Prognostic Factors for Functional Improvement After *Pars Plana* Vitrectomy and Epiretinal Membrane Peeling

Fatores de Prognósticos de Melhoria Funcional Após Vitrectomia *Pars Plana* e Pelagerm de Membrana Epiretiniana

Edgar Lopes [1], Catarina Mota [1], Afonso Murta [1], Lívio Costa [1], João Branco [1]

[1] Department of Ophthalmology, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal

Recebido/Received: 2023-12-19 | **Aceite/Accepted:** 2024-05-19 | **Published online/Publicado online:** 2024-09-11 | **Publicado/Published:** 2024-12-20

DOI: https://doi.org/10.48560/rspo.34044

ABSTRACT

INTRODUCTION: Earlier studies confirmed that the integrity of the photoreceptor layer may influence visual outcome after *pars plana* vitrectomy (PPV) and epiretinal membrane (ERM) peeling. Recently, distortion of inner retinal architecture has been studied. Our study examines prognosis factors for visual improvement post-surgery in a Portuguese tertiary hospital.

METHODS: The medical records of 234 patients were retrospectively reviewed. Forty-nine eyes of 49 patients with idiopathic ERM treated by PPV and membrane peeling were included in the study. Govetto classification, ERM connection type, central foveal subfield thickness (CST), maximum retinal thickness (MRT), intraretinal cystoid changes, inner retinal changes (presence and thickness of ectopic inner foveal layer (EIFL), ganglion cell-inner plexiform layer (GC-IPL) thickness, and disorganization of retinal inner layers (DRIL)) and outer retinal changes (cotton ball, foveolar detachment, acquired vitelliform lesion, integrity of the ellipsoid zone and interdigitation zone) were studied pre-operatively, at 3, 6 and 12 months after surgery. Correlations between baseline OCT measures and visual outcome were analyzed.

RESULTS: No correlation was found between age and concurrent cataract surgery on post-op best-corrected visual acuity (BCVA). A positive correlation was established between pre-operative and post-operative BCVA. Pre-operative CST had a significant inverse correlation with BCVA at all follow-up timepoints. Govetto score showed a positive correlation with pre-operative CST, MRT, and DRIL score, and negative correlation with pre-operative and post-operative BCVA. The presence of DRIL at baseline predicted decreased BCVA at 3-month and 1-year post-operative assessments. Pre-operative EIFL thickness did not significantly influence BCVA at any evaluation point. Eyes with pre-operative intraretinal cysts showed significantly lower BCVA at baseline and at the 12-month follow-up. Disruptions in the IZ and EZ lines pre-operatively were associated with lower baseline BCVA and poorer post-operative visual outcomes. The other evaluated parameters did not influence the final BCVA.

CONCLUSION: The study reveals the influence of preoperative BCVA, CST, DRIL, intraretinal cysts, IZ and EZ disruptions, and Govetto score on postoperative visual acuity in iERM patients. These findings emphasize the value of comprehensive preoperative retinal assessments for improved surgical decision-making in iERM treatment.

KEYWORDS: Epiretinal Membrane/diagnostic imaging; Epiretinal Membrane/surgery; Prognosis; Tomography, Optical Coherence; Visual Acuity; Vitrectomy/methods.

RESUMO

INTRODUÇÃO: Estudos anteriores confirmaram que a integridade da camada de fotorreceptores influencia o resultado visual após vitrectomia *pars plana* (VPP) e pelagem de membrana epirretiniana (MER). Recentemente, foi estudada a influência das alterações da retiniana interna no prognóstico visual. O nosso estudo examina os fatores de prognóstico para a melhoria visual pós-cirurgia num hospital terciário português.

MÉTODOS: Os registos médicos de 234 pacientes foram revistos retrospetivamente. Foram incluídos quarenta e nove olhos com MER idiopática tratados por VPP foram incluídos. Classificação de Govetto, tipo de conexão da MER, espessura foveal central (EFC), espessura máxima da retina (EMR), alterações cistóides intrarretinianas, alterações da retina interna (presença e espessura da camada foveal interna ectópica (CFIE), espessura da camada plexiforme interna e das células ganglionares (CG-CPI) e a desorganização das camadas internas da retina (DCIR)) e as alterações retinianas externas (*cotton ball*, descolamento foveolar, lesão viteliforme adquirida, integridade da zona elipsóide (ZE) e zona de interdigitação (ZI)) foram estudados no pré-operatório, 3, 6 e 12 meses após a cirurgia. As correlações entre as características pré-operatórias do OCT e o resultado visual final foram analisadas.

RESULTADOS: Não foi encontrada correlação entre a idade e cirurgia de catarata concomitante na melhor acuidade visual corrigida (MAVC) pós-operatória. Foi estabelecida uma correlação positiva entre a MAVC pré e pós-operatória. A EFC pré-operatória teve uma correlação inversa com a MAVC em todos os momentos de avaliação. A pontuação de Govetto mostrou uma correlação positiva com a EFC pré-operatória, EMR e pontuação de DRIL, e correlação negativa com a MAVC pré-operatória e pós-operatória. A presença de DRIL pré-operatório correlacionou-se com uma MAVC inferior aos 3 meses e 1 ano. A espessura da CFIE pré-operatória não influenciou significativamente a MAVC em nenhum momento. Quistos intrarretinianos pré-operatórios correlacionam-se com menor MAVC pré e pós-operatória. Alterações pré-cirúrgicas nas ZE e ZI correlacionam-se com menor MAVC inicial e pós-operatória. Os outros parâmetros não influenciaram a MAVC final.

CONCLUSÃO: A MAVC pré-operatória, EFC, DCIR, cistos intrarretinianos, disrupções ZI e ZE e pontuação de Govetto pré-operatórios influenciam a MAVC pós-operatória. Estes resultados destacam a importância de uma avaliação pré-cirúrgica detalhada utilizando OCT para otimizar as decisões no tratamento de ERMi.

PALAVRAS-CHAVE: Acuidade Visual; Membrana Epirretiniana/diagnóstico por imagem; Membrana Epirretiniana/cirurgia; Prognóstico; Tomografia de Coerência Ótica; Vitrectomia/métodos.

INTRODUCTION

Epiretinal membrane (ERM) is a prevalent retinal disease primarily affecting older individuals, with a wide-ranging occurrence rate (2.2%-28.9%).[1] ERMs, typically idiopathic, are associated with contractile cellular proliferation on the macula's inner surface, often a consequence of spontaneous posterior hyaloid detachment.[2]

Treatment often includes *pars plana* vitrectomy (PPV) with ERM and internal limiting membrane (ILM) peeling. However, visual improvement varies, and risks are involved. Therefore, efforts have been devoted to predicting surgical outcomes, specifically leveraging optical coherence tomography (OCT) imaging.

Numerous studies have investigated the macular anatomical changes caused by ERM that may contribute to visual impairment. Earlier studies have presented conflicting results on the correlation between central foveal thickness (CFT) and postoperative visual acuity. A consistent association, however, has been noted between outer retinal damage and poor visual outcomes post-ERM removal.[3–5] Meanwhile, recent studies have begun to focus on the impact of inner retinal changes due to ERM traction, uncovering links between these changes and visual results, and identifying

new predictive factors for surgical success.[6–8]

This study aims to investigate the effects of pre-surgical inner and outer retina changes on post-surgical best-corrected visual acuity (BCVA) following ERM surgery. Additionally, it seeks to clarify the relationship between OCT biomarkers and BCVA in individuals diagnosed with idiopathic ERM (iERM).

METHODS

SAMPLE SELECTION

A retrospective study reviewed consecutive iERM patients treated with PPV and iERM peeling at Centro Hospitalar Universitário de Lisboa Central, Portugal. Pre- and postoperative data from 234 eyes were collected at 3-, 6-, and 12-months post-surgery. iERM diagnosis was established through fundoscopy and OCT. This study was performed accordingly to the principles of the Declaration of Helsinki. All data was saved and shared anonymously.

Exclusion criteria included prior intraocular surgeries (excluding uncomplicated phacoemulsification), retinal detachment, intermediate or advanced age-related macular degeneration, proliferative diabetic retinopathy, non-proliferative diabetic retinopathy with a history of clinically significant macular edema, macular holes, retinal vascular occlusions, advanced glaucoma, optic neuropathy, or any other cause of vision loss unrelated to iERM. In addition, patients who did not undergo evaluations at the specified time points were also excluded.

CLINICAL EVALUATION

All patients underwent a comprehensive assessment, including slit lamp examination and indirect fundoscopy. BCVA was measured in decimal scale. Heidelbedg Spectralis spectral-domain (SD) OCT (Heidelberg Engineering, Germany) was used in all cases, and a single blinded investigator graded all images based on Spectralis OCT patterns. All cases included at least two forms of OCT imaging as outlined by Govetto *et al*.[2]

SD-OCT IMAGING

Horizontal scans covering the central 2000 μm diameter area were assessed. The Heidelberg Eye Explorer's automated retinal thickness map analysis protocol was used for central foveal subfield thickness (CST) and maximal retinal thickness (MRT) measurements. iERMs were classified according to the 4-grade staging system proposed by Govetto *et al*.[2] OCT scans were also used to detect intraretinal cystoid changes. All parameters were measured subfoveally using the Heidelberg OCT "caliper" tool. Both outer and inner retinal architecture distortions were analyzed.

ANALYZING RETINAL ARCHITECTURE DISTORTIONS

Outer Retinal Distortions

The 'Cotton ball sign' was defined as a diffuse or roundish hyper-reflective region between the ellipsoid zone (EZ) and interdigitation zone (IZ) at the fovea center and was not considered a disruption of the EZ.[9] EZ or IZ defects were identified as the loss of a hyperreflective line at the fovea. Foveolar detachment was defined as a central pocket of subneurosensory hyporeflectivity or subretinal fluid. Acquired vitelliform lesion was seen as dome-shaped subretinal hyperreflective material positioned external to the EZ and internal to preserved retinal pigmented epithelium (RPE).

Inner Retinal Distortions

The presence and severity of disorganization of retinal inner layers (DRIL) were assessed using SD-OCT scans. DRIL was defined as the disorganization of inner retinal layers in the fovea. A DRIL severity score was assigned for statistical analysis, as published by Zur *et al*.[10] Ganglion cell-inner plexiform layer (GC-IPL) thickness was measured as the distance from the inner border of GC layer to the outer border of IPL. Ectopic inner foveal layer (EIFL) was detected as a continuous hypo- or hyper-reflective band extending from the inner nuclear layer and inner plexiform layer across the foveal region.[2] The type of connection between the retina and iERM was classified into complete or multiple junctions.

SURGERY

Several proficient vitreoretinal surgeons performed a 23-gauge transconjunctival, 3-port PPV. Double staining using trypan blue and brilliant blue was employed. The iERM was systematically removed using end-gripping forceps within the boundaries of the vascular arcades across a zone up to 3-disc diameters around the fovea. The decision to peel the ILM was determined case-by-case. Phakic patients over 55 years of age or those with existing cataract underwent a combined phacoemulsification and intraocular lens implantation procedure.

STATISTICAL ANALYSIS

All statistical analyses were conducted R Project version 3.5.3 (R Core Team, Vienna, Austria). For continuous variables, we utilized the mean and standard deviation (SD), while counts and percentages were employed for categorical variables. Data normality was confirmed by Shapiro-Wilk test. Paired t-test analyzed normally distributed mean measurements, while non-parametric data utilized the Wilcoxon signed-rank test. Pearson or Spearman tests determined variable correlations. Parameter changes over time were analyzed via repeated measures ANOVA or Friedman test, with significant results undergoing post hoc tests using Benja-

Table 1. Population Characteristics and comparation with BCVA.

Characteristics	N = 49	Pre-op (*p*-value)	12 m post-op (*p*-value)
Side			
Right (%)	22 (44.9)	0.713	0.812
Left (%)	27 (55.1)		
Age			
Mean (SD)	73.06 (7.298)	0.607*	0.724*
Median	74 (7)		
Gender			
Male (%)	26 (53.06)	0.974	0.983
Female (%)	23 (46.94)		
Cataract surgery			
Before PPV (%)	16 (32.65)	0.531	0.055
During PPV (%)	33 (67.35)		

* Pearson correlation.

mini-Hochberg correction or Tukey HSD. BCVA improvement was correlated with changes from pre-op BCVA at follow-up intervals. Univariate linear regression analyses identified variables independently affecting visual acuity, complemented by multivariate analyses to determine the OCT parameters significantly impacting visual function. Statistical significance was attributed to *p* values under 0.05.

RESULTS

DEMOGRAPHICS AND BASELINE STATISTICS

We retrospectively reviewed the records of 234 ERM patients; 185 were excluded, leaving 49 qualified for analysis. Demographics and baseline OCT findings are summarized in Tables 1 and 2. Table 3 depicts the mean BCVA across all visits. No age-related impact on BCVA improvement was found. Concurrent cataract surgery was noted in 33 patients (67.35%); the remaining were pseudophakic, undergoing only PPV. Postoperative BCVA showed no significant difference between the two groups.

Table 2. Preoperative OCT characteristics.

Characteristics	N = 49
Govetto Classification	
stage 1 (%)	1
stage 2 (%)	3 (6.12)
stage 3 (%)	39 (79.6)
stage 4 (%)	6 (12.24)
EIFL (%)	43 (91.49)
GC-IPL (%)	21 (42.9)
Intraretinal cysts (%)	18 (37.5)
DRIIL (%)	26 (53.06)
Cotton ball sign (%)	10 (20.41)
Foveolar detachment (%)	2 (4.08)
Acquired viteliforme lesion (%)	3 (6.12)
EZ defect (%)	3 (6.12)
IZ disruption (%)	7 (15.22)

OCT BIOMARKERS FOR VISUAL ACUITY

Univariate Analysis

We conducted univariate linear regression models, with BCVA as the dependent variable and each OCT factor as an independent variable. Upon analysis, only CST ($p<0.001$) and MRT ($p<0.001$) measurements, DRIL ($p=0.002$) and its associated score ($p=0.023$), GC-IPL thickness ($p=0.043$), the Govetto score ($p<0.001$), and the presence of intraretinal cysts ($p=0.009$) showed a significant correlation with deteriorated BCVA.

Multivariable Analysis

To understand BCVA variation, we built a multivariate model with variables showing potential significance in univariate analysis ($p<0.2$). We pruned for multicollinearity, refining the model iteratively through variance analysis, which ultimately highlighted MRT and IZ line defects as key factors. MRT exhibited a negative coefficient of -0.001 ($p<0.001$), indicating that with every 100 µm increase in MRT, a 0.1 reduction in BCVA can be expected, when other variables are held steady. In the same vein, an IZ line defect was negatively associated with BCVA, with a coefficient of -0.206 ($p=0.027$), signifying a 0.206 D BCVA decrease compared to eyes without the defect

Furthermore, the Akaike Information Criterion value of -150.924 for the MRT indicates a strong model fit, showing that incorporating MRT as a predictor substantially enhances the model's explanatory ability regarding BCVA outcomes.

Table 3. BCVA progression during follow-up.

BCVA (N = 49)	Pre-op	3 months	Difference to Pre-op	6 months	Difference to Pre-op	1 year	Difference to Pre-op	*p*-value (test)
Mean (SD)	0.35 (0.175)	0.55 (0.259)	+0.2 (0.23)	0.67 (0.222)	+0.32 (0.205)	0.73 (0.212)	+0.38 (0.225)	<0.001 (Friedman)
Median (IQR)	0.4 (0.3)	0.6 (0.3)	+0.2 (0.38)	0.6 (0.3)	+0.3 (0.3)	0.8 (0.3)	+0.4 (0.25)	

Pairwise Wilcoxon tests with Benjamini-Hochberg correction.

	Pre-op	3 months	6 months	1 year
Pre-op	-	<0.001	<0.001	<0.001
3 months	<0.001	-	0.068	0.002
6 months	<0.001	0.068	-	0.138
1 year	<0.001	0.002	0.138	-

PREDICTORS OF VISUAL ACUITY AFTER PPV AND ERM PEELING

Visual Acuity

The 1-year BCVA was significantly different from the 3 months and pre-op BCVA (p<0.001 and p=0.003) but was not significantly different from the 6 months BCVA (p=0.174). BCVA progression during follow-up is represented in Table 3. Preoperative BCVA was positively correlated with postoperative BCVA at 3, 6 and 12 months (p<0.001, p<0.001, p=0.019, respectively). A significant negative association was observed between preoperative BCVA and 12-month post-iERM removal vision improvement (r=-0.46, p=0.001), as shown in Fig. 1.

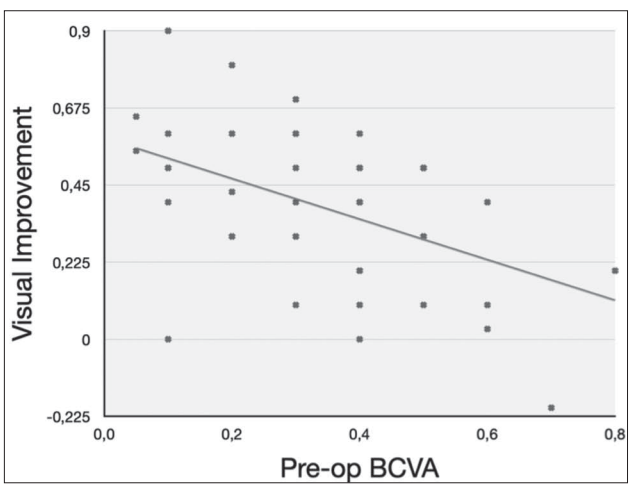


Figure 1. Correlation between visual improvement (postoperative - preoperative BCVA) and preoperative BCVA.

Central Foveal Subfield Thickness and Maximal Retinal Thickness

Mean CST and MRT progression during follow-up are displayed in Figs. 2A and 2B. Pre-op CST was negatively correlated with pre-op (p=0.001, r=-0.443) and 3-, 6-, and 12-months post-op BCVA (p=0.001, r=-0.449; p=0.037, r=-0.299; p=0.005, r=-0.399, respectively). Similarly, pre-op MRT demonstrated negative correlations with preoperative BCVA (p<0.001, r= -0.465), BCVA at 3 months (p<0.001, r= -0.465), BCVA at 6 months (p=0.031, r=-0.038), and BCVA at 12 months (p=0.005, r=-0.0399) postoperatively.

Govetto Score

A significant positive correlation was observed between Govetto score and preoperative CST (p<0.001, r=0.59), MRT (p<0.001, r=0.578), and DRIL score (p<0.001, r=0.61). However, these correlations did not persist postoperatively. Govetto staging was also negatively correlated with preoperative (p<0.001, r=-0.583) and postoperative BCVA at 3, 6, and 12 months (p=0.019, r=-0.333; p=0.007, r=-0.382; p=0.016, r=-0.369, respectively).

Disorganization of Retinal Inner Layer

Pre-operatively, DRIL was noted in in 26 eyes (53.06%), with an average score of 2.38. Eyes with DRIL displayed greater preoperative CST (528µm vs 439µm, p<0.001), with a positive correlation observed between score and preoperative CST (p<0.001, r= 0.669). Moreover, higher BCVA was reported in eyes without DRIL, compared to those with preoperative DRIL (0.43 (0.15) vs 0.28 (0.169), respectively; p=0.003). After 12 months, 19 eyes (38.78%) still displayed DRIL, with a mean score of 1.54. DRIL presence before surgery was associated with lower postoperative BCVA at 3-months (0.48 (0.264) vs 0.65 (0.217), p=0.026) and 1-year (0.65 (0.202) vs 0.82 (0.192), p=0.008). However, no significant association was found between preoperative DRIL and 6-months postoperative BCVA (0.63 (0.213) vs 0.72 (0.221), p=0.139). The preoperative DRIL score was inversely correlated with BCVA at the preoperative stage (p=0.04, r= -0.405) and at 3 (p=0.013, r= -0.481), 6 (p=0.001, r= -0.6), and 12 months (p=0.024, r= -0.449) following surgery.

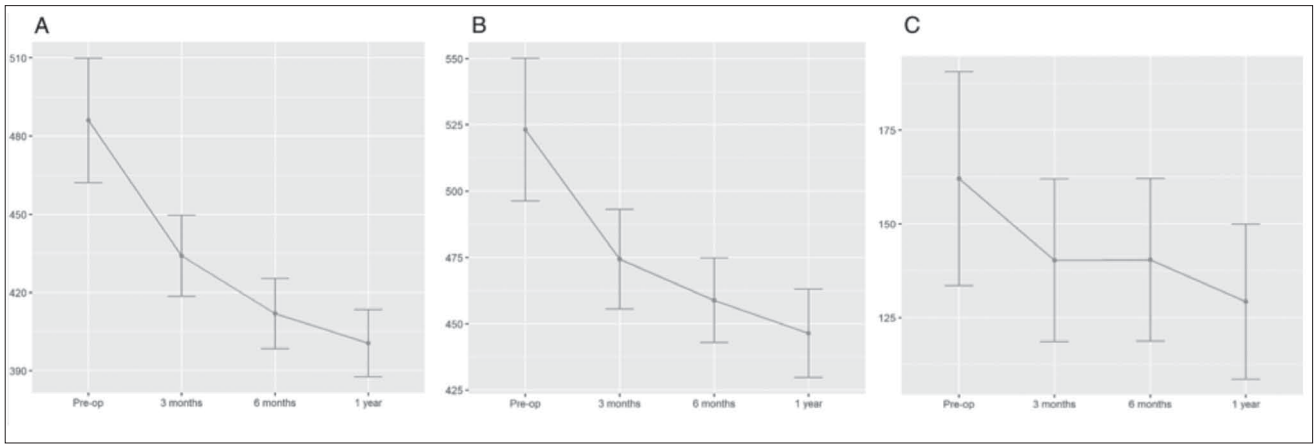


Figure 2. Graph depicting mean values at follow--up intervals; error bars denote standard deviation. A) Mean central retinal thickness (μm), B) Mean maximum retinal thickness (μm), C) Ectopic inner foveal layer thickness (μm).

Ectopic Inner Foveal Layer

In the preoperative evaluation, EIFL was detected in 45 eyes (91.8%), and at the 12-months post-operative follow-up visit, it persisted in 43 eyes (87.8%). The average thickness of EIFL reduced from an initial 164.15 μm (92.633) pre-surgery to 134.06 μm (68.231) a year post-surgery (Fig. 2C). A significant positive correlation was noted between the pre-operative EIFL thickness and pre-operative CST (p<0.001, r=0.749), which persisted throughout the entire follow-up period. No statistically significant difference in BCVA was found between patients with and without EIFL at any evaluation. Moreover, no significant correlation was found between the preoperative EIFL thickness and BCVA at any assessment point.

Intraretinal Cysts

The presence of intraretinal cysts was observed in 18 eyes (36.7%) during preoperative evaluation. Eyes with preoperative cysts exhibited lower BCVA compared to those without (0.27 (0.163) vs 0.41 (0.168), p=0.017). At 12 months postoperative follow-up, there was a significant lower BCVA in eyes with intraretinal cysts compared to those without (0.65 (0.22) vs 0.78 (0.197), p=0.046). However, this association was not observed at the 3- and 6-month postoperative time points.

Outer Retinal Layers

Before surgery, IZ disruptions were detected in 7 eyes (14.4%) and EZ defects in 3 (6.1%), with all EZ disruptions rated Govetto grade 4. Significantly lower pre-op BCVA was seen in those with IZ disruptions (0.24 (0.127) vs 0.37 (0.178), p=0.042). Although lower BCVA was also noted in subjects with EZ defects, it was not statistically significant (0.17 (0.058) vs 0.37 (0.175), p=0.052). Pre-op CST was higher in patients with EZ defects (594 μm vs 483 μm, p=0.006) and those with IZ disruptions (545 μm vs 479 μm, p=0.053). This pattern persisted into the postoperative period. After surgery, patients with preoperative IZ disruptions had significantly lower BCVA at all follow-up points. At 1-year, their BCVA averaged 0.55 (0.245) vs 0.76 (0.191) in patients without IZ disruptions (p=0.038). For EZ defects, BCVA was significantly lower at 3 months (0.2 (0.173) vs 0.58 (0.244), p=0.019) and 6 months (0.33 (0.208) vs 0.69 (0.203), p=0.015), but not at 12 months (0.51 (0.365) vs 0.75 (0.195), p=0.29). Although the number of eyes with EZ defects remained constant, the number of eyes with IZ line defects increased after surgery, with 13 eyes (28.26%) at 3 months and 12 eyes (26.09%) at 12 months showing defects.

Other

No significant correlation was found between acquired vitelliform lesion, cotton ball sign, foveolar detachment, thickness of GC-IPL and iERM connection, and postoperative BCVA.

Best-corrected Visual Acuity Improvement

Eyes with IZ disruption showed an inferior improvement at 3-months post-operatively (P=0.046); while this trend persisted throughout the follow-up period, the difference did not reach statistical significance. Similarly, eyes with EZ disruption and the presence of a cotton ball sign exhibited inferior improvement in visual function at 3- and 6-months post-surgery, but these differences were not statistically significant. Preoperative BCVA was significantly correlated with visual improvement at 12 months following ERM removal (r=-0.46, p=0.001) (Fig. 1). No other correlations were noted.

DISCUSSION

This research provides a comprehensive understanding on the impact of preoperative structural retinal changes in the functional improvement after iERM removal. Additionally, it sheds light in the multiple retinal determinants that affect visual acuity in patients diagnosed with iERM

Our examination of individual OCT factors in rela-

tion to BCVA, using univariate linear regression models, revealed that only a select few, notably CST and MRT measurements, DRIL with its score, GC-IPL thickness, the Govetto score, and the presence of intraretinal cysts, had significant correlations with declining BCVA. This emphasizes the potential clinical value of these specific metrics in the assessment of iERM patients. The multivariable analysis further accentuated the significance of specific variables. Within this framework, MRT and IZ line defects stood out as dominant predictors.

It is noteworthy BCVA significantly improved one year postoperatively compared to preoperative and 3-month assessments. However, this improvement did not significantly differ from the BCVA at the 6-month follow-up, indicating a plateau in visual acuity recovery.

Our study found that better preoperative BCVA correlates with superior postoperative BCVA, highlighting its importance in predicting visual recovery post iERM surgery. However, eyes with lower pre-operative BCVA demonstrated greater improvement after 12 months - but achieved inferior final BCVA - suggesting even those with poorer initial vision can benefit from surgery. This underscores pre-operative BCVA's role as a predictive factor for post-operative outcomes in iERM patients.

The correlation between macular thickness and visual acuity in iERM patients has been a focal point of various studies. Govetto *et al*[11] elucidated that a higher CST was significantly linked to a lower preoperative BCVA. Shiono *et al*[12] postulated that post-ERM extraction visual prognosis was not largely determined by CST, a finding mirrored in the work of Hosoda *et al*.[4] On the other hand, Jeon *et al*[13] found a short-term positive association between CST and BCVA post-ERM removal, but it did not persist in later follow-ups. In our study, higher pre-operative CST and MRT correlated with lower BCVA both before and after surgery at all timepoints. This indicates their potential as valuable prognostic markers. MRT, in particular, stood out as a strong predictor for visual acuity in multivariate analysis.

Our study highlights the prognostic significance of the Govetto score, an indicator of iERM severity, as it strongly correlates with pre-operative CST, MRT, and DRIL score. A higher Govetto score, reflecting advanced iERM, is associated with greater retinal thickness and disrupted architecture, which can negatively impact visual outcomes. Additionally, Govetto staging consistently predicts both pre-operative and post-operative BCVA at all follow-up intervals.

In DREAM study,[10] the first to explore the predictive capabilities of DRIL in determining visual outcomes in iERM patients, a significant association was identified between DRIL scores and both functional and anatomical outcomes. Furthermore, eyes with severe DRIL experienced limited benefits from surgery. Our study supported these findings. Pre-op BCVA was poorer, and CST was higher in cases presenting DRIL, especially those with a more severe DRIL score. Furthermore, individuals with pre-op DRIL and those with higher score had a lower final post-op BCVA.

The presence of intraretinal cysts, another feature of retinal disorganization, was similarly associated with worse pre-operative and 1-year post-operative visual acuity.

The specific pathogenesis of EIFL and DRIL remains to be fully elucidated. According to Zur *et al*,[10] prolonged tractional forces could lead to inner retinal layer irregularity and synaptic disconnection between photoreceptors and ganglion cells, explaining the poor visual prognosis in severe DRIL cases. Moreover, cellular damage to bipolar, Müller, amacrine, and horizontal cells could also influence visual outcomes in ERM cases.[14,15] As Govetto *et al*[2] proposed, these abnormalities could represent progressive stages of ERM development, initiated by outer nuclear layer stretching that subsequently evolves into EIFL, and ultimately DRIL. This theory aligns with our findings, as the poorest visual outcomes were observed in patients exhibiting DRIL, nevertheless being the similar for patients with or without EIFL. This suggest that DRIL is present in more advanced iERM.

Assuming that higher CST, MRT, DRIL and Govetto score, and presence of intraretinal cysts are more prevalent in advanced stages, the findings suggest that earlier surgery for iERM may yield greater benefits.

The thickness of the inner retina may play a role in determining the visual outcome post-surgery. Jeon *et al*[13] suggested a lack of a strong association between preoperative or postoperative visual acuity and inner retinal thickness in eyes that underwent ERM surgical treatment. Conversely, according to a study by Joe *et al*,[16] the thickness of the inner retina emerged as a primary factor in determining vision for ERM patients. Considering the mixed findings on the impact of inner retinal thickness on visual outcomes, our study focused on evaluating specific inner retinal changes such as EIFL presence and thickness, GC-IPL thickness, and the type of connection between the retina and iERM.

According to Doguizi *et al*,[1] a positive correlation was observed between visual acuity and the thickness of the EIFL. Additionally, their multivariate analysis identified the presence of EIFL as an independent determinant of BCVA. Govetto *et al*[2] introduced a novel SD-OCT staging system, which is centered on the presence of EIFL. They observed a gradual decline in visual acuity from stage 1 to stage 4. Moreover, in eyes that underwent ERM surgical removal, a relationship was found between EIFL thickness and decreased preoperative visual acuity. Nawrocka *et al*[17] found that while EIFL initially influences surgical outcomes, its impact decreases over time possible due to retinal tissue regeneration. In contrast, DRIL, indicative of severe retinal distortion, persists as the primary factor affecting visual acuity 1 ½ years post-surgery. Two possible theories explain the link between EIFL and reduced vision: EIFL could act as a barrier, hindering light from reaching photoreceptors, or the long-term displacement of the inner retina may damage photoreceptors and other neuronal cells within the retina, impairing normal neural transmission.[18] Our findings oppose these results, possibly due to the low proportion of patients in our study without EIFL (8.16%). In our study, the presence of EIFL and its thickness was not associated with post-op BCVA. Moreover, despite a reduction in thickness, EIFL did not disappear in any pa-

tient during the follow-up period. This could be due to our shorter follow-up time or because patients underwent surgery at a later stage of disease progression.

The association between the thickening of the GC-IPL complex and a decreased vision following surgical removal was previously studied. Song *et al*[7] proposed that greater GC layer thickness might indicate more damaged tissue, possibly due to bloated cells or intercellular edema, which they considered irreversible. However, Cho *et al*[6] found no significant correlation between GC-IPL thickness and postoperative BCVA. In our study there was no correlation between GC-IPL thickness in any evaluation point.

In ERM patients, its proposed that tangential contractile forces exerted by Müller cells might alter the interface between the photoreceptor outer segment tip and the RPE, leading to a defect in the IZ zone. This disruption could extend further, resulting in an EZ defect.[12,13,19] This study corroborates this hypothesis, as we found EZ line defects were uncommon and only observed in patients where the disruption surpassed the IZ line. Additionally, all these patients were categorized as grade 4 according to Govetto's staging.

In iERM surgery, disruptions of outer retinal layers, particularly the IZ and EZ, and its effects in visual acuity in eyes were extensively studied.

Some reports found a significant correlation between preoperative EZ disruption on OCT and postoperative visual function in surgically treated eyes.[5,7,20,21] Additionally, EZ disruption exhibited a strong association with preoperative visual acuity in various other studies.[1,11,22] However, there are varying conclusions among researchers. Oster *et al*[19] showed that the integrity of the photoreceptor EZ was a statistically significant prognostic factor for visual acuity, whereas Shiono *et al*[12] concluded that EZ disruption was a poor visual predictor. Additionally, Jeon *et al*[13] revealed that EZ defect was not strongly connected with visual improvement after ERM removal. Nawrocka *et al*[17] found that preoperative defects in the IZ line were linked to lower BCVA until 24 months after surgery, but not thereafter.

Our research revealed that eyes with disruptions in the IZ exhibited lower BCVA both pre- and post-surgery. However, the degree of visual improvement observed 12 months post-surgery was comparable to that in eyes without such disruptions (0.31 vs 0.39). Similarly, eyes EZ defects had diminished BCVA during the 3- and 6-month postoperative evaluations. At the one-year mark, their BCVA was statistically similar to those without EZ defects, despite clinical differences. Our study indicates patients with EZ or IZ line defects may experience limitations in visual improvement, but there is still an improvement in vision one year postoperatively, indicating that surgical intervention for iERM remains an option. Nevertheless, the authors acknowledge the influence of the condition of the IZ and EZ lines presurgery on the functional results post-surgery.

Our research has uncovered that specific features such as acquired vitelliform lesions, cotton ball signs, foveolar detachment, epiretinal membrane connection, and the thickness of the outer nuclear layer do not have a discernible impact on the ultimate visual acuity. This discovery emphasizes the complexity of the factors that determine visual outcomes after surgery and underlines the essential need for further research in this field.

Tsunoda *et al*[9] suggested that the cotton ball sign in ERM cases might result from consistent inner retinal strain, particularly at the fovea, that would resolve post traction alleviation. Govetto *et al*[23] argued that tractional stress via Müller cells might displace foveal cones upward, not disturbing the integrity of EZ and ELM. This was verified by the patients' retained visual function in our study.

This study holds significant value as it explores the potential variability of treatment responses in different patient groups. The efficacy of treatment methods such as PPV and ERM peeling may differ across various groups due to variability in disease progression, patient demographics, or surgical procedures. By investigating these factors within the Portuguese population, we aim to validate established prognostic indicators and comprehend disease-specific characteristics in this demography.

However, our research has limitations. Firstly, the cohort, based on patients treated at a single specialized vitreoretinal center, may not be representative of the Portuguese population with iERM, thus potentially introducing selection bias. Secondly, with a sample size of 49 eyes, it might limit the strength of conclusions, especially when multiple factors are under analysis. Thirdly, the retrospective nature of the study could lead to data inaccuracies and the 12-month follow-up period may not capture long-term outcomes. However, it is important to highlight that the study revealed a significant improvement in visual acuity within the initial six months after surgery, suggesting that pre-operative factors play a more influential role during this timeframe. Furthermore, the study's lack of a standardized treatment protocol and focus primarily on best-corrected visual acuity might also introduce confounders and overlook other relevant functional and anatomical parameters, such as contrast sensitivity or macular sensitivity. We should account for the impact of cataract. To circumvent this, our study included patients who were either pseudophakic or underwent cataract surgery during PPV.

In summary, our study offers a detailed analysis of factors affecting visual acuity post iERM surgery in a Portuguese cohort. Notably, OCT parameters like CST, MRT, Govetto score, and DRIL emerged as crucial predictors of visual outcomes. These insights highlight the importance of such metrics in iERM management. Our observations also highlighted the significance of pre-operative visual acuity in predicting post-surgical outcomes and accentuated the benefit of early surgical intervention.

The variation in outcomes reported by other researchers underscores the intricate interplay of factors affecting visual acuity post-ERM surgery. Our research reinforces the need for a comprehensive approach in assessing visual prognosis in iERM treatment.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

EL: Data collection, data analysis, writing
CM and AM: Data analysis, writing
LC and JB: Reviewing the scientific content of the article
All the authors approved the final version to be published.

EL: Recolha de dados, análise de dados, escrita
CM e AM: Análise de dados, escrita
LC e JB: Revisão do conteúdo científico do artigo
Todos os autores aprovaram a versão final a ser publicada.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

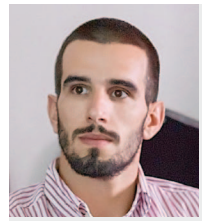
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

REFERENCES

1. Doguizi S, Sekeroglu MA, Ozkoyuncu D, Omay AE, Yilmazbas P. Clinical significance of ectopic inner foveal layers in patients with idiopathic epiretinal membranes. Eye. 2018;32:1652-60. doi:10.1038/S41433-018-0153-9
2. Govetto A, Lalane RA, Sarraf D, Figueroa MS, Hubschman JP. Insights Into Epiretinal Membranes: Presence of Ectopic Inner Foveal Layers and a New Optical Coherence Tomography Staging Scheme. Am J Ophthalmol. 2017;175:99-113. doi:10.1016/J.AJO.2016.12.006
3. Kim HJ, Kang JW, Chung H, Kim HC. Correlation of foveal photoreceptor integrity with visual outcome in idiopathic epiretinal membrane. Curr Eye Res. 2014;39:626-33. doi:10.3109/02713683.2013.860990
4. Hosoda Y, Ooto S, Hangai M, Oishi A, Yoshimura N. Foveal Photoreceptor Deformation as a Significant Predictor of Postoperative Visual Outcome in Idiopathic Epiretinal Membrane Surgery. Invest Ophthalmol Vis Sci. 2015;56:6387-93. doi:10.1167/IOVS.15-16679
5. Kim JH, Kim YM, Chung EJ, Lee SY, Koh HJ. Structural and functional predictors of visual outcome of epiretinal membrane surgery. Am J Ophthalmol. 2012;153:103-10.e1. doi:10.1016/J.AJO.2011.06.021
6. Cho KH, Park SJ, Cho JH, Woo SJ, Park KH. Inner-Retinal Irregularity Index Predicts Postoperative Visual Prognosis in Idiopathic Epiretinal Membrane. Am J Ophthalmol. 2016;168:139-49. doi:10.1016/J.AJO.2016.05.011
7. Song SJ, Lee MY, Smiddy WE. Ganglion cell layer thickness and visual improvement after epiretinal membrane surgery. Retina. 2016;36:305-10. doi:10.1097/IAE.0000000000000705
8. Kromer R, Vogt C, Wagenfeld L, Spitzer MS, Stemplewitz B. Predicting Surgical Success in Patients with Idiopathic Epiretinal Membrane Using the Spectral-Domain Optical Coherence Tomography Segmentation Module for Single Retinal Layer Analysis. Curr Eye Res. 2018;43:1024-31. doi:10.1080/02713683.2018.1467931
9. Tsunoda K, Watanabe K, Akiyama K, Usui T, Noda T. Highly reflective foveal region in optical coherence tomography in eyes with vitreomacular traction or epiretinal membrane. Ophthalmology. 2012;119:581-7. doi:10.1016/J.OPHTHA.2011.08.026
10. Zur D, Iglicki M, Feldinger L, Schwartz S, Goldstein M, Loewenstein A, et al. Disorganization of Retinal Inner Layers as a Biomarker for Idiopathic Epiretinal Membrane After Macular Surgery-The DREAM Study. Am J Ophthalmol. 2018;196:129-35. doi:10.1016/J.AJO.2018.08.037
11. Govetto A, Virgili G, Rodriguez FJ, Figueroa MS, Sarraf D, Hubschman JP. Functional and anatomical significance of the ectopic inner foveal layers in eyes with idiopathic epiretinal membranes: Surgical Results at 12 Months. Retina. 2019;39:347-57. doi:10.1097/IAE.0000000000001940
12. Shiono A, Kogo J, Klose G, Takeda H, Ueno H, Tokuda N,et al. Photoreceptor outer segment length: a prognostic factor for idiopathic epiretinal membrane surgery. Ophthalmology. 2013;120:788-94. doi:10.1016/J.OPHTHA.2012.09.044
13. Jeon S, Jung B, Lee WK. Long-term prognostic factors for visual improvement after epiretinal membrane removal. Retina. 2019;39:1786-93. doi:10.1097/IAE.0000000000002211
14. Watanabe A, Arimoto S, Nishi O. Correlation between metamorphopsia and epiretinal membrane optical coherence tomography findings. Ophthalmology. 2009;116:1788-93. doi:10.1016/J.OPHTHA.2009.04.046
15. Okamoto F, Sugiura Y, Okamoto Y, Hiraoka T, Oshika T. Inner nuclear layer thickness as a prognostic factor for metamorphopsia after epiretinal membrane surgery. Retina. 2015;35:2107-14. doi:10.1097/IAE.0000000000000602
16. Joe SG, Lee KS, Lee JY, Hwang JU, Kim JG, Yoon YH. Inner

retinal layer thickness is the major determinant of visual acuity in patients with idiopathic epiretinal membrane. Acta Ophthalmol. 2013;91:e242-3. doi:10.1111/AOS.12017
17. Nawrocka ZA, Trebinska M, Nawrocka Z, Nawrocki J. Idiopathic epiretinal membranes: postoperative changes in morphology. Can J Ophthalmol. 2023;58:582-91.doi:10.1016/J.JCJO.2022.06.023
18. Karasavvidou EM, Panos GD, Koronis S, Kozobolis VP, Tranos PG. Optical coherence tomography biomarkers for visual acuity in patients with idiopathic epiretinal membrane. Eur J Ophthalmol. 2021;31:3203-13. doi:10.1177/1120672120980951
19. Oster SF, Mojana F, Brar M, Yuson RMS, Cheng L, Freeman WR. Disruption of the photoreceptor inner segment/outer segment layer on spectral domain-optical coherence tomography is a predictor of poor visual acuity in patients with epiretinal membranes. Retina. 2010;30:713-8. doi:10.1097/IAE.0B013E3181C596E3
20. Mitamura Y, Hirano K, Baba T, Yamamoto S. Correlation of visual recovery with presence of photoreceptor inner/outer segment junction in optical coherence images after epiretinal membrane surgery. Br J Ophthalmol. 2009;93:171-5. doi:10.1136/BJO.2008.146381
21. Inoue M, Morita S, Watanabe Y, Kaneko T, Yamane S, Kobayashi S, et al. Preoperative inner segment/outer segment junction in spectral-domain optical coherence tomography as a prognostic factor in epiretinal membrane surgery. Retina. 2011;31:1366-72. doi:10.1097/IAE.0B013E318203C156
22. Watanabe K, Tsunoda K, Mizuno Y, Akiyama K, Noda T. Outer retinal morphology and visual function in patients with idiopathic epiretinal membrane. JAMA Ophthalmol. 2013;131:172-7. doi:10.1001/JAMAOPHTHALMOL.2013.686
23. Govetto A, Bhavsar K V., Virgili G, Gerber MJ, Freund KB, Curcio CA, et al. Tractional Abnormalities of the Central Foveal Bouquet in Epiretinal Membranes: Clinical Spectrum and Pathophysiological Perspectives. Am J Ophthalmol. 2017;184:167-80. doi:10.1016/J.AJO.2017.10.011



Corresponding Author/
Autor Correspondente:

Edgar Lopes
Alameda de Santo António
dos Capuchos,
1169-050 Lisboa, Portugal
E-mail: edgar.m.lopes@gmail.com

ORCID: 0000-0002-1700-2921