Cross-Sectional Imaging Analysis of Epiretinal Membrane Involvement in Unilateral Open-Angle Glaucoma Severity

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Purpose. To determine the relevance of epiretinal membranes (ERMs) in primary open-angle glaucoma (POAG) and potential risk for glaucoma severity.

Methods. Sixty eyes of 30 patients with POAG who had a unilateral ERM were analyzed; 60 nonglaucomatous eyes of 30 patients with a unilateral ERM also were recruited in this institutional cross-sectional study. Patients underwent swept-source (SS) optical coherence tomography (OCT) imaging and visual field testing. Intraindividual differences in the SS-OCT retinal nerve fiber layer (RNFL) disc cupping area measurements and visual field outcomes were analyzed in the two groups.

Results. In patients with POAG, the mean circumpapillary RNFL thickness in the eyes with an ERM was 75.6 ± 16.5 μm superiorly and 71.8 ± 26.0 inferiorly compared with the fellow eyes without an ERM (87.2 ± 23.6 μm, $P = 0.0061$ and 81.3 ± 27.7 μm, $P = 0.034$, respectively). The areas of disc cupping and cup-to-disc ratio seen on OCT horizontal and vertical B-scans were larger in eyes with an ERM than in the fellow eyes without ERM ($P = 0.0004$ and $P = 0.0011$, respectively). The average mean deviations were −11.6 ± 7.5 dB in the ERM group and −8.19 ± 6.4 dB in the group with no ERM ($P = 0.029$). Eyes with an ERM received more antiglaucoma eye drops ($P = 0.018$). Those differences were not seen between eyes with an ERM or fellow eyes in patients without glaucoma.

Conclusions. The presence of an ERM can be a potential risk factor for unilateral severity in eyes with POAG.

Keywords: epiretinal membrane, glaucoma, inner retina

Epiretinal membranes (ERMs) are fibrocellular matrices that contain glial cells, fibroblasts, and hyalocytes that overlay the internal limiting membrane (ILM).[1,2] The resultant contraction of the ERMs can affect the macular microanatomy and cause increased retinal thickness, formation of ectopic inner foveal layers, and disruption of the outer and inner retinal layers.[1,2]

Numerous studies have reported the risk factors for glaucoma that include age, race, sex, positive family history, myopia, diabetes mellitus, disc hemorrhage, large diurnal fluctuations in intraocular pressure (IOP), and central corneal thickness.[3–6] We frequently observe large intereye difference in the severity of normal tension glaucoma (NTG); however, to date, few risk factors have been identified for the unilaterally predominant severity of NTG or primary open-angle glaucoma (POAG).

Recently, structural changes in the optical coherence tomography (OCT) findings on the inner retina of eyes with glaucoma have been reported. Multiple groups have reported peripapillary retinoschisis associated with transient increases in retinal nerve fiber layer (RNFL) thickness in glaucomatous eyes as determined by OCT.[7,8] However, glaucoma or nonglaucoma-associated optic neuropathies can lead to thickening and edema in the inner nuclear layer, termed microcystic macular edema (MME).[9,10] Nerve fiber damage and the subsequent retrograde loss of ganglion cells are thought to cause dysfunction of the Müller cells in both peripapillary retinoschisis and MME.[7,10] In addition, retinal traction might be sufficient to cause inner nuclear layer (INL) spaces in both disease processes.[8,11]

Some investigators have reported that ERMs are associated with glaucoma in some cases. Asrani et al.[12] found that more than 10% of glaucomatous eyes had an ERM responsible for the artifacts seen in OCT macular scans. Although the prevalence rates of ERMs have been reported to be approximately 2% to 10%,[13] the number of eyes with an ERM may be underestimated because only a few population-based large-scale studies have used OCT to diagnose ERMs.[14,15]

To detect POAG severity, visual field loss or thinning of the ganglion cell layer at the macula usually are evaluated. Because those parameters are complicated by the presence of an ERM, we analyzed the optic disc imaged by swept-source (SS) OCT to determine if the ERMs affected unilaterally progressing POAG in the current study.

Methods

Data Collection

The Institutional Review Board of Osaka University Hospital approved this study, which adhered to the tenets of the

Table 1. Exclusion Criteria in the Present Study

Any previous intraocular surgery excluding uncomplicated phacoemulsification
History of retinal detachment
Intermediate or advanced age-related macular degeneration
History of choroidal neovascularization of any etiology
Central serous chorioretinopathy
Proliferative diabetic retinopathy
Nonproliferative diabetic retinopathy with a history of clinically significant diabetic macular edema
Tractional and degenerative lamellar macular holes
History of central or branch retinal vein occlusion and central or branch retinal artery occlusion
History of inflammatory eye disorders
History of endophthalmitis or any other intraocular infection
Retinal dystrophies
Unreliable visual field tests
Poor-quality SS-OCT scans

Declaration of Helsinki. The study was a retrospective consecutive case series of POAG associated with unilateral ERMs in patients who visited the Department of Ophthalmology of Osaka University Hospital from October 2014 through November 2017. We retrospectively reviewed the medical records of 348 consecutive patients with bilateral OAG, including 30 patients with a unilateral ERM during the follow-up glaucoma evaluations. We identified the current cases by searching the medical records using Topcon IMAGEnet software (Topcon Corp., Tokyo, Japan). POAG and NTG were defined based on the following criteria: the presence of an open angle on gonioscopic examination; the glaucomatous optic disc appearance, that is, diffuse or localized rim thinning, a notch in the rim, or a vertical cup-to-disc ratio exceeding 0.6 or higher than that of the fellow eye by more than 0.2; and glaucomatous visual field loss, that is, a cluster of three points with a probability of <5% on the pattern deviation map in more than one hemifield, including more than one point with a probability of <1%, or a cluster of two points with a probability of <1% on two qualifying visual fields. Two glaucoma specialists (S.U. and A.M.) confirmed the two criteria. The inclusion criterion for association of the ERMs in this study was the presence of a unilateral ERM diagnosed by SS-OCT based on the report of Govetto et al.[2] The exclusion criteria are summarized in Table 1. The demographic and clinical information were reviewed and recorded. Age-matched subjects with an ERM also were recruited from among the patients in the hospital if they had an IOP of 21 mm Hg or lower and an optic nerve head (ONH) that appeared normal on a fundus examination.

Examinations

We measured the best-corrected visual acuity (BCVA), the axial length using the IOLMaster 500 (Carl Zeiss Meditec, San Diego, CA, USA), and the mean deviation (MD) of the visual field examination obtained using the 30-2 program of the Humphry field analyzer (Carl Zeiss Meditec); SS-OCT examinations (DRI OCT-1, Topcon Corp.) and color fundus photography (TRC-50, Topcon Corp.) also were performed. The refractive error was measured by autorefractometry (ARK-530, Nidek Co., Ltd., Gamagori, Japan). The central corneal thickness was evaluated by noncontact specular microscopy (CEM-530, Nidek Co., Ltd.). POAG was diagnosed based on the presence of glaucomatous optic neuropathy (localized or diffuse neuroretinal rim thinning and/or a RNFL defect) and an associated visual field defect.

Swept-Source OCT

A commercially available SS-OCT device (DRI-OCT, Topcon Corp.) was used to image the ONH and the macula. Three-dimensional cube scans (resolution, 512 × 256 pixels) were obtained from a 6 × 6-mm area centered on the optic disc. The axial and transverse resolutions in tissue in this instruments are 8 and 20 μm, respectively. The center wavelength is 1050 nm, and the scanning speed is 100,000 axial scans/s. With deeper penetration and higher scan speed, this machine is suitable for en-face imaging, especially of the deep structures. Eyes were imaged using the three-dimensional scan mode, of which the A-scan density was 512 lines (horizontal) × 256 lines (vertical), within the scan time of 1.3 seconds. Poor-quality images such as those with poor contrast due to media opacity or poorly fixated images were excluded. The thicknesses of the circumpapillary (cp) RNFL and ganglion cell complex (GCC) in the superior, temporal, inferior, and nasal quadrants of the optic disc or macula were measured using the DRI-OCT software. Segmentation of RNFL and GCC was checked in masked fashion in all cases. Vertical and horizontal cup-disc ratios were calculated using oblique B-scan images extracted from the cube images of the optic disc. The disc margin was defined manually as the retinal pigment epithelium/Bruch's membrane complex (RPE/BM) border. The cup margin was defined manually as the intersection of the ILM and the RPE/BM border reference line. The horizontal or vertical cup area was defined as the region surrounded by the ILM, surface of the lamina cribrosa, and RPE/BM border reference line, respectively (Supplementary Fig. S1). EnView software (Topcon Corp.) and ImageJ (National Institutes of Health, Bethesda, MD, USA) were used to measure these parameters of the optic disc.[16,17]

Statistical Analysis

The data were analyzed using GraphPad Prism (GraphPad Software, La Jolla, CA, USA). One-way analysis of variance, Mann-Whitney *U* test, and the paired *t*-test were performed as appropriate. $P < 0.05$ was considered significant.

Results

Patient Characteristics

The study population included 30 patients with POAG (mean age, 68.7 ± 9.4 years) and 30 patients without glaucoma with a unilateral ERM (mean age, 68.4 ± 11.1 years). The baseline characteristics of the two groups including age and sex did not differ significantly. In the patients with POAG, the mean logarithm of the minimum angle of resolution (logMAR) BCVAs of the eyes with a unilateral ERM and the fellow eyes without an ERM were 0.13 ± 0.27 (range, –0.18 to 1.00) and –0.04 ± 0.14 (range, –0.18 to 0.40), respectively. In patients without glaucoma, the mean BCVAs of the eyes with a unilateral ERM and the fellow eyes without an ERM were 0.23 ± 0.26 (range, –0.08 to 1.00) and 0.014 ± 0.13 (range, –0.18 to 0.30). Table 2 shows the clinical and ocular characteristics of the study population.

The intraindividual analyses in patients with POAG showed no differences between both eyes in the mean central corneal thickness, spherical equivalent refractive error, and IOP (paired *t*-test, $P > 0.05$ for all comparisons). However, the eyes with an ERM had a worse mean visual field MD (–11.6 ± 7.5 dB) compared with the fellow eyes without an ERM (–8.19 ± 6.4 dB; $P = 0.029$) (Table 3). We also found significant decreases in eyes with an ERM in both the upper and lower total deviations (Table 3). Eyes with an ERM received more antiglaucoma eye drops than eyes without one ($P = 0.018$) (Table 3). The eyes

Table 2. Demographics and Ocular Characteristics of the Study Population

	Glaucoma (30 Subjects)		No Glaucoma (30 Subjects)		Difference Between Patients With and Without Glaucoma
	ERM Affected Eye	ERM Unaffected Eye	ERM Affected Eye	ERM Unaffected Eye	
No. eyes	30		30		
Age, y	68.7		68.4		$P = 0.600$
Sex (%)					
Male	9 (30.0)		13 (56.7)		
Female	21 (70.0)		17 (43.3)		$P = 0.422$
DM	1 (3.3)				$P = 0.353$
HBP	13 (43.3)		13 (43.3)		$P = 1.000$
CVD	7 (23.3)		1 (3.3)		$P = 0.052$
Axial length, mm	24.8	24.7	24.6	24.5	$P = 0.868$
Glaucoma type					
POAG	11 (36.7)				
NTG	19 (63.3)				
VA, logMAR	0.13 ± 0.27	−0.04 ± 0.14	0.23 ± 0.26	0.014 ± 0.13	$P = 0.868$*, $P = 0.107$†
ERM stage (%)					$P = 0.392$
1	7 (23.3)		7 (23.3)		
2	11 (36.7)	NA	17 (56.7)	NA	
3	8 (26.7)	NA	6 (20.0)	NA	
4	1 (3.3)	NA	0 (0.0)	NA	
Central foveal thickness, µm	385.0 ± 73.6	250.9 ± 34.5	353.6 ± 82.8	266.0 ± 53.5	$P = 0.126$*, $P = 0.200$†
Average retinal thickness, µm	309.4 ± 33.7	262.8 ± 49.8	315.2 ± 36.8	273.8 ± 34.8	$P = 0.529$*, $P = 0.325$†
Presence of PVD	25 (83.3)	28 (93.3)	23 (76.7)	24 (80.0)	$P = 0.748$*, $P = 0.254$†

DM, diabetes mellitus; HBP, high blood pressure; CVD, cardiovascular disease; PVD, posterior vitreous detachment; NA, not applicable.
* Glaucoma vs. nonglaucoma in ERM affected eyes.
† Glaucoma vs. nonglaucoma in ERM unaffected eyes.

with an ERM had thinner cpRNFLs in the superior and inferior quadrants (75.6 ± 16.5 µm and 71.8 ± 26.0 µm, respectively) compared with the fellow unaffected eyes (87.2 ± 23.6 µm and 81.3 ± 27.7 µm; $P = 0.006$ and $P = 0.034$, respectively) (Table 4; Figs. 1, 2). Moreover, the horizontal and vertical ratios of the cup to the disc were 0.684% ± 0.144% and 0.685% ± 0.186%, respectively, in eyes with an ERM and 0.607% ± 0.157% and 0.605% ± 0.177% ($P < 0.001$ and $P = 0.003$), respectively, in the fellow eyes without an ERM (Fig. 3). The area of disc cupping in the horizontal and vertical B-scans analyzed with SS-OCT were 0.380 ± 0.311 mm^2 and 0.443 ± 0.368 mm^2, respectively, which were significantly larger than those in eyes without an ERM (0.269 ± 0.264 mm^2 and 0.323 ± 0.264 mm^2, respectively ($P < 0.001$ and $P = 0.001$) (Table 4; Fig. 3). When we compared the superior cpRNFL and inferior cpRNFL in the same patient with glaucoma with an ERM, there was no significant difference ($P = 0.393$). In addition, contrary to our findings in the cpRNFL, the GCC in eyes with an ERM was thicker than in eyes without an ERM (Table 4).

The intraindividual analysis of patients without glaucoma showed that there were no differences in the characteristics excluding the VA and macular status between both eyes. The intraindividual analysis in the patients without POAG did not show a worse mean visual field MD, thinner cpRNFL, or enlargement of the disc cupping (Table 4).

Table 3. Glaucoma Severity Parameters

	Glaucomatous Eyes (30 Subjects)			Nonglaucomatous Eyes (30 Subjects)		
	ERM (30 Eyes)	No ERM (30 Eyes)	*P* Value	ERM (30 Eyes)	No ERM (30 Eyes)	*P* Value
CCT, mm	0.511 ± 0.035	0.512 ± 0.033	0.447	0.526 ± 0.031	0.527 ± 0.031	0.537
IOP, mm Hg	13.6 ± 2.5	13.8 ± 2.4	0.513	14.2 ± 2.6	14.3 ± 2.9	0.819
SAP MD, dB	−11.6 ± 7.5	−8.19 ± 6.4	0.029	−2.6 ± 2.2	−2.3 ± 2.2	0.344
SAP TD, dB						
Upper	−11.8 ± 9.6	−7.6 ± 6.3	0.024	−3.2 ± 2.1	−2.3 ± 2.0	0.156
Lower	−10.4 ± 6.9	−7.2 ± 6.6	0.047	−2.5 ± 2.0	−2.5 ± 2.2	0.910
Topical glaucoma medications (%)			0.018			
0	5 (16.7)	13 (43.3)		NA	NA	
1	14 (46.7)	10 (33.3)		NA	NA	
2	4 (13.3)	2 (6.7)		NA	NA	
3	4 (13.3)	2 (6.7)		NA	NA	
4	1 (3.3)	1 (3.3)		NA	NA	
5	1 (3.3)	1 (3.3)		NA	NA	

CCT, central corneal thickness; SAP MD, standard automated perimetry MD; SAP TD, standard automated perimetry total deviation; NA, not applicable.

Table 4. SS-OCT Parameters on Glaucoma Severity

	Glaucoma (30 Subjects)			Non-Glaucoma (30 Subjects)		
	ERM (30 Eyes)	Non-ERM (30 Eyes)	*P* Value	ERM (30 Eyes)	Non-ERM (30 Eyes)	*P* Value
cpRNFL thickness, μm						
Superior	75.6 ± 16.5	87.2 ± 23.6	0.006	116.2 ± 14.9	114.5 ± 19.7	0.589
Temporal	71.3 ± 17.2	69.7 ± 16.4	0.652	91.4 ± 27.7	84.7 ± 20.1	0.186
Inferior	71.8 ± 26.0	81.3 ± 27.7	0.034	117.1 ± 22.3	117.6 ± 25.6	0.877
Nasal	60.4 ± 18.6	58.9 ± 16.8	0.5653	69.7 ± 16.0	68.4 ± 14.0	0.643
Area of cupping on B-scan, mm^2						
Horizontal	0.380 ± 0.311	0.296 ± 0.264	<0.001	0.0836 ± 0.083	0.0855 ± 0.083	0.779
Vertical	0.443 ± 0.368	0.323 ± 0.246	0.001	0.108 ± 0.117	0.0938 ± 0.091	0.225
C/D ratio						
Horizontal	0.684 ± 0.144	0.607 ± 0.157	<0.001	0.369 ± 0.145	0.380 ± 0.154	0.584
Vertical	0.685 ± 0.186	0.605 ± 0.177	0.003	0.434 ± 0.162	0.416 ± 0.139	0.521
mGCC thickness						
Superior	123.7 ± 30.0	107.0 ± 16.6	0.008	156.2 ± 41.8	119.5 ± 21.1	<0.001
Temporal	106.4 ± 29.4	90.1 ± 15.7	0.005	146.4 ± 37.2	110.7 ± 24.8	<0.001
Inferior	105.6 ± 24.1	95.9 ± 22.1	0.082	150.6 ± 32.5	121.4 ± 24.1	<0.001
Nasal	125.8 ± 35.1	103.8 ± 17.8	0.003	153.5 ± 33.6	116.5 ± 20.2	<0.001

C/D, cup-to-disc; mGCC, macular GCC.

Discussion

The association between POAG and ERMs has not been clarified. We documented for the first time that the mean cpRNFL was thinner in eyes with a unilateral ERM than in the fellow eyes without an ERM in the same patients with POAG but not in patients without glaucoma. The area of disc cupping and the cup-to-disc ratio were larger in the eyes with a unilateral ERM than in the fellow eyes without an ERM. The mean MD was lower in the group with an ERM compared with

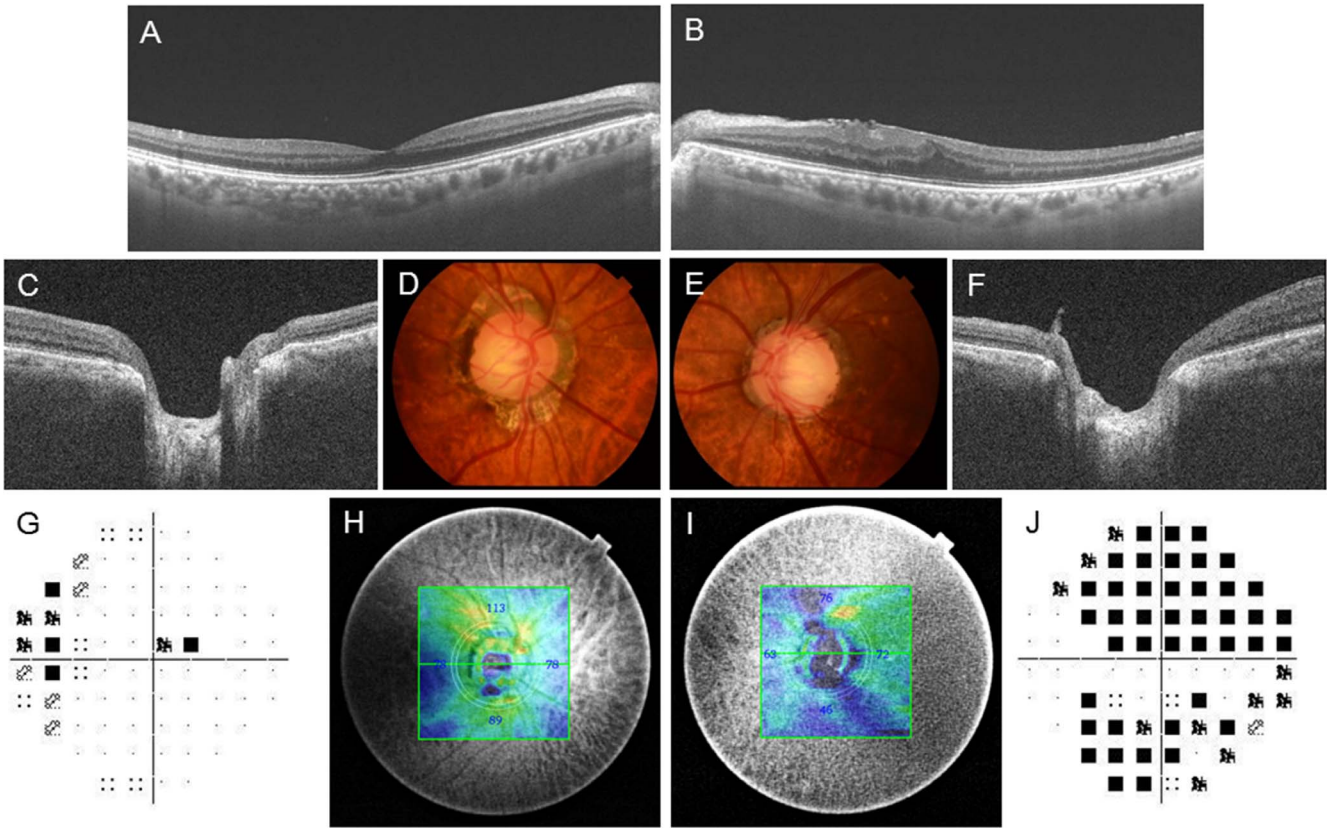

Figure 1. A 79-year-old woman with bilateral open-angle glaucoma associated with unilateral ERM in left eye. A B-scan image at the macula obtained by SS-OCT in the left eye shows a stage 3 ERM (**B**) according to Govetto et al.[2] and in the right eye without an ERM (**A**). A horizontal B-scan image at the center of the disc shows greater cupping in the left eye with an ERM (**F**) than that of the right eye (**C**). A color fundus photograph of the optic disc of the left eye shows an ERM (**E**) and the right eye without an ERM (**D**). An en-face image obtained by SS-OCT shows inferior and superior RNFL thinning (**I**) in an eye with an ERM compared to the right eye (**H**). Decreased visual field sensitivity is shown in the left eye with an ERM (**J**) compared to the right eye (**G**).

Investigative Ophthalmology & Visual Science

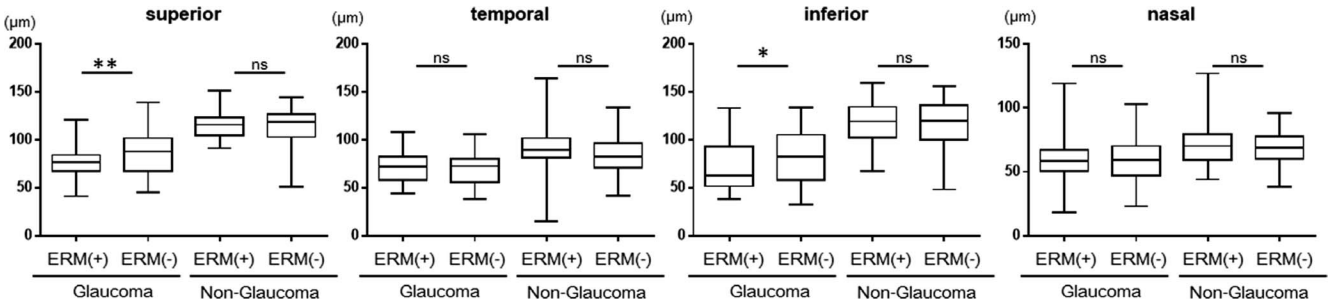

FIGURE 2. Boxplots show an average RNFL in the superior, temporal, inferior, and nasal sectors around the optic disc measured by SS-OCT in an eye with an ERM and a fellow eye without an ERM in subjects with and without. $^{*}P < 0.05$, $^{**}P < 0.01$. NS, not significant.

the group without an ERM. In addition, eyes with an ERM were treated with more antiglaucoma eye drops.

The prevalence of POAG is approximately 5% in patients 40 years old and older[18] and an ERM is present in from 2% to 10%.[4,19–21] Care should be taken considering that epidemiologic research has not yet disclosed the relationship between those two diseases. In clinical practice, OCT is more efficient than retinal photography for detecting epiretinal disorders.[1,22,23] Thus, theoretically, the use of both photography and OCT should detect more ERMs; however, studies in which OCT also was performed have reported lower prevalence rates than those studies in which OCT was not performed.[13,15] Further research is needed to assess the performance of OCT in diagnosing ERMs before the technology is included in epidemiologic studies to clarify its prevalence and association with glaucoma.

Although the pathogenesis of glaucoma is not fully understood, the level of IOP is associated strongly with retinal ganglion cell death. IOP can cause mechanical stress and strain on the lamina cribrosa.[24] IOP-induced mechanical strain can result in disruption of axonal transport and resultant retinal ganglion cell death.[25] Nonetheless, loss of microcirculation,[26] immunogenicity,[27] excitotoxicity,[28] and oxidative stress[29] that affect neurons also can cause glaucomatous progression.

In eyes with an ERM, the anatomic changes that occur in the outer retina[30,31] and the central foveal thickness[32] may be correlated with visual outcomes. However, the mechanical stress induced by ERM traction can involve all retinal layers, including the inner retina, causing a spectrum of macular disorders. Recently, multiple studies have reported the visual outcomes in eyes with an ERM, in which retinal ganglion or inner nuclear layer cellular damage was induced, owing to inner retinal layer traction, through the inner retinal thickness or the ganglion cell-inner plexiform layer (GC-IPL) thickness.[33,34] Increasing GC-IPL thickness at the macula and irregularity of the inner retinal layers seen on OCT images were associated significantly with decreased VA.[35,36] The current findings indicated that the pathogenesis of glaucomatous severity in eyes with an ERM can attribute to development of ERM traction on the inner retina. We propose that the centripetal traction induced by ERMs may cause mechanical stress on the neural fibers in a vertical direction to the optic disc cup. In the eyes with an ERM, thinner cpRNFLs were found in the superior and posterior quadrants, which seem to be more susceptible to the loss of retinal ganglion cells in OAG.[37] As those changes were not seen in patients without glaucoma, the current study suggested that the inner retinal layers in glaucomatous eyes may be sensitive to the tractional stress due to neural vulnerability. In this study on glaucoma patients, the cpRNFL difference between ERM eye and non ERM eye was more prominent in superior quadrant compared to inferior quadrant (Table 4). Even though this difference was not significant ($P = 0.3932$) in the comparison in the same patients with glaucoma and an ERM, the inferior cpRNFL especially tended to be thinner and is reportedly more vulnerable than the superior RNFL.[37] Thus, we speculate this cpRNFL damage in superior quadrant is attributed from vascular insults caused by ERM traction. ERMs can be caused by vascular factors.[20] Considering glaucoma is also associated with loss of microcirculation,[26] it is possible that progressed glaucoma and ERM were caused by loss of blood flow in this study.

Despite findings that ERMs in patients with glaucoma might have been involved in the increased glaucoma severity via mechanical stress induced by the centripetal traction, those changes did not dramatically affect the parameters associated with glaucoma and were limited to the locations of the superior and inferior quadrants. We can speculate that there might be a specific POAG type that is affected by ERMs. In addition, an important possible hypothesis is that ERMs might develop simultaneously or even subsequently with glaucomatous retinal ganglion cell death. Tsuchiya et al.[38] reported recently that visual field sensitivity can deteriorate even after

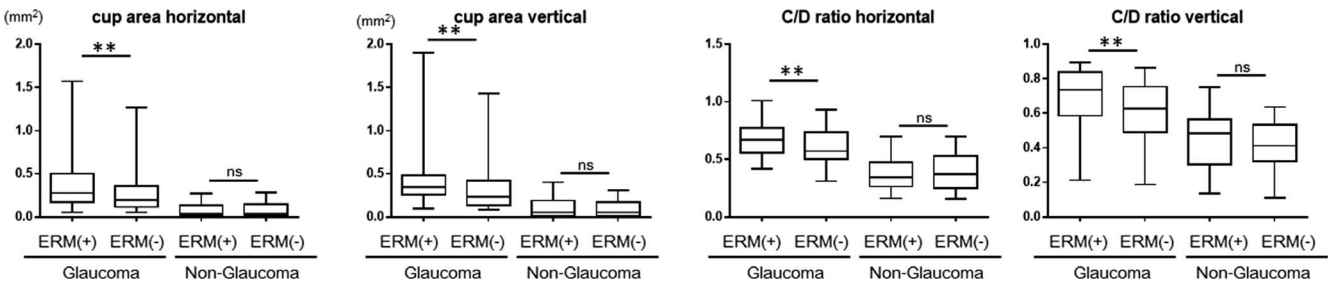

FIGURE 3. The boxplots show areas (mm^2) of disc cupping or cupping/disc ratio measured by horizontal or vertical B-scan image of the optic disc obtained using SS-OCT. The medians are represented by *horizontal lines* in the *gray boxes*. *Error bars* denote interquartile range. $^{**}P < 0.01$. C/D, cupping/disc; NS, not significant.

removal of ERMs, indicating that relieving the mechanical stress does not improve the glaucoma outcomes. We found the association but not causality by the ERMs in the current patients with glaucoma. Thus, a longitudinal study with detailed imaging analyses is still warranted; however, the current study identified a potential novel risk factor for glaucomatous severity, which can occur predominantly unilaterally.

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