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Analysis of retinal microstructure and electrophysiology in eyes following pars plana vitrectomy and membrane peeling for vitreomacular interface disorders

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Abstract

Purpose To investigate the relationship between retinal structural biomarkers using spectral-domain optical coherence tomography (SD-OCT) and macular function before and after surgery.

Methods Forty-four eyes of 44 patients were included. Ophthalmological examinations included visual acuity (VA), intraocular pressure, OCT angiography (OCTA), and multi-focal electroretinography (mf-ERG) at baseline (pre-surgery) and post-operative follow-up. The ILM texture during peeling was graded by the surgeon as follows: Grade 1, fragile; Grade 2, easy to peel in a sheet; and Grade 3, sticky. The cross-sectional area of the ganglion cell layer and central retinal thickness in the fovea were evaluated using ImageJ software of SD-OCT. The presence of a dissociated optic nerve fiber layer (DONFL) was evaluated using en face OCTA images. mf-ERG results are shown as the ratio between the average amplitudes from rings 1 and 2 (central) and rings 4 and 5 (peripheral): the P1 ratio.

Results Based on the SD-OCT morphological characteristics of the foveal area, 14 cases were classified into ERM group 1 (mainly outer retinal thickening or more tenting of the outer retina), 11 into ERM group 2 (prominent inner retinal thickening), 9 into ERM group 3 (ERM with macular hole), and 10 into ERM group 4 (full thickness macular hole without ERM and vitreomacular traction without ERM). Morphological characteristics were correlated with ILM texture ($p = 0.0031$) and DONFL ($p < 0.0001$). Group 2 and group 3 ERM had a stickier ILM when peeling and showed DONFL in 100% of the cases. Group 1 ERM had a more fragile ILM when peeling and did not result in DONFL. ILM texture was also correlated with DONFL ($p < 0.0001$), in which sticky ILM resulted in DONFL after the operation. Eyes with DONFL showed a greater decrease in ganglion cell complex/central retinal thickness in the foveal area, slow P1 ratio recovery, and slower VA improvement.

Conclusions ERM with prominent inner retinal structural changes are likely to have a stickier ILM when peeled, leading to a subsequently DONFL. The appearance of DONFL results in an initial decrease in macular function recovery and slower post-operative visual improvement. Surgeons should be more delicate when peeling sticky ILM, especially in eyes with ERM with prominent inner retinal thickening or macular holes.

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Keywords Vitreomacular interface disorders, Internal limiting membrane peeling, Vitreoretinal surgery, Multi-focal electroretinogram, Dissociated optic nerve fiber layer (DONFL), Epiretinal membrane

Introduction

Pars plana vitrectomy (PPV) and membrane peeling are currently the preferred procedures for the management of vitreomacular interface disorders such as macular holes (MH), epiretinal membranes (ERM), and vitreomacular traction (VMT). While internal limiting membrane (ILM) peeling has been shown to decrease ERM recurrence [1] and enhance MH closure rates [2], ILM has been investigated in recent macular surgery and holds significant importance. The ILM is a 10-μm-thick transparent structure formed by the basement membrane of the retinal Müller cells. It plays an important role in homeostasis and maintenance of inner retinal layers, and is composed mainly of collagen fibers, glycosaminoglycans, laminin, and fibronectin [3], which are responsible for the biochemical properties of the retina [4]. The consequences of ILM peeling and how it may damage the retina remain controversial and require further study. Swelling of the arcuate retinal nerve fiber layer (SANFL), macular retinal displacement, and dissociated optical nerve fiber layer (DONFL) were reported in some cases [5].

The DONFL appears as an indentation seen on the retinal nerve fiber layer (RNFL) on cross-sectional optical coherence tomography (OCT) images [Figure 1]. In en face OCT images, the DONFL appears as numerous black holes, which the direction is same as the optic nerve fibers. Several studies have demonstrated a strong link between ILM peeling and DONFL formation. Some believe that DONFL occurs without loss of the nerve fiber layer and thought that DONFL is caused by macular nerve fiber layer rearrangement and reorganization rather than true mechanical damage [6, 7]. However, some believe that the DONFL involves deeper damage under the RNFL [8, 9], or the thickness decrease more in the temporal retina than in the nasal retina [9]. To date, it is not known which ILM texture corresponds to the formation of the DONFL. The pathogenesis of DONFL and its influence on macular function are not well understood.

This study aimed to evaluate the association between the morphological characteristics revealed on spectral-domain optical coherence tomography (SD-OCT) images, the texture of the ILM during peeling, and the development of DONFL. We also analyzed the changes in visual acuity, retinal structure, and macular function using mf-ERG for 3 months and more than 6 months of follow-up to explore the risk factors and influence of DONFL on macular function. We hope that this study will provide additional information for clinical practice to improve surgical procedures.

Methods

Study participants

This study was a non-randomized retrospective consecutive case series. The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E (II)-20230113) and adhered to the tenets of the Declaration of Helsinki. Patients who underwent ILM peeling between January 2020 and September 2022 at Kaohsiung Medical University Hospital were enrolled in this study. We excluded patients with ocular diseases such as retinal breaks, diabetic retinopathy, retinal vein occlusion, and uveitis. Eyes with uncontrollable ophthalmic diseases such as glaucoma, corneal opacity, or optic nerve diseases were also excluded. Those who did not have a follow-up of at least 6 months were also excluded from the study.

Clinical data, including visual acuity, SD-OCT measurements (Heidelberg Engineering, Heidelberg, Germany), and mf-ERG (Espion E3—Diagnosys LLC, MA, USA) values, were recorded at baseline and post-operatively. The ganglion cell complex includes the retinal nerve fiber, ganglion cell, and inner plexiform layers. The thickness was measured using ImageJ software (SD-OCT), which we adapted the concept from Pichi F et al. [5]. mf-ERG was performed following the International Society for Clinical Electrophysiology of Vision (ISCEV) recommendations associated with Borrelli et al. [10] and Lumi at al.'s [11] procedure using Dawson, Trick, and Litzkow (DTL) electrodes with a 61-scaled hexagons protocol. The pupils were dilated with 1% tropicamide (Mydriacyl®, Alcon, Belgium) and the examination was performed in each eye separately, while the other eye was occluded. Refractive errors were corrected with +3.50 diopters due to the dilated pupils. With a 45-in. monitor, an array of 61 hexagons was projected and driven at a frame rate of 75 Hz, covering the central 60-degree area surrounding the fovea. The black and white hexagons have luminances of 1000 and 0 cd/m^2, respectively. The DTL Plus electrodes were applied to the conjunctiva at the inferior limbus. The ground electrode was attached to the forehead. Assuming that retinal adaptation may affect mf-ERG values, the participants were exposed to the same pre-exposure light, and the examination room's illumination was moderate and same for all participants. The distance between the stimuli was 260 mm. The diameter of the stimulus was 60° and the patient was instructed to fixate on the center of the fixation cross that extended to

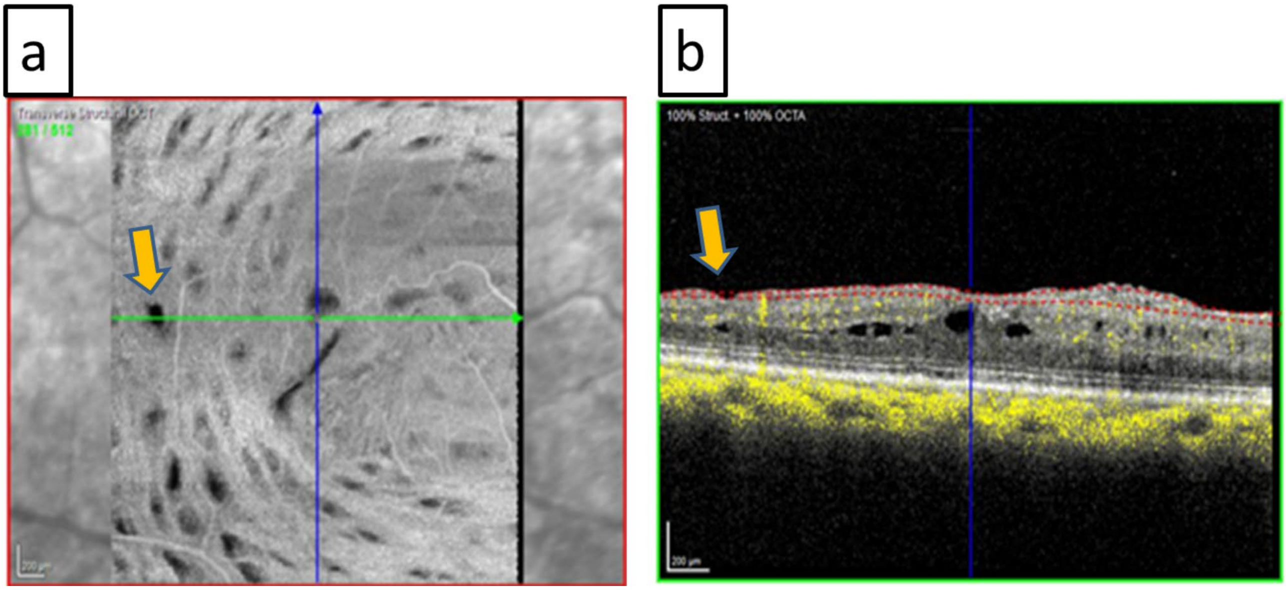

Fig. 1 En face OCT image (**a**) of one case in our study showed numerous black holes, which the direction is same as the optic nerve fibers. Focal dimple corresponding to dark spots on green line in (**a**), were visible in the RNFL on B-scan OCT images in (**b**) (yellow arrow)

all four corners of the screen to facilitate central fixation (the diameter of the fixation cross was 60°). The stability of the fixation was monitored using a camera placed in front of the patient. The participants were coached on steady fixation, and the recording trial was repeated in cases of inappropriate fixation. The examination was performed monocularly, with a registration time of at least 4 min per eye, and repeated in cases of eccentric fixation, unstable fixation, or the presence of movement artifacts. Signals were processed through a 5–100-Hz band-pass filter and amplified through a 30,000 gain.

Outcome measures were the absence or appearance of DONFL, the ratio of ganglion cell complex to central retinal thickness in the foveal area, and the P1 ratio of mfERG. To normalize the response amplitudes and equalize the intra-individual variability, a P1 ratio was calculated between the average of the amplitudes measured on central rings 1 and 2 divided by the average found on rings 4 and 5. [Figure 2]

Surgical technique

All surgical procedures were performed by a single surgeon. The surgical procedures included standard 25-G vitrectomy (Constellation; Alcon, Fort Worth, TX). For macular pucker, both the ERM and ILM were peeled. The ILM flap was preserved with a 15% C3F8 gas tamponade in patients with macular holes. ILM peeling was facilitated by staining with indocyanine green (0.25% diluted with 50% glucose water). 25G serrated forceps (EYE TECHNOLOGY, Essex UK) were utilized for the peeling process. Combined surgery with phacoemulsification was done if the surgical view was obscured by cataract.

The ease of ILM peeling was graded by the surgeon as follows: Grade 1, fragile; Grade 2, easy to peel in a sheet; and Grade 3, sticky. [Figure 3]

Statistics analysis

Statistical analysis was performed using JASP software (version 0.16.1; JASP Team [2022]). A *p* value of <0.05 was considered statistically significant in all analyses. Fisher's exact test, Cochran–Armitage trend test, and Cramer's V test were used to evaluate the correlation between different diagnoses, macular hole, high myopia, DONFL, and ILM texture. Repeated measures analysis of variance (ANOVA) was used to evaluate the changes in mean differences of visual acuity logMAR, the ratio of ganglion cell complex thickness to central retinal thickness in the foveal area, and the P1 ratio using the generalized model, from baseline to each scheduled visit (1.5, 3, and more than 6 months) after surgery as the dependent variable.

Results

A total of 44 eyes of 44 patients were included. Patient characteristics including age, sex, duration of disease, and lens status were recorded in Tables 1 and 2. Based on the SD-OCT morphological characteristics at the foveal area, 14 eyes (31.8%) were categorized into ERM group 1 (mainly outer retinal thickening or more tenting of the outer retina), 11 eyes (25%) into ERM group 2 (prominent inner retinal thickening), 9 eyes (20.5%) into ERM group 3 (ERM with macular hole), 10 eyes into ERM group 4 (7 eyes (15.9%) had a full-thickness macular hole (FTMH) without ERM, and 3 eyes (6.8%) had

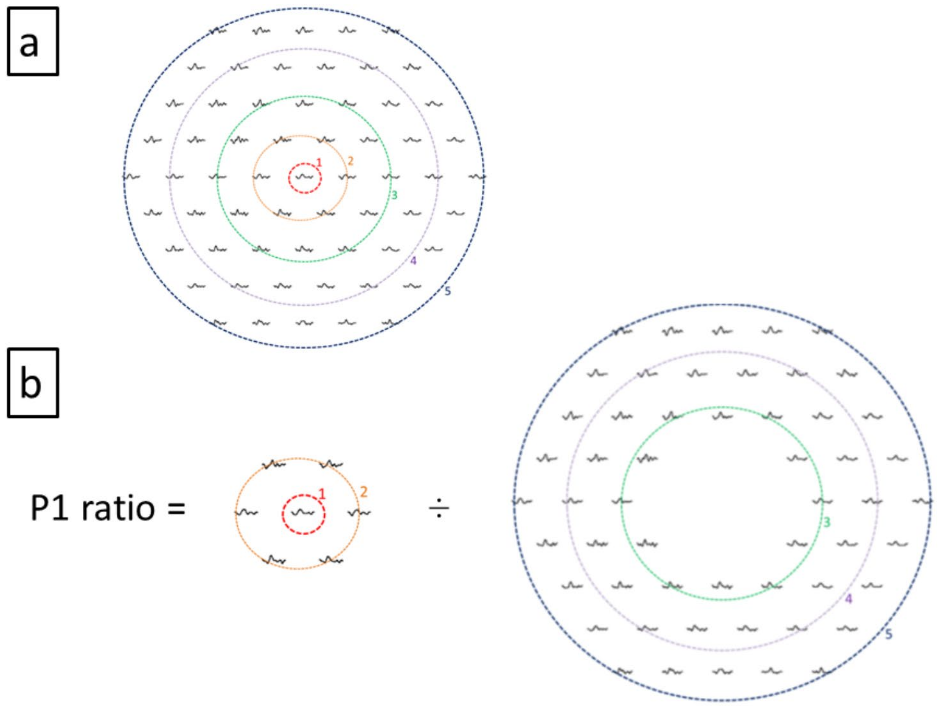

Fig. 2 (**A**) The hexagons used as mfERG stimuli protocol and the respective electric responses. (**B**) Illustrative panel for the calculation made to determine P1 ratio using the 2 central rings divided by the 2 peripheral rings

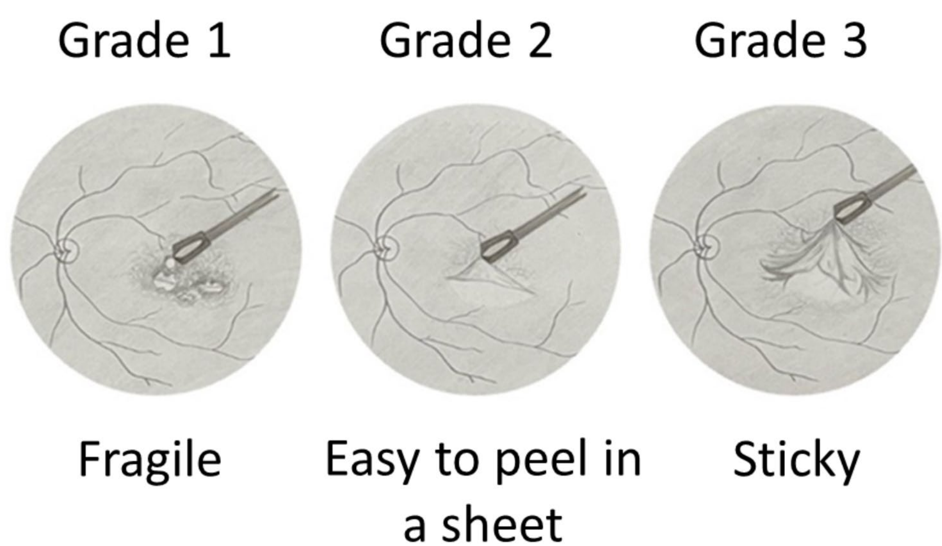

Fig. 3 The ease of ILM peeling

Table 1 Patient characteristics

	ERM group 1	ERM group 2	ERM group 3	ERM group 4	*p* value
Number, eyes	14	11	9	10	
Sex (female/male)	8/6	7/4	7/2	10/0	0.0885
Age, years	67.86 ± 9.95	63.55 ± 7.49	66 ± 10.62	58.6 ± 6.67	0.0961
Initial Lens status (phakic/pseudophakic)	14/0	9/2	7/2	10/0	0.1136
Duration of symptoms, months (mean/median)	10.5/9.0	5.55/6.0	6.67/6.0	8/6.50	0.0969/0.1026
High myopia, number	2	1	2	4	

Table 2 The correlation of morphological characteristics and ILM texture

ILM texture	Grade 1	Grade 2	Grade 3	Fisher exact test, *p*	Trend test, *p*	Cramer's V
Number of eyes (%)	7 (15.9)	24 (54.5)	13 (29.5)			
Diagnosis, number of eyes (%)				0.0007	0.0015	0.51
ERM group 1	5 (71.4)	9 (37.5)	0 (0.0)			
ERM group 2	0 (0.0)	6 (25.0)	5 (38.5)			
ERM group 3	0 (0.0)	2 (8.3)	7 (53.8)			
ERM group 4	2 (28.6)	7 (29.2)	1 (7.7)			
With macular hole, number of eyes (%)	1 (14.3)	8 (33.3)	8 (61.5)	0.0971	0.0281	0.33
With high myopia, number of eyes (%)	0 (0.0)	5 (20.8)	4 (30.8)	0.3625	0.1165	0.25
With DONFL, number of eyes (%)	0 (0.0)	10 (41.7)	13 (100.0)	< 0.0001	< 0.0001	0.68

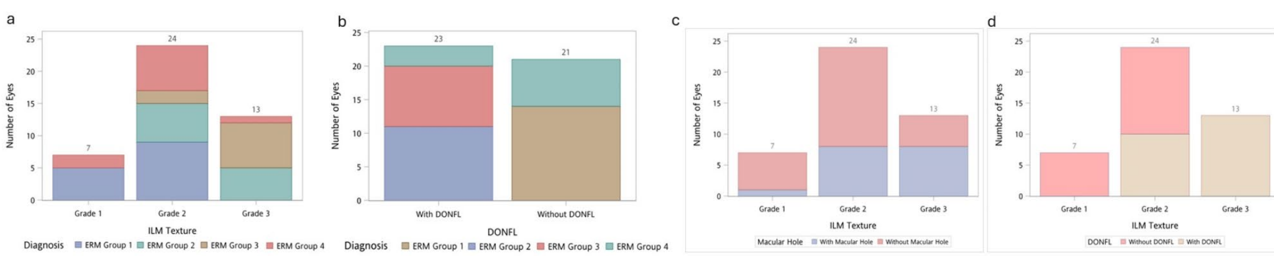

Fig. 4 (**A**) The correlation of the diagnosis of vitreomacular disorder and ILM texture (Fisher exact test, $p = 0.0031$, Cramer's V = 0.55). (**B**) The correlation of the diagnosis of vitreomacular disorder and the development of DONFL (Fisher exact test, $p < 0.0001$, Cramer's V = 0.9). (**C**) The correlation of macular hole and ILM texture (Trend test, $p = 0.0031$, Cramer's V = 0.33). (**D**) The correlation of ILM texture and DONFL (Trend test, $p = < 0.0001$, Cramer's V = 0.68)

vitreo-macular traction (VMT) without ERM). The ILM texture was graded as fragile (grade 1) in seven eyes, easy to peel in a sheet (grade 2) in 24 eyes, and sticky (grade 3) in 13 eyes. Of these, 9 eyes had high myopia (defined as >-6D). Post-operatively, DONFL developed in 23 (52.3%) eyes.

Morphological characteristics correlated with ILM texture (Fisher's exact test, $p = 0.0031$, Cramer's V = 0.55) [Figure 4A] and the development of DONFL (Fisher's exact test, $p < 0.0001$, Cramer's V = 0.9) [Figure 4B]. ERM with prominent inner retinal thickening (group 2) or with a macular hole (group 3) tended to have a stickier ILM when peeling (Fig. 4A. Fisher's exact test, $p = 0.0031$, Cramer's V = 0.55) and developed DONFL in 100% of the cases (Fig. 4B. Fisher exact test, $p < 0.0001$, Cramer's V = 0.9). In contrast, patients in Group 1 ERM had more fragile ILM when peeling and did not develop DONFL in all cases. We showed 2 cases in Fig. 5: Case 1 showed ERM with mainly outer retinal thickening, categorized as ERM group 1, which had no DONFL after the operation; Case 2 showed ERM with prominent inner retinal thickening, categorized as ERM group 2. The patient had DONFL after the operation. The presence of a macular hole itself predicts sticky ILM (trend test, $p = 0.0031$, Cramer's V = 0.33 [Figure 4C], but high myopia did not. The ILM texture is also correlated with DONFL (trend test, $p = < 0.0001$, Cramer's V = 0.68) [Figure 4D], in which stickier ILM would likely to develop DONFL after operation.

When compared with eyes without DONFL, eyes with DONFL showed a greater decrease in the ratio of ganglion cell complex/central retinal thickness in the foveal area, less VA LogMAR improvement, and slower P1 ratio recovery in 3-month follow-up (Table 3; Figs. 5 and 6 a ~ c). However, the vision and P1 ratio of patients with DONFL improved after a longer follow-up (≧6-months), although the improvement was not as obvious as that in the group without DONFL (VA logMAR: $p = 0.0468$, P1 ratio: $p = < 0.0001$).

Table 4 Presents the results of a sub-analysis of the initial and final VA LogMAR for preoperative lens status and a comparison of eyes with or without subsequent cataract surgery during the follow-up period. Cataract surgery was performed on 14 eyes. 4 eyes were pseudophakic before the surgery. Our results revealed that the initial lens status and cataract surgery was not related to visual acuity.

Discussion

As an increasing number of retinal disorders are being identified for ILM peeling, there has been a persistent concern about potential mechanical and traumatic changes to the retinal microstructure, such as the DONFL. Previous studies have demonstrated a strong link between ILM peeling and DONFL formation. Tadayoni et al. first described the appearance of DONFL [12], typically observed 1–3 months after surgery in 42–62% of eyes that underwent ILM peeling. Mitamura et al. [6] found that DONFL was present in 62.2% of

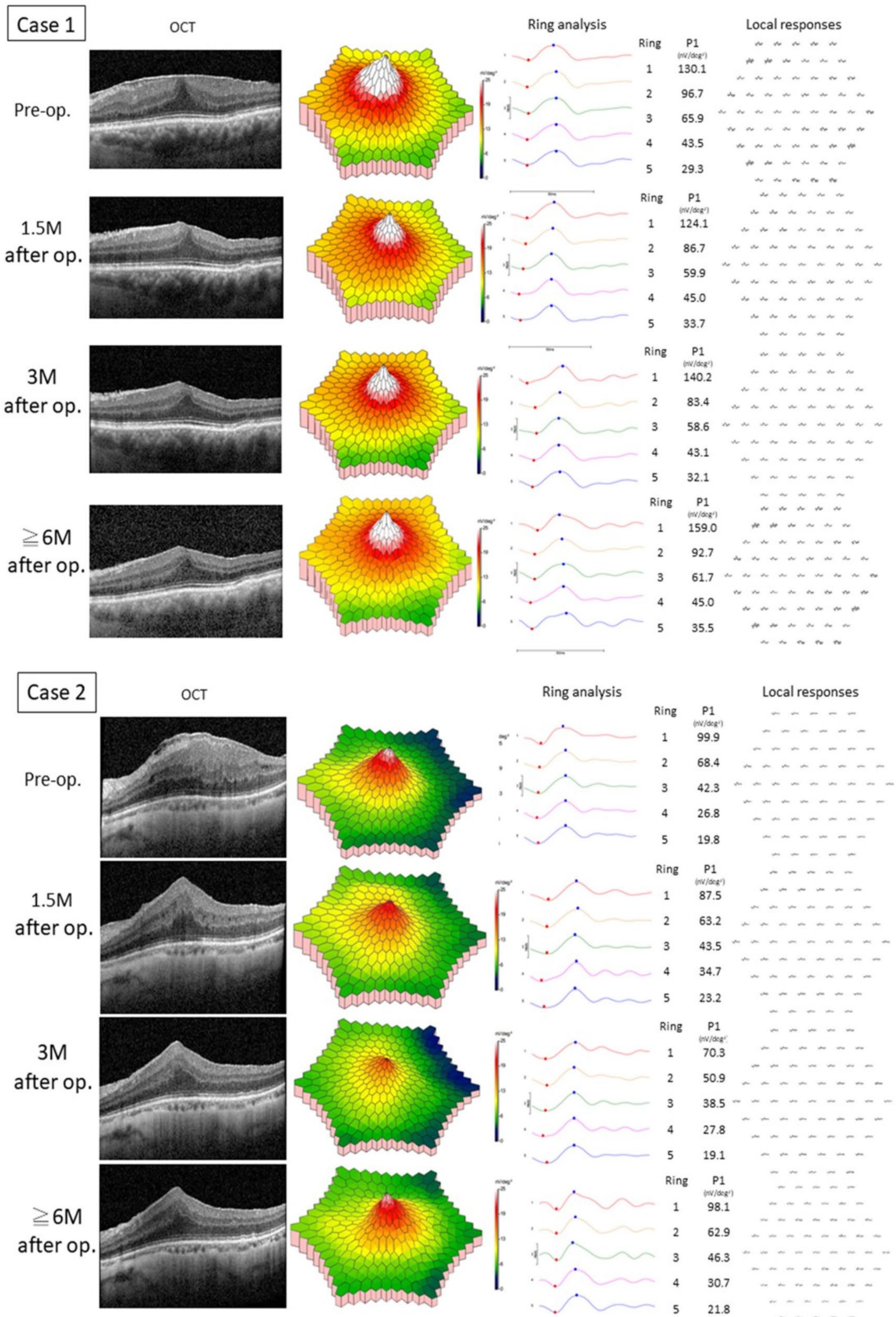

Fig. 5 (See legend on next page.)

(See figure on previous page.)

Fig. 5 OCT and mf-ERG of two patients. Case 1: ERM group 1 (mainly outer retinal thickening) and Case 2: ERM group 2 (prominent inner retinal thickening). **Case 1**: SD-OCT showed ERM with mainly outer retinal thickening, categorized as ERM group 1. The patient had no DONFL after the operation. (1) P1 amplitude of pre-op was 130.1 nV/deg^2, 96.7 nV/deg^2, 65.9 nV/deg^2, 43.5 nV/deg^2, 29.3 nV/deg^2 in R1, R2, R3, R4, and R5, respectively. P1 ratio was 130.1 + 96.7/43.5 + 29.3 = **3.1154**. (2) P1 amplitude of 1.5 M after op. was 124.1 nV/deg^2, 86.7 nV/deg^2, 59.9 nV/deg^2, 45.0 nV/deg^2, 33.7 nV/deg^2 in R1, R2, R3, R4, and R5, respectively. P1 ratio was 124.1 + 86.7/45.0 + 33.7 = **2.67**. (3) P1 amplitude of 3 M after op. was 140.2 nV/deg^2, 83.4 nV/deg^2, 58.6 nV/deg^2, 43.1 nV/deg^2, 32.1 nV/deg^2 in R1, R2, R3, R4, and R5, respectively. P1 ratio was 140.2 + 83.4/43.1 + 32.1 = **2.97**. (4) P1 amplitude of 6 M after op. was 159.0 nV/deg^2, 92.7 nV/deg^2, 61.7 nV/deg^2, 45.0 nV/deg^2, 35.5 nV/deg^2 in R1, R2, R3, R4, and R5, respectively. P1 ratio was 159.0 + 92.7/45.0 + 35.5 = **3.12**. **Case 2**: SD-OCT showed ERM with prominent inner retinal thickening, categorized as ERM group 2. The patient had DONFL after the operation. (5) P1 amplitude of pre-op was 99.9 nV/deg^2, 68.4 nV/deg^2, 42.3 nV/deg^2, 26.8 nV/deg^2, 19.8 nV/deg^2 in R1, R2, R3, R4, and R5, respectively. P1 ratio was 99.9 + 68.4/26.8 + 19.8 = **3.61**. (6) P1 amplitude of 1.5 M after op. was 87.5 nV/deg^2, 63.2 nV/deg^2, 43.5 nV/deg^2, 34.7 nV/deg^2, 23.2 nV/deg^2 in R1, R2, R3, R4, and R5, respectively. P1 ratio was 87.5 + 63.2/34.7 + 23.2 = **2.60**. (7) P1 amplitude of 3 M after op. was 70.3 nV/deg^2, 50.9 nV/deg^2, 38.5 nV/deg^2, 27.8 nV/deg^2, 19.1 nV/deg^2 in R1, R2, R3, R4, and R5, respectively. P1 ratio was 70.3 + 50.9/27.8 + 19.1 = **2.58**. (8) P1 amplitude of 6 M after op. was 98.1 nV/deg^2, 62.9 nV/deg^2, 46.3 nV/deg^2, 30.7 nV/deg^2, 21.8 nV/deg^2 in R1, R2, R3, R4, and R5, respectively. P1 ratio was 98.1 + 62.9/30.7 + 21.8 = **3.11**

the ILM peeling group, limited to areas with ILM peeling, and in 0.0% of the non-ILM peeling group. Another study reported that the incidence of DONFL was as high as 100% after idiopathic full-thickness macular hole (FTMH) surgery [13]. However, it is still debatable whether retinal nerve fiber layer (RNFL) reorganization or damage deeper than the RNFL occurs in the DONFL. Moreover, the type of ILM that causes DONFL remains unknown. Even with DONFL, most of this micro-damage does not appear to affect macular function as measured by visual acuity, microperimetry [14], or subjective automated visual field testing [15] in previous studies. Therefore, elucidating the association among preoperative morphology, ILM histopathological characteristics, subsequent DONFL, and the impact of visual acuity and macular function may help surgeons take measures to prevent irreversible retinal damage and achieve favorable post-operative visual outcomes.

Our results show that ERM with the presence of inner retinal thickening or with a macular hole predicts sticky ILM texture during peeling and the subsequent development of DONFL. Numerous theories have been proposed regarding the morphological progression of ERMs. Wang et al. [16] revealed that ERMs with high cellularity and glial cell density may damage the inner retinal structure. Based on these results, we speculated that the inner retinal structural changes caused by ERM might influence the ILM texture. When the ILM becomes sticky and difficult to peel, peeling itself might lead to a greater chance of retinal damage, and possibly DONFL, postoperatively. In our patients, DONFL appeared in 100% of ERM groups 2 and 3. However, none developed DONFL in ERM group 1. As for FTMH, with the small number of cases in our analysis (seven cases), further evaluation is needed to clarify the association between FTMH and DONFL. We also divided the patients into those with and without macular holes and those with high myopia. Patients who presented with macular holes showed a correlation with sticky ILM (trend test, $p = 0.0031$, Cramer's V = 0.33), but those with high myopia did not. We speculated that the presence of a macular hole, including eyes with ERM/VMT or even FTMH, might have more traction force. This force caused by the ERM/VMT/posterior hyaloid, distorted the inner retinal structure, and then influenced the ILM structure, which made the ILM hard to peel.

Regarding DONFL, in our study, eyes with DONFL showed a greater decrease in the ratio of ganglion cell complex/central retinal thickness, which is consistent with previous studies [8, 9, 12]. Thinning of the inner retina may be related to the loss or damage of Müller cells. The endfeet of Müller cells participate in the formation of the ILM. Stripping the ILM may deprive Müller cells of their endfeet function, causing the remainder to degenerate. As for visual acuity, every participant in this study showed VA improvement after ILM peeling. However, eyes in the DONFL group showed slower and lesser VA LogMAR improvements than those in the non-DONFL group. In terms of macular function, a previous study suggested that ILM peeling may damage the inner retinal layers and Müller cell function, which have negative effects on the P1 wave of multifocal ERG [17]. It is believed that N1 is generated by photoreceptors in the outer retinal layer and P1 is generated by Müller and bipolar cells [18, 19]. Eyes in the DONFL group in our study showed a downward trend in the P1 ratio through the 3-month trend, but slowly recovered and increased after 6 months; this is statistically different from the non-DONFL eyes, which showed a decrease in the P1 ratio at 1.5 months but recovered and increased at 3 and 6 months. We propose that decreased inner retinal thickness and more micro-damage to the inner retina in eyes with DONFL may result in a greater decrease in the P1 ratio and less VA improvement in the first 3 months; however, the damage recovered with longer follow-up, similar to vision and the P1 ratio.

The main limitations of this study are as follows: (1) This study was retrospective, the sample size of patients was relatively small, and the post-operative follow-up period was relatively short. (2) This was a single-center study, and a multicenter study is necessary for further analysis. (3) We did not analyze the immunohistopathological properties of ILM. (4) ILM texture was graded by a single experienced surgeon during peeling, which

Table 3 The correlation between DONFL, and the ratio of GCC complex/central retinal thickness, visual acuity LogMAR and P1 ratio

	With DONFL			**Without DONFL**			**With DONFL vs. Without DONFL**	
	LS-Means (SE)	**Difference of LS-Means (95% CI)**	***p* value**	**LS-Means (SE)**	**Difference of LS-Means (95% CI)**	***p* value**	**Difference of LS-Means (SE; 95% CI)**	***p* value**
GCC complex/central retinal thickness								
Baseline	0.35 (0.02)	Reference		0.29 (0.02)	Reference		Reference	
1.5 months	0.27 (0.02)	-0.08 (-0.10 to -0.05)	< 0.0001	0.24 (0.01)	-0.04 (-0.07 to -0.02)	0.0017	-0.03 (0.02; -0.07 to 0.002)	0.0633
3 months	0.23 (0.01)	-0.12 (-0.15 to -0.09)	< 0.0001	0.25 (0.01)	-0.04 (-0.06 to -0.01)	0.0088	-0.09 (0.02; -0.13 to -0.04)	< 0.0001
≧6 months	0.25 (0.01)	-0.10 (-0.13 to -0.06)	< 0.0001	0.26 (0.01)	-0.03 (-0.06 to -0.001)	0.0399	-0.07 (0.02; -0.11 to -0.02)	0.0045
Trend: from baseline to ≧6 M		-0.03 (-0.04 to -0.02)	< 0.0001		-0.01 (-0.02 to 0.001)	0.0628	-0.02 (0.01; -0.04 to -0.01)	0.0009
VA LogMar								
Baseline	0.69 (0.06)	Reference		0.84 (0.09)	Reference		Reference	
1.5 months	0.65 (0.07)	-0.04 (-0.13 to 0.05)	0.3789	0.71 (0.09)	-0.13 (-0.33 to 0.07)	0.2126	0.09 (0.11; -0.13 to 0.31)	0.4262
3 months	0.47 (0.05)	-0.21 (-0.26 to -0.17)	< 0.0001	0.35 (0.04)	-0.48 (-0.64 to -0.33)	< 0.0001	0.27 (0.08; 0.11 to 0.43)	0.0010
≧6 months	0.26 (0.04)	-0.42 (-0.53 to -0.32)	< 0.0001	0.24 (0.04)	-0.60 (-0.78 to -0.42)	< 0.0001	0.17 (0.11; -0.04 to 0.38)	0.1068
Trend: from baseline to ≧6 M		-0.14 (-0.18 to -0.11)	< 0.0001		-0.21 (-0.28 to -0.15)	< 0.0001	0.07 (0.04; 0.001 to 0.14)	0.0468
P1 ratio								
Baseline	3.54 (0.14)	Reference		2.84 (0.11)	Reference		Reference	
1.5 months	2.87 (0.11)	-0.66 (-0.86 to -0.47)	< 0.0001	2.79 (0.12)	-0.05 (-0.27 to 0.17)	0.6748	-0.61 (0.15; -0.91 to -0.32)	< 0.0001
3 months	2.84 (0.13)	-0.69 (-0.83 to -0.56)	< 0.0001	3.27 (0.21)	0.43 (0.03 to 0.83)	0.0339	-1.12 (0.21; -1.54 to -0.70)	< 0.0001
≧6 months	3.10 (0.14)	-0.43 (-0.62 to -0.25)	< 0.0001	3.58 (0.17)	0.74 (0.40 to 1.09)	< 0.0001	-1.18 (0.20; -1.57 to -0.78)	< 0.0001
Trend: from baseline to ≧6 M		-0.13 (-0.19 to -0.08)	< 0.0001		0.27 (0.15 to 0.39)	< 0.0001	-0.40 (0.07; -0.54 to -0.27)	< 0.0001

LS-means: least squares means; SE: standard error; CI: confidence intervals;

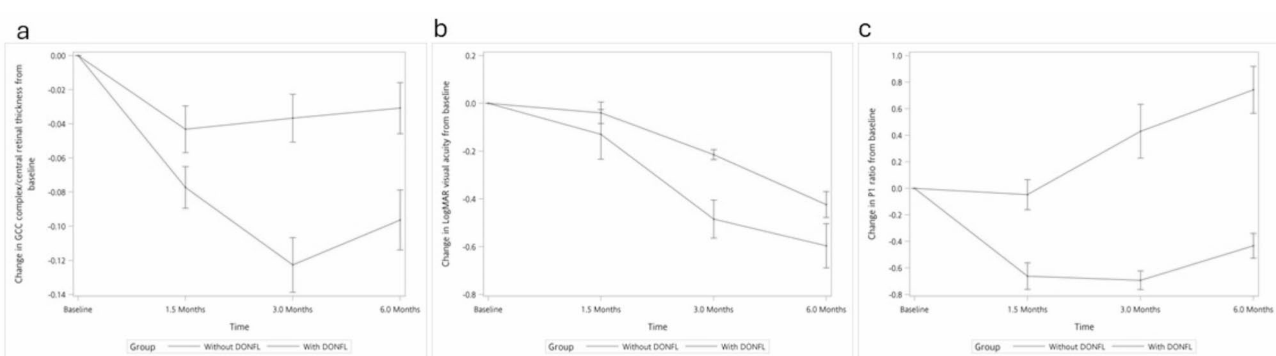

Fig. 6 (**a**) Eyes with DONFL showed more decrease of the ratio of ganglion cell complex /central retinal thickness in the fovea area in ≧6-months follow up (Least Squares Means= -0.02, standard error = 0.01, 95% confidence intervals=-0.04 to -0.01, $p = 0.0009$). (**b**) Eyes with DONFL showed less VA LogMAR improvement in ≧6-months follow up (Least Squares Means = 0.07, standard error = 0.04, 95% confidence intervals = 0.001 to 0.14, $p = 0.0468$). (**c**) Eyes with DONFL showed slower P1 ratio recovery in ≧6-months follow up (Least Squares Means= -0.40, standard error = 0.07, 95% confidence intervals=-0.54 to -0.27, $p < 0.0001$)

may have been subjective. (5) The classification system we used for ERM was based on our subjective interpretation of SD-OCT scan images. (6) 26 eyes may develop some degree of cataract at the 6-month follow-up. This outcome may have resulted in an underestimation of visual recovery after ILM peeling. However, after adjustment for the initial and final lens status, we found that it was not significantly related to visual acuity.

Table 4 Preoperative and Postoperative VA in Terms of Lens Status and Cataract Surgery

	Initial VA logMAR	*p* value	Final VA logMAR	*p* value
Initial lens status		0.3175		0.7827
Phakia, 40 eyes	0.7755/0.6990		0.2545/0.2218	
Pseudophakia, 4 eyes	0.5797/0.699		0.2249/0.2280	
Cataract surgery		0.5023		0.6002
Yes, 14 eyes	0.7201/0.6990		0.2308/0.2218	
No, 26 eyes	0.8054/0.6990		0.2674/0.2218	

Values are mean/median

VA: Visual acuity; logMAR: logarithm of the minim angle of resolution

Conclusion

The present study identified OCT biomarkers and their correlation with ILM texture and DONFL development. ERM with prominent inner retinal structural damage or with macular holes is likely to have a stickier ILM when peeling, leading to a subsequently DONFL. The appearance of DONFL results in an initial decrease in macular function recovery and slower post-operative visual improvement. Surgeons should be more delicate when peeling sticky ILM, especially in eyes with ERM with prominent inner retinal thickening or macular holes.

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Author contributions
Material preparation, data collection and analysis were performed by IHC, MSL, CLT, HPT, and SJS. The first draft of the manuscript was written by IHC. MSL, CLT, HPT, and SJS commented on previous versions of the manuscript. IHC, MSL, CLT, HPT, and SJS read and approved the final manuscript.

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Data availability
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Written informed consent from the parent/legal guardian of participants was not required for this retrospective study in accordance with the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E (II)-20230113). The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E (II)-20230113) and adhered to the tenets of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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