

Evaluation of optical coherence tomography biomarkers in patients with idiopathic epiretinal membrane

Dogukan Comerter¹, Eyup Duzgun¹

ABSTRACT

Purpose: To evaluate the effects of optical coherence tomography (OCT) biomarkers on visual acuity in patients with idiopathic epiretinal membrane (iERM).

Materials and Methods: iERM patients admitted to the retina outpatient clinic were divided into stages by OCT and best corrected visual acuity (BCVA), OCT parameters (central macular thickness (CMT), macular volume (MV), maximum retinal thickness (MRT), outer nuclear layer (ONL) and ectopic inner foveal layer (EIFL) thickness) were determined and biomarkers (cotton ball sign, cystoid macular edema (CME), vitreomacular traction (VMT), retinoschisis, external limiting membrane-ellipsoid zone (ELM-EZ) disruption, disorganized retinal inner layers (DRIL)) were evaluated.

Results: There was a statistically significant difference between the patients regarding BCVA, CMT, MV, MRT, ONL, and EIFL thickness according to their OCT stages. ($p < 0.0001$) BCVA was the lowest in Stage 4, with the highest CMT, MV, and MRT values. A statistically significant positive correlation was found between the patient's BCVA and CMT, MV, MRT, OCT stage, ONL, and EIFL thickness values. ($p < 0.05$) Visual acuity was significantly lower in patients with VMT, retinoschisis, ELM-EZ disruption, and DRIL than those without. ($p = 0.017$, $p = 0.002$, $p = 0.043$, $p = 0.02$, respectively) No statistically significant difference was found between the patients regarding BCVA according to the presence of cotton ball sign and CME. ($p > 0.05$) No statistically significant difference was found between the presence of cotton ball sign and gender, hypertension, diabetes, lens status, OCT stage, ONL, and EIFL thickness. ($p > 0.05$)

Conclusion: Retinoschisis, VMT, ELM-EZ defects, and DRIL should be considered negative prognostic factors for visual acuity. The presence of cotton ball sign and CME was not found to affect visual acuity in this study.

Keywords: Cotton ball sign, Ectopic inner foveal layers, Epiretinal membrane, Optical coherence tomography, Outer nuclear layer.

INTRODUCTION

Epiretinal membrane (ERM) is a vitreoretinal interface pathology that arises from the proliferation of fibroblasts, glial cells, and astrocytes on the internal limiting membrane (ILM). Its prevalence varies between 2.2% and 28.9% and increases with age.^{1,2} ERMs are typically idiopathic and may remain asymptomatic for years. However, macular ERMs can lead to symptoms such as reduced visual acuity, metamorphopsia, micropsia, macropsia, and monocular diplopia.^{3,4} Before advanced imaging techniques were available, ERMs were most commonly classified according to schemes such as those proposed by Gass.⁵ Because

tests that functionally assess vision, like multifocal ERG and microperimetry, are impractical, Optical Coherence Tomography (OCT) has become the gold standard for evaluating ERM, guiding surgical decisions, and postoperative follow-up due to its rapid and accessible imaging capabilities. Advances in OCT technology have enabled higher image resolution and faster data processing, allowing for detailed cross-sectional or three-dimensional imaging of retinal layers.

The primary goals of ERM research are to determine the stages of ERM, identify prognostic parameters affecting

1- Department of Ophthalmology, Sultan Abdülhamid Han Training and Research Hospital, University of Health Sciences, İstanbul, Türkiye

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Correspondence author:

Dogukan Comerter

Email: dcomerter@hotmail.com

visual acuity, and establish surgical indication criteria, allowing for the formulation of an appropriate treatment plan using the correct technique at the right time. Although there is no consensus on the optimal timing of surgery, recent studies suggest that certain microstructural changes observed on OCT may be useful in predicting final visual acuity.^{6,7} The structural integrity of retinal layers, particularly photoreceptors, macular thickness, macular volume, ellipsoid zone, interdigitation zone integrity, cotton wool spots, and acquired vitelliform lesions, have been investigated for their impact on visual function.⁸⁻¹⁰ Subsequent studies have evaluated the role of prognostic biomarkers related to inner retinal layers, such as the presence of an ectopic inner retinal layer (EIFL), disorganization of inner retinal layers, and thickness of the inner nuclear layer, nerve fiber layer, and ganglion cell layer.⁶ The most widely accepted current OCT-based staging system is the scheme proposed by Govetto et al., which considers morphological changes caused by ERM and includes the presence of EIFL, which is associated with lower visual acuity. Researchers analyzed ERM in four stages based on OCT findings and reported that advanced stages are correlated with decreased visual acuity.¹¹

Our study aims to evaluate the effects of OCT parameters and biomarkers on visual acuity using the OCT staging system in patients with ERM.

MATERIALS AND METHODS

Ethics committee approval was obtained from Health Sciences University Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2024/07/802) and the study was conducted in accordance with the Declaration of Helsinki. The study included 150 cases of idiopathic epiretinal membrane presenting to the retina outpatient clinic of Sultan 2nd Abdülhamid Han Training and Research Hospital. Age, gender, systemic and ocular diseases, best corrected visual acuity (BCVA), intraocular pressure (IOP), anterior segment, and fundus examination findings were recorded from patient files. Central macular thickness (CMT), macular volume (MV), maximum retinal thickness (MRT), outer nuclear layer thickness (ONL), and ectopic inner foveal layer (EIFL) thickness were recorded. The presence of cotton ball sign, cystoid macular edema (CME), vitreomacular traction (VMT), retinoschisis, external limiting membrane-ellipsoid zone (ELM-EZ) abnormality, and disorganized retinal inner layers (DRIL) were also evaluated.

BCVA was evaluated with the Snellen chart and converted to logMAR for statistical analysis. OCT images were acquired with Spectral Domain OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) using a horizontal OCT scan (25 lines 240 mm apart; 30° x 20°). Images with poor image quality were not included in the study. CMT, MRT, and MV data were measured with the automatic software function via the thickness map module of the device. ONL and EIFL thicknesses in the foveal region were measured manually with the 'caliper' function of the device. Retinal layers were named according to the dictionary defined by the IN-OCT consensus.¹² EIFL was defined as the presence of an uninterrupted hyporeflective or hyperreflective band extending from the inner nuclear layer (INL) and inner plexiform layer (IPL), visible in all OCT scans centered on the fovea. ELM-EZ disturbance was defined as disruption of the EZ integrity. At the same time, the presence of a circular hyperreflective area between the ellipsoid region at the center of the fovea and the cone outer segment line was termed a 'cotton ball' sign as described by Tsunoda et al.¹³ The presence of hyporeflective intraretinal cystoid spaces with ERM was considered as a possible traction-induced CME as described by Johnson.¹⁴

Statistical Analysis

Statistical analyses were performed with SPSS software (SPSS Version 20.0; SPSS Inc., Chicago, USA). Descriptive statistics were calculated for all variables in the study. The conformity of continuous variables to normal distribution was evaluated by the Shapiro-Wilk test. Mean and standard deviation (SD) values for continuous variables and frequency and percentage values for categorical variables were calculated. Parametric and nonparametric tests (ANOVA, Kruskal-Wallis Test, Mann-Whitney U) were used to compare quantitative variables, and the Chi-Square test was used to compare the rates among the study population. Spearman Correlation Analysis was used to evaluate the relationship between dependent parameters. A p-value <0.05 was considered statistically significant in all statistical analyses.

RESULTS

A total of 150 patients were included in the study; 82 (54.6%) were male, 68 (45.3%) were female, and the mean age was 71.84±7.8 years. Twenty-six patients had hypertension and 20 patients had diabetes mellitus without retinopathy.

Thirty-six eyes (24%) were classified as stage 1, 45 (30%) as stage 2, 58 (38.6%) as stage 3, and 11 (7.3%) as stage

4 ERM. There was a statistically significant difference between the patients according to OCT stages in terms of BCVA, CMT, MRT, MV, ONL, and EIFL thickness ($p < 0.0001$) (Table 1). Visual acuity was found to be the lowest in stage 4, with the highest values of CMT, MV, and EIFL. There was a statistically significant positive correlation between visual acuity and OCT stage, CMT, BCVA, MRT, MH, ONL, and EIFL thickness ($p < 0.05$) (Table 2 and 4).

Visual acuity was significantly lower in eyes with retinoschisis, VMT, ELM-EZ disruption, and DRIL ($p = 0.017$, $p = 0.002$, $p = 0.043$, $p = 0.02$, respectively). There was no statistically significant difference between the presence of cotton ball sign and CME in terms of BCVA ($p > 0.05$) (Table 2). There was no statistically significant correlation between the presence of cotton ball sign and gender, hypertension, diabetes, lens status, OCT stage, ONL, and EIFL thickness. ($p > 0.05$) (Table 3)

DISCUSSION

Recent meta-analyses show that the majority of evidence in the literature points to photoreceptor integrity as the most consistent OCT marker of better visual acuity after surgery. These findings point to the importance of analyzing the interdigitation and EZ regions as well as the photoreceptor outer segment length.¹⁵ Depending on the changes in these layers, it is known that the lower the preoperative visual acuity level and the worse the metamorphopsia, the higher the rate of improvement in both in the postoperative period. Another accepted fact is that the final visual acuity is better in eyes with better preoperative visual acuity and intact EZ.¹⁶ Based on this, we can say that the factors affecting preoperative visual acuity are the main determinants of successful ERM surgery. The initial BCVA threshold value for good visual prognosis has been reported to be 20/44 according to Snellen's chart.¹⁶ Considering this visual acuity level as a criterion, it may be a correct approach to prefer surgery from the second stage when the outer layers

Table 1: Comparison of visual acuity and OCT findings depending on the stage of ERM

	Stage 1 (n=36)	Stage 2 (n=45)	Stage 3 (n=58)	Stage 4 (n=11)	p
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Visual Acuity (logMAR)	0,29± 0,2	0,48± 0,3	0,45± 0,3	0,62± 0,2	0,0001*
Central Macular Thickness (µm)	351,25± 60,9	426,84± 81,8	457,12± 74,5	531,45± 49,1	0,0001**
Maximum Retinal Thickness (µm)	411,81± 59	461,33± 84,7	491,83± 83,9	575,18± 56,6	0,0001*
Macular Volume (mm3)	9,29± 0,7	10,16± 1,3	10,29± 1,1	11,03± 1,3	0,0001*
ONL Thickness (µm)	136,36± 53,1	281,07± 93,2	206,19± 65,1	250,09± 85,1	0,0001*
EIFL Thickness (µm)	-	-	149,22± 65,5	230,82± 73,9	0,0001*

* Kruskal Wallis test, ** Analyze of Variance ANOVA, $p < 0,05$
OCT: Optical coherence tomography, ONL: Outer nuclear layer, EIFL: Ectopic inner foveal layer

Table 2: The effect of OCT biomarkers on visual acuity

OCT Biomarkers	Visual Acuity						
	-			+			p
	n	Med.	Mean±SD	n	Med.	Mean±SD	
Cotton Ball Sign	120	0,4	0,43± 0,3	30	0,4	0,45± 0,3	0,482
Cystoid Macular Edema	123	0,4	0,42± 0,3	27	0,5	0,51± 0,3	0,072
Retinoschisis	129	0,4	0,4± 0,3	21	0,5	0,62± 0,3	0,002
Vitreomacular Traction	139	0,4	0,42± 0,3	11	0,7	0,61± 0,2	0,017
ELM-EZ Defect	132	0,4	0,42± 0,3	18	0,5	0,55± 0,3	0,043
DRIL	138	0,4	0,42± 0,3	12	0,6	0,58± 0,2	0,02

Mann whitney U test; $p < 0,05$
OCT: Optical Coherence Tomography, ELM: External Limiting Membrane, EZ: Elipsoid Zone DRIL: Disorganised Retinal Inner Layers

Table 3: Demographic distribution of Cotton Ball Sign

	Cotton Ball Sign		p
	- (n=120)	+ (n=30)	
Gender			0,1
Female	50 (41,7)	18 (60)	
Male	70 (58,3)	12 (40)	
Hypertension			0,914
-	99 (82,5)	25 (83,3)	
+	21 (17,5)	5 (16,7)	
Diabetes			0,084
-	98 (81,7)	20 (66,7)	
+	22 (18,3)	10 (33,3)	
Status of Lens			0,682
Phakic	70 (58,3)	16 (53,3)	
Pseudophakic	50 (41,7)	14 (46,7)	
OCT Stage			0,255
1	32 (26,7)	4 (13,3)	
2	32 (26,7)	13 (43,3)	
3	47 (39,2)	11 (36,7)	
4	9 (7,5)	2 (6,7)	

Chi-square test; p<0,05
OCT: Optical coherence tomography

start to deteriorate. Our study demonstrated that ERM surgery performed at stage 2 resulted in significantly better visual results and anatomical improvement.¹⁷

Although early studies confirmed the fact that the outer retinal layers play an important role in postoperative visual outcomes, recent studies have proven the importance of the inner retinal layers. Although idiopathic ERM affects the volume of all retinal layers, the inner retina is the most variable layer. A strong correlation was found between visual acuity and inner retinal layer thickness in patients with healthy photoreceptor layers.¹⁸ In 2013, Joe et al.¹⁹ showed inner retinal layer thickness at the fovea as the main determinant of visual acuity in their study classifying ERM and reported that it may provide important information about the optimal timing of surgical intervention.

The new OCT staging system proposed by Govetto et al. is considered to meet the clinical need to a large extent.¹⁵ This system is based on the arrangement of the foveal contour, and the presence of EIFL and DRIL, and is considered to be a guide in determining the preoperative grading of ERM and the prognosis of surgical outcomes. The presence of EIFL along the foveal region is an independent risk factor for low visual acuity.¹¹ In our study, the OCT stage according to these criteria was correlated with the increase in total retinal thickness as well as retinal layers. We found that increased retinal thickening was associated with decreased visual acuity as demonstrated in previous studies. In light of the data obtained from our study, we can say that this staging system with simple parameters will be useful in patient follow-up and surgical decision-making, provided that visual acuity is taken as the main criterion. While the presence of EIFL is associated with severe preoperative visual deterioration and is a negative factor for postoperative anatomical healing, there are also reports that it has no significant effect on postoperative visual acuity.^{15,20}

Previous studies have shown a significant correlation between CMT and visual acuity.²¹ It is also known that high preoperative CMT is associated with poor anatomical recovery.^{16,22} In our study, the mean CMT increased significantly as the ERM stages progressed. This may be explained by the fact that the main factors causing the increase in CMT thickness were ONL in stage 2, while the increase in EIFL thickness was the main determinant in stages 3 and 4. In contrast, Govetto et al. reported that initial CMT had no significant effect on preoperative visual acuity, but higher preoperative CMT values were associated with greater improvement in postoperative visual acuity.

Table 4: Relation between OCT parameters and visual acuity

		Visual Acuity
OCT Staging	r	,307**
	p	0,0001
Central Macular Thickness (µm)	r	,319**
	p	0,0001
Maximum Retinal Thickness (µm)	r	,292**
	p	0,0003
Macular Volume (mm3)	r	,182*
	p	0,026
ONL Thickness (µm)	r	,223**
	p	0,006
EIFL Thickness (µm)	r	,227**
	p	0,005

Spearman correlation analysis *: p<0,05; **: p<0,01
OCT: Optical coherence tomography, **ONL:** Outer Nuclear Layer, **EIFL:** Ectopic inner foveal layer

Although the presence of EIFL is known to be associated with lower visual acuity, it has been reported that each 100 pm increase in EIFL thickness leads to a 0.086 logMAR decrease in BCVA. Kim et al. showed that preoperative INL thickness is closely related to preoperative and postoperative visual acuity.²³ Similarly, the relationship between preoperative and postoperative INL thickness and metamorphopsia is also known.²⁴

The retrospective nature of this study made it difficult to evaluate metamorphopsia and the thickness of the INL was excluded from the study. Retinoschisis involving this layer was found to have a negative effect on visual acuity, but unlike previous studies, macular edema had no negative effect on visual acuity. This different result may be due to the inability to differentiate retinoschisis from microcystoid macular edema. The fact that the number of retinoschisis and microcystoid macular edema were close to each other in all stages according to the OCT stage suggests that the severity of focal traction and changes in retinal microstructure are independent of the stage.

The presence of DRIL, which can be seen in both severe diabetic retinopathy and ERM, has been accepted as a negative prognostic indicator in addition to being associated with worse visual acuity. DRIL affects the inner retinal layers by blocking the visual input from photoreceptors to ganglion cells. Zur et al.²⁵ reported that ERM with DRIL had the worst visual acuity after surgery. In our study, the visual acuity of patients with DRIL were found to be significantly lower.

The cotton ball sign, which is one of the findings defined as a central bouquet, is thought to be caused by continuous traction of the inner retinal layers in the early to middle stages of ERM before disorganization. In our study, cotton ball sign was detected in 30 eyes, with a higher rate of cotton ball sign in eyes with stages 2 and 3 ERM. The higher incidence in these stages suggests that it may be due to increased vertical traction in the outer retinal layers. There was no significant correlation between the presence of gender, hypertension, diabetes, pseudophakia, and cotton ball sign development. There was no difference between the distribution of ERM stages in cases with and without cotton ball sign. It has been reported in previous studies that the presence of a cotton ball sign is not a prognostic marker.²⁶ In this study, eyes with cotton ball sign showed good visual acuity. It is not considered a prognostic marker because it disappears after surgery without leaving any damage. 20% of the patients with cotton ball sign were found to have simultaneous ELM-EZ defects and there is

not enough data to suggest that the two lesions are related to each other.

OCT-based staging systems and biomarkers are the main criteria to be considered in the follow-up and surgical decision-making process of ERM to predict a good visual rehabilitation and postoperative clinical course. This study revealed that biomarkers in the outer layers of the retina such as EZ-ELM and pathologies involving the inner layers of the retina such as retinoschisis, VMT, and DRIL may have negative effects on visual acuity preoperatively. The presence of cotton ball sign was not significantly associated with visual acuity. Although the EIFL staging scheme is an objective, easy, and reproducible method that correlates with visual acuity in ERM patients, the presence of additional factors affecting visual acuity should be considered in OCT-based evaluations. The proportional effects of these pathologies on visual functions after surgery form the basis of our future studies.

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