Optical coherence tomography biomarkers for visual acuity in patients with idiopathic epiretinal membrane

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Abstract:

Purpose: To investigate the correlation between outer and inner retina optical coherence tomography (OCT) biomarkers and visual acuity in patients with idiopathic epiretinal membrane (iERM) and identify which of them may be predictive of visual function.
Methods: A retrospective cross-sectional single-centre study was conducted that included patients diagnosed with iERM. Spectral domain OCT images were obtained and assessed qualitatively and quantitively. The association of OCT parameters with best corrected visual acuity was analysed.
Results: Charts of 97 eyes of 97 patients were reviewed. Central foveal thickness, maximal retinal thickness (MRT), photoreceptor outer segment length, outer foveal thickness, ganglion cell-inner plexiform layer complex thickening, inner retinal thickness and inner retinal layer irregularity index were among the major outcome measures. OCT scans were also assessed for the presence of cotton ball sign, ellipsoid zone disruption, ectopic inner foveal layer, disorganisation of retinal inner layers (DRIL), intraretinal fluid, subretinal fluid (SRF) and epimacular membrane rip. Univariate analysis showed statistically significant association between all the aforementioned parameters with worse vision, except for cotton ball sign and SRF. Multivariate analysis found that MRT and severe DRIL were strongly correlated with worse vision ($p<0.001$).
Conclusion: MRT and severe DRIL should be considered as negative prognostic factors for visual acuity.

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Keywords: biomarkers, idiopathic epiretinal membrane, optical coherence tomography, visual acuity

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INTRODUCTION

Epiretinal membrane (ERM) is a relatively common retinal disorder with a prevalence of 2.2% to 28.9% in the general population, which is significantly associated with aging.[1] Most cases are idiopathic, but may also develop secondary to ocular inflammatory conditions, retinal vascular diseases, trauma, tumors or retinal detachments.[2]

Idiopathic ERM (iERM) is a macular condition characterized by abnormal fibrocellular proliferation on the inner retinal surface, above the internal limiting membrane (ILM).[2] Histologic studies showed that iERMs are composed of retinal and extraretinal cells and proteins of extracellular matrix (ECM). Various cell types have been found, including glial cells (retinal Müller cells, microglia and astrocytes), macrophages, hyalocytes, fibroblasts, myofibroblasts and retinal pigment epithelium (RPE) cells.[3]

At early stages of iERM there are commonly no symptoms, whereas in advanced cases of the disease, patients may complain of visual impairment, distortion, macropsia or monocular diplopia affecting their quality of life.[4,5]

In recent years, the development of spectral domain optical coherence tomography (SD-OCT) with higher resolution images gave ophthalmologists the opportunity for detailed visualization of macular microstructure and evaluation of anatomic alterations in patients with ERM. Many OCT studies have been conducted in order to identify the anatomic changes of the macula region of eyes with ERM that are associated with visual loss. Parameters correlated with outer retina, such as disruption of ellipsoid zone (EZ), photoreceptor outer segment (PROS) length and outer foveal thickness (OFT) were found to be associated with postoperative visual function.[3] However, analysis of outer retina alterations failed to predict sufficiently the final visual outcome after surgical treatment of ERM. Thus, recent studies have focused on the evaluation of inner retinal anatomy which is primarily affected by ERM mechanical traction.

The purpose of this study is to investigate the correlation between outer and inner retina OCT biomarkers and visual acuity in patients diagnosed with iERM. Additionally, we aim to identify which of these factors may be predictive of visual function.

MATERIALS AND METHODS

Patient selection

This was a cross-sectional, observational and consecutive chart review carried out at a single vitreoretinal referral centre (Ophthalmica clinic, Thessaloniki, Greece). Our study group consisted of patients that were examined between January 2013 and March 2019 and diagnosed with unilateral or bilateral iERM. Approval from institution's review board and ethics committee was obtained and the study was conducted with adherence to the tenets of the declaration of Helsinki.

Fundoscopic evaluation along with OCT findings confirmed the diagnosis of iERM. Exclusion criteria are featured in Table 1.

EXCLUSION CRITERIA	• History of intraocular surgery not including uncomplicated cataract surgery • History of retinal tear or detachment • Advanced age-related macular degeneration • Proliferative or non-proliferative diabetic retinopathy with previous clinically significant diabetic macular edema • Lamellar holes or pseudoholes • History of retinal vein/artery occlusion • Advanced glaucoma or any other optic neuropathy • History of inflammatory ocular diseases • Severe cataract • Previous ocular trauma • Any other pathology causing visual loss except ERMs

Table 1 Exclusion criteria

Clinical assessment and SD-OCT imaging

Comprehensive ophthalmological evaluation, including slit lamp examination and indirect fundus ophthalmoscopy, was performed in all patients. Best corrected visual acuity (BCVA) was measured in logarithm of the minimum angle of resolution (logMAR) for statistical analysis and all eyes were scanned with the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). SD-OCT images were graded by a single masked investigator and all quantitative measurements were based on Spectralis OCT patterns. At least two forms of OCT imaging were used in all cases, as described by Govetto et al.[2]

The automated retinal thickness map analysis protocol of the Heidelberg Eye Explorer with nine Early Treatment Diabetic Retinopathy Study (ETDRS) subfields was selected for the measurement of central foveal thickness (CFT) and maximal retinal thickness (MRT). CFT was set as the mean retinal thickness of the 1mm diameter circular region around the foveola.[6]

PROS length was defined on OCT as the distance between the inner boundary of inner segment/outer segment (IS/OS) junction and the outer boundary of the RPE, while OFT was determined as the distance between the superior border of external limiting membrane (ELM) and the inferior border of RPE (Figure 1). In all eyes, both parameters were measured subfoveally with the Heidelberg OCT "caliper" tool and images were adapted to 1:1 µm aspect ratio.[7] A discontinuous ellipsoid band appearing in the fovea was defined as disruption of EZ.[2]

Tsunoda et al[8] described cotton ball sign as a diffuse or roundish hyper-reflective region between the EZ and the interdigitation zone (IZ) at the centre of the fovea (Figure 2). The presence of a continuous hypo or hyper-reflective band that extended from the inner nuclear layer (INL) and inner plexiform layer (IPL) over the foveal zone was described as continuous ectopic inner foveal layer (EIFL) on OCT.[2] In all cases, ERMs were also classified based on the 4-grade staging system proposed by Govetto et al,[2] as depicted in Figure 3.

In addition, SD-OCT scans were evaluated for the presence and severity of disorganization of retinal inner layers (DRIL). The borders between the ganglion cell (GC)-IPL complex and INL, and between the INL and outer plexiform layer (OPL) were examined within a 2000µm central area for the ability to get identified between the layers and for regularity of borders. The horizontal area in which borders between layers were not recognizable was measured in μm with the OCT calliper function. A DRIL severity score was obtained for statistical analysis (Table 2).[6]

CGIPL – INL borders	Identifiable=0	Unidentifiable=1
	Regular=0	Irregular=1
INL – OPL borders	Identifiable=0	Unidentifiable=1
	Regular=0	Irregular=1

Table 2 DRIL severity grading score: score 0 corresponds to the absence of DRIL, scores 1-3 to the presence of mild DRIL and score 4 to the presence of severe DRIL

The distance between the inner retinal surface and the outer boundary of the INL was defined as inner retinal layer thickness.[9] GC-IPL thickness was set as the distance between the inner border of GC layer and the outer border of IPL. Both parameters were measured manually using the calliper instrument of OCT (Figure 4a). Inner retinal layer irregularity index (IRII) was described as the fraction of the length of IPL inferior boundary over RPE layer length (Figure 4b).[10] Image J, a free software for image analysis, was used for the calculation of IRII, following the same protocol presented by Cho et al.[10]

Epimacular membrane (EMM) rip was demonstrated on OCT as a well-defined edge of torn EMM and ILM with a scrolled flap. Depending on the presence of the scrolled edge within 500μm of the center of the fovea, as measured with the OCT calliper tool, EMM rips were listed in two categories: Type 1 or fovea-involving and Type 2 or extrafoveal (Figure 5).[11]

Finally, SD-OCT scans of eyes with iERM were examined for the presence of intraretinal cystoid changes or subretinal fluid (SRF).

Statistical analysis

All statistical analyses were conducted using SPSS version 25 (IBM Corp; Armonk, NY) for Windows, R Project for Statistical Computing version 3.5.3 (R Core Team, Vienna Austria) and MedCalc ver. 18 (MedCalc Software bv, Ostend, Belgium; 2018). Descriptive statistics were measured for all study variables. Continuous variables were recorded as mean and SD values, whereas categorical variables were recorded as frequency and percentage. Shapiro-Wilk test was used to assess data distribution, whereas t-test and Mann-Whitney were used to determine statistical significance between sets of data. Univariate linear regression analyses were performed to identify independent variables significantly associated with visual acuity. Multivariate analyses were also performed in order to identify the most significant OCT parameters that affect visual function. P values below 0.05 were considered statistically significant.

RESULTS

We retrospectively analysed the medical charts of 305 patients with ERMs, of which 208 were not enrolled according to the study exclusion criteria. Ninety-seven patients (97 eyes) were finally included, of which 41 (42.3%) were male and 56 (57.7%) were female with a mean age of 74.5±8.1 years (range 26-89). Of the 97 eyes with ERMs, 45 (46.4%) were pseudophakic, 42 (43.3%) were phakic with no opacities and 10 (10.3%) had early cataract. Mean BCVA of our sample was 0.23±0.27 logMAR. The presence of cotton ball sign was recorded in 26 (26.8%) of 97 eyes and disruption of inner segment EZ in 6 (6.2%) of them. EIFL was found in 31 (32%) of enrolled patients and absence of foveal pit in 68 (70.1%). Of 97 eyes with ERMs, 29 (29.9%) had ERM stage 1, 37 (38.1%) stage 2, 23 (23.7%) stage 3 and 8 (8.3%) stage 4. The mean values of PROS length, OFT and GC-IPL complex thickening were 70.67±8.1μm, 96.45±8.17μm and 115.81±25.17μm respectively. Mean inner retinal thickness was 60.91±92.89μm. However, in 7 of 97 eyes with ERMs, inner retinal thickness measurements were not reliable due to remarkable retinal disorganisation. Therefore, they were not taken into account in thickness analysis. In our sample, mean CFT was measured at 418.35±92.74μm and mean MRT at 462.77±116.87μm. Of 97 patients, DRIL severity score 0 was recorded in 52 (53.6%), 1 in 18 (18.6%), 2 in 16 (16.5 %), 3 in 3 (3.1 %) and 4 in 8 (8.2%). Mean value of IRII was 1.015±0.209, although measurement was not reliable in one eye owing to significant retinal disruption. Thus, this particular measurement was not considered in analysis. The presence of IRF was identified in 27 cases (27.8%) and the presence of SRF in 2 (2.1%). EMM rip was confirmed in 19 eyes (19.6 %) of which it was classified as type 1 in 7 (7.2%) and type 2 in 12 (12.4%).

Univariate analysis

To investigate the potential association of BCVA with the OCT factors we recorded and measured, we created a number of univariate linear regression models. In each model we used BCVA as the response variable and each OCT factor as explanatory variables.

Results of linear regression analysis of factors including the presence of cotton ball sign, the presence of EIFL, ERM stage, disruption of inner segment EZ, absence of foveal pit, PROS length, OFT, inner retinal thickness, GC-IPL complex thickening, CFT, MRT, DRIL severity score, IRII, IRF, SRF and EMM rip, showed that only the presence of cotton ball sign and SRF were not significantly correlated with worse vision (Figure 6).

The presence of EIFL proved to be significantly associated ($p<0.001$) with worse visual acuity (Figure 7a). There was statistical significance between ERM stages in terms of BCVA, with stage 3 and 4 being related with worse vision ($p=0.0015$ and $p<0.001$ respectively), (Figure 7b). Disruption of inner segment EZ was also found to be highly associated ($p=0.0016$) with worse visual function (Figure 7c), so was the absence of foveal pit ($p=0.011$). Analysis revealed that greater PROS length and OFT were strongly correlated ($p=0.0097$ and $p=0.004$ respectively) with slightly better visual acuity (Figure 8). Results confirmed that greater inner retinal thickness was associated significantly ($p=0.015$) with worse vision (Figure 9). Greater GC-IPL complex thickening, IRII, CFT and MRT showed statistically significant correlation ($p<0.001$) with lower vision (Figure 10). The presence of DRIL was robustly associated ($p<0.001$) with worse BCVA only for severity scores 2 and 4 (Figure 11a). Lower visual acuity was highly correlated ($p<0.001$) with both the presence of IRF and EMM rip of any type [Figure 11(b,c)].

Multivariable analysis

To adjust our analysis for every factor we used, we aimed to create the best possible multivariable model that would explain the variation of BCVA according to our factors. To achieve the best possible model, we initially included every variable whose univariate model had a p-value<0.2. We removed the variables that created multicollinearity one by one, comparing the nested models with an analysis of variance between models. The best possible model was determined as the one with the least possible Akaike's Information Criterion and the best possible adjusted R^2. The best model we reached (AIC= -60.2, R^2=0.6) included two parameters: MRT and DRIL severity score. MRT found to be strongly associated with visual acuity (p<0.001, 95%CI: 0.0009 to 0.0017) with an effect of 7 logMAR letters decrease per 100μm. Mild DRIL (severity score 1-3) did not appear to affect vision significantly, as compared with no DRIL. On the other hand, severe DRIL (severity score 4) was robustly related with worse vision by almost 3 logMAR lines (p<0.001, 95%CI: 0.13 to 0.45).

The results of the univariate and multivariate analyses are included in Table 3.

Variable		**Univariate**		**Multivariate**	
		p-value	**95% CI**	**p-value**	**95% CI**
Cotton ball sign		0.058	-0.24-0.004	**--**	**--**
EIFL		<0.001	0.2-0.4	--	--
ERM	**stage 2**	0.69	-0.08-0.22	--	--
	stage 3	0.0015	0.07-0.12	--	--
	stage 4	<0.001	0.49-0.82	--	--
Disruption of inner segment ellipsoid zone		0.0016	0.14-0.58	0.73	-0.25-0.18
Absence of foveal pit		0.011	0.04-0.27	0.92	-0.56-0.58
PROS length		0.0097	-0.016-(-0.002)	0.92	-0.005-0.004
OFT		0.004	-0.016-0.003	--	--
Inner retinal thickness		0.015	0.0001-0.013	0.48	-0.00057-0.00027
GC-IPL complex thickening		<0.001	0.0025-0.0065	0.85	-0.002-0.0017
CFT		<0.001	0.0015-0.0024	--	--
MRT		<0.001	0.0015-0.0021	<0.001	0.0009-0.0017
DRIL	**severity score 1**	0.14	-0.03-0.2	--	--
	severity score 2	<0.001	0.14-0.38	--	--
	severity score 3	0.06	-0.01-0.48	--	--
	severity score 4	<0.001	0.47-0.79	<0.001	0.13-0.45
IRII		<0.001	4.62-7.73	0.8	-2.47-2.15
IRF		<0.001	0.1-0.34	0.35	-0.05-0.13
SRF		0.19	-0.13-0.64	0.053	-0.003-0.5
EMM rip	**Type 1**	<0.001	0.16-0.56	0.7	-0.13-0.2
	Type 2	<0.001	0.016-0.33	0.34	-0.06-0.18

Table 3 Univariate and multivariate analysis for OCT biomarkers for visual acuity in patients with iERM

DISCUSSION

Inner and outer retinal damage and their relationship with BCVA in ERM cases have been described in several studies in the past. However, an agreement on the best biomarker has not been reached yet. In this study, we explored the correlations of all previously reported predictive factors with BCVA and found that MRT and severe DRIL were associated with worse visual acuity in eyes with iERM.

To the best of our knowledge, this is the first study to investigate the effect and prognostic value of both inner and outer retina OCT biomarkers on visual function of iERM patients.

Univariate analysis showed statistically significant association between CFT, MRT and BCVA. MRT, unlike CFT, proved to be a strong prognostic factor for visual function through multivariate analysis. Various studies have investigated the relationship between macular thickness and visual acuity in ERM patients. Shiono et al[7] reported that CFT was not a strong predictor for visual outcome after ERM removal. Hosoda et al[12] also reached to the same conclusion. Jeon et al[9] found that CFT was correlated with BCVA change at 24 months postoperatively, suggesting that greater macular thickness resulted in better vision. Similar results were presented by Govetto et al,[13] who additionally demonstrated that preoperative CFT was significantly associated with worse preoperative BCVA. Two studies identified macular thickness as an independent predictive factor for reduced visual function in ERM cases.[1,14]

Our research revealed that DRIL severity score 4 was robustly correlated with visual acuity in patients with iERM. Particularly, we showed that severe DRIL was significantly associated with worse vision by almost 3 logMAR lines. DRIL has been primarily recognized as an OCT parameter for visual prognosis in eyes with diabetic macular oedema (DMO).[15-17] Zur et al[6] were the first to explore the predictive value of DRIL for visual and structural outcome in ERM patients that underwent pars-plana vitrectomy (PPV) and ERM peeling. DREAM study found that eyes without or mild DRIL preoperatively, experienced greater visual improvement postoperatively than eyes with severe DRIL over a 12-month follow-up period. Negative prognosis for visual acuity in patients with severe DRIL was attributed to the continuous mechanical traction leading to inner retinal layer deformation. This condition could develop and result in distortion and disruption of the synapses between photoreceptors and ganglion cells. Additionally, they hypothesised that visual outcome in ERM cases may be affected by cellular damage of the bipolar, Müller, amacrine and horizontal cells.

In the present study, univariate regression analysis demonstrated that, unlike SRF, IRF presence in patients diagnosed with iERM was significantly correlated with BCVA. Nevertheless, multivariate analysis proved that both biomarkers were not strong prognostic factors for visual function. Previous reports have also confirmed that the presence of cystoid macular oedema had no notable effect on vision and was a poor predictor for visual acuity in ERM patients.[1,18]

Except DRIL, other inner retina biomarkers that were evaluated were IRII, inner retinal thickness and GC-IPL complex thickening. Univariate analysis results presented statistically significant correlation between these parameters with BCVA. However, multivariate analysis showed that IRII, inner retinal thickness and GC-IPL could not be used as predictors for visual function. Various previous studies tried to explore the relationship between those inner retina biomarkers with visual acuity and their prognostic value in patients with iERM. Cho et al[10] found a strong association between IRII and postoperative visual outcome and suggested this parameter as the most reliable predictive factor for visual improvement after ERM removal. Their speculation was based on the following mechanism: prolonged mechanical traction caused irregularity of inner retinal layers, especially INL, that might lead to deformation of the layer or disruption of the synaptic connections between photoreceptors and ganglion cells and consequent cellular damage of Müller, bipolar, amacrine, and horizontal cells, which are the main INL components. Although IRII proved to be a reliable biomarker, its use on daily basis may be difficult because of the demanding measurements that have to be obtained.[19] Jeon et al[9] indicated that inner retinal thickness was not correlated strongly with preoperative or postoperative visual acuity in eyes that had surgical treatment for ERM. Nevertheless, in a report by Joe et al,[20] inner retinal thickness appeared as the major parameter determining vision in ERM patients. GC-IPL complex thickening was robustly associated with decreased vision after surgical removal of ERM in some studies.[21,22] Song et al[22] assumed that greater GC layer thickness depicted more damaged tissue, because of bloated cells or intercellular oedema, which was irreversible. On the other hand, Cho et al[10] showed that there was not significant correlation between GC-IPL thickness and postoperative BCVA but they presumed that their results were not reliable due to measurement limitations.

Several reports have explored the effect of EIFL on visual acuity in ERM patients. Doguizi et al[1] found that EIFL presence was significantly correlated with worse vision in eyes with iERM and, in particular, BCVA was strongly associated with stage 3 ERM. Moreover, they demonstrated that the presence of EIFL was an independent predictor for lower visual acuity in this group of patients. Similar results were presented by Govetto et al.[2] It has been suggested that EIFL development was caused by inner retinal layer displacement combined with Müller cell proliferation, which was activated by the mechanical traction of the retina. Lower visual acuity in ERM patients has been connected to the greater inner retinal layer thickness of the fovea.[1] Govetto et al,[13] who proposed a new SD-OCT staging system based on EIFL presence showed that, as the stage of ERM increased, vision decreased remarkably. In eyes that underwent surgical ERM removal, they also found that EIFL thickness was robustly associated with lower preoperative visual acuity, whereas preoperative EIFL presence was strongly correlated with worse postoperative visual outcome. This connection between EIFL and visual acuity was explained by two possible mechanisms: The first suggested that the ectopic inner retinal layer prevented afferent light from reaching photoreceptors, behaving as a natural barrier. Therefore, the projection of visual image on the foveal cones was blocked or degraded. The second mechanism attributed decreased vision to the compromised normal neural transmission caused by the damage of photoreceptors and other neural cells of the retina, due to the longstanding inner retina displacement. González-Saldivar et al[19] who investigated the role of EIFL staging scheme in the prognosis of visual outcome after ERM removal, indicated that stage 2 ERM had considerably better visual results compared to stage 3 and 4 over a follow-up period of 12 months. Our study examined the association between the presence of EIFL and visual acuity. Univariate analysis revealed that stage 3 and 4 ERM were significantly correlated with worse vision. However, EIFL was excluded from our multivariable model because of multicollinearity with DRIL.

Regarding outer retina parameters, in this research we found that PROS length and OFT were significantly associated with visual acuity in eyes with iERM, although multiple regression analysis revealed that they were not strong predictive factors. Various studies have explored the association between PROS length, OFT and BCVA in ERM patients. Shiono et al[7] demonstrated that PROS length was a robust indicator of visual function in patients diagnosed with iERM, as well as a predictor for postoperative visual outcome after surgical treatment of ERM. OFT also reflected postoperative visual acuity. However, PROS length was more strongly correlated with visual acuity than OFT. They assumed that assessment of PROS length may be more precise than assessment of OFT in visual prognosis due to the presence of the main components of visual substance (opsin and all-trans-retinal) in the outer segment.

Disruption of EZ was significantly associated with worse vision through univariate analysis, whereas multivariate analysis indicated that this was not a strong prognostic factor for visual acuity. Many studies have investigated the connection between the integrity of IS/OS junction and visual acuity in eyes with iERM. Some reports found a significant correlation of preoperative disruption of the IS/OS layer on OCT with postoperative visual function in eyes that were treated surgically.[18,23-27] EZ disruption was robustly associated with preoperative visual acuity in other studies.[1,13,28] Oster et al[14] showed that the integrity of photoreceptor IS/OS junction was a statistically significant prognostic factor for visual acuity in ERM patients, whereas Shiono et al[7] concluded that the disruption of EZ was a poor visual predictor in these patients. Jeon et al[9] also revealed that EZ defect was not strongly connected with visual improvement after ERM removal. They hypothesized that, in ERM patients, the tangential contractile forces distributed by Müller cells could change the interface between the photoreceptor outer segment tip and the RPE, resulting in the cone outer segment tip (COST) line defect. Extension of the disruption beyond the COST line could lead to EZ defect. Based on this assumption, they supported that ERM patients with low vision and preoperative outer retinal damage had limited odds for visual improvement, even after postoperative structural restoration on OCT images.

Our statistical analysis revealed that the presence of cotton ball sign was poorly correlated with visual acuity. Tsunoda et al[8] supported that, in ERM cases, cotton ball sign possibly resulted from the continuous inward mechanical traction on the outer retina over the foveal region. This explained its disappearance once the traction was released. Such chronic tension could affect the photoreceptors, causing microstructural damage and visual impairment. However, Govetto et al[29] indicated that Müller cell-mediated tractional stress may lead to upward displacement of foveal cones without jeopardizing the anatomical integrity of EZ and ELM. Their speculation was confirmed by the good visual function the study patients preserved. Thus, cotton ball sign may not be necessarily associated with decreased vision and may operate as a biomarker for visual impairment caused by prolonged inward traction on the fovea of ERM patients.

EMM rip, a newly proposed OCT parameter, and its association with visual acuity were investigated in our study. Univariate analysis found statistically significant association between the presence of EMM rip (both types) with worse vision, whereas multivariate analysis indicated that this biomarker had not prognostic value for visual function. Sigler et al[11] showed that the classification of EMM rip into its two types may be connected with presenting visual function as well as visual improvement after surgical treatment of ERM. Their study demonstrated that foveal involvement (type 1 EMM rip) was correlated with lower vision at diagnosis and worse visual outcome after ERM removal. Extrafoveal EMM rip was also associated with presenting visual symptoms. In this report by Sigler et al,[11] the scrolled edge of EMM, which was depicted as a thicker border of retina on SD-OCT images, was assumed to result anatomically from residual tangential mechanical force following surface ILM tearing.

This study had certain limitations. First of all, it was limited by its retrospective nature. Secondly, the cataract effect should be taken into consideration. In order to avoid it, we used a sample of patients that were pseudophakic or phakic with no opacities or early cataract. Finally, the reproducibility of the grading of OCT parameters was the most important limitation. SD-OCT findings were interpreted subjectively and in some cases, for the measurement of IRII, GC-IPL complex thickness and inner retinal thickness, autotracking of retinal layers was not available due to retinal deformation, thus switch to manual tracking was inevitable. Progress in automated segmentation algorithms needs to be made so as to improve the ability to assess and measure OCT biomarkers more accurately.

In conclusion, this study demonstrated highly significant association between MRT and severe DRIL on SD-OCT images with visual acuity in patients diagnosed with iERM. Based on these results, these OCT biomarkers should be considered as negative indicators for visual function in iERM cases.

Declaration of conflicting interests

The authors declare that they have no conflict of interest.

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Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Patient consent

Not applicable.

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FIGURE LEGENDS

Figure 1. Spectral domain optical coherence tomography (SD-OCT) image showing the measurement of parameters photoreceptor outer segment (PROS) length and outer foveal thickness (OFT).

Figure 2. Spectral domain optical coherence tomography (SD-OCT) image depicting cotton ball sign between the inner segment ellipsoid zone (EZ) and the interdigitation zone (IZ) in the central fovea (white arrows).

Figure 3. Spectral domain optical coherence tomography (SD-OCT) staging system of epiretinal membranes (ERMs): Stage 1. Insignificant morphological alterations. The foveal pit is present and all retinal layers are clearly defined. Stage 2. More anatomical modifications with loss of foveal depression but all retinal layers are still well identified. Stage 3. Continuous ectopic inner foveal layers (EIFLs) (white arrows) cross the foveal region. All retinal layers are clearly defined and the foveal pit is absent like in Stage 2. Stage 4. Significant macular thickening and anatomical disruption. EIFLs are present (white arrows), foveal pit is lost and all retinal layers are disorganized.

Figure 4. (a) Spectral domain optical coherence tomography (SD-OCT) image showing the measurement of inner retinal layer thickness (IRLT) and GC-IPL complex thickening (white arrows) and **(b)** the measurement of inner retinal irregularity index (IRII).

Figure 5. Spectral domain optical coherence tomography (SD-OCT) classification of epimacular membrane (EMM) rips: **(a)** Type 1 or fovea-involving and **(b)** Type 2 or extrafoveal.

Figure 6. Correlation of BCVA in logMAR with **(a)** Cotton ball sign and **(b)** Subretinal fluid (SRF).

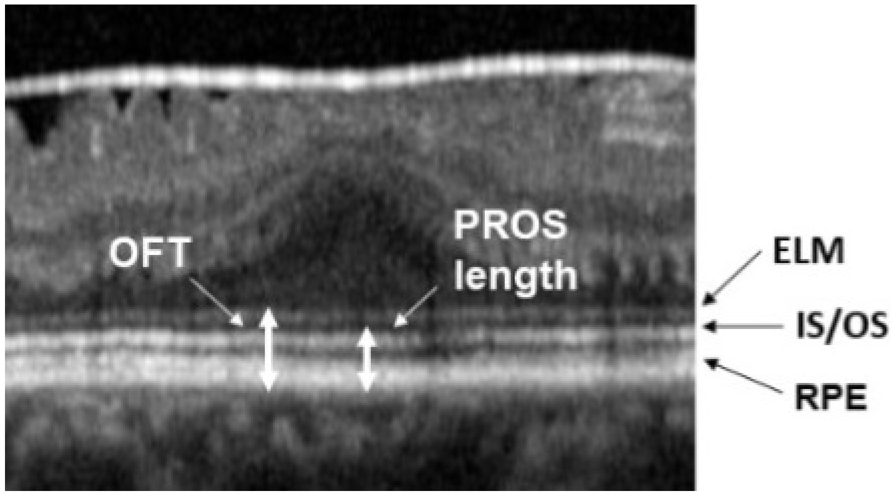
Figure 7. Correlation of BCVA in logMAR with **(a)** Ectopic inner foveal layer (EIFL), **(b)** Epiretinal membrane (ERM) stage and **(c)** Disruption of ellipsoid zone (EZ).

Figure 8. Scattered diagrams showing a negative correlation between **(a)** Photoreceptor outer segment (PROS) length and BCVA and **(b)** between outer foveal thickness (OFT) and BCVA. Pearson correlation coefficient (r) and p value for the slope of the regression line are noted.

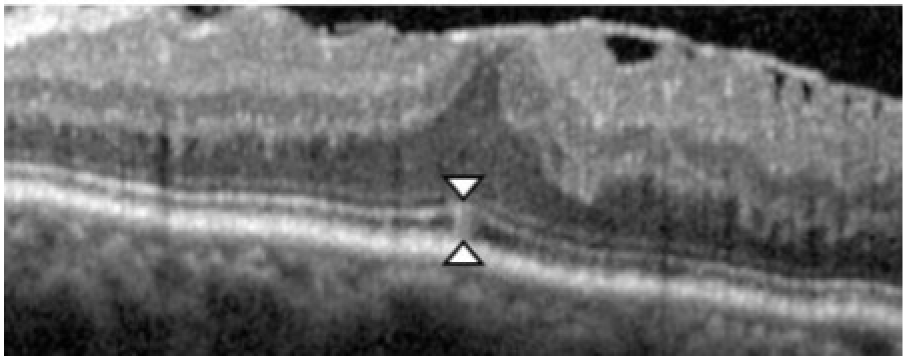
Figure 9. Scattered diagram showing a positive correlation between inner retinal thickness and BCVA. Pearson correlation coefficient (r) and p value for the slope of the regression line are noted.

Figure 10. Scattered diagram showing a positive correlation between **(a)** Ganglion cell-inner plexiform (GC-IPL) complex thickening and BCVA, **(b)** Inner retinal irregularity index (IRII) and BCVA, **(c)** Central foveal thickness (CFT) and BCVA and **(d)** Maximal retinal thickness (MRT) and BCVA. Pearson correlation coefficient (r) and p value for the slope of the regression line are noted.

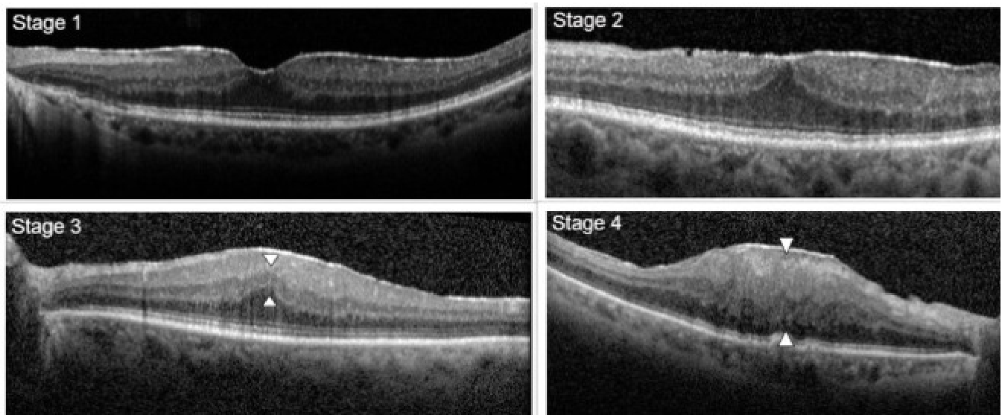
Figure 11. Correlation of BCVA in logMAR with **(a)** Disorganization of retinal inner layers (DRIL), **(b)** Epimacular membrane (EMM) tear and **(c)** Intraretinal fluid (IRF).



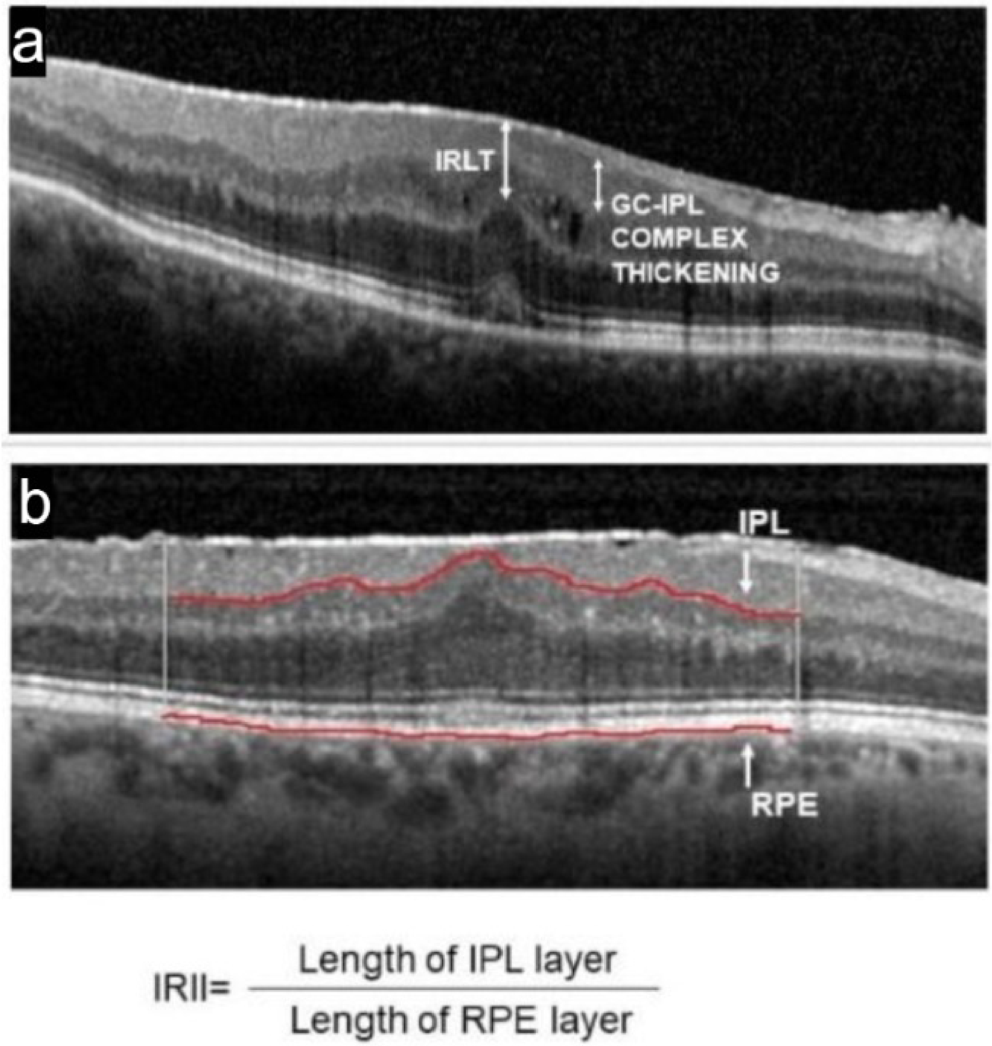
Spectral domain optical coherence tomography (SD-OCT) image showing the measurement of parameters photoreceptor outer segment (PROS) length and outer foveal thickness (OFT).



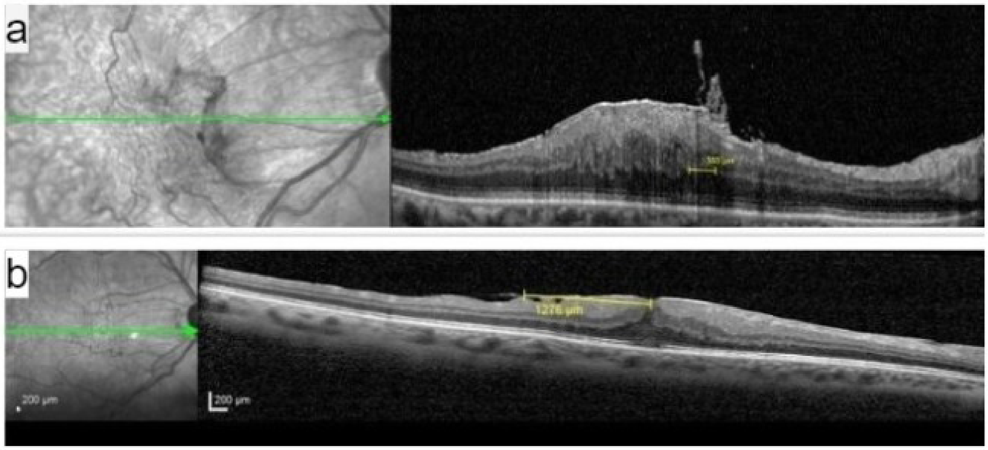
Spectral domain optical coherence tomography (SD-OCT) image depicting cotton ball sign between the inner segment ellipsoid zone (EZ) and the interdigitation zone (IZ) in the central fovea (white arrows).



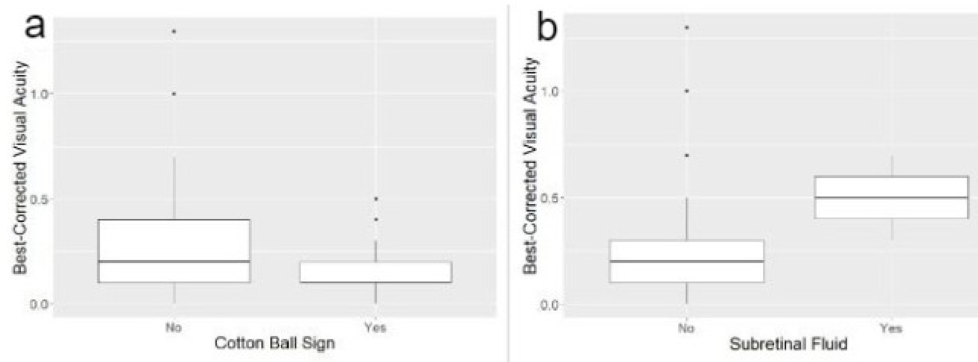
Spectral domain optical coherence tomography (SD-OCT) staging system of epiretinal membranes (ERMs): Stage 1. The foveal depression is present and all retinal layers are clearly identified. Stage 2. All retinal layers are still well identified but the foveal depression is lost. Stage 3. Like stage 2, all retinal layers are well identified and the foveal depression is absent. Continuous ectopic inner foveal layers (EIFLs) (white arrows) cover the foveal area. Stage 4. EIFLs are present (white arrows), there is no foveal depression and all retinal layers are disorganized.



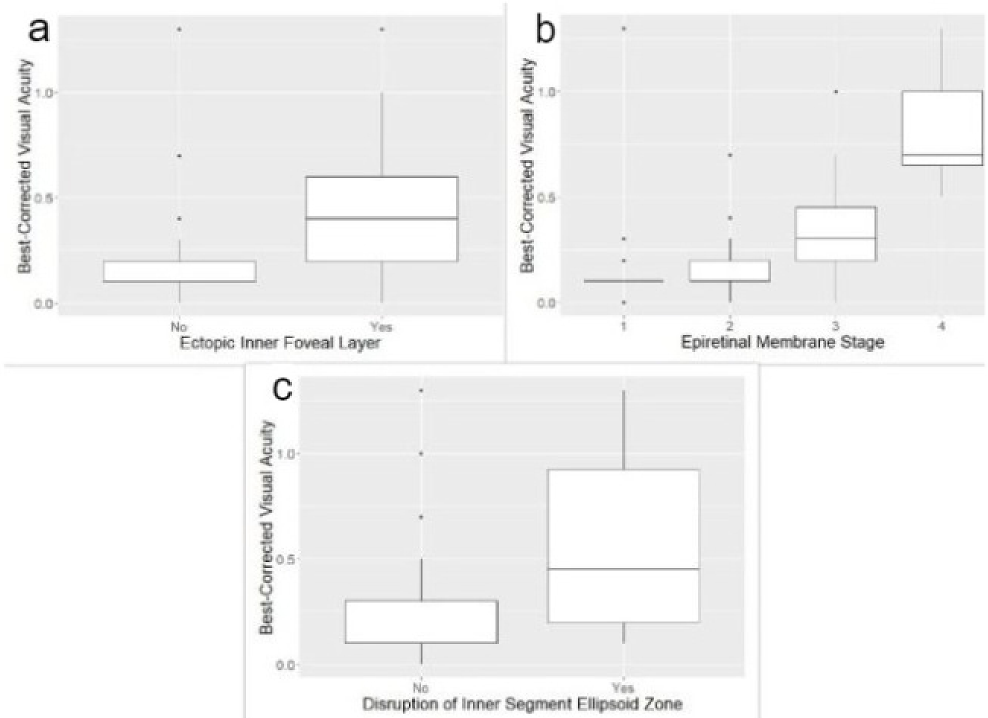
(a) Spectral domain optical coherence tomography (SD-OCT) image showing the measurement of inner retinal layer thickness (IRLT) and GC-IPL complex thickening (white arrows) and (b) the measurement of inner retinal irregularity index (IRII).



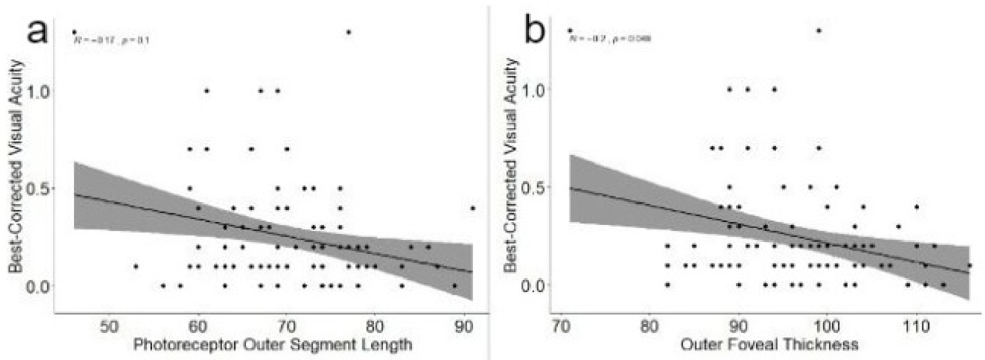
Spectral domain optical coherence tomography (SD-OCT) classification of epimacular membrane (EMM) rips: (a) Type 1 or fovea-involving and (b) Type 2 or extrafoveal.



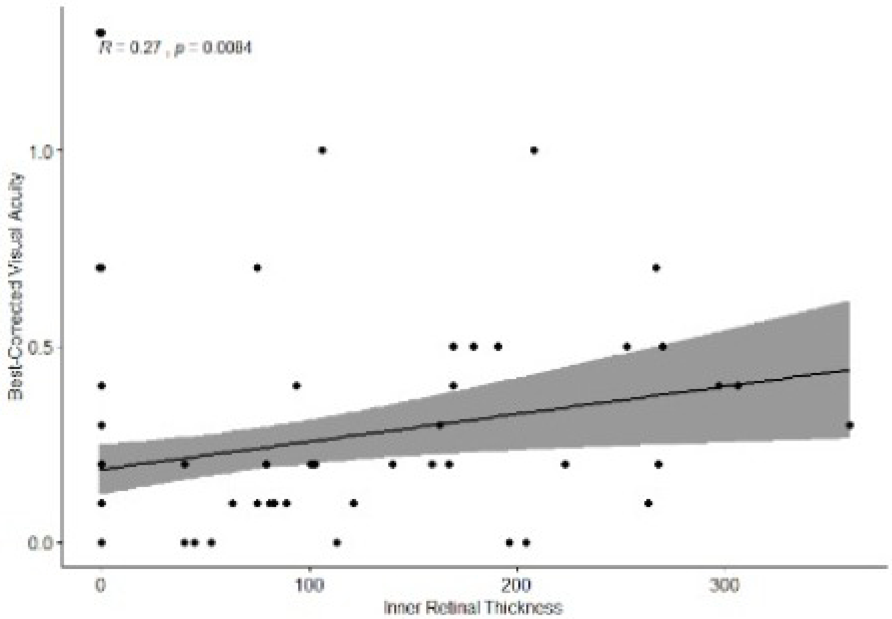
Correlation of BCVA in logMAR with (a) Cotton ball sign and (b) Subretinal fluid (SRF).



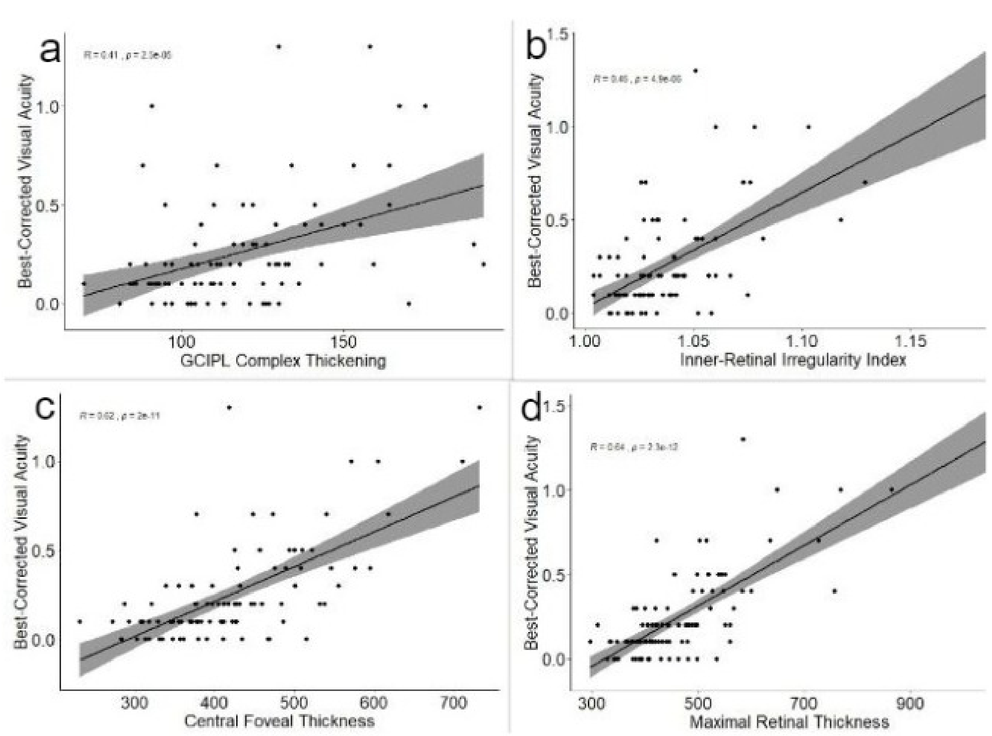
Correlation of BCVA in logMAR with (a) Ectopic inner foveal layer (EIFL), (b) Epiretinal membrane (ERM) stage and (c) Disruption of ellipsoid zone (EZ).



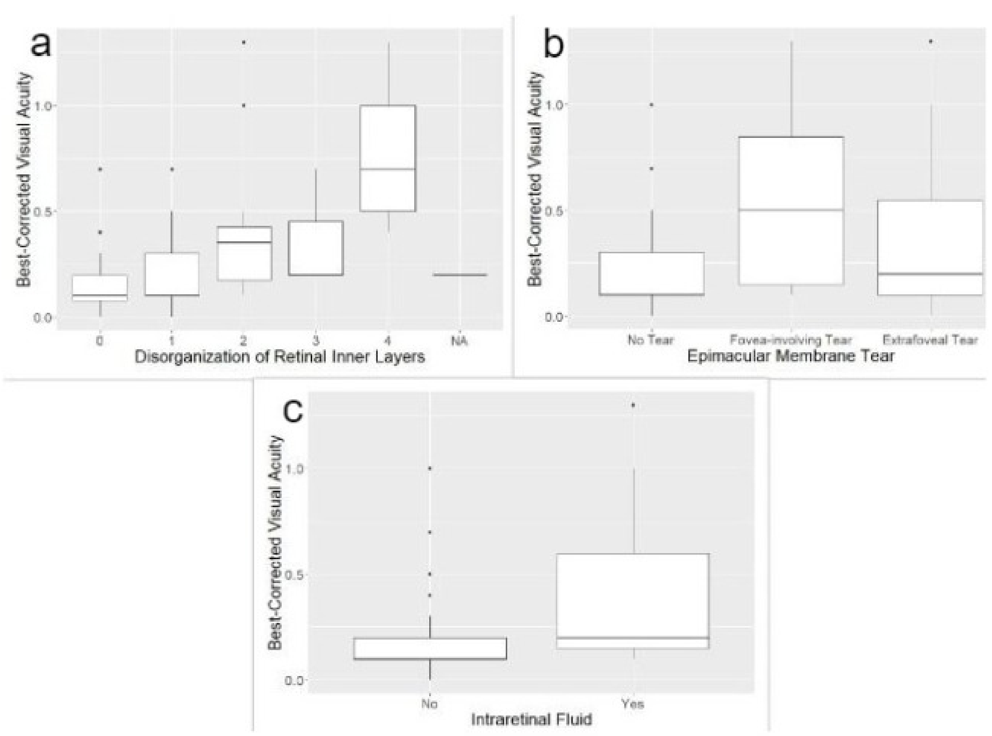
Scattered diagrams showing a negative correlation between (a) Photoreceptor outer segment (PROS) length and BCVA and (b) between outer foveal thickness (OFT) and BCVA. Pearson correlation coefficient (r) and p value for the slope of the regression line are noted.



Scattered diagram showing a positive correlation between inner retinal thickness and BCVA. Pearson correlation coefficient (r) and p value for the slope of the regression line are noted.



Scattered diagram showing a positive correlation between (a) Ganglion cell-inner plexiform (GC-IPL) complex thickening and BCVA, (b) Inner retinal irregularity index (IRII) and BCVA, (c) Central foveal thickness (CFT) and BCVA and (d) Maximal retinal thickness (MRT) and BCVA. Pearson correlation coefficient (r) and p value for the slope of the regression line are noted.



Correlation of BCVA in logMAR with (a) Disorganization of retinal inner layers (DRIL), (b) Epimacular membrane (EMM) tear and (c) Intraretinal fluid (IRF).