• Clinical Research •

Intraocular retinal thickness asymmetry in early stage of primary open angle glaucoma and normal tension glaucoma

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Abstract

• AIM: To investigate the intraocular retinal thickness asymmetry of peripapillary retinal nerve fiber layer (pRNFL) and macular layers measured by spectral-domain optical coherence tomography (SD-OCT) in patients with early stage of primary open angle glaucoma (POAG) and normal tension glaucoma (NTG).

• METHODS: A total of 117 patients with early stage of glaucoma (54 patients with POAG and 63 patients with NTG) and 32 normal subjects were recruited for the study. The pRNFL thickness, total macular layer (TML) thickness, and isolated inner macular layer (IML) thickness were measured by SD-OCT. Hemisphere TML thickness asymmetry measured by the posterior pole asymmetry scan was evaluated. Thickness differences of pRNFL and IML between superior and inferior quadrants were calculated. Asymmetry indices (AIs) of the pRNFL, TML and isolated IML were also computed. Areas under the receiver-operating characteristic curves (AROCs) were generated to determine the diagnostic capabilities of different parameters.

• RESULTS: Intraocular pRNFL thickness differences and AIs between the superior and inferior quadrants were significantly different between normal and NTG groups (*P*=0.009 and *P*<0.001, respectively). Intraocular pRNFL thickness differences and AIs between the temporal-superior and temporal-inferior sectors were also significantly different between normal and NTG groups (*P*=0.035 and *P*<0.001, respectively). The thickness differences and AIs of TML between superior and inferior hemispheres were significantly different between normal and NTG groups (*P*=0.001 and *P*=0.001, respectively) and between normal and POAG groups (*P*=0.032 and *P*=0.020, respectively). The thickness differences and AIs of macular ganglion cell layer (mGCL) between superior and inferior quadrants were significantly different between normal and NTG groups (*P*=0.013 and *P*=0.004, respectively), and between NTG and POAG groups (*P*=0.015 and *P*=0.012, respectively). The thickness difference of TML between superior and inferior hemispheres showed the highest diagnostic capability for early NTG eyes (AROC=0.832).

• CONCLUSION: Intraocular retinal thickness asymmetry in pRNFL, TML and mGCL are found in early stage of NTG. Hemisphere TML thickness asymmetry is also found in POAG eyes. Asymmetry analysis of retinal thickness can be an adjunctive modality for early detection of glaucoma.

• KEYWORDS: retinal nerve fiber layer; macular thickness; primary open angle glaucoma; normal tension glaucoma; hemisphere retinal asymmetry; optical coherence tomography

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INTRODUCTION

Glaucomatous optic neuropathy is associated with progressive ganglion cell layer (GCL) and retinal nerve fiber layer (RNFL) loss, structural changes of optic nerve head (ONH) and characteristic visual field (VF) defects. More than 35% to 40 % of retinal ganglion cell (RGC) axons can be lost before a measurable VF defect becomes evident in early glaucoma[1]. The structural evaluations for ONH, GCL and RNFL become important issues for early detection of glaucoma. However, there are a wide range of optic disc and cup sizes, variable configuration of the blood vessels, variable optic nerve morphology with titled and rotated disc, and peripapillary changes in the general population[2]. Variable optic disc size, optic disc tilt, peripapillary optic disc atrophy and vitreous traction can result in errors in measurements

of the peripapillary RNFL (pRNFL) thickness, especially in highly myopic patients[3-4]. While the optic discs have variable sizes and peripapillary atrophic changes, the macula shape is generally less variable than the ONH. About half of the RGCs located within the macula and the RGCs together with RNFL constitutes 40% of the retinal thickness[5]. Because glaucomatous damage involves progressive loss of RGCs and their axons, macular thickness measurement can be an alternative tool for early detection of glaucomatous change in the absence of maculopathy[6-10]. The measurements of pRNFL and inner macula layers (IML) by spectral-domain optical coherence tomography (SD-OCT) have been shown in several studies to be significantly thinner in glaucomatous eyes compared to healthy eyes[11-14].

In clinical setting, there is a wide overlap in the thickness distribution of the structure parameters between normal and early glaucomatous eyes. It is sometimes difficult to detect early glaucoma by measuring the thickness changes of the pRNFL and IML. The distribution of RGC axons and soma is highly symmetrical between the superior and inferior halves of the retina in normal eyes. The thickness profiles of the pRNFL, GCL, ganglion cell-inner plexiform layer (GCIPL), and ganglion cell complex (GCC) in the macula measured with SD-OCT are also highly symmetrical in upper and lower retinal hemispheres in normal eyes[15-16]. Glaucoma is usually an asymmetric disease entity, and the asymmetry of optic disc cupping is suspected of glaucoma clinically. The glaucomatous VF defects are also commonly asymmetric, and the VF loss can affect predominantly at superior or inferior VF at the time of diagnosis[17-19]. As regard to structure changes, it was reported that the difference between retinal hemispheres of total macular layer (TML) thickness measured by Posterior Pole Asymmetry Analysis (PPAA) (Heidelberg Engineering, Dossenheim, Germany) could be an indicator of early glaucomatous damage. The analysis of TML thickness asymmetry showed good sensitivity and specificity for early glaucoma detection and the glaucoma discriminating ability was similar to pRNFL thickness[20-25]. The structural and functional differences existed between normal tension glaucoma (NTG) and primary open angle glaucoma (POAG) in previous studies[26-28]. A more localized RNFL defect, thinner neuroretinal rim, and a deeper and more central VF defect closer to fixation point were more common in NTG than in POAG. Since NTG is associated with earlier involvement of the central VF, significant RGC damage may occur so that the IML thickness asymmetry can exist in NTG eyes. In the present study, we investigated the thickness differences and asymmetry indices (AIs) of pRNFL and IML parameters between superior and inferior quadrants, and hemisphere TML thickness differences and AIs in patients with early stage of POAG and NTG. Areas under the receiver operating characteristic curves (AROCs) were calculated to summarize diagnostic capabilities of the asymmetry parameters.

SUBJECTS AND METHODS

This cross-sectional study investigated POAG and NTG patients who attended the Glaucoma Clinic of Kaohsiung Chang Gung Memorial Hospital. The normal subjects were from patients coming for routine ophthalmic examination and hospital staff who had no ocular disease and had not received ocular surgery or laser procedures. The design of this study adhered to the tenets of the Declaration of Helsinki and was reviewed and approved by the institutional review board and ethics committee at Chang Gung Memorial Hospital.

All subjects underwent a thorough ophthalmologic examination, including best-corrected visual acuity, refraction, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy, central corneal thickness (CCT), ophthalmoscopy, red-free fundus photography (TRC-50EX, TOPCON, Japan), standard automatic perimetry (SAP) and SD-OCT exam. The refraction was expressed as spherical equivalence (SE), which was calculated as sphere plus half of the cylinder. To be included, patients had to have a best-corrected visual acuity of 20/40 or better, spherical refraction within ±6.0 diopters, cylinder correction within ±3.0 diopters, open angle on gonioscopy and the IOP less than 21 mm Hg under medication control. All glaucoma patients were at an early stage with a mean deviation (MD) value greater than -6 dB on SAP exam. Patients who had corneal lesions, chronic uveitis, secondary glaucoma, optic neuropathy other than glaucoma, retinal pathology, maculopathy and previous ocular trauma history were excluded from this study.

CCT was measured by Non-Contact Specular Microscope (SP-3000P, TOPCON, Tokyo, Japan) and SAP examination was performed with Swedish Interactive Threshold Algorithm standard (SITA) 30-2 Humphrey field analyzer (HFA; Carl Zeiss Meditec, Dublin, CA, USA). Unreliable VF test with fixation loss of more than 20% and false positive or false negative rates of more than 20% were excluded. A glaucomatous VF defect was defined as 3 or more significant (P<0.05) non-edge contiguous points with at least 1 at the P<0.01 level on the same side of the horizontal meridian in the pattern deviation plot and graded outside normal limits in the glaucoma hemifield test. Glaucomatous VF defects were confirmed by two reliable VF exams. Glaucomatous optic disc was defined as thinning or notching of the neuroretinal rim and excavation of the optic disc on stereoscopic color fundus photographs. POAG was defined as an IOP greater than 21 mm Hg on more than two occasions without medication, a glaucomatous optic disc, RNFL defects with corresponding glaucomatous VF defects and open anterior chamber angles on gonioscopy. NTG was defined as an IOP less than 21 mm Hg on

more than two occasions without medication, a glaucomatous optic disc, RNFL defects with corresponding glaucomatous VF defects and open anterior chamber angles on gonioscopy. All the normal subjects had normal anterior segments, open angles, and normal posterior segment findings, as well as normal OHN in their ophthalmic examinations. The IOP measurements were lower than 21 mm Hg, and SAP exams were within normal limits. Spectral-domain imaging was performed with the Spectralis OCT (Heidelberg Engineering, Dossenheim Heidelberg, Germany). The fast RNFL thickness protocol was used for calculating the pRNFL thickness. The scan circle was 3.4 mm in diameter. The pRNFL thickness values were divided into 4 quadrants. The superior and inferior quadrants were further divided into nasal and temporal sectors. The OCT parameters, including global RNFL thickness, average RNFL thickness in four quadrants and in four sectors were generated automatically in the analysis reports. For TML thickness measurement, retinal thickness map analysis was used to display thickness measurements. The average retinal thickness of 1 mm diameter circle within the central fovea on the Early Treatment Diabetic Retinopathy Study grid was calculated. Two concentric circles with diameters of 3 and 6 mm outside the fovea central circle represented the inner and outer sectors of macula, respectively. The concentric circles were further divided into superior, temporal, inferior, and nasal quadrants. After the TML data were obtained, the IML were segmented automatically using the software Multi-Layer Segmentation Tools to get the thicknesses of the macular GCL (mGCL) and macular RNFL (mRNFL). For assessment of TML thickness asymmetry, the PPAA scan was performed. The superior and inferior hemisphere thicknesses and fovea thickness were automatically generated in the PPAA report. The thickness differences between the superior and inferior quadrants, between the temporal-superior and temporal-inferior sectors, and between the nasal-superior and nasal-inferior sectors, were calculated from the RNFL thickness reports. The macular asymmetry which was assessed by TML thickness differences between the superior and inferior hemispheres were calculated from the PPAA reports. The thickness differences between the superior and inferior quadrants of mGCL and mRNFL were calculated from the Multi-Layer Segmentation reports. The AIs for all the parameters were calculated as: (thickness differences between the superior and inferior retinal layers/ average thickness of the superior and inferior retinal layers)×100. Only image quality of at least 20 in SD-OCT were used for this study. Each patient underwent scans to measure RNFL and macular layer thickness at the same visit. If both eye fulfilled the inclusion criteria, only the eye with better OCT image quality was used for analysis.

Statistical Analysis Data from the POAG, NTG, and normal groups were compared using one-way ANOVA followed by Bonferroni's multiple comparison procedure for continuous data, and Chi-square test for categorical data. The correlations between MD of SAP and retinal thickness asymmetry parameters were analyzed by Pearson's correlation coefficient. The diagnostic capabilities for thickness difference parameters of pRNFL and macular layer for differentiating early glaucoma from normal subjects were demonstrated by AROCs. The AROC was calculated using the standard formula. An AROC value of 1.0 represented perfect discrimination, whereas an AROC of 0.5 represented discrimination no better than chance. The diagnostic capabilities of thickness differences and AIs for pRNFL, TML and IML parameters were compared using *Z* test between POAG and NTG groups. All the statistical analyses were performed by using the SPSS version 17.0 (SPSS, Chicago, IL, USA). A *P* value less than 0.05 was considered to be statistically significant.

RESULTS

This study included 32 healthy eyes of 32 normal subjects and 117 glaucomatous eyes of 117 subjects (54 eyes with POAG and 63 eyes with NTG). The mean ages were 56.6±7.8y in the normal group, 60.4±16.1y in the POAG group, and 60.6±11.9y in the NTG group. The demographic data were shown in Table 1. The MD and pattern standard deviation (PSD) showed significant differences between patients with glaucoma and normal group ($P<0.01$), but there were no significant differences in MD and PSD between the POAG and NTG groups.

In comparison of the pRNFL thickness parameters, there were significant differences between normal and POAG groups, and between normal and NTG groups in the superior and inferior quadrants, and in the temporal-superior, temporal-inferior, nasal-superior, and nasal-inferior sectors (Table 2). Regarding the thickness asymmetry between normal and NTG groups, there were significant thickness differences between superior and inferior quadrants and between temporal-superior and temporal-inferior sectors ($P=0.009$ and $P=0.035$, respectively). The AIs of all pRNFL parameters were significantly different between normal and NTG groups. The AIs of pRNFL between superior and inferior quadrants and between nasal-superior and nasal-inferior sectors were also significantly different between normal and POAG groups ($P=0.019$ and $P=0.008$, respectively).

In comparison of the macular thickness parameters from the PPAA report, the TML thicknesses in the superior and inferior hemispheres were significantly greater in the normal group than in the NTG and POAG groups, but there were no differences between the NTG and POAG groups. The thicknesses of mGCL and mRNFL were significantly thinner in the POAG and NTG groups than in normal group (Table 3). Regarding the thickness asymmetry between

Table 1 Demographic data of normal subjects, POAG and NTG patients

Parameters	N (*n*=32)	POAG (*n*=54)	NTG (*n*=63)	*P*		
				Normal *vs* POAG	Normal *vs* NTG	POAG *vs* NTG
Age (y)	56.6±7.8	60.4±16.1	60.6±11.9	0.487	0.462	1.0
Male/Female	9/23	37/17	35/28	0.0009	0.033	0.452
CCT (μm)	541.4±33.5	508.9 ±132.5	487.1±149.6	0.862	0.209	1.0
SE (diopters)	-1.29±2.32	-1.25±2.63	-1.37±2.48	1.0	1.0	1.0
IOP (mm Hg)	14.1±3.4	15.9±3.9	12.7±3.0	0.068	0.177	<0.001
VF						
MD (dB)	-0.28±0.98	-2.89±1.54	-2.95±1.61	<0.001	<0.001	1.0
PSD (dB)	1.89±0.56	3.10±1.83	3.57±1.83	0.004	<0.001	0.370

POAG: Primary open angle glaucoma; NTG: Normal tension glaucoma; CCT: Central corneal thickness; SE: Spherical equivalence; IOP: Intraocular pressure; VF: Visual field; MD: Mean deviation; PSD: Pattern standard deviation. Chi-square test for categorical data and one-way ANOVA followed by Bonferroni's multiple comparison procedure for continuous data.

Table 2 Thickness parameters, thickness differences and asymmetry indices of pRNFL fiber layer in normal subjects, POAG and NTG patients

pRNFL (μm)	Normal (*n*=32)	POAG (*n*=54)	NTG (*n*=63)	*P*		
				Normal *vs* POAG	Normal *vs* NTG	POAG *vs* NTG
Global	105.8±9.3	85.7±13.2	83.3±14.6	<0.001	<0.001	1.0
Superior quadrant	131.8±15.0	108.1±20.3	103.5±22.3	<0.001	<0.001	0.658
Inferior quadrant	134.7±14.7	104.1±23.0	102.0±24.8	<0.001	<0.001	1.0
S-I pRNFL D	11.1±8.7	16.1±12.0	19.5±15.0	0.254	0.009	0.465
AI of S-I pRNFL D	7.4±5.6	15.8±12.7	20.0±16.9	0.019	<0.001	0.285
Temporal-superior	150.9±15.4	117.7±24.5	115.2±26.1	<0.001	<0.001	1.0
Temoral-inferior	164.1±17.2	123.0±30.9	116.7±35.0	<0.001	<0.001	0.797
TS-TI pRNFL D	18.3±15.4	21.8±15.0	28.2±21.2	1.0	0.035	0.170
AI of TS-TI pRNFL D	11.7±9.9	19.1±14.3	27.7±23.2	0.201	<0.001	0.032
Nasal-superior	112.3±19.4	98.0±24.1	91.3±25.5	0.023	<0.001	0.394
Nasal-inferior	104.9±21.7	84.6±22.7	86.9±21.3	<0.001	0.001	1.0
NS-NI pRNFL D	12.9±9.1	22.3±16.9	20.4±16.6	0.021	0.082	1.0
AI of NS-NI pRNFL D	12.5±8.4	25.6±20.4	24.4±22.1	0.008	0.015	1.0

POAG: Primary open angle glaucoma; NTG: Normal tension glaucoma; pRNFL: Peripapillary retinal nerve fiber layer; S-I pRNFL D: Difference of peripapillary retinal nerve fiber layer thickness between superior and inferior quadrants; TS-TI pRNFL D: Difference of peripapillary retinal nerve fiber layer thickness between superior-temporal and inferior-temporal sectors; NS-NI pRNFL D: Difference of peripapillary retinal nerve fiber layer thickness between superior-nasal and inferior-nasal sectors; S-I MT D: Difference of macular thickness between superior and inferior hemispheres; AI: Asymmetry index. One-way ANOVA followed by Bonferroni's multiple comparison procedure.

normal and NTG groups, there were significantly different in thickness differences and AIs between superior and inferior hemispheres of TML (*P*=0.001 and *P*=0.001, respectively) and between superior and inferior quadrants of mGCL (*P*=0.013 and 0.004, respectively). The thickness difference and AI between superior and inferior hemispheres of TML were also significantly different between normal and POAG groups (*P*=0.032 and *P*=0.020, respectively).

The correlations between global pRNFL and MD, between average TML and MD, between thickness difference and MD, and between AIs and MD were shown in Table 4. The correlations between global pRNFL thickness and MD and between average TML thickness and MD were statistically significant (both *P*<0.001). However, the thickness differences and AIs were not significantly correlated with MD of SAP.

The AROCs for thickness differences and AIs of pRNFL, TML, mGCL and mRNFL for differentiating early glaucoma from normal eyes were shown in Figures 1 and 2. For diagnosing early stage of NTG, the AROC for thickness difference of TML between the superior and inferior hemispheres was 0.832 and the AROC for AI of TML between superior and inferior hemispheres was 0.845 (Table 5).

Table 3 Thickness parameters, thickness differences and asymmetry indices of macular layers in normal subjects, POAG and NTG patients

Macular layer (μm)	Normal (*n*=32)	POAG (*n*=54)	NTG (*n*=63)	*P*		
				Normal *vs* POAG	Normal *vs* NTG	POAG *vs* NTG
Average TML	292.3±12.2	279.9±14.1	279.2±16.8	0.001	<0.001	1.0
Superior TML	293.3±12.4	283.5±16.6	275.8±16.5	0.018	<0.001	0.029
Inferior TML	291.5±12.2	276.6±14.1	272.3±18.1	<0.001	<0.001	0.438
S-I TML D	3.7±2.5	8.8±11.7	10.6±7.9	0.032	0.001	0.785
AI of S-I Macula D	1.2±0.9	3.1±4.1	3.8±2.7	0.020	0.001	0.725
Sup-Q mGCL	45.6±2.9	40.1±5.2	40.4±4.3	<0.001	<0.001	1.0
Inf-Q mGCL	43.7±2.8	38.8±4.7	37.5±5.5	<0.001	<0.001	0.409
S-I mGCL D	1.9±1.6	2.2±2.2	3.8±3.8	1.0	0.013	0.015
AI of S-I mGCL D	4.3±3.7	5.8±6.2	10.4±11.2	1.0	0.004	0.012
Sup-Q mRNFL	33.7±4.2	29.0±5.0	28.9±4.5	<0.001	<0.001	1.0
Inf-Q mRNFL	34.7±3.9	30.4±4.8	28.6±5.4	<0.001	<0.001	0.155
S-I mRNFL D	3.0±2.3	3.2±2.7	3.8±3.2	1.0	0.493	0.789
AI of S-I mRNFL D	8.6±6.5	11.1±8.9	13.7±11.5	0.734	0.048	0.449

POAG: Primary open angle glaucoma; NTG: Normal tension glaucoma; TML: Total macular layer; mGCL: Macular ganglion cell layer; mRNFL: Macular retinal nerve fiber layer; Sup-Q mGCL: Superior quadrant macular ganglion cell layer; Inf-Q mGCL: Inferior quadrant macular ganglion cell layer; Sup-Q mRNFL: Superior quadrant macular retinal nerve fiber layer; Inf-Q mRNFL: Inferior quadrant macular retinal nerve fiber layer; S-I TML D: Difference of total macular layer thickness between superior and inferior hemispheres; S-I mGCL D: Difference of macular ganglion cell layer thickness between superior and inferior quadrants; S-I mRNFL D: Difference of macular retinal nerve fiber layer thickness between superior and inferior quadrants; AI: Asymmetry index. One-way ANOVA followed by Bonferroni's multiple comparison procedure.

Table 4 Analysis of correlation coefficients between mean deviation and retinal thickness, between mean deviation and thickness differences, and between mean deviation and asymmetry indices in all glaucoma patients (*n*=117)

Retinal layers	*R*	*P*
Thickness		
Global pRNFL	0.470	<0.001
Average TML	0.400	<0.001
Thickness difference		
pRNFL	0.081	0.384
TML	-0.101	0.277
mGCL	-0.090	0.333
mRNFL	-0.014	0.884
Asymmetry Index		
pRNFL	0.021	0.823
TML	-0.120	0.196
mGCL	-0.116	0.213
mRNFL	-0.034	0.712

pRNFL: Peripapillary retinal nerve fiber layer; TML: Total macular layer; mGCL: Macular ganglion cell layer; mRNFL: Macular retinal nerve fiber layer. Pearson's correlation coefficient.

DISCUSSION

Glaucoma is usually a bilateral but asymmetric disease, which represents VF defect predominantly at superior or inferior hemifield at the time of diagnosis. In early stage of glaucoma, functional changes usually develop in one hemifield. It is considered that structural change precedes functional loss, asymmetric retinal changes may occur in early stage of glaucoma[17-19]. In the present study, the thickness differences and AIs of pRNFL between the superior and inferior quadrants, between the temporal-superior and temporal-inferior sectors, and between the nasal-superior and nasal-inferior sectors were significantly different between normal and NTG eyes. The thickness difference and AI of pRNFL between the nasal-superior and nasal-inferior sectors were also significantly different between normal and POAG eyes. Our results were different from previous studies. Sullivan-Mee *et al*[21] reported that there was no significant thickness difference between superior and inferior quadrants of pRNFL in early stage of POAG. They found that the intraocular macular thickness asymmetry was significantly higher in glaucoma group than in normal group, whereas the pRNFL asymmetry was not different between groups. Khanal *et al*[22] also reported that intraocular pRNFL thickness asymmetry was not different between normal and NTG, between normal and POAG and between NTG and POAG. There are a wide range of optic disc and cup sizes, variable angle of the optic nerve tilt and peripapillary changes in the general population. The pRNFL thickness showed high degree of variability in different individuals. The asymmetry of pRNFL may be not apparent between normal and glaucoma groups in different studies.

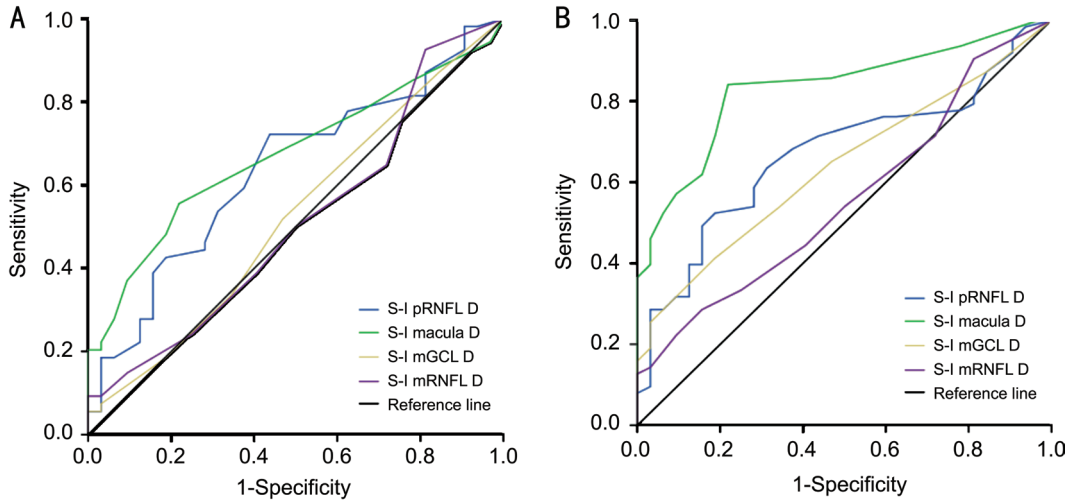

Figure 1 ROC curves for thickness differences of pRNFL and macular layers for discriminating glaucoma patients from normal subjects
A: For discriminating POAG eyes from normal eyes, the AROCs for thickness differences of pRNFL, TML, mGCL and mRNFL were 0.637, 0.673, 0.522, and 0.512, respectively; B: For discriminating NTG eyes from normal eyes, the AROCs for thickness differences of pRNFL, TML, mGCL and mRNFL were 0.672, 0.832, 0.638, and 0.559, respectively.

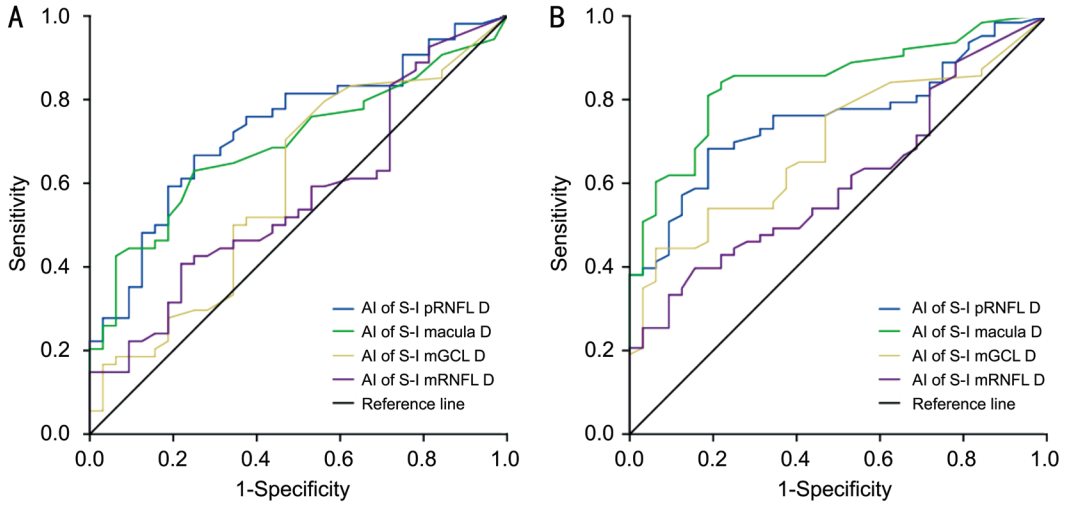

Figure 2 ROC curves for asymmetry indices of pRNFL and macular layers for discriminating glaucoma patients from normal subjects
A: For discriminating POAG eyes from normal eyes, the AROCs for asymmetry indices of pRNFL, TML, mGCL and mRNFL were 0.733, 0.695, 0.594, and 0.567, respectively; B: For discriminating NTG eyes from normal eyes, the AROCs for asymmetry indices of pRNFL, TML, mGCL and mRNFL were 0.756, 0.845, 0.693, and 0.607, respectively.

Table 5 Diagnostic capabilities of thickness differences and asymmetry indices of pRNFL and macular layers for differentiating normal tension glaucoma from normal subjects and for differentiating POAG from normal subjects

AROC curve	POAG (95%CI)	NTG (95%CI)	*P*
S-I pRNFL D	0.637 (0.518-0.757)	0.672 (0.562-0.781)	0.671
AI of S-I pRNFL D	0.733 (0.626-0.839)	0.756 (0.661-0.853)	0.752
S-I TML D	0.673 (0.561-0.786)	0.832 (0.750-0.914)	0.025
AI of S-I TML D	0.695 (0.585-0.805)	0.845 (0.767-0.924)	0.029
S-I mGCL D	0.522 (0.395-0.650)	0.638 (0.527-0.749)	0.182
AI of S-I mGCL D	0.594 (0.467-0.720)	0.693 (0.588-0.799)	0.232
S-I mRNFL D	0.512 (0.384-0.639)	0.559 (0.440-0.678)	0.599
AI of S-I mRNFL D	0.567 (0.443-0.691)	0.607 (0.493-0.721)	0.646

AUROC: Area under the receiver operating characteristic curve; S-I pRNFL D: Difference of peripapillary retinal nerve fiber layer thickness between superior and inferior quadrants; S-I TML D: Difference of total macular layer thickness between superior and inferior hemispheres; S-I mGCL D: Difference of macular ganglion cell layer thickness between superior and inferior quadrants; S-I mRNFL D: Difference of macular retinal nerve fiber layer thickness between superior and inferior quadrants; AI: Asymmetry index. *Z* test.

It was reported that the thickness difference of TML between retinal hemispheres is an indicator of early glaucomatous damage. Um *et al*[23] defined five zones in the superior and inferior hemispheres of the macular thickness map and compared the differences in average retinal thickness between corresponding pairs in each of the five zones. Hemisphere asymmetry in TML thickness was found and the macular hemifield test showed better performance than the average pRNFL thickness measurements in eyes with early-stage of glaucoma. Sullivan-Mee *et al*[21] calculated the thickness difference of TML between superior and inferior hemispheres and found an increase in macular thickness asymmetry in early stage of POAG. They found that hemisphere asymmetry of TML parameters had good sensitivity and specificity for early detection of POAG, and the glaucoma discriminating ability was similar to that of pRNFL parameters. Khanal *et al*[22] investigated the macular asymmetry between POAG and NTG eyes with MD of -5.85 dB and -3.10 dB, respectively. They calculated TML thickness difference between superior and inferior hemispheres and found significant thickness differences among normal, NTG and POAG groups. The TML thickness asymmetry was significantly higher in POAG eyes compared to NTG eyes. Our result was different from Khanal's study. We noted that the TML thickness between superior and inferior hemispheres was significantly different between normal and NTG groups, and between normal and POAG groups. The AIs between superior and inferior hemispheres were also significantly different between normal and NTG groups and between normal and POAG groups, but there was no difference between POAG and NTG groups. Very early stage of glaucoma patients with MD of -2.89 dB for POAG group and -2.95 dB for NTG group were included in the present study. The TML thickness parameters were decreased and the TML asymmetry measurements were also significantly different between normal and glaucoma patients, however, we did not find significant difference in TML asymmetry between POAG and NTG eyes.

Recent studies showed that the thickness of the GCL, GCIPL, and GCC in the macula measured by SD-OCT are highly symmetric in superior and inferior retinal hemispheres in normal eyes. In early stage of glaucoma, structural changes usually develop in one hemisphere, and the other hemisphere is also involved as the glaucoma progresses. Lee *et al*[29] analyzed the macular thickness asymmetry of TML, mRNFL, GCIPL, and GCC with swept-source OCT and found statistically significant differences between glaucoma and normal groups. Hwang *et al*[30] found that the GCIPL thickness difference and AI between superior and inferior hemispheres had good diagnostic capabilities in early stage of glaucoma. The AI had a better glaucoma diagnostic capability than absolute GCIPL thickness difference for various stages of glaucoma. Yamada *et al*[31] measured the macular thickness and calculated the thickness difference and AI in normal subjects and glaucoma patients. They found that the thickness differences between the superior and inferior hemispheres decreased with the severity of glaucoma, whereas AI did not. The AI in glaucoma eyes had less overlap than the AI in normal eyes as compared the thickness difference of retinal layers. Besides, the mGCL asymmetry analysis had excellent glaucoma diagnostic capability, regardless of glaucoma severity. In the present study, the thickness parameters in superior and inferior quadrants of mGCL and mRNFL were decreased. The asymmetric decrease of mGCL thickness in one hemisphere was apparent in NTG eyes, but not in POAG eyes. The thickness difference and AI of mGCL between superior and inferior quadrants was significantly different between NTG and normal groups, but not between POAG and normal groups. The structural and functional differences exist between NTG and POAG. NTG eye commonly has a more localized RNFL defect, a thinner neuroretinal rim, and a deeper and more central VF defect closer to fixation point than POAG eyes[26-28]. Thonginnetra *et al*[28] reported that NTG eyes had a higher percentage of abnormal test points in the central subfields on multifocal visual-evoked potential and SAP than POAG eyes. Since NTG is associated with earlier involvement of the central visual field, significant RGC damage may occur so that there can be significant difference in the mGCL thickness asymmetry between POAG and NTG eyes.

Though the mGCL thickness asymmetry was noted in early stage of NTG, the mRFNL thickness asymmetry was not found in early stage of NTG and POAG. More than 50% of RGC somas reside within 5 mm or 16° of the fovea and are stacked up to six layers thick[5]. Small losses of RGC can be detectable by analyzing the mGCL thickness. The mRNFL was thinner than the mGCL in the macular area. The thickness of mRNFL decreased in early glaucoma eyes, but it did not show asymmetric decrease between superior and inferior quadrants in the present study.

Glaucomatous optic neuropathy is associated with RGC apoptosis and RNFL atrophy. Both pRNFL thickness and macular thickness are thinner in glaucomatous eyes. Yamada *et al*[31] reported that the thickness parameters decreased with the severity of glaucoma, whereas AIs did not. The correlations of thickness of macular layers and MD of SAP were good (r=0.475-0.552) for eyes with glaucoma. In contrast, there were no significant correlations between AIs and MD values except in the mGCL, but the correlation was low (r=-0.257). In the present study, we also found that the correlations between thickness of global pRNFL and MD and between thickness of TML and MD were good (r=0.470 and 0.400, respectively), but the thickness differences and AIs were not significantly correlated with MD. The thickness measurements were

dependent on the severity of glaucoma, and they correlated well with MD. The AIs are independent on the severity of glaucoma and they did not have significant correlation with MD.

With the advent of PPAA, macular thickness measurement was used for detection of early glaucoma. The pRNFL consists of axons of both macular RGCs and peripheral RGCs, which pass through the macular area, whereas the mGCL contains RGC soma only in the corresponding macular area. Sullivan-Mee *et al*[21] evaluated the diagnostic capabilities of differences in pRNFL thickness and TML thickness for identifying early POAG[22]. In their study, TML thickness asymmetry was one of the best parameters for identifying early glaucoma, and the AROC was 0.860, but the AROC of pRNFL thickness asymmetry was 0.595. Our study is similar with theirs as the pRNFL thickness asymmetry parameter has low AROC (0.672), the TML thickness asymmetry parameter has high AROC (0.832), and the AI of TML between superior and inferior hemispheres had good diagnostic performance for early NTG (AROC=0.845).

Yamada *et al*[31] analyzed thickness asymmetry of the pRNFL, mGCL and mGCC between upper and lower hemispheres to predict glaucoma. The AROCs for thickness measurements increased with increasing glaucoma severity, whereas AROCs for AIs did not have clear ranges for glaucoma severity. The discriminating ability was most prominent for AI of mGCL, followed by AIs of GCC and TML. Lee *et al*[29] used the swept-source OCT to analyze the hemisphere thickness difference of pRNFL, GCC, GCIPL and TML. The GCC thickness difference (AROC=0.894) and pRNFL thickness difference (AROC=0.862) were the best for discriminating glaucomatous eyes. Kim *et al*[32] applied a MATLAB-based computer program of GCIPL hemifield test for automated detection of GCIPL thickness difference across the horizontal raphe by using Cirrus high-definition OCT and assessed its glaucoma diagnostic performance. A positive GCIPL hemifield test result was observed more frequently in the glaucomatous eyes than in the normal eyes. The AROC of the GCIPL hemifield test (0.962) was greater than that of the inferotemporal GCIPL thickness (0.938) and the average GCIPL thickness (0.912) in early glaucoma. Hwang *et al*[30] investigated the glaucoma diagnostic ability of GCIPL asymmetry analysis. All of the GCIPL parameters showed good glaucoma diagnostic ability (AROCs≥0.817). The GCIPL thickness differences and AIs showed the highest AROCs in early and moderate glaucoma diagnosis and lower AROCs in preperimetric and advanced-to-severe glaucoma detection. In the present study, we segment the IML and calculated the thickness difference and AIs between superior and inferior macula. Though the TML thickness difference and AI of TML showed good discriminating abilities, however, thickness differences in mGCL and mRNFL thickness between superior and inferior quadrants had fair glaucoma diagnostic capabilities. Our results cannot show good diagnostic performance for early glaucoma by thickness asymmetry of mGCL and mRNFL may be due to the very early stage of glaucoma in our patients. As the severity of disease increases, the discriminating ability for glaucoma increases. The severity of disease could be an important factor for evaluating the utility of asymmetry analysis for glaucoma diagnosis.

Khanal *et al*[22] evaluated the diagnostic capability of pRNFL and TML thickness difference measurements for the discrimination of NTG and POAG. The pRNFL thickness difference had the lowest AROC as well as the least sensitivity for identifying NTG from normal subjects (AROC=0.626, sensitivity=30%), and for identifying POAG from normal subjects (AROC=0.644, sensitivity=37%). The AROCs for TML thickness difference were significantly larger for discriminating NTG from normal subjects (AROC=0.893) and for discriminating POAG from normal subjects (AROC=0.882) than those of pRNFL thickness difference. In the present study, the diagnostic capabilities of pRNFL thickness difference between POAG and NTG were not different, but the diagnostic capabilities of TML thickness difference between POAG and NTG were significantly different. The AROC for TML thickness difference was better in NTG (0.832) than that of POAG (0.673). NTG is associated with earlier involvement of the central visual field and macular RGC, so macular asymmetry parameter of NTG has a better discriminating ability for glaucoma than that of POAG in the present study.

There were some limitations in our study. First, our study was limited by the relatively small sample size and we only evaluated the diagnostic performance of the intraocular macular thickness and pRNFL thickness asymmetry measurements in early stage of NTG and POAG. Further studies including a larger sample and different stages of glaucoma are needed to clarify the retinal thickness asymmetry in glaucoma diagnosis. Second, the macular scan only measures the central macular thickness and it may be erroneous due to operator factors, scan quality, segmentations errors, or other coexisting retinal pathology. More studies are needed to optimize the role of macular asymmetry in glaucoma care. Third, our study only included Taiwanese subjects, and thus lacked ethnic variety. Fourth, PPAA of Spectralis OCT compares TML based on the BMO to the fovea axis. It is different from other OCT devices that the horizontal line passing through the fovea was used in the inter-hemispheric asymmetry analysis. There can be different results between different OCT instruments. Besides, asymmetry analysis for glaucoma might have disadvantages in the glaucoma patients presenting symmetric damage, such as advanced to severe stage of glaucoma.

In conclusion, intraocular retinal thickness asymmetry in pRNFL, TML and mGCL were found in early stage of NTG.

Hemisphere TML thickness asymmetry was also found in POAG eyes. Eyes with significant retinal thickness asymmetry may indicate glaucomatous damage. Asymmetry analysis of retinal thickness can be an adjunctive tool for early detection of glaucoma.

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Conflicts of Interest: Lin PW, None; **Chang HW,** None; **Lai IC,** None; **Tsai JC,** None; **Poon YC,** None.

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CORRIGENDUM

Induction of significant intraocular pressure diurnal fluctuation in rats using a modified technique of microbead occlusion

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The authors wish to amend the wording of the following sentence on page 1117, replacing ‘Weber and Zelenak[13] injected 8 to 12 times per week before an initial sustained IOP elevation in rhesus monkeys.’ with ‘Weber and Zelenak[13] injected 8 to 10 times before an initial sustained IOP elevation in rhesus monkeys.’

The authors apologize for any inconvenience caused by this error.