.052)	0.677	-0.012 (-0.046 to 0.023)	0.496	-0.007 (-0.043 to 0.030)	0.723	-0.009 (-0.027 to 0.010)	0.347
Temporal	-0.005 (-0.028 to 0.019)	0.685	-0.008 (-0.026 to 0.011)	0.407	0.007 (-0.013 to 0.027)	0.490	-0.003 (-0.013 to 0.007)	0.517

VF: Visual field; MD: Mean deviation; PSD: Pattern standard deviation; mGCIPLT: Macular ganglion cell-inner plexiform layer thickness; ONH: Optic nerve head; C/D ratio: Cup-to-disc ratio; cpRNFLT: Circumpapillary retinal nerve fiber layer thickness; CI: Confidence interval; OCT: Optical coherence tomography.

Table 3 Univariable linear regression analysis with GEE method describing the relationships of the OCT-derived parameters with VF sensitivity in advanced glaucoma

OCT-derived parameters	24-2 MD glaucoma		24-2 PSD glaucoma		10-2 MD glaucoma		10-2 PSD glaucoma	
	β (95%CI)	*P*	β (95%CI)	*P*	β (95%CI)	*P*	β (95%CI)	*P*
mGCIPLT (μm)								
Average	0.397 (0.199 to 0.595)	<0.001	0.244 (0.124 to 0.364)	<0.001	0.762 (0.485 to 1.038)	<0.001	0.091 (-0.078 to 0.260)	0.284
Minimum	0.463 (0.216 to 0.710)	<0.001	0.272 (0.120 to 0.424)	0.001	0.879 (0.527 to 1.232)	<0.001	0.058 (-0.152 to 0.267)	0.581
Superior	0.359 (0.193 to 0.526)	<0.001	0.193 (0.087 to 0.299)	0.001	0.529 (0.264 to 0.794)	<0.001	0.100 (-0.044 to 0.244)	0.168
Inferior	0.304 (0.063 to 0.545)	0.015	0.201 (0.057 to 0.346)	0.007	0.741 (0.409 to 1.073)	<0.001	-0.001 (-0.191 to 0.190)	0.994
Superonasal	0.257 (0.121 to 0.392)	<0.001	0.171 (0.091 to 0.251)	<0.001	0.476 (0.28 to 0.672)	<0.001	0.122 (0.013 to 0.232)	0.030
Inferonasal	0.242 (0.070 to 0.414)	0.007	0.174 (0.073 to 0.275)	0.001	0.586 (0.356 to 0.816)	<0.001	0.079 (-0.057 to 0.215)	0.249
Superotemporal	0.444 (0.271 to 0.618)	<0.001	0.252 (0.142 to 0.362)	<0.001	0.599 (0.310 to 0.888)	<0.001	0.113 (-0.046 to 0.271)	0.160
Inferotemporal	0.310 (0.040 to 0.581)	0.025	0.188 (0.024 to 0.353)	0.026	0.801 (0.428 to 1.174)	<0.001	-0.04 (-0.251 to 0.171)	0.703
ONH parameters								
Rim area (mm^2)	19.921 (11.166 to 28.676)	<0.001	12.365 (7.088 to 17.642)	<0.001	37.616 (25.637 to 49.594)	<0.001	6.15 (-1.492 to 13.791)	0.112
Average C/D ratio	-52.756 (-73.809 to -31.702)	<0.001	-30.829 (-43.928 to -17.730)	<0.001	-85.396 (-117.349 to -53.443)	<0.001	-10.975 (-30.246 to 8.297)	0.257
Vertical C/D ratio	-33.152 (-54.474 to -11.83)	0.003	-20.194 (-33.167 to -7.220)	0.003	-62.842 (-94.163 to -31.521)	<0.001	-1.26 (-18.685 to 16.165)	0.885
cpRNFLT (μm)								
Average	-0.025 (-0.235 to 0.185)	0.811	0.008 (-0.12 to 0.135)	0.904	-0.003 (-0.329 to 0.323)	0.984	0.027 (-0.128 to 0.181)	0.731
Superior	0.067 (-0.082 to 0.216)	0.371	0.084 (-0.003 to 0.172)	0.059	0.028 (-0.206 to 0.262)	0.810	0.101 (-0.006 to 0.208)	0.063
Inferior	-0.133 (-0.277 to 0.011)	0.070	-0.069 (-0.158 to 0.019)	0.121	-0.074 (-0.305 to 0.158)	0.525	-0.015 (-0.126 to 0.095)	0.781
Nasal	0.043 (-0.181 to 0.267)	0.699	0.038 (-0.098 to 0.174)	0.578	0.197 (-0.147 to 0.541)	0.254	-0.005 (-0.171 to 0.161)	0.953
Temporal	-0.028 (-0.192 to 0.137)	0.737	-0.039 (-0.138 to 0.06)	0.431	-0.103 (-0.357 to 0.15)	0.416	-0.046 (-0.167 to 0.074)	0.443

VF: Visual field; MD: Mean deviation; PSD: Pattern standard deviation; mGCIPLT: Macular ganglion cell-inner plexiform layer thickness; ONH: Optic nerve head; C/D ratio: Cup-to-disc ratio; cpRNFLT: Circumpapillary retinal nerve fiber layer thickness; CI: Confidence interval; OCT: Optical coherence tomography.

Table 4 Comparison of OCT-derived parameters and VF sensitivity between the early glaucomatous eyes with and without CVFDs

Parameters	With CVFDs (*n*=22 eyes)	Without CVFDs (*n*=23 eyes)	*P*
Age (y)	47.88±19.84	44.47±16.25	0.581[a]
Gender (M/F)	9/7	10/5	0.716[b]
IOP (mm Hg)	21.33±6.12	18.80±4.25	0.127[c]
SE (D)	-1.74±1.49	-1.64±2.01	0.865[c]
VF parameters (dB)			
24-2 VF MD	-3.46±1.52	-2.79±1.35	0.154[c]
24-2 VF PSD	2.42±1.29	2.01±1.05	0.307[c]
10-2 VF MD	-2.89±1.25	-2.45±1.26	0.269[c]
10-2 VF PSD	1.54±0.86	1.29±0.26	0.298[c]
mGCIPLT (μm)			
Average	75.45±7.41	80.91±6.69	0.022[c]
Minimum	70.36±10.13	76.04±11.05	0.101[c]
Superior	75.68±10.05	82.22±6.83	0.036[c]
Inferior	73.09±6.83	78.52±7.81	0.018[c]
Superonasal	78.59±9.87	85.22±7.35	0.026[c]
Inferonasal	76.27±8.01	81.30±6.22	0.019[c]
Superotemporal	75.18±9.20	78.87±6.83	0.218[c]
Inferotemporal	73.82±7.53	79.96±8.06	0.012[c]
ONH parameters			
Rim area (mm^2)	1.12±0.26	1.12±0.19	0.930[c]
Average C/D ratio	0.65±0.11	0.62±0.13	0.373[c]
Vertical C/D ratio	0.61±0.10	0.57±0.14	0.294[c]
cpRNFLT (μm)			
Average	87.82±15.70	94.91±10.69	0.083[c]
Superior	107.5±23.57	116.74±22.02	0.151[c]
Inferior	107.91±25.72	119.48±15.36	0.069[c]
Nasal	66.23±9.53	66.61±11.54	0.905[c]
Temporal	69.45±22.95	76.48±14.67	0.228[c]

M: Male; F: Female; IOP: Intraocular pressure; SE: Spherical equivalent; VF: Visual field; MD: Mean deviation; PSD: Pattern standard deviation; dB: Decibels; mGCIPLT: Macular ganglion cell-inner plexiform layer thickness; ONH: Optic nerve head; C/D ratio: Cup-to-disc ratio; cpRNFLT: Circumpapillary retinal nerve fiber layer thickness. [a]Comparison by independent Student's *t*-test; [b]Comparison by Chi-square test; [c]Comparison by GEE method.

the normal limits and temporal cpRNFLT were borderline in the sector map (Figure 2D). The superonasal, superior and superotemporal mGCIPLT were outside the normal limits and inferotemporal mGCIPLT were borderline in the sector map (Figure 2H). Another case of an advanced glaucomatous eye (Figure 2I-2P) with central VF damage showed more details of VF defects on the 10-2 VF test (Figure 2N) than on the 24-2 VF test (Figure 2J). The superior and inferior cpRNFLT appeared as abnormal (Figure 2L), while all mGCIPLTs (Figure 2P) appeared as abnormal in the sector map. However, in the thickness map, the remaining variable thickness of mGCIPLT (Figure 2O) was greater than that of cpRNFLT (Figure 2K).

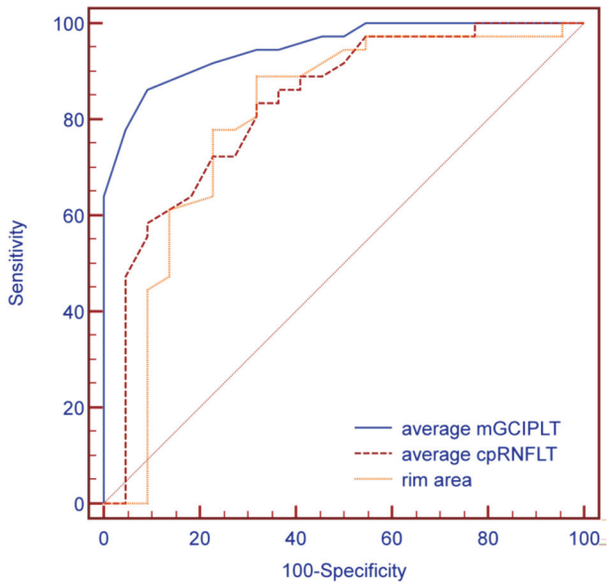

Figure 1 ROC curves for discriminating performance of best mGCIPLT, cpRNFLT and ONH parameters in early glaucomatous eyes with CVFDs versus normal eyes CVFDs: Central 10° of the VF damages; ROC: Receiver operating characteristic; mGCIPLT: Macular ganglion cell-inner plexiform layer thickness; cpRNFLT: Circumpapillary retinal nerve fiber layer thickness; ONH: Optic nerve head.

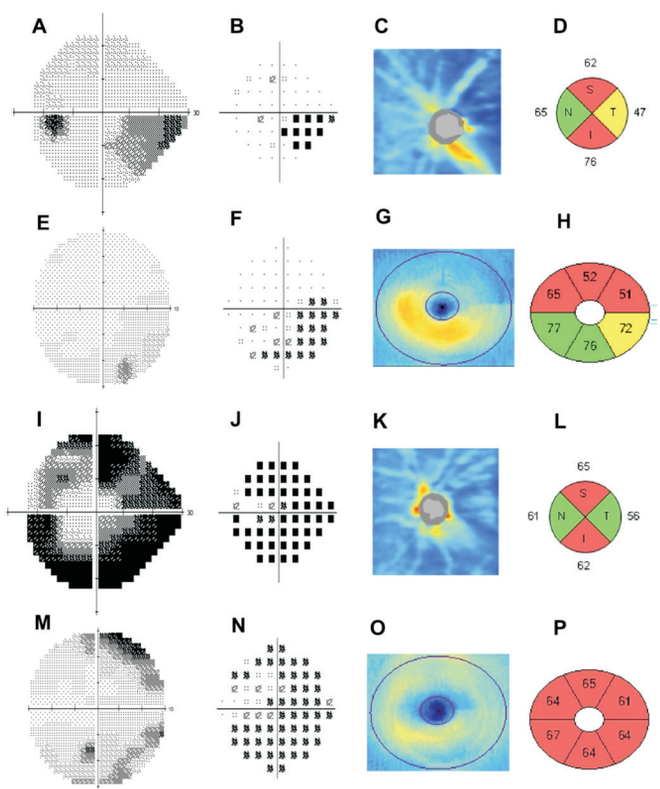

Figure 2 Cases of early glaucoma (A-H) and advanced glaucoma (I-P) A, I: The 24-2 VF gray scale printout diagram; B: The 24-2 VF pattern deviation probability plot; C, K: cpRNFLT map; D, L: cpRNFLT in 4 sectors; E, M: The 10-2 VF gray scale printout diagram; F: The 10-2 VF pattern deviation probability plot; G, O: mGCIPLT map; H, P: mGCIPLT in 6 sectors; J: The 24-2 VF total deviation probability plot; N: The 10-2 VF total deviation probability plot. VF: Visual field; cpRNFLT: Circumpapillary retinal nerve fiber layer thickness; mGCIPLT: Macular ganglion cell-inner plexiform layer thickness.

Table 5 The AUC and sensitivity at fixed specificities of OCT-derived parameters in early glaucomatous eyes with CVFDs versus normal eyes

Parameters	AUC (95%CI)	*P*	Sensitivity at 90% specificity (95%CI), %	Sensitivity at 95% specificity (95%CI), %
mGCIPLT (μm)				
Average	0.949 (0.868 to 0.982)	<0.001	81.36 (43.66 to 97.27)	61.82 (24.66 to 89.09)
Minimum	0.925 (0.822 to 0.975)	<0.001	82.12 (36.36 to 95.45)	50.00 (18.18 to 79.09)
Superior	0.910 (0.804 to 0.961)	<0.001	72.73 (50.00 to 86.36)	70.91 (44.88 to 89.96)
Inferior	0.929 (0.826 to 0.976)	<0.001	81.36 (31.82 to 99.14)	50.00 (10.77 to 85.45)
Superonasal	0.887 (0.765 to 0.952)	<0.001	68.73 (47.62 to 86.36)	68.18 (45.45 to 86.36)
Inferonasal	0.927 (0.837 to 0.971)	<0.001	73.64 (45.45 to 93.64)	59.09 (31.52 to 80.00)
Superotemporal	0.889 (0.779 to 0.955)	<0.001	77.27 (53.64 to 95.45)	61.82 (13.18 to 86.36)
Inferotemporal	0.902 (0.794 to 0.956)	<0.001	66.06 (36.36 to 85.91)	53.64 (13.64 to 77.27)
ONH parameters				
Rim area (mm^2)	0.799 (0.610 to 0.907)	<0.001	57.27 (9.09 to 77.27)	45.45 (4.55 to 72.27)
Average C/D ratio	0.761 (0.620 to 0.873)	<0.001	35.45 (9.09 to 59.06)	30.91 (0.00 to 58.18)
Vertical C/D ratio	0.746 (0.597 to 0.855)	<0.001	31.82 (2.73 to 57.59)	8.18 (0.00 to 36.36)
cpRNFLT (μm)				
Average	0.827 (0.674 to 0.918)	<0.001	52.73 (22.73 to 74.55)	47.27 (13.64 to 72.73)
Superior	0.806 (0.650 to 0.907)	<0.001	36.36 (5.23 to 77.27)	29.09 (11.57 to 68.29)
Inferior	0.793 (0.625 to 0.905)	<0.001	67.27 (22.73 to 86.36)	31.82 (4.55 to 74.14)
Nasal	0.511 (0.354 to 0.651)	0.883	4.55 (0.00 to 21.19)	4.55 (0.00 to 13.64)
Temporal	0.748 (0.563 to 0.871)	<0.001	46.36 (22.27 to 72.73)	39.09 (17.90 to 60.39)

CVFDs: Central 10° of the VF damages; mGCIPLT: Macular ganglion cell-inner plexiform layer thickness; ONH: Optic nerve head; C/D ratio: Cup-to-disc ratio; cpRNFLT: Circumpapillary retinal nerve fiber layer thickness; AUC: Area under the curve; CI: Confidence interval; OCT: Optical coherence tomography.

DISCUSSION

Glaucoma affects retinal ganglion cells and their axons, and is considered as a disease in which central VF can damage in early glaucoma and is relatively well preserved in advanced glaucoma[3-4]. There were significant differences in all ONH parameters, mGCIPLT and cpRNFLT except for the nasal cpRNFLT among the groups. The optic disc area of the advanced glaucoma group was larger than that of the early glaucoma and healthy participants group. However, there was no significant difference in optic disc area between the early glaucoma and healthy participants groups. These results are similar to those of a previous study comparing optic disc area in glaucoma patients with different severity[22]. In our study, the cpRNFLT and mGCIPLT were significantly decreased as the severity of glaucoma increased. Our findings are similar to previous studies, which demonstrated that mGCIPLT and cpRNFLT decreased as the glaucoma severity increased[2,23-24].

The mGCIPLT were significantly associated with 10-2 VF PSD, while the superior, inferior and average cpRNFLT, and superotemporal mGCIPLT were significantly correlated with 24-2 VF PSD. The findings were explained as follows: First, it is likely due to the macular damage occurs even in early glaucoma, and the damage is related to central VF sensitivity loss[25]. Second, glaucomatous damages were mainly located in the inferior or superior temporal cpRNFL in the early stage of the disease[26]. Third, this result was observed because mGCIPLT is measured in the macula falling within the 10-2 VF, while the cpRNFL is distributed in the entire retina[27]. Finally, the PSD is more sensitive in early glaucoma, because it is a global measurement for quantifying VF loss and highlighting local VF defects. Lee *et al*[28] reported that there were significant associations were found between 10-2 VF loss and mGCIPLT in early glaucoma

In our study, the mGCIPLT was significantly associated with the 24-2 VF MD, 10-2 VF MD and 24-2 VF PSD in advanced glaucoma, while the cpRNFLT parameters were not. A previous longitudinal study has reported that the rates of mGCIPLT change were statistically significant in severe glaucoma, while the average rates of cpRNFLT change were not[29]. The mGCIPLT showed a significant association with 10-2 VF even after the cpRNFLT had reached the lower limit of measurement[30]. A previous cross-sectional study demonstrated that the mGCIPLT was significantly related to VF parameters in advanced glaucoma, while cpRNFLT was not[15]. Our study suggested that mGCIPLT and 10-2 VF measurements are useful for evaluating the severity of advanced glaucoma in group level.

In our study, the decrease of mGCIPLTs in early glaucomatous eyes with CVFDs on 24-2 VF were more severe than those of early glaucomatous eyes without CVFDs on 24-2 VF, except for the minimum and superotemporal mGCIPLT, although the degree of VF loss and RNFL defect were similar. Park

et al[7] found that the mGCIPLT was significantly thinner in glaucomatous eyes with parafoveal scotomas compared with those without parafoveal scotomas on the 10-2 VF test, while the average cpRNFLT, 24-2 VF MD were similar. The decrease in the mGCIPLT in glaucomatous eyes with parafoveal scotoma was more severe than that with peripheral nasal step, while the VF damage was similar[12,31].

The discriminating ability of mGCIPLT was similar to those of the currently recognized cpRNFLT and ONH parameters for glaucoma diagnosis[2,10-11]. In our study, the average mGCIPLT can provide better performance compared with those of average cpRNFLT in early glaucoma eyes with CVFDs. The results are similar to previous studies, which found that the AUC of the average mGCIPLT of the parafoveal scotoma group was significantly larger than those of the peripheral scotoma group[12,31].

Although 10-2 VF testing revealed damage in many eyes with early glaucomatous VF loss missed by 24-2 VF test (35.4%), the number of central damages detected by 24-2 and 10-2 VF tests (92.8% and 81.5%, respectively) was similar[3]. Progressive mGCIPLT thinning and progressive cpRNFLT thinning occur simultaneously and they were predictive indicators of VF progression[32]. Park *et al*[7] reported that early glaucoma eyes with VF damage in the central 10° of 24-2 VF that is related to mGCIPL thinning should be examined using the 10-2 VF testing. Chakravarti *et al*[33] demonstrated that early glaucoma eyes with VF damage in the central 5° of 24-2 VF deserve attention to determine VF damage by performing 10-2 testing. Kim *et al*[34] reported that the discriminating abilities of mGCIPLT parameters increased as the cpRNFLT defects approaches the fovea in preperimetric glaucoma. Our study suggested that early glaucoma patients with CVFDs should be taken seriously and could be further assessed with mGCIPLT and 10-2 VF measurement of macular damage.

However, our study had several limitations. First, the study was a cross-sectional study, longitudinal studies will provide more powerful evidence. Second, the sample size was relatively small, and a larger sample size will further support our findings. Third, all of the participants in our study were Chinese, thus, our results may not represent populations of other races. Fourth, our study used linear regression to explore the structure-function relationship in early or advanced glaucoma patients, while the method would be much better to use in glaucoma patients with a wide range of disease severities.

Clinically, the diagnosis of early glaucoma and follow-up of advanced glaucoma are relatively difficult. Evaluating all patients using both the 24-2 and 10-2 VF test or optic disc and macular scanning is time-consuming and costly. Our study suggested that early glaucoma patients with CVFDs and advanced glaucoma should be taken seriously and could be further assessed with mGCIPLT and 10-2 VF measurements. In conclusion, the 10-2 VF and Mgciplt parameters are complementary to 24-2 VF, cpRNFLT and ONH parameters, especially in detecting early glaucoma with CVFDs on 24-2 VF and evaluating the severity of advanced glaucoma in group level.

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