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Epiretinal Membrane: Evaluating the Prognostic Impact of Recent Optic Coherence Tomography-based Classification

ARTIGO CIENTÍFICO ORIGINAL

ÁREA CIENTÍFICA DE OFTALMOLOGIA

Trabalho realizado sob a orientação de:

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Avaliação do Impacto Prognóstico dos atuais Sistemas de Classificação de Membranas Epirretinianas

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LIST OF ABBREVIATIONS

BCVA – best corrected visual acuity

CFT – central foveal thickness

CHUC – Coimbra University Hospital Centre

COST – cone outer segment tips

EIFL – ectopic inner foveal layers

ERM – epiretinal membrane

GCC – ganglion cell-inner plexiform layer complex

ILM – internal limiting membrane

IPL - inner plexiform layer

IRF – intraretinal fluid

IS/OS – inner segment/outer segment

OCT – optical coherence tomography

ONL – outer nuclear layer

PHACO – phacoemulsification and intraocular lens implantation

PPV – pars plana vitrectomy

PROS – photoreceptor outer segment

PVD – posterior vitreous detachment

RE – right eye

RPE – retinal pigment epithelium

Schisis - macular retinal schisis

SD – standard deviation

SD-OCT – spectral-domain optical coherence tomography

SRF – subretinal fluid

VA – visual acuity

RESUMO

INTRODUÇÃO: A membrana epirretiniana (MER) define-se como uma proliferação fibrocelular da superfície interna da retina. Com o recurso à tomografia de coerência ótica, diversos parâmetros estruturais e sistemas de classificação das MER foram descritos com potencial impacto prognóstico, anatómico e funcional.

OBJETIVO: Este trabalho propõe caracterizar o impacto prognóstico de biomarcadores avaliados através da tomografia de coerência ótica de domínio spectral (SD-OCT) - camada interna ectópica foveal (EIFL), espessura macular central (EMC), sinal de *cotton ball*, integridade da camada elipsoide, presença de líquido intraretiniano ou subretiniano e esquisis – em olhos submetidos a vitrectomia *pars* plana (VPP) por MER e pelagem membrana limitante interna.

MÉTODOS: Trata-se de um estudo retrospetivo, longitudinal, de coorte. Foram incluídos, de forma consecutiva, olhos com diagnóstico de MER idiopática, submetidos a VPP 23/25-gauge, com tempo mínimo de follow-up pós-cirúrgico de 12 meses. Foram avaliadas imagens de SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany), preoperatoriamente, aos 6 e 12 meses pós-operatório, por 2 médicos especialistas independentes. Com o recurso à função de “caliper”, foi registada a espessura EIFL medida na vertical e horizontal, em b-*scans* centrados na fóvea. A associação entre a espessura da EIFL e de outros biomarcadores do SD-OCT, previamente descritos, com a melhor acuidade visual corrigida (MAVC) foi avaliada. O nível de significância estabelecido foi $p<0.05$.

RESULTADOS: Foram incluídos cento e dezoito olhos, de 108 doentes (idade média 76,52±7,09; 65% do sexo masculino). Pré-operativamente, a MAVC média foi 55,52±12,44 letras e, 70,00±13,34 letras aos 12 meses pós-operatório, a evolução média da MAVC foi de 13,45±14,15 letras (p<0,001). Pré-operativamente, a EIFL estava presente em 59 olhos (50%). A espessura média da EIFL, medida na horizontal e vertical, foi 239,31±89,27μm e 228,48±85,67 μm, respetivamente. A medição na vertical e horizontal está correlacionada, pré-operativamente, com a CFT (rho=0,63 e rho=0,55; *p*<0,001, respetivamente). No entanto, apenas a camada ectópica medida na vertical demonstrou ter impacto prognóstico na MAVC final, independentemente da CFT pré-operatória (ß=-0,12±0,05; p=0,01). De facto, a espessura da EIFL medida na vertical demonstrou ser o marcador individual de prognóstico visual mais sensível (ß=-0,07±0,01; *p*<0,001).

CONCLUSÃO: Este estudo revela que a camada ectópica medida na vertical pode ser um importante preditor da evolução da acuidade visual pós-cirurgia. Isto é, um aumento na espessura da EIFL medida na vertical, antes da cirurgia, esteve relacionada com pior prognóstico funcional final. Este parâmetro parece ser um biomarcador mais sensível e melhor preditor do *outcome* visual, prevalecendo sobre outros biomarcadores previamente descritos.

PALAVRAS-CHAVE: membrana epirretiniana, vitrectomia, prognóstico, biomarcadores

ABSTRACT

INTRODUCTION: Epiretinal membrane (ERM) is a fibrocellular proliferation above the inner surface of the retina. Optical coherence tomography (OCT) structural features and new classifications schemes have been proposed as prognostic biomarkers for anatomical and functional postoperative improvement.

PURPOSE: To characterize the prognostic impact of baseline spectral domain optical coherence tomography (SD-OCT) biomarkers - ectopic inner foveal layer (EIFL), cotton ball sign, ellipsoid disruption, intra and subretinal fluid - in eyes with idiopathic ERM who underwent pars plana vitrectomy (PPV) with ERM and internal limiting membrane peeling.

METHODS: Retrospective longitudinal cohort study. Consecutive eyes with idiopathic ERM that underwent 23- or 25-gauge PPV and had a minimum follow-up of 12 months after surgery were included. SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) scans were graded at baseline (preoperatively), and at 6 and at 12 months postoperatively by two independent medical graders (JPM and MR). Two EIFL thickness measures were manually obtained using the caliper function: a horizontal EIFL based on a horizontal b-scan centered at the fovea and a vertical EIFL based on a vertical b-scan also centered at the fovea. The association of EIFL thickness and others SD-OCT biomarkers (cotton ball sing, ellipsoid sone disruption, intraretinal and subretinal fluid, macular retinal schisis and CFT) with best corrected visual acuity (BCVA) change was evaluated. Significance was considered at $p<0.05$.

RESULTS: One-hundred and eighteen eyes of 108 patients (mean age 76.52 ± 7.09; 65% males) were included. Preoperatively, mean BCVA was 55.52 ± 12.44 letters and a mean BCVA change of 13.45 ± 14.15 letters was observed at 12 months ($p<0.001$). EIFL was present in 59 eyes (50%) preoperatively. Horizontal mean EIFL thickness was 239.31 ± 89.27 µm and vertical mean EIFL thickness was 228.48 ± 85.67 µm. Both were correlated with preoperative central foveal thickness (CFT) (rho=0.63 and rho=0.55; $p<0.001$, respectively). Nonetheless, only vertical EIFL thickness demonstrated a prognostic impact on final BVCA, independent of preoperative CFT (ß= -0.12 ± 0.05; $p=0.01$). Indeed, vertical EIFL thickness was the most important visual individual prognostic biomarker (ß= -0.07 ± 0.01; $p<0.001$)

CONCLUSION: Our study revealed that vertical EIFL thickness may reflect the true impact of this ectopic layer on visual prognosis. That is, an increased preoperative vertical EIFL thickness predicted worst anatomical and functional outcomes. This parameter seems to be a reliable biomarker to predict final visual outcome, surpassing other common OCT biomarkers.

KEYWORDS: epiretinal membrane, vitrectomy, prognosis, biomarkers

INTRODUCTION

Epiretinal membrane (ERM) is a common vitreoretinal disease, first described by Iwanoff, in 1865[1]. It is a fibrocellular membrane proliferation on the inner surface retina along the internal limiting membrane (ILM), affecting the retina over the macula.

Progression occurs from a thin and translucid avascular tissue to a semitranslucent, thicker membrane, with contractile capacity, ultimately, resulting in macular dysfunction. This phenomenon can also be identified as "macular pucker", "preretinal macular fibrosis", "epimacular proliferations" "epiretinal fibrosis or gliosis" or "surface wrinkling retinopathy" or "cellophane maculopathy".

Based on etiology, this macular disease is classified into idiopathic or secondary[2]. Idiopathic ERM is the most common type, when there is no identifiable etiology. Secondary ERM is associated with chronic ocular disease, intraocular surgery, tumors or trauma. Nowadays, is clear the association between idiopathic ERM, aging[3] and posterior vitreous detachment (PVD)[4].

The pathological mechanism of ERM that induces visual loss persists unclear, although is thought to be based in a fibrotic process. Bellhorn *et al*[5] defined "epipapillary membrane" as a heterogeneous network of glial cells, mainly astrocytes and Müller cells, that migrate through breaks in the ILM toward the vitreous. ERM induces contractile forces resulting in inward movement of the outer nuclear layer (ONL)[6].The development of intense traction leads to disarrangement of the cells polarities in each retinal layer and disturbance of normal neurotransmission[6]. The most likely theory is the migration of retinal pigment epithelium (RPE) cell through microbreaks in the internal limiting membrane that occurs during the PVD[7].

Histologically, it is possible to identify cellular and extracellular matrix components, such as glial cells, hyalocytes, macrophages, retinal pigment epithelial cells, fibroblast and myofibroblast.

Manifestation

The majority of patients are asymptomatic and are diagnosed on routine examination.

Most common clinical visual manifestation are: metamorphopsia, aniseikonia, photopsia, loss of central vision and monocular diplopia [8–10].

Prevalence and incidence

ERM prevalence ranges from 4% to 6.2%, increasing significantly with age.[2,11,12].

In 1997, Mitchell et al[2], in the Blue Mountain Eye Study, regarding 3654 Australian residents with 49 years of age or older, reported a prevalence of 6.2%.

In 2003, Miyazaki et al[11], conducted a study in a Japanese population with 1775 participants and the prevalence of ERM was of 4%.

In 2005, McCarty et al[12], performed another Australian study with 4313 participants. They concluded that the global prevalence is, like other population-based studies, around 6%, but they found a significant increase by age group (0.5% for 40 to 49 years, 2.6% for 50 to 59 years, 9.4% for 60 to 69 years, 15.1% for 70 to 79 years, and 11.3% for 80 years and older).

Still regarding the Blue Mountain Study, Fraser-Bell et al[13], in a five-year cohort study obtain a cumulative incidence rate for ERM of 5.3%. Regarding the natural history, this study concluded that the progression of ERM is very slow and the rate of progression is between 16% and 33%. Almost 39% of the eyes maintained a stable vision and only 25% of the cases had a visual acuity (VA) decrease, during the study.

Imaging

Initially, stereoscopic biomicroscopy, stereoscopic color fundus photography, fluorescein angiography and red free fundus imaging were the methods used for assessing this macular pathology.

Recently, optical coherence tomography (OCT) and more specifically spectral-domain optical coherence tomography (SD-OCT) became the gold-standard to study the macular morphology. This exam plays a major role in the diagnosis and management of ERM. It is a high-resolution noninvasive imaging exam that allows a cross-sectional retina analysis, with a precise and quantitative evaluation of intraretinal layers and vitreomacular interface.

In this exam, ERM is defined as a single, hyperreflective, discrete and irregular line, contiguous or anterior to the inner retinal surface, typically associated with underlying retina wrinkling and presence of hyporreflective space between the ERM hyperreflectivity and ILM.

Treatment

Concerning ERM treatment, in 1978, Machemer first described the established surgical correction for symptomatic ERM as pars plana vitrectomy (PPV) with removal of the ERM[14].

Several studies have shown significant visual improvement after surgery for ERM. Margherio *et al*[15] reported 328 cases that underwent vitreous surgery to remove ERM and 74% improved two or more lines in VA. In 1986, McDonald *et al*[16] performed a study in 33 consecutive cases of idiopathic ERM, who underwent PPV, with a median of 10 months of follow up. Improvement of BCVA was verified in 79% treated eyes.

In patients with symptomatic idiopathic ERM, specialty with significant VA loss and/or incapacitant visual distortion, PPV with ERM removal and ILM peeling, is the gold standard procedure for retinal anatomic restauration and functional improvement[17]. This technique shows lower rates of recurrence without adverse visual outcome. Patients with poor preoperative VA have been associated more frequently with a greater improvement in BCVA[18].

Biomarkers

Nonetheless, the right moment for surgery remains unclear. Surgeons must evaluate the severity of ERM and predict postoperative visual rehabilitation. It is essential to weight the benefits and risks of the intervention, allowing a careful selection of candidates and the ideal timing for surgical treatment. Therefore, efforts have been applied to identify visual prognosis biomarkers.

With the development of SD-OCT, many investigators made an effort to demonstrate morphological findings as potential prognosis predictors of postoperative visual outcome after ERM surgery.

Higher preoperative central foveal thickness (CFT) is correlated with poor preoperative VA[10,19–21] and negatively correlated with postoperative best corrected visual acuity (BCVA)[19,20].

Photoreceptor outer segment (PROS) length (distance between photoreceptors inner segment (IS) and outer segment (OS) junction and RPE) was found to be a prognostic valuable factor for the postoperative VA[9,22].

The ellipsoid zone (EZ) corresponds to the photoreceptors IS/OS junction and the integrity of EZ is associated with functional status. Disruption of the IS/OS junction has been associated with poor postoperative VA[23,24].

Cone outer segment tips (COST) is an hyperreflective line between the EZ and RPE. Disruption of COST suggests photoreceptor damage and, possibly, a deterioration of VA[25]. Preoperative length of the COST line defect is associated with poor postoperative BCVA[25]. Continuous COST in association with integrity of IS/OS junction is a favorable prognosis factor after ERM surgery[26].

The cystoid macular edema (CME) is defined by hyporeflective roundish-elliptical intraretinal cystoid spaces on OCT scans and their presence have been reported as a poor functional prognostic sign[27].

Recent studies shifted the attention to the inner retina layers biomarkers, pointed out as primary affected area of stress mechanism involved. Inner retinal layers have the largest variability of thickness and are the main responsible for the repercussion on VA, in patients with idiopathic ERM[28]. Furthermore, Jeon *et al*[29] suggested that, in ERM patients, reduced BCVA with damage in outer retinal structure had less chance to improve VA, since it reflects long-lasting damage of photoreceptors. In contrast, when reduction of visual capacity is due to inner retinal changes, relatively reversible and potential long-term vision improvement is possible.

Retina thickening is secondary to traction of ERM, a tangential and unidirectional force with origin in the inner surface of the retina. The uneven mechanical stress on the retina results in different thickness changes for each layer. Previous studies showed that inner nuclear layer (INL) had the highest variability and was strongly associated with BCVA changes[28]. Preoperative INL thickness is a good indicator of metamorphopsia, preoperatively and postoperatively, in patients with idiopathic ERM[30,31].

Kim *et al*[21] reported that INL thickness was the stronger structural variable, significantly associated with postoperative VA. And, also, ganglion cell-inner plexiform layer complex (GCC) thickness was negatively associated with postoperative VA[21]. Lee et al[32] achieved that the postoperative GCC was thinner than normal controls, and a thinner GCC was correlated with poor visual outcomes.

Yang *et al*[33] reported that the postoperative degree of inner retinal anatomic restauration was mostly associated with visual function recovery. Decreased vision in eyes with ERM has mainly attributed to thickening of inner foveal retinal layer and CFT. The major prognosis factor of postoperative visual recovery were preoperative central inner retinal layers thickness and duration of disease. Also, Joe *et al*[6] found that this abnormal inner foveal layer thickening was the main predictor of VA, even compared with central subfield thickness, outer retinal layer thickness and IS/OS disruption.

Furthermore, higher CFT/GCL ratio has been described as a significant predictor of postoperative VA improvement[34].

In 2017, Govetto *et al*[26] introduced a new classification scheme, practical and reproducible, based on ectopic inner foveal layers (EIFL), defined as a continuous hyperreflective band on the OCT scans, extending from the INL and inner plexiform layer (IPL) across the foveal region. The authors concluded that presence of EIFL was an independent risk factor for preoperative VA and postoperative lower anatomic and functional rehabilitation.

Classification

In the clinical field, remains difficult to predict the postoperative visual outcome and with this purpose, many authors created different classifications systems.

In 1996, Wilkins *et al*[35], reported the first OCT based classification, regarding the adherence to the retinal surface.

In 2012, Hwang *et al*[36], classified idiopathic ERM according to characteristics of foveal morphology on the SD-OCT, into five subtypes: outer retinal thickening with minimal inner retinal change (stage 1A); outer retinal inward projection and inner retinal thickening (stage 1B); prominent thickening of the inner retinal layer (stage 1C); formation of macular pseudohole (stage 2A) and foveal-sparing ERM schicis-like intraretinal splitting (stage 2B).

In 2012, Chalam et al[31] described a classification scheme regarding clinically relevant SD-OCT findings, namely CFT and inner segment ellipsoid band integrity.

In 2013, Konidaris *et al*[37], reported a more extensive classification OCT-based, based morphologic and PVD.

The latest staging system for ERM was proposed by Govetto *et al*[38]. Is a SD-OCT staging scheme based on the presence of EIFL and foveal anatomy: Stage 1 - ERM with negligible morphological distortion and foveal depression preserved; Stage 2 - ERM with retinal layers well defined, stretching of ONL and loss of foveal depression; Stage 3 - ERM with EIFL but well-defined retinal layers and loss of foveal depression; Stage 4 - ERM with EIFL associated with remarkable retinal layers disorganization.

Few studies have documented the impact of EIFL in the functional prognosis in patients with idiopathic ERM.

In 2017, Govetto *et al*[39] reported a retrospective cohort study including 111 eyes. They found that baseline EIFL presence and thickness, had a significant and direct negative effect in BCVA, both preoperative and postoperative, independently from CTF and other confounders. Postoperatory EIFL thinning had no effect on BCVA change during the follow up. EIFL persisted in 91% at 12 months, with poor anatomical restauration and lower surgical visual outcomes, suggesting irreversible retinal damage. In conclusion, this new classification and the presence of EIFL were proposed as predicters for postoperative anatomical and functional recovery.

In 2018, Donguizi *et al*[40] presented a prospective, cross-sectional design study with 121 eyes and reported that BCVA values were correlated negatively with EIFL and CFT thickness. Sato *et al*[41] performed a retrospective study with 77 eyes, which showed significant better VA in eyes without an EIFL. Also, González-Saldivar *et al*[7] reported a retrospective study with 88 pseudophakic eyes, with 12 months follow-up and they found that stage 2 ERM had better VA and anatomic outcome, when compared with stage 3 and 4 (where EIFL is present). Therefore, for a better prognosis, ERM surgery is desirable before EIFL development.

Objectives

The aim of this study was to characterize the impact of EIFL thickness and CFT along with other structural biomarkers on the functional and anatomical prognosis in eyes with idiopathic ERM who underwent PPV with ERM and ILM peeling. Additionally, we aimed to compare the prognostic capacity of several SD-OCT-based ERM classification schemes.

METHODS

Study Design

We performed a single-center, retrospective, longitudinal cohort study at a tertiary care hospital in Portugal. The study protocol was approved by the local Ethics Committee (Nº CHUC-150-20) and this biomedical research followed the tenets of the Declaration of Helsinki. An informed consent was signed by all the included participants.

Consecutive patients diagnosed with idiopathic ERM submitted to PPV with ERM and ILM peeling ± phacoemulsification and intraocular lens implantation, between January 2014 and December 2017, and with a minimal follow-up of 12 months after surgery, were included.

Patients submitted to previous intra-ocular surgery other than uncomplicated phacoemulsification or diagnosed with other intraocular entities were excluded.

Ophthalmologic evaluation

Medical records were reviewed by the authors to retrieved demographics and medical and surgical information. BCVA was recorded in terms of Snellen fraction preoperatively, at 6 months and at 12 months following surgery.

SD-OCT imaging and quantitative measurements

SD-OCT scans were assessed at baseline and at 6 and 12 months postoperatively by two independent medical graders (JPM and MR), who were blinded to the clinical data. Scans were obtained using Heidelberg Spectralis SD-OCT with eye-tracking dual-beam technology (Heidelberg Engineering GmbH, Heidelberg Germany) and analyzed with the Heidelberg Eye Explorer using the HRA/Spectralis Viewing Module. SD-OCT scan patterns were used for all quantitative measurements and qualitative evaluation. Retinal layers were identified using the terminology proposed by the international OCT Consensus[42].

Preoperatively, the following parameters were evaluated: "cotton ball" sing (presence of a round and diffused hyperrefletive area between the EZ and the cone outer segment tip line at the center of the fovea, as described by Tsunoda *et al*[43]), EZ disruption, intraretinal fluid (IRF), subretinal fluid (SRF), macular retinal schisis (schisis) and mean CFT (defined as the average thickness encountered in the 1mm central subfield located at the fovea, was obtained automatically from the "thickness map" function of the Heidelberg software). Vertical and horizontal EIFL thickness were measured manually, using the "caliper" function, of the Heidelberg instrument. A straight vertical line from the outer margin of INL to the inner margin of the ILM measured the abnormal EIFL layer thickness in the vertical and horizontal B-scans centered in the fovea.

At 6 and 12 months after surgery, the following measures were recorded: mean CFT and vertical and horizontal EIFL measurements.

All ERMs were classified according to three previously described staging systems: EIFL based system[38], OCT based system[36] and SD-OCT based system[37].

Surgery procedure

PPV to remove ERM was performed by 5 experienced surgeons, with or without combined cataract surgery (phacoemulsification and intraocular lens implantation – PHACO).

Patients underwent a conventional 3-port transconjuntival, suture-less, 23- or 25-gauge PPV with ERM and ILM peeling, performed using the Constellation vision system (Alcon, Fort wort, TX), under local anesthesia. Both ERM and ILM were peeled using Grieshaber ILM forceps (Alcon), with the assistance of 0.025% brilliant blue G (DORC, Zuidland, the Nertherlands). At the end of the surgery, air-fluid exchange was performed. All patients received a standard postoperative protocol of topical antibiotic and anti-inflammatory medication. All patients were evaluated at baseline and at 6 and 12 months after surgery. Postoperative complications were record at any point during the follow up period.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26 (IBM, Corporation, Armonk, NY, USA). The significance level was considered for a *p* value inferior to 0.05. All BCVA values were converted to the logarithm of the minimum angle of resolution (logMAR) scale for statistical analysis purposes. Descriptive analyzes were calculated for all variables of interest. Continuous variables are expressed as mean ± standard deviation for continuous variables (logMAR (BCVA), CFT, EIFL thickness). Frequency and percentage were estimated for categorical variables (sex, eye involved, preoperative lens status, type of surgery, “cotton ball” sing, EZ disruption, IRF, SRF and schisis). All the data samples shown non-normal distribution and the variance between groups of ERM stages was not similar. Therefore, were used non-parametric tests for analyses purpose. The significance of the difference between the independent groups was examined with Mann-Whitney U test for two groups and with the Kruskal-Wallis test for more than two groups. Spearman’s rank correlation test was used to explore the significance of the relationship among continuous variables. Friedman repeated measures analysis of variance on ranks was performed to compare the BCVA, SD-OCT parameters and measurements and to analyze its evolution, within the same subject, at different periods (baseline, 6 months and 12 months).

Univariate and multivariate linear or logistic regression was used to assess association between SD-OCT findings and BCVA longitudinal change, the most significant independent predictor of VA in ERM eyes. Linear mixed-effects models with subjects as random intercept and time as random slope were used to investigate predictors of change in BCVA during follow up. Structural equation modeling was used to fit mediation analyses and to assess whether SD-OCT findings and measurements affects BCVA directly or only indirectly.

Covariates included in univariate and multivariate models were preoperative CFT, EIFL thicknesses, IRF and baseline and postoperative BCVA. In the ERM staging process, the Cohen kappa coefficient was used to measure interobserver agreement for categorial variables. Bonferroni correction for multiple tests was performed as a pos hoc test.

RESULTS

One hundred and eighteen eyes with idiopathic ERM were included in the study. Baseline demographics of our study population are summarized in the Table 1. There were no significant differences in BCVA regarding preoperative lens status and type of surgery performed (PPV or PHACO+PPV).

Table 1 – Baseline patients demographics and ocular characteristics

Age (years, mean ± SD)	76.52 ± 7.09 (range: 56-92 age)	
Sex (male, n,%)	65	55.1%
RE (n, %)		48.3%
Preoperative lens status (pseudophakia, n,%)	24	20.3%
Surgery (n,%)		
PPV	35	29.7%
PHACO + PPV	83	70.3%

Abbreviations: SD, standard deviation. RE, right eye. PPV, pars plana vitrectomy. PHACO, phacoemulsification and intraocular lens implantation.

Preoperatively, mean BCVA was 55.52 ± 12.44 letters. Mean VA at 6 and 12 months after surgery was 67.54 ± 10.93 and 70.00 ± 13.34 letters, respectively. BCVA significantly improved at 6 months and 12 months post-surgery when compared with baseline values (p<0.001, Fig.1A) and, also, between 6 and 12 months of follow up (p=0.03).

Correlation of BCVA with SD-OCT measurements

Preoperative mean CFT thickness was 492.79 ± 80.22 µm. CFT significantly decreased from baseline to 6 and 12 months after surgery (p=0.03; p<0.001 respectively) and, finally, between 6 and 12 months of follow up (p=0.03, Fig. 1B).

Preoperative mean horizontal EIFL thickness was 239.31 ± 89.27 µm and mean vertical EIFL thickness was 228.48 ± 85.67 µm. Horizontal and vertical EIFL thickness significantly decreased from baseline to 6 and 12 months after ERM surgery (p≤0.001, Fig. 1C and 1D). CFT showed a statistically significant correlation with both baseline horizontal EIFL (rho=0.63, p<0.001) and vertical EIFL (rho=0.55, p<0.001).

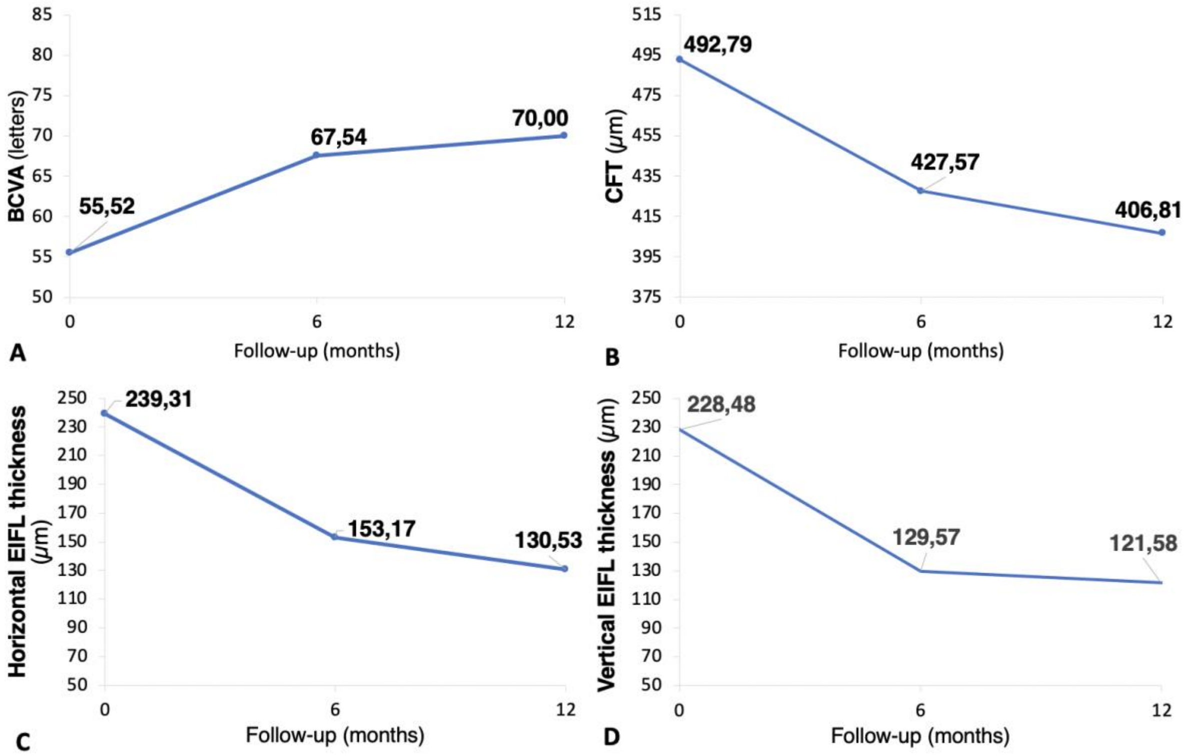

Figure 1 - Best corrected visual acuity, central foveal thickness and ectopic inner foveal layer thickness evolution during follow-up.

(1A) BCVA evolution during follow-up. **(1B)** CFT evolution during follow-up **(1C)** Horizontal EIFL thickness evolution during follow-up. **(1D)** Vertical EIFL thickness evolution during follow-up. Abbreviations: BCVA, best corrected visual acuity. CFT, central foveal thickness. EIFL, ectopic inner foveal layer.

Preoperative BCVA significantly correlated with both vertical and horizontal EIFL and CFT thickness. Additionally, vertical and horizontal EIFL thickness were correlated with preoperative CFT. Correlation data are summarized in Table 2.

Table 2 - Correlation coefficients of BCVA and SD-OCT measurements

	CFT		**Vertical EIFL thickness**		**Horizontal EIFL thickness**	
	rho	*p*	rho	*p*	rho	*p*
Preoperative BCVA	-0.33	<0.001	-0.29	0.02	-0.28	0.03
Final BCVA	-0.17	0.13	-0.31	0.04	-0.08	0.61
CFT	----------------------		0.55	<0.001	0.63	<0.001
Horizontal EIFL thickness	0.63	<0.001	0.52	<0.001	----------------------	

Abbreviations: BCVA, best corrected visual acuity. SD-OCT, spectral-domain optical coherence tomography. CFT, central foveal thickness. EIFL, ectopic inner foveal layer. Data are presented as rho; p value, using Spearman's rho.

Clinically interpreting the coefficients included in Table 3, comparing BCVA with OCT parameters, we found that an addiction of 100 µm of preoperative CFT, was associated with an approximate mean reduction of 5 letters in initial BCVA, an addiction of 100 µm of preoperative horizontal EIFL thickness, was associated with an approximate mean reduction of 4 letters in preoperative BCVA and, finally, an addiction of 100 µm of preoperative vertical EIFL thickness, was associated with an approximate mean reduction of 3.5 letters in initial BCVA.

Table 3 - Association between BCVA, EIFL thickness, CFT and IRF

	Independent variables							
	Horizontal EIFL thickness		**Vertical EIFL thickness**		**Preoperative CFT**		**IRF**	
Dependent variables	ß	*p*	ß	*p*	ß	*p*	ß	*p*
Preoperative BCVA	-0.04	0.007	-0.04	0.03	-0.06	<0.001	-5.86	0,04
Final BCVA	-0.01	0.62	-0.06	0.03	-0.07	0.004	-8.12	0.03

Abbreviations: BCVA, best corrected visual acuity. EIFL, ectopic inner foveal layer. CFT, central foveal thickness. IRF, intraretinal fluid. Data are presented as ß, p value, using ANOVA.

In the mixed-effects model, only preoperative vertical EIFL thickness demonstrated an independent prognostic impact on evolution of BCVA (ß= -0.03, *p*=0.045). In this model, the direct effect of preoperative vertical EIFL thickness on final BCVA was an approximate mean reduction of 3.4 letters per 100 µm. Preoperative horizontal EIFL thickness and CTF did not demonstrated a prognostic impact on BVCA evolution in the multivariate analysis (*p*=0.89 and *p*=0.06, respectively).

Correlation of BCVA with SD-OCT structural parameters

"Cotton ball" sign was not correlated with BCVA preoperatively (*p*=0.05) or at 6 or 12 months postoperatively (*p*=0.95 and *p*=0.82, respectively). Ellipsoid band disruption had preoperative association with worst BCVA (*p*=0.02). However, postoperatively had no prognosis capacity at 6 months or at 12 months (*p*=0.27 and *p*=0.59 respectively). Subretinal fluid and schisis were not associated with BCVA either preoperatively (*p*=0.24 and *p*=0.46) or at 6 months (*p*=0.33 and *p*=0.72) or 12 months (*p*=0.36 and *p*=0.75) postoperatively.

Presence of intraretinal fluid was associated with poorer initial VA (*p*=0.02). IRF maintained the negative effect during the follow up period (*p*=0.003 and *p*=0.01, respectively at 6 months and at 12 months). Presence of preoperative IRF was associated with an approximate mean inferiority of 8 letters in final BCVA (Table 4).

Table 4 - Prognostic capacity of SD-OCT biomarkers (compared to BCVA evolution)

			Prognosis significance	
	n	%	ß	p
"Cotton ball" sing	33	29.2%	-0.49	0.78
EZ disruption	14	12.1%	-4.19	0.13
IRF	25	21.6%	-7.51	0.002
SRF	5	4.3%	-6.14	0.19
Schisis	7	6.0%	0.48	0.91

Abbreviations: SD-OCT, spectral-domain optical coherence tomography. BCVA, best corrected visual acuity. EZ, ellipsoid zone. IRF, intraretinal fluid. SRF, subretinal fluid. Schisis, macular retinal schisis. Using mixed-effects model adjusted to variable time. Data are presented as n (%).

Correlation of BCVA with classification systems

OCT-based classification was not able to stratify patients preoperatively (p=0.34) and had no prognostic significance at 6 months and at 12 months (*p*=0.36 and *p*=0.28 respectively).

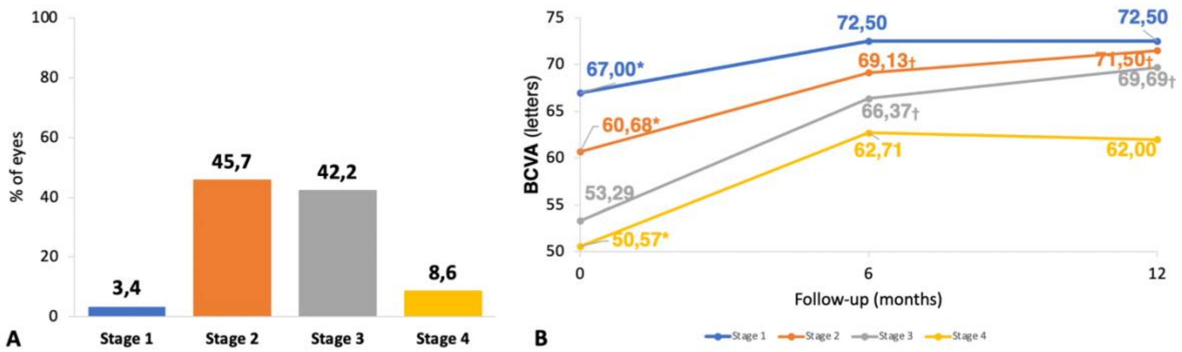

Figure 2 - Ectopic inner foveal layer-based classification.

(2A) Preoperative staging according to EIFL preoperative classification. EIFL was present preoperatively in 59 eyes, 50%, stage 3 and 4. **(2B)** BCVA evolution, according to EIFL preoperative classification. *statistically significant: stage 1 (*p*=0.02), 2 (*p*=0.049 not adjusted) vs stage 4, using Pairwise multiple comparison with Bonferroni corrected p value. †The improvement in VA in relation to initial BCVA was statistically significant in stage 2 and 3 at 6 months of follow up (*p*=0.005 and *p*=0.001, respectively) and at 12 months of follow up (*p*=0.001 and *p*<0.001, respectively, using Bonferroni correction for multiple tests). Abbreviations: BCVA, best corrected visual acuity. EIFL, ectopic inner foveal layer.

EIFL-based classification was able to stratify preoperatively VA (p=0.007, Fig. 2A and 2B). There was a significant difference in BCVA between stage 1 and 2 when compared with stage 4 (p=0.02 and p=0.049 respectively).

SD-OCT-based classification was able to stratify a BCVA preoperative with a statistically significant difference in BCVA between stage B and stage C (p=0.02). However, it had no prognostic capacity at 6 months and at 12 months (p=0.27 and p=0.59 respectively).

Inter-observers' agreement for eye stratification showed a strong correlation (k=0.69) for OCT-based classification and very strong coefficient (k=0.82) for EIFL-based classification.

The evolution of BCVA according to the different classifications, was calculated using Friedman's two-way analysis of variance by ranks. OCT-based classification showed statistically significant differences in VA over time for stages stage 1B, 1C and 2A (p<0.001). No statistical significance was reached for stage 1A (p=0.37). For stage 1B, the improvement in vision was statistically significant at 12 months of follow up (p=0.001). Regarding stage 1C, the improvement in vision was statistically significant at 6 months and at 12 months of follow up (p<0.001). For stage 2A, the improvement in vision was statistically significant at 6 months and at 12 months of follow up (p<0.001).

EIFL-based classification was significantly associated with the evolution of BVCA during the follow-up period, but only for specific stages. In stages 2 and 3, VA evolved over time, with initial and postoperative BCVA being statistically distinct (p<0.001). The improvement in vision between stages 2 and 3 was statistically significant at 6 months of follow up (p=0.005 and p=0.001, respectively) and persisted at 12 months (p≤0.001 for both). However, in stage 1 and 4, BCVA did not change significantly during the follow up period (p=0.14 and p=0.07).

Regarding the SD-OCT-based classification, in stage B, BCVA improved over the follow-up period (p<0.001 at 6 and 12 months). However, in stage C no difference in BCVA was found (p=0.10).

DISCUSSION

This study explored the clinical significance of SD-OCT, qualitative and quantitative findings, and evaluated the prognosis capacity of different classification schemes in 118 eyes diagnosed, with idiopathic ERM, who underwent VPP with ERM and ILM peeling. In the present study differences in the postoperative time course of changes in VA, SD-OCT characteristics were evaluated, and prognostic factors were distinct among our population.

Our study shows that preoperative VA has prognostic value for postoperative BCVA. A mean improvement of 3 lines in BCVA was observed during the follow up period. Higher preoperative VA was found to be associated with better postoperative visual outcome. Also, lower preoperative VA results in a greater improvement of letters, reflecting the ceiling effect. Prognostic capacity of preoperative BCVA has been reported by several authors, with consistent results[20,24,26,44,45].

Additionally, we evaluated three classifications schemes as prognostic factors for visual outcome in our population. All three classifications did not show significant prognostic impact.

OCT-based scheme was not able to stratify preoperatively patients and due to subjective interpretation of foveal morphological characteristics has lower reproducibility. Therefore, this classification showed poor clinical relevance for the therapeutic orientation of ERM.

The present study suggests that classification based on EIFL shown clinical relevance in prognosis implication on vision acuity and layer thickness, for stage 2 and 3. Similarly, Govetto *et al*[38] demonstrated the prognostic value of their classification, outcomes were significant different between the 3 ERM stages, with Stage 2 and 4 ERMs at opposite ends. In our study, this classification was able to preoperatively stratify patients according to preoperative VA, stage 1 plus stage 2 *versus* stage 4. Preoperative presence of EIFL formation was significantly associated with lower postoperative BCVA. Similarly, Govetto *et al*[38] found an association between EIFL and lower preoperative BCVA.[39] A possible explanation proposed is that EIFL interposed between afferent light and photoreceptors and may degrade the visual image projected on the foveal cone photoreceptors[38]. The extent of this optical obstruction was directly related with EIFL thickening[39].

In our study, only in stage 2 and stage 3 EIFL ERM occurred a significant visual improvement over follow-up. Previous studies reported significantly better outcomes after surgery on stage 2 EIFL ERM[7] and higher rate of improvement for stage 3[39]. Theses subgroups have a higher postoperative anatomical and functional recovery and suggested that the restoration of foveal depression unobstruct the pathway for incoming light to strike directly the photoreceptors[7].

Regarding SD-OCT qualitative features, only disruption of ellipsoid band and IRF, when present preoperatively, proved to be significantly associated with worst baseline BCVA. During the follow up period, only IRF demonstrated negative prognosis impact. Previous studies reported that preoperative IRF was related to significantly worse preoperative VA and lower postoperative vision improvement[46–48].

Other structural biomarkers were evaluated, including "cotton ball" sign, ellipsoid band integrity and presence of SRF, but did not reach statistical significance as prognostic factors. Other studies did not find significant prognostic value of integrity of ellipsoid band[21,49]. Although, multiples studies pointed that EZ integrity has a positive correlation in visual prognosis in eyes with MER[10,19,23,24,45].

Regarding SD-OCT quantitative findings, during the follow up period was observed a decrease of both CFT and EFIL thicknesses. Baseline CFT did not predict the VA evolution, as well as in multiples studies[45,26,50,41]. However, several other studies have demonstrated that CFT may be a predictor of worse postoperative BCVA[10,19,38,40,51].

To the best of our knowledge, in similar studies from literature, only horizontal scans were evaluated to access prognostic impact of EIFL formation. When comparing direct effect of both EIFL thickness, in our study, only preoperative vertical EIFL thickness demonstrated an independent and negative predictor of BCVA evolution. Vertical EIFL thickness was significant associated with inferior letters of improvement.

Preoperatively, BCVA was negatively correlated with CTF and EIFL thicknesses. However, CFT and EIFL thicknesses were also positively correlated between them, meaning that these variables shared an effect on BCVA. Our study found different correlations coefficients between CFT and EIFL thicknesses. Strongest correlation was found with horizontal EIFL thickness, when compared with vertical EIFL thickness. Kinoshita *et al*[49] evaluated metamorphopsia scores for horizontal and vertical lines in eyes with ERM. Their study concluded that horizontal metamorphopsia was greater, when compared with vertical metamorphopsia. ERM severity was significantly correlated with horizontal metamorphopsia score but not with vertical metamorphopsia score. Also suggested that this correlation may be explain by the directionality of retinal plasticity. A possible justification pointed is that vertical displacement on the retina is larger than horizontal contraction in ERM patients. The optic disc and the horizontal course of axons of retinal ganglion cells may restrict horizontal displacement of the posterior retina, in advance stage of ERM[49,52]. And, therefore, vertical plasticity of posterior retina may be greater. Such explanation supports our results.

The strengths of our study include a large cohort with a long follow-up period when compared with similar studies. Also, inclusion of several parameters, namely mostly used ERM classifications and structural findings with potential prognostic impact. SD-OCT qualitative evaluation was performed independently by two medical graders. The use of SD-OCT eye-tracking system allowed precise analysis and comparation of all exams during the follow up for each patient. Limitations of this study are inherent to its retrospective and single-center nature. Others possible sources of bias are the multiple surgeons performing surgeries and, in some cases, the combination with cataract surgery.

CONCLUSION

In conclusion, few studies have documented the prognostic value of EIFL in eyes with ERM. Our results fulfil that gap and corroborate recent literature. Our study revealed that only the vertical EIFL thickness reflect the true impact of this ectopic layer on visual prognosis. That is, an increased preoperative vertical EIFL thickness predicted worst anatomical and functional outcomes. This parameter seems to be a reliable biomarker to predict final visual outcome, surpassing other common OCT biomarkers.

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