Predictive Value of Ectopic Inner Foveal Layer Without Internal Limiting Membrane Peeling For Idiopathic Epiretinal Membrane Surgery

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Research Article

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Abstract

Purpose: To investigate the clinical importance of ectopic inner foveal layer (EIFL) grading (mild to severe) diagnosed with idiopathic epiretinal membrane (iERM) patients who were peeled up only ERM in eyes with EIFL.

Materials and Methods: Patients diagnosed with iERMs who have undergone PPV including only ERM peeling were enrolled into the study; and follow-up findings were recorded at baseline, months 3, 6, 12, and final examinations, retrospectively. EIFL was divided into four grades from mild to severe. Pre- and postoperative anatomical changes were measured by spectral domain optical coherence tomography (SD-OCT) imaging method. The association between EIFL and other SD-OCT parameters with best corrected visual acuity (BCVA) was assessed before and after PPV surgery.

Results: One-hundred thirty eight eyes of 106 patients with EIFL (mild to severe) were included in the study. The higher thickness of EIFL was significantly correlated with lower baseline BCVA ($r = 0.575$, $p = 0.020$) and final BCVA ($r=0.748$, $p= 0.001$). Although, EIFLs continued in advanced stage cases (stage 3 and 4) (64 eyes (82%)) at final visit, observed in 8 eyes (23 %) in early stage (stage 2) of iERMs. Above all, a strong positive correlation was found between EIFL thickness and ERM recurrence rate ($r=0.876$, $p <0.001$). Recurrence ERM was detected in 27 eyes, which were found in 2 eyes (%7) at stage 1, 3 eyes (%9) at stage 2, 10 eyes (%23) at stage 3, and 12 eyes (%33) at stage 4 ($p<0.001$).

Conclusion: A negative relationship was found between the severity of EIFL and postoperative anatomical and visual recovery. In terms of surgical timing, early stages (stage 1 and 2) may be preferred for providing good anatomical and visual recovery and low recurrence rate following surgery. In relation to further anatomical and visual yields, additional internal limiting membrane peeling may not be an essential procedure for early grades of iERMs (stage 1 and 2).

Introduction

The pars plana vitrectomy (PPV) with epiretinal membrane (iERM) peeling is the most acceptable surgical procedure for symptomatic ERMs. Despite superiority of anatomical achievements, visual prognosis is occasionally unpredictable following the surgery [1–4]. Therefore, several studies have been conducted to identify sensitive prognostic biomarkers that may estimate postoperative achievement visually. In line with recent advances in technology of spectral domain optical coherence tomography (SD-OCT), faster data acquirement and higher resolution have improved due to significantly higher scanning speeds. Furthermore, SD-OCT imaging is a valuable imaging method in order to evaluate the ERM before and after surgery, and to determine the prognosis [5, 6].

Various biomarkers have been presented to the literature as predictors of visual acuity following surgery in idiopathic ERMs (iERMs), such as integrity and continuity of both ellipsoid and interdigitation zone, and length of the photoreceptor outer segment [3, 7, 8]. Whereas, prognostic evaluation of such parameters maintains controversial because assessment of outer retinal integrity may not be analysed in

some eyes with iERMs due to the artefacts present in SD-OCT [9]. Since analysis of outer retinal changes may be inadequate to predict postoperative visual result, studies of inner retinal layers which are one of the main regions affected by ERM-related mechanical stress should be considered first [10–14].

In a recent study, existence of ectopic inner foveal layers (EIFLs) in central foveal zone on eyes with iERMs was characterized by SD-OCT. The formation of EIFL formation may symbolize a substantial part of ERM development; and it is crucial for newly recommended SD-OCT staging diagram in iERMs [15]. Although the presence of EIFL was related with lower baseline best corrected visual acuity (BCVA), the prognostic effect of EIFL on postoperative BCVA has not been clarified due to the controversial results of studies on this issue [14, 15].

Outcomes of both visual and anatomical surgery were analysed in the patient cohort diagnosed with iERMs who had PPV with solely ERM peeling in order to investigate clinical importance of EIFL.

Materials And Methods

Medical records of 138 eyes of 106 iERM patients who have undergone PPV in a tertiary hospital and screened by two independent evaluators (BK and AC) between September 2013 and March 2019 were reviewed retrospectively.

Patients were allocated into four stages in terms of ERM types;

Stage 1 – 26 eyes,

Stage 2 – 34 eyes,

Stage 3 – 42 eyes,

Stage 4–36 eyes.

The study protocol was conducted in accordance with the principles of the Helsinki Declaration and approved by the local ethics committee.

Inclusion criteria were presence of iERM which was followed up regularly and treated through PPV and membrane peeling (only ERM), and a follow-up period of at least 13 months.

Ophthalmic assessment was performed as a comprehensive ophthalmologic examination including BCVA and IOP assessment, slit lamp biomicroscopy, fundus examination, and SD-OCT imaging at the baseline and months 3, 6, 12, and final visit following PPV surgery. BCVA was evaluated with Snellen chart at each visit and subsequently converted to the logarithm of the minimum resolution angle (logMAR).

Exclusion Criteria were as follows;

Any history of intraocular surgery except for phacoemulsification surgery, previous retinal detachment history, all types of age-related macular degeneration (AMD), history of choroidal neovascularization (CNV), pachychoroid spectrum diseases and all subtypes, all forms of diabetic retinopathy that cause macular edema, retinal dystrophies, previous history of all types of retinal vein and artery occlusion, any history of advanced glaucoma and optic neuropathy, history of ocular trauma, history of endophthalmitis or any intraocular infection, macular telangiectasia, history of Irvine–Gass syndrome, other reasons that may cause vision decrement other than ERM.

Ectopic inner fovea layers were characterized by SD-OCT scans in the fovea as follows: the presence of hyporeflective and hyperreflective bands spreading from the inner nuclear layer and the inner plexiform layer along with the fovea region are shown in Fig. 1. The EIFL thickness in the central fovea region was manually measured through Heidelberg Spectralis as a vertical line between the outer edge of the inner nuclear layer and the lower face of the central ERM (Fig. 1) [15].

Mean central macular thickness (CMT) were measured automatically by the Heidelberg programme. In SD-OCT, ERM was generally described as single, irregular lines above the ILM as the underlying retinal wrinkle and hyperreflective band among the ERM and ILM. In present study, all ERMs were based on a four-grade staging system as in the ERM classification by Govetto et al. [15] as shown in Fig. 1.

Staging scheme of ERMs by SD-OCT:

Stage 1. Indicates mild ERM with several anatomical changes. The foveal depression and contour are maintained, and all retinal layers are well selected. It has a thin cellophane-like membrane appearance.

Stage 2. There are more anatomical modifications. Foveal depression has disappeared, but all retinal layers are still well visible.

Stage 3. Sustained EIFLs overlap the entire foveal base (white arrows). Similar to grade 1 ERMs, foveal depression has lost and all retinal layers are well displayed.

Stage 4. Indicates ERM with irregularity and disorganization in all layers of the fovea. Thick EIFLs entirely enclose the foveal area (white arrows), foveal depression is not observed and whole retinal layers are distorted.

Cystoid macular edema (CME) was characterized as the existence of multiple hyperreflective intra-retinal cystoid spaces on OCT. The definition of pseudohole which was determined on the B-scan OCT image findings established by the International Vitreomacular Traction Working Group was accepted [16].

The presence of a discontinuity of ellipsoid band at the fovea was identified as an indicator of ellipsoid zone disruption. Surgical procedures were performed as ERM peeling with a standard 3-port 23 gauge PPV system. A combination surgery with the same time phacoemulsification was implemented in the event of advanced cataracts as N3, C3, P3 or further lens opacity (LOCS III) [17].

The Surgical procedure:

Anterior and core vitrectomy were performed initially and following the posterior hyaloid was detached with the aid of visualization by triamcinolone acetonide; ERM were stained by membrane blue dual dye and peeled up to the vascular arcades. At the end of the operation, partial air fluid exchange was performed on all patients. The operation was terminated by applying topical and subconjunctival antibiotics onto the eye.

Statistical analysis

Descriptive statistics were calculated for all variables. Mean and SD values were expressed in continuous variables; categorical variables were expressed in frequency and percentage for categorical variables. The distribution of data was determined through Kolmogorov-Smirnov test and the Levene test was used to delineate variance homogeneity. The t-test or ANOVA test were used to analyze inter-group data with a regular distribution and equal variance. Non-normally distributed and ranked data for inter-group analysis were implemented by Mann-Whitney U test or Kruskal Wallis test. Chi-square test was used to compare rates between the groups. Friedman test was used for data changes that did not conform the normal distribution during the follow-up periods, and the MANOVA test was used for data that were normally distributed. Pearson's correlation test was used to evaluate the association between continuous functional and anatomical variables. Generalized equation estimation (GEE) analysis was used for statistical analysis, since the double eyes were included in the study in some patients. Baseline BCVA and CMT as well as alterations in CMT and EIFLs thickness from baseline were involved as variables included in the univariate and multivariate models. SPSS (version 22.0, SPSS Inc., Chicago, IL, USA) program was used for statistical analysis. Any p value below 0.05 ($p < 0.05$) was set out as statistically significant.

Results

The mean age of the participants was 69.25 ± 7.81 years (range, 48–86 years) with mean follow-up time was 26.18 ± 13.07 months (range, 13–68 months). Fifty-one (%48) patients were male and 55 (%52) patients were female.

Our surgical intervention criteria were BCVA > 0.20 log MAR at the time of diagnosis or metamorphopsia that compromises visual quality if BCVA was < 0.20 log MAR. Combined procedure was implemented in 16 of 26 eyes (%61.5) in stage 1, 23 of 34 eyes (67%) in stage 2, 26 of 42 eyes (62%) in stage 3 and 23 of 36 eyes (64%) in stage 4 ($p = 0.067$).

Twenty-one eyes were excluded from the study. Seventeen eyes were excluded due to poor OCT image quality ($n = 12$) and choriocleral interface that could not be imaged ($n = 5$). Four eyes were excluded due to macular diseases such as CNV ($n = 4$).

There were no statistically differences in age ($p = 0.952$), follow-up time ($p = 0.908$), gender ($p = 0.244$), side ($p = 0.994$), anterior segment status ($p = 0.219$), baseline IOPs ($p = 0.673$), baseline BCVA ($p = 0.019$),

implementing number of combined procedure ($p = 0.067$).

Recurrence ERM was detected in 27 of 138 eyes, which were found in 2 eyes (%7) at stage 1, 3 eyes (%9) at stage 2, 10 eyes (%23) at stage 3, and 12 eyes (%33) at stage 4 ($p < 0.001$).

The clinical data of participants is summarized in Table 1. Baseline findings of the study were presented in Table 2.

Table 1
The demographic and clinical data of patients

Groups	Grade 1	Grade 2	Grade 3	Grade 4	p values
Eyes	26	34	42	36	
Gender	12♀14♂	11♀12♂	15♀17♂	11♀14♂	0.244*
Age (mean $\pm$ SD)	67.58 $\pm$ 9.41	68.76 $\pm$ 6.31	69.62 $\pm$ 8.18	70.84 $\pm$ 7.69	0.952*
Side	13♀13♂	14♀20♂	20♀22♂	14♀22♂	0.994*
Follow up (months) (mean $\pm$ SD)	25.33 $\pm$ 10.36	26.23 $\pm$ 13.48	28.81 $\pm$ 17.40	27.53 $\pm$ 8.83	0.908*
Follow up (months) (range)	13 to 57	13 to 54	13 to 68	13 to 52	
ERM recurrences	2/26 (%7)	3/34 (%9)	10/42 (%23)	12/36 (%33)	< 0.001†
*ANOVA test, † Chi square test					
SD, standard deviation; ♀ female, ♂ male; ♀ right, ♂ left; ERM, epiretinal membrane; ♀phakic, ♀pseudophakic					

Table 2
Baseline findings of the study

ERM (number)	Stage 1 (n = 26)	Stage 2 (n = 34)	Stage 3 (n = 42)	Stage 4 (n = 36)	p value
BCVA (log MAR) (Snellen)	(0.46 ± 0.22) (20/57)	(0.51 ± 0.24) (20/64)	(0.68 ± 0.20) (20/93)	(0.71 ± 0.25) (20/100)	0.019*
CMT (µm)	312.08 ± 50.76	419.84 ± 57.94	488.37 ± 46.10	545.61 ± 40.34	< 0.001*
CME (%)	6/26 (%23)	7/34(%20)	9/42(%21)	8/36(%22)	0.091†
Pseudohole (%)	4/26(%15)	6/34(%17)	7/42(%16)	5/36(%13)	0.284†
Ellipsoid zone disruption (%)	0	1/34(%2)	6/42(%14)	8/36(%22)	0.002†
EIFL thickness(µm)	0	161.49 ± 34.79	189.78 ± 47.84	254.18 ± 54.74	0.021*
*P-value: ANOVA test. †P-value: chi-square test.					

Stage 1;

Best corrected visual acuity increased from baseline 0.46 ± 0.22 log MAR (20/57 equivalent) to 0.11 ± 0.12 log MAR (20/25 equivalent) in the final visit (p < 0.001). CMT decreased from baseline 312.08 ± 50.76 µm to 248.08 ± 41.63 µm in the final visit (p < 0.001). IOP decreased from baseline 14.66 ± 1.15 mmHg to 14.25 ± 2.45 mmHg in the final visit (p = 0.467).

Stage 2;

Best corrected visual acuity increased from baseline 0.51 ± 0.24 log MAR (20/64 equivalent) to 0.15 ± 0.18 (20/28 equivalent) log MAR in the final visit (p = 0.021). CMT decreased from baseline 419.84 ± 57.94 µm to 366.84 ± 60.09 µm in the final visit (p < 0.001). IOP decreased from baseline 14.76 ± 1.16 mmHg to 16.07 ± 5.28 mmHg in the final visit (p = 0.147).

Stage 3;

Best corrected visual acuity increased from baseline 0.68 ± 0.20 log MAR (20/93 equivalent) to 0.40 ± 0.38 log MAR (20/50 equivalent) in the final visit (p = 0.015). CMT decreased from baseline 488.37 ± 46.10 µm to 396.18 ± 28.03 µm in the final visit (p < 0.001). IOP decreased from baseline 15.12 ± 1.58 mmHg to 14.62 ± 1.92 mmHg in the final visit (p = 0.230).

Figure 2 shows SD-OCT images of two different patients who underwent PPV at the 2nd and 3rd stages during follow-up periods.

Stage 4;

Best corrected visual acuity increased from baseline 0.71 ± 0.25 log MAR (20/100 equivalent) to 0.48 ± 0.32 log MAR (20/60 equivalent) in the final visit ($p < 0.001$). CMT decreased from baseline 545.61 ± 40.34 μm to 401.46 ± 46.97 μm in the final visit ($p < 0.001$). IOP decreased from baseline 14.92 ± 0.27 mmHg to 15.38 ± 2.75 mmHg in the final visit ($p = 0.200$).

Comparison of each stages according to the follow-up periods among patients revealed a significant change in stage 1 for CMT (month 3 $p < 0.001$; month 6 $p = 0.041$; month 12 $p = 0.001$, final visit $p < 0.001$).

As for BCVA, significant change was observed in stage 1 for according to all follow ups between other stages (month 3, $p = 0.012$; month 6, $p = 0.039$; month 12, $p = 0.043$; final visit, $p = 0.028$). The changes in measurements at baseline and all follow-up periods are summarized in Table 3.

Table 3
The results of the study

ERM types	Baseline	3rd month	6th month	12th month	Final visit	p values
Stage 1						
BCVA (logMAR)	0.46 ± 0.22	0.21 ± 0.20	0.17 ± 0.21	0.14 ± 0.16	0.11 ± 0.12	< 0.001
CMT (µm)	312.08 ± 50.76	279.75 ± 49.39	262.16 ± 66.54	257.08 ± 40.47	248.08 ± 41.63	< 0.001
IOP (mmHg)	14.66 ± 1.15	14.16 ± 2.28	14 ± 2.76	13.75 ± 1.60	14.25 ± 2.45	0.467
EIFL (µm)	-	-	-	-	-	-
Stage 2						
BCVA (logMAR)	0.51 ± 0.24	0.45 ± 0.34	0.29 ± 0.27	0.22 ± 0.23	0.15 ± 0.18	0.021
CMT (µm)	419.84 ± 57.94	435.07 ± 58.48	389.84 ± 58.74	373.69 ± 57.38	366.84 ± 60.09	< 0.001
IOP (mmHg)	14.76 ± 1.16	14.23 ± 2.12	13.84 ± 2.47	14.46 ± 2.43	16.07 ± 5.28	0.147
EIFL (µm)	161.49 ± 34.79	105.94 ± 22.45	71.79 ± 15.45	59.31 ± 12.78	52.44 ± 10.92	< 0.001
Stage 3						
BCVA (logMAR)	0.68 ± 0.20	0.60 ± 0.28	0.56 ± 0.41	0.50 ± 0.32	0.40 ± 0.38	0.015
CMT (µm)	488.37 ± 46.10	434.31 ± 34.11	415.93 ± 36.26	399.93 ± 30.46	396.18 ± 28.03	< 0.001
IOP (mmHg)	15.12 ± 1.58	14.56 ± 2.65	14.37 ± 2.55	13.87 ± 2.12	14.62 ± 1.92	0.230
EIFL (µm)	189.78 ± 47.84	131.46 ± 29.90	113.82 ± 22.94	91.47 ± 19.34	82.92 ± 23.56	< 0.001
Stage 4						
BCVA (logMAR)	0.71 ± 0.25	0.77 ± 0.41	0.63 ± 0.35	0.54 ± 0.29	0.48 ± 0.32	< 0.001
CMT (µm)	545.61 ± 40.34	473 ± 50.38	414.15 ± 49.55	402.23 ± 39.81	401.46 ± 46.97	< 0.001
IOP (mmHg)	14.92 ± 0.27	15.23 ± 1.36	16.92 ± 4.97	17.38 ± 5.66	15.38 ± 2.75	0.200
EIFL (µm)	254.18 ± 54.74	163.42 ± 39.73	134.97 ± 33.81	117.84 ± 26.43	107.84 ± 24.93	< 0.001
P-value: MANOVA test.						

A correlation was found between lower baseline BCVA with both higher baseline CMT ($p < 0.001$, $r = 0.574$) and higher baseline EIFL thicknesses ($r = 0.575$, $p = 0.020$). The higher thickness of baseline EIFL was correlated with lower final BCVA ($r = 0.748$, $p = 0.001$).

In addition, CMT was correlated with EIFL thickness ($p < 0.001$, $r = 0.476$); this may be explained as the effect of these variables on visual acuity. Although EIFLs continued in advanced stage cases (stage 3 and 4) on 64 of 78 eyes (82%) at the final visit, it was observed on 8 of 34 (23 %) eyes in the early stage (stage 2).

At the final visit, foveal pit was formed on 20 of 26 eyes (76 %) with stage 1 ERM, on 19 of 34 eyes (55 %) with stage 2 ERM, on 5 of 42 eyes (12%) with stage 3 ERM, and on 3 of 36 eyes (8%) with stage 4 ERM. These results were significantly differ when compared between groups ($p = 0.031$). Figure 3 shows the formation of foveal depression according to the pre- and postoperative follow-up periods.

Positive correlation detected between baseline CMT and final CMT ($r = 0.575$, $p = 0.020$). A positive correlation was found between EIFL thickness and recurrence rate ($p < 0.001$, $r = 0.694$). Figure 4 shows ERM recurrence by EIFL thickness amount between groups.

Discussion

This study investigated the clinical importance of EIFL grading (mild to severe) in a cohort of 138 eyes diagnosed with iERMs and exposed to PPV (solely ERM peeling); and a significant relationship was detected between higher baseline thickness of EIFL and high recurrence rate, lower baseline and final BCVA over long-term follow-ups ($p < 0.05$).

There is not any common consensus on the timing of surgery on eyes with iERMs. Determining the severity of ERM and assessment of the prognosis by surgical removal may be difficult [15]. The characterization of reliable prognostic biomarkers is thereby crucial among surgeons who predict postoperative functional and anatomical results in eyes with iERMs. It has been shown in various studies that ILM peeling with ERM does not provide an anatomical and visual benefit compared to ERM peeling alone in iERM patients. The rate of recurrent ERM and the need for repetition of ERM surgery were found to be lower in eyes that peeled up with ILM and ERM [18–20]. Although similar rates were observed in our study, we found a positive correlation between ERM recurrence and EIFL thickness. This study may contribute to the hypothesis of visual and anatomical disruption of Müller cells in the development of EIFLs.

Up to date, there is numerous number of OCT studies which analyse the prognostic role of inner retinal changes on decrement of BCVA in iERMs. In fact, recent studies suggest that impairment of external retinal layers may be inadequate in order to explain vision deterioration precisely in ERM formation. However, the integrity of the photoreceptor and the outer retinal layer had an important prognostic value in final visual acuity during long-term follow-ups [10–14, 15]. In this context, we have classified the

presence of EIFL in a subset of iERMs and associated this incidence of anatomical findings with poor initial BCVA.

Govetto et al. evaluated the effect of EIFL on anatomical and functional outcomes on 111 eyes of 107 patients with iERMs that both ERM and ILM were peeled up in a retrospective study for 12 months. The presence of EIFL had a respectable impact on the initial and final BCVA; and it was observed that the higher the EIFL correlated with lower the initial BCVA. The EIFLs were detected in 56 of 111 eyes (50.4%) before ERM and ILM peeling surgery. EIFL continued to exist on 51 (91%) of 56 eyes after the surgery due to the diagnosis of stage 3 and 4 iERMs. Although thickness of the EIFL manifested a decrease after the surgery ($p < 0.001$), the reduction of EIFL in postoperative period did not cause to any change in final BCVA. They suggested that presence of EIFL may be a negative prognostic factor for postoperative anatomical and visual recovery [21]. Predicting prognostic efficacy of inner retinal changes on visual function may cause bias for assessment of such analysis due to the strong correlation between inner retinal thickness and CMT. Previous studies have demonstrated independent relationships among the inner retinal thickness and visual acuity in iERMs; however, the automated software may usually take analyses corresponding to the incorrect retinal layer rather than inner retinal parameters [13, 22]. In our study, EIFL was present at baseline in 98/138 (71%) of patients in our study and decreased in 72/138 (52%) post-surgery but did not disappear completely. In current study, we may suppose that excess amount of EIFL had a negative prognostic effect in terms of ERM recurrence rate, visual acuity improvement, and recovery of foveal anatomy.

In a recent study by Mavi Yıldız et al., both ERM and ILM were peeled up in 112 eyes of 112 patients, and less visual and anatomical gains were achieved in advanced stages (stage 3 and 4) [23]. In our study, after solely performing ERM peeling, both the number of recurrences were higher and the visual and anatomical gains were less for advanced stage (stage 3 and 4).

Ectopic inner foveal layer thickness decreased during postoperative follow ups [24]. This decrement was evident up to 6 months, and minimum between 6 months and 12 months following ERM surgery in our study. However, it showed that postoperative EIFL thinning did not directly affect alterations of postoperative visual acuity. This fact could be raised new questions about EIFL-associated visual deterioration and limited functional and anatomical recovery following ERM surgery. In fact, recent studies suggested that the more the thickness of the EIFL, the lower the final BCVA [22, 25]. It may be considered that ectopic retinal tissue can act as a physical barrier effect on image formation by being located between afferent light and photoreceptors, which obstructs or distorts the visual image projected onto the foveal cones. The severity of this image distortion may be directly proportional to the increase in EIFL thickness [25].

In the presence of EIFL, various changes may develop in retinal microstructures. Chronic inner foveal displacement may lead to damage and disruption on photoreceptors and other retinal cells resulting with disturbances in normal neural conduction, visual deterioration, and metamorphosia on eyes with iERM [15, 22, 26, 27]. This fact may be particularly associated with stage 4 ERMs which are involved by

complete foveal irregularity and lower postoperative visual achievements. As stated in the study of Matthews et al., complete recovery of foveal depression in the long follow-up periods after surgery gradually decreased with increment of ERM grade [28]. Persistence of EIFL following ERM surgery in most eyes with stage 3 and 4 ERM may clarify the low postoperative anatomical gain and lower visual outcomes in these groups. Ellipsoid zone disruption and outer retinal layers changes in stage 4 might have affected final visual acuity in present study.

The presence of EIFL in the absence of traction suggests that it may result in mechanical displacement of the inner retinal tissue, possibly as a result of other molecular reactions caused by Müller cells [15]. Müller cell activation may be responsible for inner retinal reorganization on fovea in postoperative period in eyes with stage 2 ERM, and symbolize a reparative reaction following ERM surgery. Therefore, internal limiting membrane peeling has negligible effect on visual results following ERM surgery. ERM recurrences are minimized by peeling of the ILM, nevertheless most recurrences are clinically insignificant [19, 20]. In a study by Ahn et al., better outcomes were found in terms of anatomical and functional recovery in patients with iERM whose ILM was not peeled in the 1st month. They declared that in line with visual outcome and photoreceptor integrity, supplementary ILM peeling may not be an obligatory procedure [29]. Recently, the development of myocystic macular edema without vascular leakage in fluorescein angiography with ganglion cell loss and thickening of the inner nuclear layer has been termed retrograde maculopathy. This condition is common seen in patients with iERMs who had undergone both ERM and ILM peeled up [30]. In our study, none of the patients developed retrograde maculopathy and did not affect functional gains notably.

To the best of our knowledge, this is the first study to evaluate EIFL, recurrence rate, anatomical and visual outcomes according to the SD-OCT-based ERM staging scheme before and after ERM peeling alone.

The limitations of current study include the retrospective design and absence of high-density macular scanning for all cases. Despite the use of high-intensity SD-OCT imaging in most of involved eyes, the central fovea might have been overlooked by a standard macular raster or single high-definition horizontal B-scan, resulting in mismatch and overlooked classification of some iERMs.

Strengths of our study include convenient follow-ups and sample size, two blinded independent evaluators and the usage of SD-OCT eye tracking systems that enable definitive analysis of postoperative anatomical alterations in all cases. Although longer follow-up periods represent the strength of our study, it was reported that both visual acuity and SD-OCT parameters return to normal within approximately 2 years after surgery, which may support that long-term follow-up provides greater opportunities for evaluation of postoperative anatomical and visual outcomes [31].

In this study, the prognostic value of the ERM classification was investigated by SD-OCT which was convenient and accessible tool to predict functional and anatomical postoperative outcomes. The existence of EIFL should not be the main factor in the surgical decision-making process when ERM grading was assessed. However, according to this study, we may suggest that the surgical timing which

may be preferred in terms of visual improvement, postoperative anatomical gain and lower recurrence rate is stage 2 and below. Moreover, we may discuss that it is an early grades of EIFL (stage 1 and 2), the outer retinal layers are not affected, and the foveal cavity formation is higher in the postoperative period. Also, ILM peeling may not be an indispensable surgical procedure in the early grades of iERMs (stage 1 and 2). The thickness of the EIFL correlates with both baseline and final BCVAs. Furthermore, postoperative EIFL thinning and severity indirectly affect postoperative BCVA alterations. Therefore, formation of EIFL may cause irreversible retinal damage; and the existence of EIFL may reflect a negative prognostic ingredient for postoperative anatomical and visual recovery.

However, prospective studies involving large patient groups are needed to confirm our results and to evaluate the prognostic effect of the ERM staging scheme more accurately. Over and above, supplementary clinicopathological studies are needed to determine the pathophysiology of EIFL development better before performing surgical procedures. Finally, automated segmentation of inner retinal layers and further imaging methods would be crucial to advance the ability to identify and quantify of EIFL. We hope outcomes of current study would spur the design of future studies that will evolve the surgical management of these lesions.

Declarations

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained prior to every surgical procedure from all individual participants included in the study.

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Figures

Figure 1

The spectral domain-optical coherence tomography (SD-OCT) grading scheme of epiretinal membranes (ERMs) and manual measurement of ectopic inner foveal layer (EIFL) are shown (white arrows).

Figure 2

SD-OCT images of two different patients who underwent pars plana vitrectomy (PPV) at the 2nd and 3rd stages during the follow-up periods.

Figure 3

The foveal contour formation in the fovea of a stage 1 ERM patient after surgery are shown. There is no EIFL tissue at this stage at baseline period. When traction is removed (white arrows), a thin and hyperreflective inner retinal tissue begins to form a connection on the outer nuclear layer 3 months following surgery. While increment of this tissue was detected during follow-up, the parafoveal inner nuclear layer approaches the center of fovea (white arrows).

EIFL thickness (μm)

Figure 4

ERM recurrence by EIFL thickness amount between groups.