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Distinct retinal remodeling and visual prognostic factors in advanced epiretinal membranes with and without associated retinal break

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Abstract

Purpose To compare retinal remodeling and predictors of visual outcomes in advanced epiretinal membranes with retinal break (RB + ERM) and without retinal break (RB – ERM).

Methods Retrospective observational study conducted on consecutive patients with stage 3 and 4 ERM who underwent pars plana vitrectomy with ERM peeling. Baseline and post-operative clinical and optical coherence tomography parameters—including ectopic inner foveal layer (EIFL) thickness, and presence of hyperreflective foci (HF)—were assessed. Multivariate analyses were conducted separately for the two conditions to examine the relationship between postoperative best-corrected visual acuity (BCVA) and a set of predictor variables.

Results A total of 80 eyes from 80 patients were included: RB-ERM ($n = 55$) and RB + ERM ($n = 25$). At baseline, RB + ERM showed higher proportion of stage 4 ERMs compared to RB-ERM ($p = 0.004$), greater EIFL thickness ($p = 0.003$), and a higher number of HF in the EIFL ($p = 0.042$). After surgery, RB + ERM exhibited significantly greater reduction in EIFL thickness ($p = 0.036$) and in HF count within the EIFL compared to RB-ERM ($p = 0.023$). BCVA improvement was similar between the two groups ($p = 0.917$). In RB-ERM, multivariate regression identified older age, worse baseline BCVA, greater baseline EIFL and central macular thickness (CMT), and higher HF count within the EIFL as significant predictors of worse postoperative BCVA ($p < 0.05$), whereas in RB + ERM, presence of preoperative intraretinal cysts, and older age showed a significant association with worse BCVA after surgery ($p < 0.05$).

Conclusions RB + ERM demonstrated more pronounced retinal remodeling and distinct predictors of postoperative BCVA compared with RB-ERM, suggesting different underlying pathophysiology, despite similar improvements in visual outcomes. Further prospective and longitudinal studies incorporating histopathological analyses are warranted to confirm these observations.

Keywords Epiretinal membrane, OCT, Retinal break

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Introduction

Epiretinal membrane (ERM) is a proliferation of fibro-cellular tissue that forms on the internal surface of the retina and internal limiting membrane (ILM), causing disruption of retinal structure and potentially leading to visual disturbances and metamorphopsia [1–3]. Prevalence is reported to be between 2.3% and 28.9% in large population studies, with increasing prevalence in older age groups [4–7].

Idiopathic epiretinal membranes (iERM) form in otherwise healthy eyes, and are most often associated with posterior vitreous detachment [3]. Micro-damage to the ILM induced by posterior vitreous detachment appears to be the *primum movens*, inducing migration of hyalocytes from the posterior vitreous, retinal pigment epithelium (RPE) cells and activated Muller glial cells from the outer retina to the retinal surface, and subsequent proliferation and fibrocellular differentiation of these cells [8–11]. In secondary epiretinal membranes (sERM), which may represent 28–32% of all ERMs [4, 12], the progression of such processes is promoted and amplified by various pre-existing ocular alterations, such as previous ocular surgery, diabetic retinopathy and the presence of peripheral retinal breaks [4, 12–16]. Posterior vitreous detachment (PVD) is found less frequently in sERM than in iERM [17], suggesting the presence of different mechanisms of activation, migration, and transdifferentiation of resident cells in these membranes, like inflammation and disruption of blood-retinal barrier [2, 18].

Advanced ERM is characterized by the presence of the ectopic inner foveal layer (EIFL), an abnormal inner retinal tissue caused by traction from the ERM [19]. Although the exact mechanism of EIFL formation is unclear, sustained anteroposterior and centripetal traction is thought to displace and reorganize the inner retinal layers, forming a continuous layer of inner and middle retinal tissue across the fovea. This traction also activates Müller cells, triggering gliosis and cell proliferation, which are likely involved in the development of EIFL [20, 21].

Previous studies have examined clinical and OCT features of iERM and ERM associated with peripheral retinal breaks, defined as retinal break-associated ERM (rbERM) [16, 22, 23]. It is thought that ERM formation in these cases may involve activation and migration of RPE cells through existing retinal breaks to the macula, potentially driven by inflammatory cytokines as part of a tissue repair response. The term macular proliferative vitreoretinopathy (macular PVR) has been proposed in different reports, suggesting a different pathogenesis between the two conditions [22, 24].

To date, no studies have specifically compared the distinct OCT features of advanced ERM with (RB + ERM) and without associated retinal breaks (RB – ERM), nor

the predictors of visual outcomes following surgical intervention. A better understanding of the differences between these entities may clarify whether they share similar pathophysiological mechanisms or represent distinct pathogenetic processes, with potential implications for patient management. Accordingly, the primary aim of this study was to compare the baseline clinical and OCT characteristics of stage 3 and 4 RB-ERM and RB + ERM, and to evaluate their morphological changes and visual outcomes after membrane peeling surgery. Additionally, we investigated potential predictors of postoperative visual acuity in each condition separately.

Materials and methods

Study population

This retrospective, observational study assessed the clinical records of a consecutive series of patients diagnosed with stage 3 and 4 ERM [19]. These individuals underwent pars plana vitrectomy (PPV) with ERM peeling at the Ophthalmology Unit of the University of Bologna between November 2021 and December 2024. We excluded eyes with secondary ERM due to retinal diseases other than retinal breaks, significant ocular media opacities (excluding cataracts), other macular conditions (e.g., intermediate/late-stage age-related macular degeneration or diabetic macular edema), poor-quality imaging, prior ocular surgeries (excluding cataract surgery), glaucoma, and axial length over 26 mm. Eligible patients were divided into two groups based on the presence of peripheral retinal breaks. The retinal break group (RB + ERM) included eyes with either untreated retinal breaks identified during preoperative dilated fundus examination or previously laser-treated retinal breaks, and the *idiopathic group* (RB-ERM) consisted of eyes without retinal breaks or other known causes of ERM. In cases previously treated with laser retinopexy, OCT examinations performed within 3 months after treatment were reviewed and did not show evidence of epiretinal membrane formation. If both eyes were eligible, the first eye to undergo PPV was selected for analysis. All procedures were conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants. The study received ethical approval from the Ethics Committee of Bologna, Italy (Code CE: 53/2025/Oss/AOUBo).

Ophthalmological assessment

At the baseline and each follow-up visits, all patients underwent a thorough ophthalmic evaluation. A comprehensive ocular history was recorded, with emphasis on any previous history of eye surgeries or laser retinopexy. The clinical assessment included measurement of best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure assessment, and a dilated fundus

examination using a 90D indirect lens. High-resolution retinal images were acquired using spectral-domain optical coherence tomography (SD-OCT) using the Spectralis HRA-OCT system (Heidelberg Engineering GmbH, Heidelberg, Germany). Baseline axial length was measured using the IOL Master 700 (Carl Zeiss Meditec, Jena, Germany). Visual acuity was tested with a Snellen chart and subsequently converted to logarithm of the minimum angle of resolution (logMAR) values for statistical purposes.

OCT images acquisition

All participants underwent standardized SD-OCT imaging following a consistent protocol, including a high-density raster scan covering a $20^\circ \times 15^\circ$ area, comprising 145 B-scans spaced 30 μm apart. In addition, horizontal and vertical line scans centered on the fovea were acquired using an automatic real-time value of at least 14 or higher. ERM was defined as a distinct, irregular, hyper-reflective band anterior to the inner retina, frequently accompanied by distortion of the retinal surface. Two independent, masked graders (G.R. and M.E.) reviewed the OCT scans to classify ERMs, focusing on stage 3 and stage 4 iERM. In cases of disagreement, a third grader (M.M.) rendered the final classification. Foveal EIFL thickness was measured manually using the caliper tool available in the Heidelberg imaging system, following previously described methodologies [20]. All images were scaled to a 1:1 mm aspect ratio. Central macular thickness (CMT) was measured manually as the vertical distance from the internal limiting membrane to the anterior boundary of the retinal pigment epithelium–Bruch's membrane complex at the foveal center. Subfoveal choroidal thickness (SFCT) was similarly assessed, defined as the distance from the hyper-reflective Bruch's membrane to the inner scleral surface, using the same caliper tool. Disruption of the ellipsoid zone (EZ) was noted when the EZ band appeared discontinuous at the foveal center. The presence of the central bouquet sign was determined based on previously established criteria, and included any of the following abnormalities within the central 100 microns of the fovea at the level of the EZ band: the cotton ball sign, a central pocket of subretinal fluid, or a central vitelliform lesion [25]. The scans were further analyzed for the presence of hyporeflective intraretinal cystoid spaces, and in select cases where present, fluorescein angiography (FA) was performed using the Heidelberg Spectralis SD-OCT. Microcystoid macular edema (MME) was differentiated from cystoid macular edema (CME) based on earlier literature [26]. The presence of finger-like projections was qualitatively assessed as previously described [22]. All OCT analysis - both qualitative and quantitative - were independently performed by two masked observers (G.R.

and M.E.). Any discrepancies in interpretation were adjudicated by a third reviewer (N.V.).

Assessment of HF in the EIFL

All SD-OCT scans were analyzed for the presence of hyperreflective foci (HF), defined as small, dot-like structures measuring 10–30 μm in diameter, with reflectivity comparable to the retinal nerve fiber layer (RNFL) and localized within the EIFL thickness within 1500 μm of the fovea. The 1500- μm central foveal area was measured using the caliper function of the Heidelberg OCT. HF were manually counted by two masked graders (G.R. and M.E.); the measurements from the first grader (G.R.) were used for analysis, while those from the second grader (M.E.) were used to assess inter-grader reliability. HF were classified as absent, few (< 10), moderate (10–20), or numerous (> 20), as previously described [21]. HF were assessed on the OCT scan (vertical or horizontal) of highest quality for each eye, using the Heidelberg Spectralis follow-up function to ensure consistent localization across visits. Additionally, HF were qualitatively assessed in the outer nuclear layer (ONL) within the same central 1500- μm area using the same criteria, with discrepancies resolved by a third masked grader (N.V.).

Surgical technique

All patients underwent a standardized surgical procedure. The choice between general and local anesthesia was determined based on patient preference and the anesthesiologist's recommendation. A 25-gauge PPV was performed using the Constellation Vision System (Alcon, USA). When indicated, cataract extraction was performed during the same surgical session. The procedure included a complete vitrectomy with careful peripheral vitreous shaving. If needed, the posterior hyaloid was separated from the retina. Both the ERM and ILM were peeled up to the vascular arcades using microforceps (Grieshaber ILM forceps, Alcon, USA). To enhance visualization during membrane peeling, Membran Blue Dual dye (DORC, Dutch Ophthalmic Research Center, Zuidland, The Netherlands) was applied to the retinal surface. At the end of surgery, air was used to evaluate the integrity of the sclerotomies.

Postoperatively, all patients followed a standardized regimen of topical antibiotics and anti-inflammatory eye drops.

Statistical analysis

Demographic and clinical characteristics were analyzed using descriptive statistics, with appropriate measures of central tendency and variability depending on whether the data were categorical or continuous. As variables were not normally distributed, they were reported as median and interquartile ranges (IQR), and non-parametric tests

were used in the statistical analysis. Associations between categorical variables were evaluated using Fisher's exact test. The Mann–Whitney test was used to evaluate the differences in demographic characteristics and quantitative OCT parameters between RB-ERM and RB+ERM. To compare preoperative and postoperative values for EIFL, CMT, SFCT, HF in EIFL and BCVA, the Wilcoxon signed-rank test was used. Spearman correlation was used to assess the relationship between HF in EIFL and EIFL thickness. A multivariate linear regression analysis was performed to investigate the relationship between BCVA at the final visit (dependent variable) and a set of predictor variables in the two conditions separately. A *p*-value less than 0.05 was considered indicative of statistical significance. All analyses were performed using IBM SPSS Statistics, version 26.

Results

Demographic data

A total of 80 eyes from 80 patients were included in the analysis: 55 eyes with RB-ERM and 25 eyes with RB+ERM. In the RB+ERM group, 21 eyes (84%) had received laser retinopexy for retinal breaks prior to surgery, with a median interval of 23 months (IQR = 10–31, range: 5–38) between retinopexy and PPV. In the remaining 4 eyes (16%), untreated peripheral retinal breaks were identified during the preoperative dilated fundus

examination and were subsequently managed with intraoperative endolaser photocoagulation. Regarding the number and location of retinal breaks: among the 25 eyes in the RB+ERM cohort with documented breaks, 18 eyes had a single break, 5 eyes had two breaks, and 2 eyes had three breaks. Breaks were located superiorly in 15/33, nasally in 5/33, temporally in 10/33, and inferiorly in 3/33. No differences regarding age and sex were observed between the two groups. The median follow-up after surgery was 5.50 months (IQR = 4–10.25), with no differences between the two groups (*p* = 0.848). Details are summarized in Table 1.

Baseline OCT assessment

At baseline, eyes with RB+ERM showed a significantly more frequent stage 4 ERM compared to the RB-ERM group (56% vs. 23.6%, *p* = 0.004) and increased EIFL thickness (*p* = 0.003). Moreover, HF in EIFL were observed more frequently in the RB+ERM group (24/25 cases) than in the RB-ERM group (38/55 cases, *p* = 0.025), and the number of HF in EIFL was greater in RB+ERM compared to RB-ERM (*p* = 0.042). No significant differences were observed in BCVA or other OCT parameters. See Table 1 for detailed comparisons. Also, no differences in EIFL thickness were observed between eyes with peripheral retinal breaks identified during the preoperative dilated fundus examination and those with

Table 1 Baseline assessment of clinical and optical coherence tomography (OCT) features in idiopathic epiretinal membranes (iERM) and retinal break-associated epiretinal membrane (rbERM)

	iERM (<i>n</i> = 55)	rbERM (<i>n</i> = 25)	<i>P</i> value
Age, median (IQR)	74 (70–78)	73 (56.75–85.25)	0.668
Sex female, number (%)	27 (49.1%)	12 (48%)	0.694
Phacoemulsification	34 (61.8%)	20 (80%)	0.439
BCVA, median (IQR) (LogMar)	0.4 (0.3–0.9)	0.4 (0.4–0.6)	0.810
CMT, median (IQR) (μm)	493 (445–534)	530.5 (461.5–617.25)	0.111
SFCT, median (IQR) (μm)	215 (162–263)	181 (149–250)	0.409
EIFL thickness, median (IQR) (μm)	149 (113–194)	219 (163.75–293.75)	0.003
ERM stage 4, number (%)	13 (23.6%)	14 (56%)	0.004
Presence of HF in EIFL, number (%)	38 (69.1%)	24 (96%)	0.025
- Few	18 (47.4%)	13 (52%)	
- Moderate	16 (42.1%)	6 (24%)	
- Numerous	4 (10.5%)	6 (24%)	
Quantity of HF in EIFL, median (IQR)	8 (0–16)	12 (7.5–22)	0.042
Presence of HF in ONL, number (%)	14 (25.5%)	4 (16%)	0.380
EZ disruption, number (%)	14 (25.5%)	6 (24%)	0.835
Intraretinal cystoid spaces, number (%)	27 (49.1%)	15 (60%)	0.270
- MME	16 (29.1%)	10 (66.7%)	0.180
- CME	11 (20%)	5 (33.3%)	0.528
Central bouquet sign, number (%)	17 (30.1%)	6 (24%)	0.350
Finger-like projections, number (%)	27 (49.1%)	16 (64%)	0.156

SD=standard deviation, BCVA=best corrected visual acuity, CMT=central macular thickness, SFCT=subfoveal choroidal thickness, EIFL=ectopic inner foveal layer, HF=hyperreflective foci, EZ=ellipsoid zone, MME=microcystoid macular edema, CME=cystoid macular edema, ONL=outer nuclear layer. (Mann-Whitney for quantitative variables, Fisher's exact test for categorical variables; significant *p* values are highlighted in bold)

Table 2 Comparison of quantitative clinical and optical coherence tomography (OCT) parameters at baseline and after surgery in idiopathic epiretinal membranes (iERM) and retinal break-associated epiretinal membrane (rbERM)

	Baseline	Follow-up	P value
BCVA, median (IQR) (LogMar)			
- iERM	0.4 (0.3–0.9)	0.1 (0.05–0.42)	0.002
- rbERM	0.4 (0.4–0.6)	0.2 (0.1–0.4)	0.007
CMT, median (IQR) (μm)			
- iERM	493 (445–534)	377.5 (326.5–446)	<0.001
- rbERM	530.5 (461.5–617.2)	421 (329.5–474)	0.002
SFCT, median (IQR) (μm)			
- iERM	215 (162–263)	193 (154.7–252)	<0.001
- rbERM	181 (149–250)	170 (127–210)	0.048
EIFL thickness, median (IQR) (μm)			
- iERM	149 (113–194)	111 (72–156)	<0.001
- rbERM	219 (163.75–293.75)	120 (58–165)	0.001
Quantity of HF in EIFL, median (IQR)			
- iERM	8 (0–16)	4 (0–8)	<0.001
- rbERM	12 (7.5–22)	5.5 (0–7.75)	0.001

IQR=interquartile range, BCVA=best corrected visual acuity, CMT=central macular thickness, SFCT=subfoveal choroidal thickness, EIFL=ectopic inner foveal layer. HF=hyper-reflective foci (Wilcoxon sign test was used; significant p values are highlighted in bold)

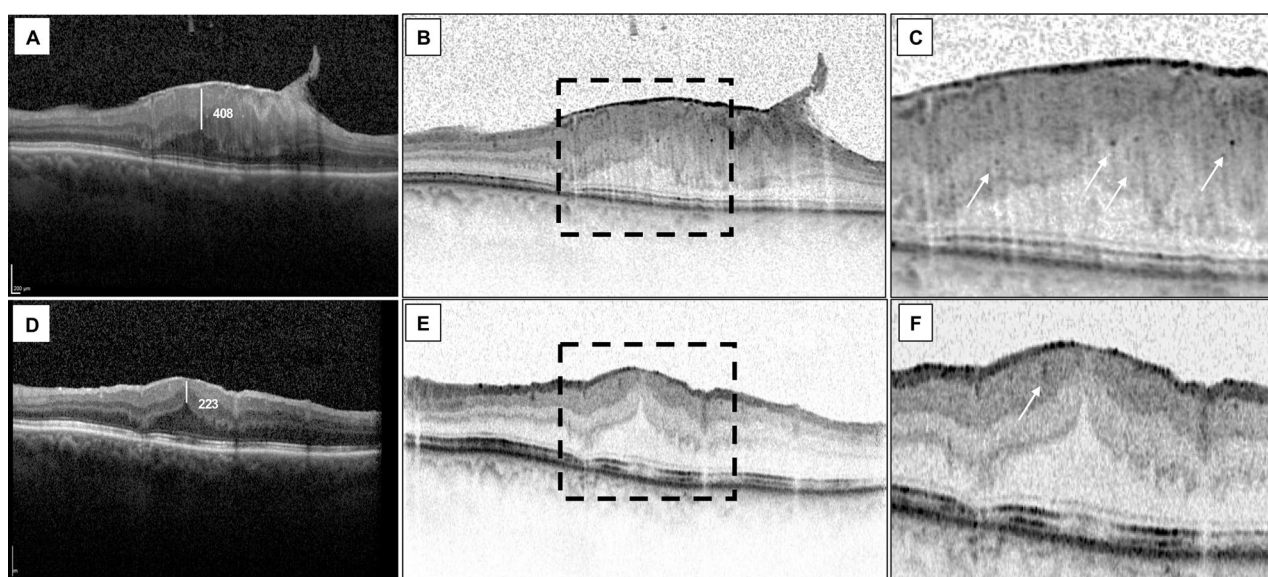


Fig. 1 Stage 4 idiopathic epiretinal membrane (RB-ERM) before and after surgery. **(A)** Optical coherence tomography (OCT) vertical B-scan in a 73 years old male patient with stage 4 RB-ERM in the left eye. Ectopic inner foveal layer thickness (EIFL) is 408 microns at baseline. **(B)** Black and white mode of the same B-scan. **(C)** Magnification of the fovea is shown. Note the presence of hyper-reflective foci (HF) in the ectopic inner foveal layer (EIFL) thickness (white arrows). **(D)** and **(E)** Vertical OCT B-scan after 7 months from ERM peeling. Note the reduction of the EIFL thickness (223 microns) **(F)** Also, note the reduction in the number of HF in the central 1500 microns

previously treated breaks (median 214.4 (IQR=158.5–251) vs. 223.1 (IQR=173.2–278.5), $p=0.567$).

Post-operative clinical and OCT assessment

Overall, a significant improvement in BCVA [pre-op median 0.4 (IQR=0.30–0.77) vs. post-op median 0.15 (IQR=0.05–0.40), $p<0.001$], and a significant reduction in CMT [pre-op median 503 (IQR=452–539) vs. post-op median 386 (IQR=328–447), $p<0.001$], SFCT [pre-op median 210 (IQR=151.5–254) vs. post-op median

190 (IQR=146–251), $p<0.001$], EIFL thickness [pre-op median 166 (IQR=118.5–219) vs. post-op median 111.5 (IQR=71.25–159), $p<0.001$], and HF in EIFL [pre-op median 10 (IQR=2–18) vs. post-op median 5.1 (IQR=1–7), $p<0.001$] was observed at the end of the follow-up. Both RB-ERM and RB+ERM showed significant improvement in quantitative parameters. See Table 2; Figs. 1 and 2. When comparing clinical data and OCT parameters, we observed that HF in EIFL were more frequently observed in the RB+ERM group

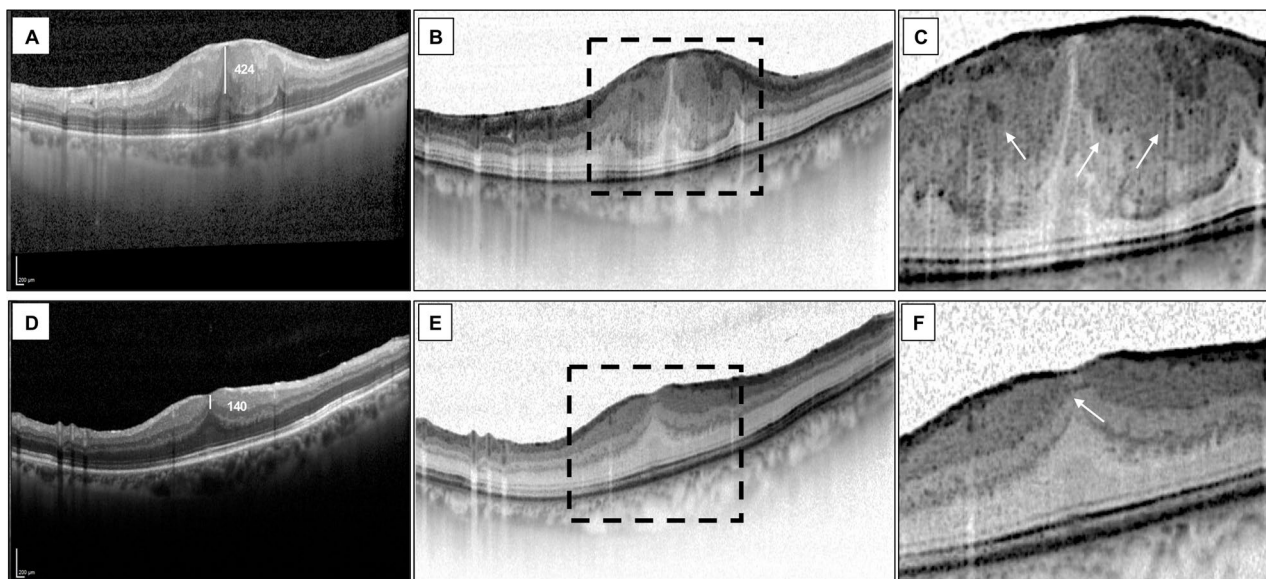


Fig. 2 Stage 4 epiretinal membrane secondary to peripheral retinal break (RB + ERM) before and after surgery. **(A)** Optical coherence tomography (OCT) vertical B-scan in a 68 years old male with stage 4 RB + ERM in the left eye. The patient had a super-temporal retinal break that was treated with laser retinopexy 7 months before. Ectopic inner foveal layer thickness (EIFL) is 424 microns at baseline. **(B)** Black and white mode of the same B-scan. **(C)** Magnification of the fovea is shown. Note the presence of numerous hyper-reflective foci (HF) in the EIFL thickness (white arrows). **(D)** and **(E)** OCT scan of the same eye after 6 months from ERM peeling. Note the reduction of the EIFL thickness (140 microns) and the improvement in the retinal structure after surgery **(F)** Magnification of the fovea is shown. Note the reduction of the HF in the EIFL thickness (white arrow)

compared to RB-ERM (64% vs. 41.81%, $p=0.043$). Intraretinal cystoid spaces were also more frequently observed in the RB + ERM group compared to the RB-ERM group (60% vs. 29.1%, $p=0.018$), and notably, they persisted in 100% of these cases postoperatively relative to the baseline assessment. See Fig. 3; Table 3. When we compared changes in visual acuity and quantitative OCT parameters between the two groups, we observed that reduction in EIFL thickness was significantly higher in RB + ERM, compared to RB-ERM ($p=0.036$). Also, reduction in HF in EIFL was significantly higher in RB + ERM compared to RB-ERM ($p=0.023$). On the other hand, no differences in BCVA, CMT and SFCT were observed. See Table 4. Overall, both reads showed a good level of agreement in counting HF in EIFL (ICC = 0.839, CI 0.771–0.884).

Predictors of visual recovery in RB-ERM and RB + ERM

Multivariate regression analysis was conducted for evaluating predictors of postoperative BCVA in RB-ERM and RB + ERMs separately. In eyes with RB-ERM, multivariate regression identified older age, worse baseline BCVA, greater baseline CMT and EIFL thickness, and higher HF count within the EIFL as significant predictors of worse postoperative BCVA ($p<0.05$). On the other hand, in RB + ERM only presence of preoperative intraretinal cysts, and older age showed a significant association with worse postoperative BCVA ($p<0.05$). See Table 5. When multivariate analysis was performed on the entire cohort,

only baseline BCVA emerged as a significant predictor of postoperative BCVA. See Table 6.

Discussion

In the present study, a greater proportion of RB + ERM presented as stage 4 membranes compared to RB-ERM at baseline. Additionally, RB + ERM showed significantly greater preoperative EIFL thickness and a higher presence of HF within the EIFL. Postoperatively, both groups showed a significant improvement in visual acuity. Eyes with RB + ERM demonstrated a significantly larger reduction in both EIFL thickness and HF count within the EIFL compared to RB-ERM eyes. Furthermore, multivariate analysis identified distinct predictors of postoperative visual outcomes in the two conditions.

The originality of the present study lies in its focus on advanced ERMs, characterized by the presence of the EIFL, an abnormal retinal tissue observed in stage 3 and 4 ERMs according to previous classification. While previous studies have examined differences in clinical presentation, OCT parameters, and outcomes between RB-ERM and RB + ERM, they included a broader spectrum of ERM stages or did not clearly define ERM severity [16, 22]. To our knowledge, this is the first study to systematically assess OCT parameters and predictors of visual outcomes in advanced RB-ERM and RB + ERM. Overall, our findings demonstrate subtype-specific surgical responses and distinct predictors of postoperative visual acuity, despite similar postoperative visual

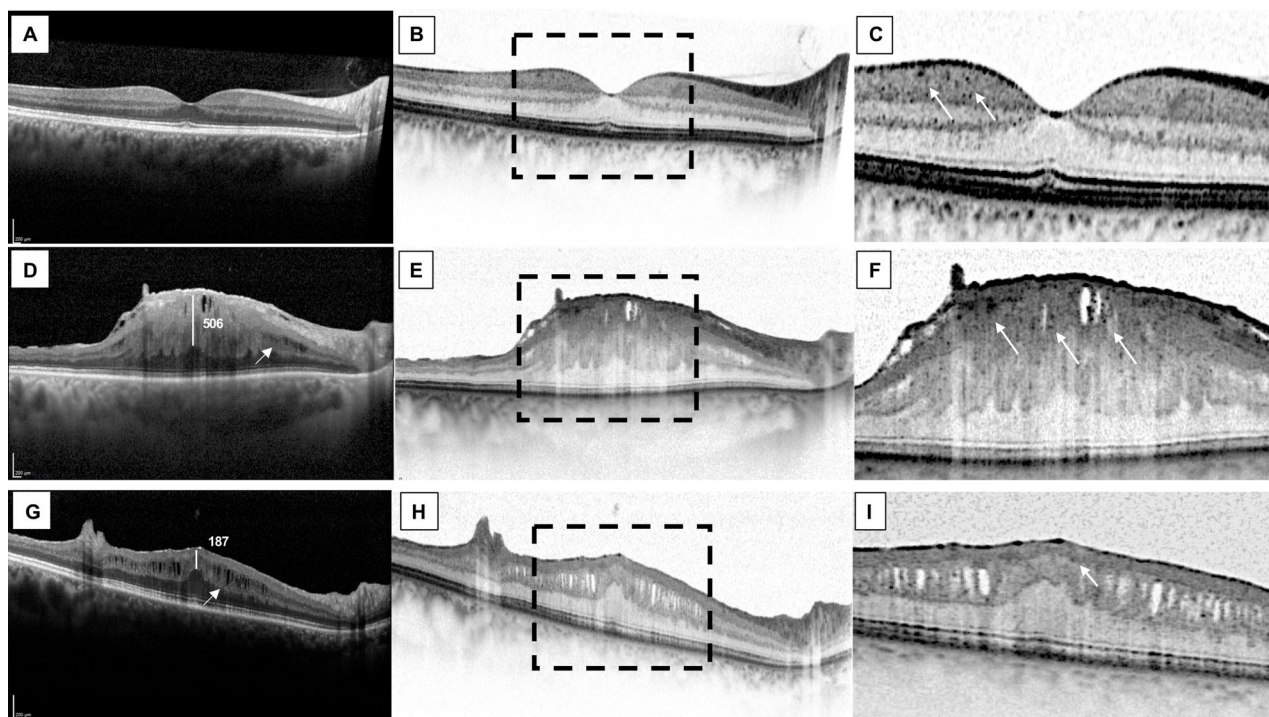


Fig. 3 Progression of stage 4 epiretinal membrane secondary to peripheral retinal break (RB + ERM), and retinal remodeling after surgery. **(A)** and **(B)** Optical coherence tomography (OCT) horizontal B-scan in the right eye of a 67 years old female patient. The patient had a superior retinal break that was treated with laser retinopexy. OCT scan was acquired before laser retinopexy. **(C)** Magnification of the fovea is shown. Note the presence of few hyper-reflective foci (HF) in the ganglion cell layer (white arrows). **(D)** OCT horizontal B-scan of the same eye after 20 months. Note the presence of a stage 4 RB + ERM. Ectopic inner foveal layer thickness (EIFL) is 506 microns, and microcystoid macular edema (MME) can be observed (white arrow). **(E)** and **(F)** Note the presence of numerous hyper-reflective foci (HF) in the EIFL thickness (white arrows). **(G)** OCT scan of the same eye after 7 months from ERM peeling. Note the reduction of the EIFL thickness (187 microns) and the persistence of the MME (white arrow). **(H)** and **(I)** Note the reduction of the HF in the EIFL thickness (white arrow)

Table 3 Post-operative assessment of clinical and optical coherence tomography (OCT) features in idiopathic epiretinal membranes (iERM) and retinal break-associated epiretinal membrane (rbERM)

	Idiopathic ERM (n = 55)	rbERM (n = 25)	P value
BCVA, median (IQR) (LogMar)	0.1 (0.05–0.42)	0.2 (0.1–0.4)	0.601
CMT, median (IQR) (μm)	377.5 (326–446)	421 (329.5–474)	0.277
SFCT, median (IQR) (μm)	193.5 (154.75–252)	185 (136–260)	0.486
EIFL thickness, median (IQR) (μm)	111 (72.75–153.75)	120 (58–165)	0.859
Presence of HF in EIFL, number (%)	23 (41.8%)	16 (64%)	0.043
- Few	16 (69.5%)	13 (81.2%)	
- Moderate	7 (30.4%)	3 (18.7%)	
- Numerous	0	0	
Quantity of HF in EIFL, median (IQR)	4 (0–8)	5.5 (0–7.75)	0.416
Presence of HF in ONL, number (%)	7 (30.4%)	6 (24%)	0.206
EZ disruption, number (%)	12 (21.8%)	10 (40%)	0.059
Intraretinal cystoid spaces, number (%)	16 (29.1%)	15 (60%)	0.018
- MME	12 (21.8%)	10 (66.7%)	0.079
- CME	5 (9.1%)	5 (33.3%)	0.335
Central bouquet sign, number (%)	10 (18.2%)	3 (12%)	0.384

IQR=interquartile range, BCVA=best corrected visual acuity, CMT=central macular thickness, SFCT=subfoveal choroidal thickness, EIFL=ectopic inner foveal layer, HF=hyper-reflective foci, EZ=ellipsoid zone, MME=microcystoid macular edema, CME=cystoid macular edema, ONL=outer nuclear layer (Mann-Whitney for quantitative variables, Fisher's exact test for categorical variables; significant p values are highlighted in bold)

Table 4 Improvement in clinical and quantitative optical coherence tomography (OCT) features in idiopathic epiretinal membranes (iERM) and retinal break-associated epiretinal membrane (rbERM) after surgery

	Idiopathic ERM (n = 55)	rbERM (n = 25)	P value
Change in BCVA, median (IQR) (LogMar)	-0.2 (0.1–0.4)	-0.2 (0.05–0.4)	0.917
Change in CMT, median (IQR) (μm)	-106.5 (53.5–184)	-96 (37–168)	0.508
Change in SFCT, median (IQR) (μm)	-17 (2–45)	-10 (5–31.5)	0.581
Change in EIFL, median (IQR) (μm)	-45 (1.25–85.75)	-97 (17.5–175.5)	0.036
Change in HF in EIFL, median (IQR) (number)	-3 (0–7.25)	-7 (1.75–9.50)	0.023

IQR=interquartile range, BCVA=best corrected visual acuity, CMT=central macular thickness, SFCT=subfoveal choroidal thickness, EIFL=ectopic inner foveal layer. HF=hyper-reflective foci (Mann-Whitney for quantitative variables; significant p values are highlighted in bold)

Table 5 Multivariate regression analysis of clinical and optical coherence tomography (OCT) features associated with post-operative best corrected visual acuity

Best corrected visual acuity

	B	95% Confidence interval		p-value
Idiopathic epiretinal membranes				
Pre-op intraretinal cysts, yes/no	+0.138	−0.179	0.456	0.394
Phacoemulsification, yes/no	−0.017	−0.272	0.238	0.893
Age, years	+0.034	0.014	0.053	0.001
Baseline BCVA, LogMar	+0.814	0.671	0.957	<0.001
Baseline CMT, μm	+0.007	0.004	0.010	<0.001
Baseline EIFL, μm	+0.008	0.003	0.012	<0.001
Baseline HF in EIFL count, number	+0.508	0.133	0.884	0.008
Baseline EZ foveal disruption, yes/no	+0.091	−0.144	0.326	0.447
Retinal break-associated epiretinal membranes				
Pre-op intraretinal cysts, yes/no	+0.212	0.019	0.404	0.031
Phacoemulsification, yes/no	−0.151	−0.354	0.051	0.143
Age, years	+0.012	0.004	0.021	0.005
Baseline BCVA, LogMar	−0.125	−0.574	0.324	0.584
Baseline CMT, μm	−0.001	−0.004	0.003	0.805
Baseline EIFL, μm	−0.003	−0.005	0.006	0.786
Baseline HF in EIFL count, number	−0.004	−0.021	0.013	0.646
Baseline EZ foveal disruption, yes/no	0.110	−0.150	0.371	0.407

The table presents the beta coefficients, 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant, with significant p-values highlighted in bold. B = unstandardized regression coefficient, HF=hyper-reflective foci, CMT = central macular thickness, EIFL = ectopic inner foveal layer, BCVA = best corrected visual acuity, EZ/ELM = ellipsoid zone/external limiting membrane

Table 6 Multivariate regression analysis of clinical and optical coherence tomography (OCT) features associated with post-operative best corrected visual acuity in the entire cohort

	B	95% Confidence interval	P value
Pre-op intraretinal cysts, yes/no	0.072	-0.229 to 0.373	0.629
Phacoemulsification, yes/no	-0.023	-0.321 to 0.275	0.876
Age, years	0.014	-0.001 to 0.029	0.062
Baseline BCVA, LogMar	0.745	0.570 to 0.920	<0.001
Baseline CMT, μm	0.001	-0.002 to 0.004	0.370
Baseline EIFL, μm	-0.003	-0.006 to 0.001	0.137
Baseline HF in EIFL count, number	0.009	-0.007 to 0.026	0.261
Baseline EZ foveal disruption, yes/no	0.104	-0.175 to 0.384	0.449
Retinal break, yes/no	0.050	-0.203 to 0.302	0.688

The table presents the beta coefficients, 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant, with significant p-values highlighted in bold. B = unstandardized regression coefficient, HF=hyper-reflective foci, CMT = central macular thickness, EIFL = ectopic inner foveal layer, BCVA = best corrected visual acuity, EZ/ELM = ellipsoid zone/external limiting membrane

outcomes between the two groups. These results may suggest differences in the underlying pathophysiological mechanisms, potentially reflecting distinct structural or cellular processes involved in each subtype.

Histopathological evidences suggest that RB + ERM may result from a distinct molecular and cellular mechanisms compared to RB-ERM. Several studies have reported a relatively higher abundance of RPE cells in RB

+ ERM and in ERMs secondary to prior retinal detachment. In contrast, the presence of RPE cells in RB-ERM has been inconsistent and, when present, typically less prominent [3, 8, 27, 28]. RPE is a prevalent cellular type in peripheral PVR membranes. Studies in animal models showed rapid expression of growth factors after induced retinal detachment, promoting activation of RPE and Müller cells [29–31]. Previous studies have shown that RPE cells within ERM tissue are linked to a higher density of myofibroblasts. These specialized contractile cells, which have features of both fibroblasts and smooth muscle cells, generate increased contractile force when activated [27]. We hypothesize that RB + ERM might contain a higher proportion of RPE cells and myofibroblasts than RB-ERM, leading to increased membrane contractility and greater tractional forces that promote EIFL formation. This process might explain both the greater preoperative EIFL thickness in RB + ERM and the more pronounced reduction in EIFL thickness after membrane peeling. However, this interpretation remains speculative, as no histopathological analysis was performed in the present study. Further studies incorporating detailed histopathological and molecular analyses of membrane specimens are needed to confirm and better understand our findings.

In RB + ERM, intraretinal cystoid spaces were present in 60% of eyes at baseline and persisted postoperatively in all of these cases (100%), indicating that no resolution occurred after ERM peeling. In contrast, RB-ERM eyes demonstrated a postoperative reduction in intraretinal cystoid spaces from 49% to 29%, suggesting a more favorable anatomical response. Similarly, in the RB + ERM group, the prevalence of EZ disruption increased from 24% at baseline to 40% postoperatively, whereas it decreased from 25.5% to 21.8% in the RB-ERM group. In a recent study, Govetto et al. reported that ERM-associated MME is more common in advanced-stage ERM and likely reflects Müller cell impairment due to tractional stress [26]. Additionally, Ishikura et al., using adaptive optics OCT, demonstrated that ERM may exert vertical traction on Müller cells via the ILM, displacing foveal cone inner segments and potentially altering mitochondrial organization [32]. Therefore, we hypothesize that the increased membrane contractility in RB + ERM, presumably secondary to a higher myofibroblast content, may exert greater mechanical stress on Müller cells, leading to persistence of microcystoid spaces and increased EZ impairment after surgery compared with RB-ERM. Despite these structural changes, the comparable visual acuity outcomes indicate that functional recovery may not directly correlate with the extent of these microstructural alterations. Future studies are needed to assess EZ integrity after surgery to determine whether these findings represent transient or permanent alterations and to

better understand their relationship with visual acuity outcomes.

Another finding of the present study was that advanced RB+ERMs demonstrate distinct predictors of postoperative BCVA compared with RB-ERM, despite similar visual outcomes. In advanced RB-ERM, older age, poorer baseline BCVA, increased EIFL and CMT, and HF within the EIFL were associated with worse visual outcomes, consistent with prior reports [20, 21]. On the other hand, in RB + ERM, only advanced age and the presence of preoperative intraretinal cysts were significantly associated with reduced postoperative visual recovery. These findings suggest that EIFL thickness in RB + ERM may have a relatively smaller impact on postoperative outcomes compared with RB-ERM. Also, our results indicate that the retina's capacity for postoperative remodeling, dependent on Müller cell integrity, may play a more critical role in visual recovery in RB + ERM, and that patient age may influence the extent of functional improvement. However, given the relatively small RB + ERM subgroup, these multivariate regression findings should be interpreted cautiously due to the increased risk of model overfitting and should be considered preliminary until validated in larger cohorts.

Also, previous studies reported that MME is more prevalent in advanced-stage ERMs, reflecting Müller cell impairment due to chronic traction, with overlapping characteristics between MME and CME, both of which can affect postoperative visual acuity [26, 33]. Overall, our results suggest that the retina's capacity for postoperative remodeling, dependent on Müller cell integrity, may play a more critical role in visual recovery in RB+ERM, and that patient age may influence the extent of visual recovery. Therefore, further studies are warranted to confirm findings, and longitudinal analyses are needed to elucidate the timing of ERM formation, which may represent a fundamental factor that could affect visual recovery and retinal remodeling following surgical peeling.

This study presents several strengths but also notable limitations. Its primary strength lies in the exclusive focus on advanced ERM, which allowed for a detailed and precise characterization of structural alterations and postoperative retinal remodeling. The inclusion of a consecutive patient cohort helped mitigate selection bias despite the retrospective design. Moreover, the application of strict inclusion and exclusion criteria, together with masked OCT assessment by independent graders, reduced potential confounding and observer-related bias.

However, several limitations should be acknowledged. The retrospective, single-center nature of the study inherently limits the generalizability of the findings. Also, although early OCT examinations after laser retinopexy did not show evidence of ERM in the RB+ERM group, the retrospective design of the study does not allow the

temporal relationship between retinal break formation and ERM development to be established with absolute certainty.

Moreover, the relatively small sample size—particularly within the RB + ERM subgroup ($n = 25$)—may limit statistical power and generalizability and increases the risk of overfitting in the multivariate regression analysis relative to the number of variables included in the model. Therefore, the predictors identified in this subgroup should be interpreted with caution and considered preliminary and hypothesis-generating. Furthermore, variability in the duration of postoperative follow-up, with a median of 5.5 months, may have introduced additional heterogeneity and limits the ability to assess the long-term stability of the observed anatomical changes, including EIFL reduction, as well as the potential for delayed visual improvement beyond 6 months after surgery. This should be taken into account when interpreting the functional outcomes.

In addition, the absence of histopathological or molecular analyses of excised membranes prevents deeper insight into the biological mechanisms underlying the retinal remodeling patterns observed on OCT.

Conclusions

Our findings suggest that advanced RB + ERM may display more pronounced retinal remodeling and a distinct set of predictors of postoperative visual outcomes compared with RB-ERM, despite similar improvements in visual outcomes. Thus, although structural alterations differ between subtypes, both groups achieved a similar degree of functional improvement after surgery, as reflected by comparable visual acuity gains over the follow-up period. These results may suggest substantial differences in the underlying pathophysiological mechanisms driving RB + ERM formation and response to surgery compared to RB-ERM, potentially involving distinct cellular and molecular processes that influence the membrane's structure and its interaction with retinal tissue.

As our study is retrospective and based on a relatively small sample, these findings should be considered hypothesis-generating rather than definitive. Further prospective and longitudinal studies incorporating histopathological analyses are warranted to confirm these observations and elucidate the mechanisms underlying retinal remodeling and the clinical implications.

Author contributions

NV, GR, MM conceived and designed the study. NV, GR, ME, AF, AM, LF, MM acquired, analyzed, and interpreted the data. NV performed statistical analysis. NV, GR, MM drafted the article. MM, LF revised it for intellectual content. The final version of the manuscript was approved by all the authors.

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Data availability

The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethical approval

All procedures were conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants. The study received ethical approval from the Ethics Committee of Bologna, Italy (Code CE: 53/2025/Oss/AOUBo). This article does not contain any studies with animals performed by any of the authors.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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