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Importance of Ectopic Inner Foveal Layer Staging in Idiopathic Epiretinal Membrane: Cross-Sectional, Retrospective Research

Ektopik İç Foveal Tabaka Evrelemesinin İdiyopatik Epiretinal Membranda Önemi: Kesitsel, Geriye Dönük Araştırma

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ABSTRACT Objective: To determine the significance of the presence of ectopic inner foveal layer (EIFL) in cases with idiopathic epiretinal membrane (iERM). **Material and Methods:** Optical coherence tomography (OCT) images of 140 cases with iERM at the initial examination were evaluated. According to their EIFL staging,the cases were divided into four stages. For all cases, best corrected visual acuity (BCVA) and obtained from OCT measurements, including the central foveal thickness (CFT), central retinal thickness (CRT), maximum retinal thickness (MRT), inner nuclear layer (INL) thickness, outer nuclear layer (ONL) thickness, inner retinal layer (IRL) thickness,outer retinal layer (ORL) thickness, and ganglion cell layer+inner plexiform layer (GCL+IPL) thicknesses, as well as total photoreceptor length (TPL), photoreceptor outer segment length (PROSL), photoreceptor deformity index (PDI), and inner retinal layer irregularity index (IRLII) were recorded. In cases where the retinal layers were clearly visualized, ORL damage, foveal bulge, and the presence of the cotton ball sign were evaluated. **Results:** According to EIFL staging, there were 22 cases in Stage 1, 45 cases in Stage 2, 44 cases in Stage 3, and 29 cases in Stage 4. BCVA was higher in Stages 1 and 2 than in Stages 3 and 4 ($p<0.001$). CFT, CRT, MRT, GCL+IPL thicknesses, and IRL and IRLII values increased higher as the EIFL stage increased ($p<0.001$ for all). INL, ONL, and ORL thicknesses, TPL, PROSL, and PDI were similar between the groups ($p>0.05$ for all). As the EIFL stage increased, ORL damage and the presence of the cotton ball sign were detected at a higher rate ($p<0.001$), whereas foveal bulge was observed less frequently ($p=0.004$). **Conclusion:** The presence of EIFL is associated with worse visual acuity in cases with iERM. As the EIFL stage increases, IRL thickness and ORL damage become more common.

Keywords: Ectopic inner foveal layer; idiopathic epiretinal membrane; inner retina; stage; visual acuity

ÖZET Amaç: Çalışmanın amacı, idiyopatik epiretinal membranlı (iERM) olgularda, ektopik iç foveal tabaka (EİFT) varlığının önemini belirlemektir. **Gereç ve Yöntemler:** iERM'si olan 140 olgunun, başlangıç muayenelerindeki optik koherens tomografi (OKT) görüntüleri değerlendirildi. EİFT evrelemesine göre olgular 4 evreye ayrıldı. Tüm olguların en iyi düzeltilmiş görme keskinlikleri (EİDGK) ile OKT görüntülerinden elde edilen; santral foveal kalınlık (SFK), santral retinal kalınlık (SRK), maksimum retinal kalınlık (MRK), iç nükleer tabaka (İNT), dış nükleer tabaka (DNT), iç retinal tabaka (İRT), dış retinal tabaka (DRT), gangliyon hücre tabaka+iç pleksiform tabaka (GHT+İPT) kalınlıkları ile toplam fotoreseptör uzunluğu (TFU), fotoreseptör dış segment uzunluğu (FDSU), fotoreseptör deformite indeks (FDİ) ve iç retinal tabaka düzensizlik indeks (İRTDİ) değerleri kaydedildi. Ek olarak retinal tabakaların net değerlendirilebildiği olgularda dış retinal katman hasarı, foveal bulge ve pamuk topu varlığı değerlendirildi. **Bulgular:** EİFT evrelemesine göre Evre 1'de 22, Evre 2'de 45, Evre 3'te 44, Evre 4'te 29 olgu mevcut idi. EİDGK, Evre 1 ve 2'de Evre 3 ve 4'e göre daha yüksek idi ($p<0,001$). SFK, SRK, MRK, GHT+İPT, İRT ve İRTDİ değerlerinin EİFT evresi arttıkça daha yüksek olduğu gözlendi (tüm değerlerde, $p<0,001$). İNT, DNT, DRT, TFU, FDSU ve FDİ değerleri evreler arasında benzerdi (tüm değerlerde $p>0,05$). Dış retinal tabaka hasarı ve pamuk topu varlığı evre yükseldikçe daha çok gözlenirken, foveal bulge daha az saptandı ($p<0,001$, $p=0,004$). **Sonuç:** iERM olgularında EİFT varlığı daha kötü görme keskinliğiyle ilişkilidir. EİFT evresi arttıkça iç retinal katman kalınlıkları artar ve dış retinal katman hasarı daha sık görülür.

Anahtar Kelimeler: Ektopik iç foveal tabaka; idiyopatik epiretinal membran; iç retina; evre; görme keskinliği

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Idiopathic epiretinal membrane (iERM) is a retinal disease characterized by glial or fibrocellular proliferation that emerges on surface of the retina, affects the macular anatomy, and presents with complaints, such as reduced visual acuity (VA) and metamorphopsia.[1] As a modality frequently preferred in practical use, optical coherence tomography (OCT) is also important in the diagnosis of iERM, along with clinical examination findings. OCT is commonly used in the assessment of retinal pathologies.[2] With the developments in the related technology, the higher resolution and reflection properties of OCT allow for a more detailed examination of retinal layers.

In this study, the spectral-domain OCT images of cases followed up for iERM were evaluated. The cases were divided into groups according to their ectopic inner foveal layer (EIFL) staging, defined in recent years, and the distribution of VA and numerical and categorical OCT parameters were examined.[3] With the results of the study, it was aimed to contribute to the literature by presenting parameters with predictive importance in the prognosis of cases with iERM.

MATERIAL AND METHODS

This cross-sectional observational design study included 140 eyes of 140 cases followed up at the Ankara Bilkent City Hospital retinal unit. Ankara City Hospital Ethics Committee (date: January 20, 2021, no: E1-21-1457) approval was obtained. After obtaining the necessary consent from the patients, the study was conducted in accordance with the principles of the Declaration of Helsinki.

The retinal unit file records of all cases were screened to evaluate age, gender, the presence of systemic and ocular diseases, the baseline best corrected visual acuity (BCVA), and lens status. An anterior segment and fundus examination was performed using a slit lamp. Lenses with nuclear sclerosis that did not reduce VA and pseudophakic cases were included in the study. Cataractous lenses (grade two and above nuclear sclerosis) were excluded.

The exclusion criteria were accepted to be conditions that could cause secondary epiretinal membrane (ERM) (retinal vascular diseases), pregnancy, or breastfeeding.

The BCVA evaluation of all cases was performed using the Snellen chart. For the statistical analysis of BCVA, the decimal representation of the VA value determined according to the Snellen chart was converted to logMAR by taking the negative logarithm.

OCT is a noninvasive imaging modality that provides detailed information about the retinal layers and is frequently used in daily practice in retina units of ophthalmology clinics. A spectralis domain OCT (Spectralis OCT; Heidelberg Engineering, Germany) device was used in our study. OCT images obtained at the first visit were examined, and the cases were divided into four groups according to the EIFL stages defined in the literature:[3]

Stage 1: Foveal contour is preserved, and retinal layers are clearly distinguished.

Stage 2: Foveal contour has disappeared, but the integrity of the retinal layers is intact.

Stage 3: The ectopic inner foveal fold is observed in the foveal region, and the inner retinal layers (IRL) can be distinguished.

Stage 4: The ectopic inner foveal fold is observed in the foveal region, but IRLs cannot be distinguished (Figure 1).

The parameters evaluated from the OCT images of all cases after EIFL staging are given below according to the order of evaluation:

- The central foveal thickness (CFT) in a one-mm field, central retinal thickness (CRT) in a 3-mm

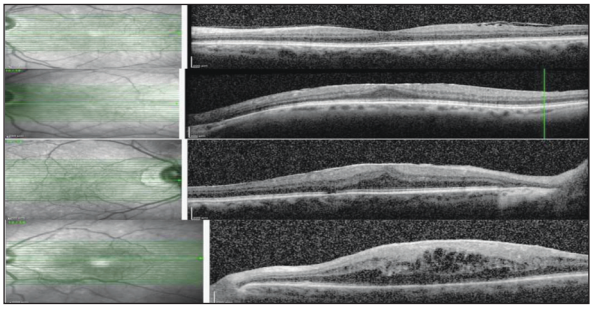

FIGURE 1: Optical coherence tomography images of the ectopic inner foveal layer stages.

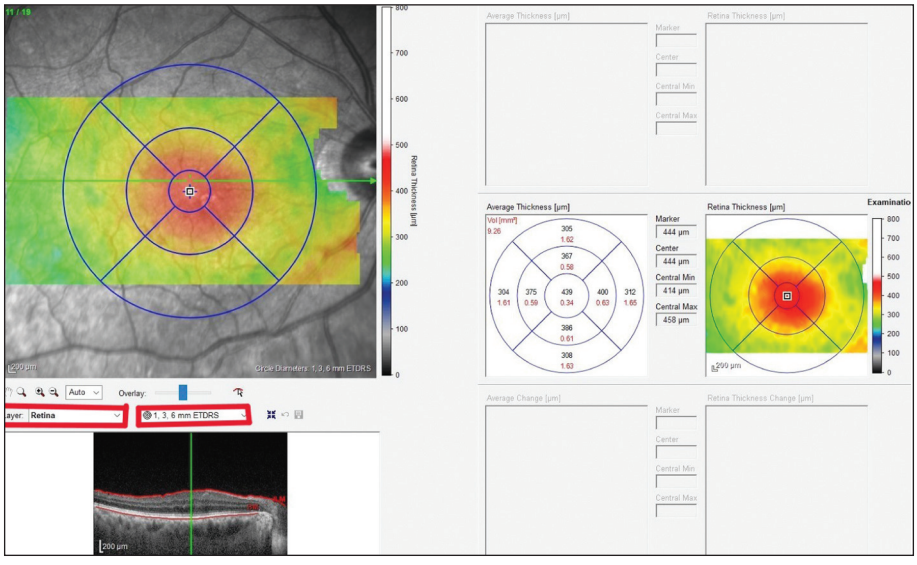

FIGURE 2: Image of the nine measurement quadrants using the Early Treatment Diabetic Retinopathy Study template.

field, and maximum retinal thickness (MRT) in a six-mm field were recorded from nine quadrants using the Early Treatment Diabetic Retinopathy Study (ETDRS) template (Figure 2).

■ The central inner nuclear layer (INL), outer nuclear layer (ONL), IRL, outer retinal layer (ORL), and ganglion cell layer+inner plexiform layer (GCL+IPL) thicknesses were measured automatically using the ETDRS template.

■ Current indices, namely total photoreceptor length (TPL), photoreceptor outer segment length (PROSL), photoreceptor deformity index (PDI), and inner retinal layer irregularity index (IRLII) were evaluated.

■ In the passing through the fovea in the ETDRS template, the normality or interruption of the integrity of the outer limiting membrane [external limiting membrane (ELM)], ellipsoid zone (EZ), and interdigitation zone (IZ), forming ORL, was evaluated.

■ The protruding appearance of EZ in the normal localization or absence of foveal contour was recorded as the presence of foveal bulge (Figure 3).

■ An oval or round hyperreflective area with unclear borders located between EZ and IZ in the fovea was noted as the cotton ball sign (Figure 4).

All measurements were performed automatically and repeated, and inconsistent and non-reproducible

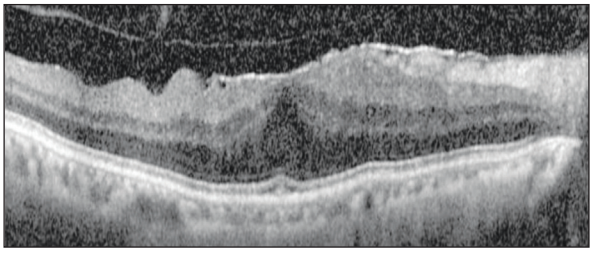

FIGURE 3: Foveal bulge appearance in an idiopathic epiretinal membrane case.

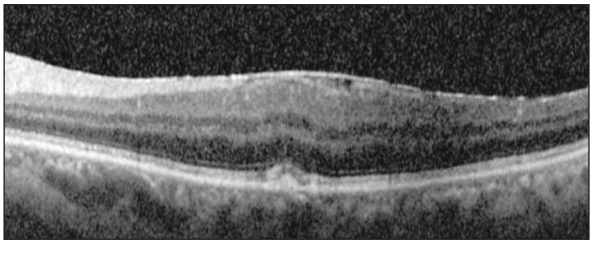

FIGURE 4: An idiopathic epiretinal membrane case with the cotton ball sign.

measurements were excluded from statistical analyses.

IBM SPSS v. 21.0 (IBM Corp., Armonk, NY) was used in the analysis of the data. The Kolmogorov-Smirnov test was used as a normality test. The Kruskal-Wallis test was conducted because the data did not show a normal distribution, and there were more than two independent groups. In cross-tables, categorical data were analyzed using the likelihood ratio test or Fisher's exact test if the expected count was lower than

five, and Pearson's chi-square test otherwise. A p value of <0.05 was considered statistically significant.

RESULTS

According to EIFL staging, there were 22 (15.7%) cases in Stage 1, 45 (32.1%) in Stage 2, 44 (31.5%) in Stage 3, and 29 (20.7%) in Stage 4 (Table 1).

TABLE 1: Distribution of groups by ectopic inner foveal layer staging.

Stage	n	%
1	22	15.7
2	45	32.1
3	44	31.5
4	29	20.7

BCVA, OCT numerical parameters, and mean and standard deviation of PDI and IRLII are shown in Table 2 according to EIFL staging. CFT, CRT, and MRT from the ETDRS measurements; INL and GCL+IPL thicknesses from the layer thickness measurements; and IRL thickness from the total thickness measurement were determined to be lowest in Stage 1 and highest in Stage 4, with a statistically significant difference being observed between the stages

TABLE 2: OCT parameters according to EIFL staging.

	EIFL stage				
	Stage 1 (n=22)	Stage 2 (n=45)	Stage 3 (n=44)	Stage 4 (n=29)	
Parameter	X̄±SD	X̄±SD	X̄±SD	X̄±SD	p value*+
Age (years)	61.5±6.6	62.7±5.8	60.8±6.0	63.1±7.4	0.25
BCVA (logMAR)	0.26±0.25	0.28±0.26	0.43±0.32	0.71±0.30	**<0.001**
CFT (µm)	278±50	355±56	422±77	466±88	**<0.001**
CRT (µm)	290±55	360±72	439±92	487±80	**<0.001**
MRT (µm)	313±58	391±80	469±87	535±92	**<0.001**
INL thickness (µm)	71±12	81±18	88±18	95±25	**<0.001**
ONL thickness (µm)	104±34	102±28	107±40	108±37	0.09
GCL+IPL thickness (µm)	115±21	121±34	152±44	166±54	**<0.001**
IRL thickness (µm)	245±38	288±58	345±77	377±74	**<0.001**
ORL thickness (µm)	81±5	85±8	90±12	88±11	0.12
TPL (µm)	84±11	89±12	91±15	85±10	0.58
PROSL (µm)	54±10	61±8	60±11	62±7	0.34
PDI	2.2±0.4	2.5±0.6	2.4±0.7	2.4±0.5	0.41
IRLII	1.04±0.03	1.05±0.03	1.06±0.04	1.07±0.05	**<0.001**
ELM integrity					
Present	22	44	40	21	**<0.001**
Absent	0	1	4	8	
EZ integrity					
Present	21	42	37	20	**<0.001**
Absent	1	3	7	9	
IZ integrity					
Present	20	40	36	19	**<0.001**
Absent	2	5	8	10	
Foveal bulge					
Present	20	38	28	14	**<0.001**
Absent	2	7	16	15	
Cotton ball sign					
Present	1	5	14	19	**0.004**
Absent	21	40	30	10	

*Kruskal-Wallis test; +Likelihood ratio test; OCT: Optical coherence tomography; EIFL: Ectopic inner foveal layer; SD: Standard deviation; BCVA: Best corrected visual acuity; CFT: Central foveal thickness; CRT: Central retinal thickness; MRT: Maximum retinal thickness; INL: Inner nuclear layer; ONL: Outer nuclear layer; GCL+IPL: Ganglion cell layer+inner plexiform layer; IRL: Inner retinal layer; ORL: Outer retinal layer; TPL: Total photoreceptor length; PROSL: Photoreceptor outer segment length; PDI: Photoreceptor deformity index; IRLII: Inner retinal layer irregularity index; EIFL: Ectopic inner foveal layer; ELM: External limiting membrane; EZ: Ellipsoid zone; IZ: Interdigitation zone.

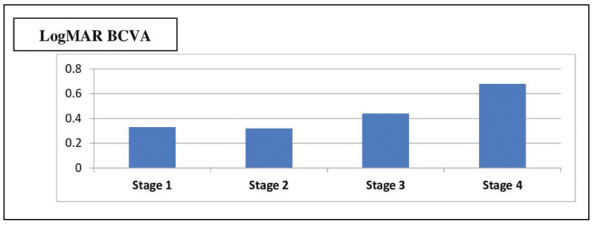

FIGURE 5: Distribution of logMAR BCVA according to ectopic inner foveal layer staging.
BCVA: Best corrected visual acuity.

($p<0.001$ for all). There was a statistically significant difference in IRLII between the Stage 1 and Stage 4 groups ($p<0.001$). INL, ONL, and ORL thicknesses from retinal thickness measurements, as well as TPL, PROSL, and PDI values among other measurements were similar between stages ($p>0.05$ for all).

Figure 5 shows the mean VA of the cases according to EIFL staging. While the mean VA of Stage 1 and 2 were similar, the VA of Stage 4 was the lowest ($p<0.001$).

Table 2 shows the distribution of categorical parameters according to EIFL staging and statistical comparisons between groups. The stage in which the integrity of ELM, EZ and IZ was preserved and the appearance of foveal protrusion was present was most frequently Stage 1 and least frequently Stage 4 ($p<0.001$ for all). The cotton ball sign was least common in Stage 1 and most common in Stage 4 ($p=0.004$).

DISCUSSION

In the current study, we evaluated the relationship between EIFL stages and VA and numerical and categorical OCT parameters in cases with iERM, with an aim to contribute new parameters with predictive significance to the literature.

Govetto et al. classified 194 eyes according to EIFL staging and reported Stage 1 in 43, Stage 2 in 88, Stage 3 in 51, and Stage 4 in 12. The authors also assessed VA, CFT, EZ damage, the presence of the cotton ball sign, and ONL thickness. They reported decreased VA, increased EZ injury, increased CFT and ONL thicknesses, and an increased incidence of the cotton ball sign from Stage 1 to Stage 4.[3] With reference to the study by Govetto et al., Takkar et al. and Yoon et al. reported that this new parameter can be used in the determination of prognosis.[3-6] In our study, there were 22 (15.7%) cases with Stage 1, 45 (32.1%) cases with Stage 2, 44 (31.5%) cases with Stage 3, and 29 (20.7%) cases with Stage 4 EIFL. The distribution of EIFL stages was similar to the previous studies conducted with large cohorts. We determined the BCVA values to be similar between Stages 1 and 2 but worse in Stages 3 and 4. The presence of EIFL was associated with lower VA. We also found that the ETDRS retinal thicknesses, especially CFT increased as the EIFL stage increased, which is in agreement with most studies in the literature. Concerning the evaluation of layer thicknesses, GCL+IPL thicknesses were lower in Stages 1 and 2, and highest in Stage 4. While most studies in the literature have evaluated the ONL thickness, there is only limited research performing the evaluation of INL and GCL+IPL thicknesses according to EIFL staging. Although the deterioration of IRL integrity affects these measurements, especially in cases with Stage 4 EIFL, in our sample, we included cases in which we were able to perform this evaluation and found a statistically significant difference between all EIFL stages in relation to the IRL thickness. The IRL thickness was lowest in Stage 1 and highest in Stage 4, while the ORL thickness did not significantly differ between the EIFL stages. This can be interpreted as that ERM primarily affects IRLs but has lower effects on ORLs.

Various signaling, especially those involved in Müller cell activation pathways are thought to play a role in the formation of EIFL, and this process is facilitated by reactive gliosis.[7] In a study based on in vitro animal models, the level of kinase regulated by extracellular signal was reported to be high when the retina was exposed to mechanical stress.[8] This pathway is involved in the mitogen-activated protein kinase cascade, which is considered to play a role in Müller cell proliferation and neuroprotection.[9] Baek et al. compared the baseline findings and vitreous cytokines between 32 iERM cases without EIFL and 28 iERM cases with EIFL. They determined that VA was worse, and CFT was thicker in the group with EIFL. There was similar between the two groups in terms of ELM and EZ damage. The main purpose of that study was to compare the vitreous cytokine lev-

els, with the authors evaluating many collagens and interleukins discussed in the etiology of ERM in the literature. Monocyte chemotactic protein-1, CD163, and macrophage colony-stimulating factor were found to be significantly higher in the group with EIFL. Although formation of EIFL remains unclear, higher levels of these cytokines indicate the importance of macrophages. It is thought that macrophages, which are one of the precursor cells in conditions such as wound healing and fibrosis may also be precursor cells in pathologies like ERM.[10]

Coppola et al. evaluated their cases in two groups according to the presence of EIFL and reported no statistically significant difference between the groups with regard to baseline VA, the cotton ball sign, and EZ integrity. Among the baseline findings, the only significant difference was observed in CFT and the ONL thickness. Both thicknesses were reported to be greater in the EIFL group.[11] Mavi Yildiz et al. reported 16 cases with Stage 1, 20 with Stage 2, 56 with Stage 3, and 20 with Stage 4 EIFL. They evaluated baseline VA, the cotton ball sign, EZ damage, ONL thickness, CFT, cystoid macular edema, EIFL length, and FAZ measurements according to EIFL stages and found that as the stage increased, VA decreased, ONL, CFT, and EIFL thicknesses increased, EZ damage and the cotton ball sign were seen more frequently, and the FAZ parameters were reduced. The authors noted no significant difference between the EIFL stages in terms of cystoid macular edema. They reported that the presence of EIFL, the cotton ball sign, and EZ damage negatively affected VA at both baseline and postoperative month 12.[12] In addition to the thickness of ORLs, their integrity may also differ between EIFL stages. Although there are many studies in the literature examining the differences in EZ integrity according to EIFL staging, only some have assessed the integrity of IZ and ELM. There are even fewer studies addressing all these three parameters. Therefore, our study may be important for the literature since it examines these three parameters together. We found that the integrity of these three ORLs was affected more frequently as the EIFL stage increased from 1 to 4. In the current study, although the ORL thicknesses did not significantly differ between the EIFL stages, there were significant differences in relation to the disruption of the integrity of these layers. It is known that in most diseases, the disruption of the integrity of the photoreceptor layer negatively affects the visual prognosis.[13-15]

In this study, foveal bulge was observed at the highest rate in Stage 1 and lowest rate in Stage 4, and there was a significant difference between the EIFL stages. The cotton ball sign was the least common In Stage 1 and most common in Stage 4. In the literature, most studies evaluating the relationship between the cotton ball sign and EIFL stages have reported a low incidence of this sign in Stage 4. In contrast, we found that the cotton ball sign was most common in Stage 4 (48%), which also resulted in a worse visual prognosis in this group.

In a systematic review, Iuliano et al. found that the absence of EIFL might be associated with better visual outcomes.[16] In a study including Stage 3 and 4 iERM cases, the baseline VA values were reported to statistically significantly differ between EIFL stages. In the same study, the metamorphopsia score, CFT, and the EIFL thickness were reported to be higher in Stage 4. The authors interpreted these findings to suggest that the decreased sensitivity of the photoreceptor layer could cause metamorphopsia, considering that EIFL was formed by the synaptic connections between horizontal, bipolar, amacrine, and Müller cells, as well as the stems of these cells.[17] In the study by Mahmoudzadeh et al., the distribution of a total of 322 eyes according to EIFL staging was as follows: 21 eyes in Stage 1, 38 eyes in Stage 2, 188 eyes in Stage 3, and 75 eyes in Stage 4. The baseline VA was determined to worsen as the stage increased. The authors also noted that the presence of EIFL was not associated with VA in the postoperative period according to the multivariate analysis.[18] Among the remaining parameters evaluated in our study, PROSL, TPL, and PDI were similar across the EIFL stages. IRLII, which has been defined in recent years, was lowest in Stage 1 and highest in Stage 4. Therefore, we consider that IRLII is an OCT parameter that can be used in cases where the outer nuclear, inner, and outer plexiform layers can be evaluated even if the integrity of IRL is disrupted.

Concerning the formation of EIFL, the following inferences can be made: the foveal configuration may be altered by the traction effect of ERM formed by perifoveal posterior vitreous detachment. With the thickening of IRLs, foveal tissue may progress toward the vitreous and cause foveal herniation. The contraction of Müller cells, especially in the outer plexiform layer can also facilitate this process.[19]

Among the limitations of our study, the first is related to the evaluation of findings obtained only at the first visit of the cases. Second, as the EIFL stage increases, the involvement of the retinal layers also increases; therefore, the evaluated numerical OCT parameter values may have differed. In order to avoid this limitation, we only included the consistent OCT parameters automatically measured using the ETDRS template in statistical analyses. Lastly, the study was designed retrospectively and conducted at a single center.

CONCLUSION

In conclusion, our results indicate that EIFL-based OCT staging, which has been defined in recent years, can be used in the determination of prognosis, as has also been reported in most studies in the literature. We consider that our study, conducted with a large number of cases and enriched with both quantitative and qualitative parameters, will guide further studies in this area.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mehmet İçöz, Mücella Arıkan Yorgun;* ***Design:*** *Mehmet İçöz, Mücella Arıkan Yorgun,Yelda Yıldız Taşçı, Yasin Toklu;* ***Control/Supervision:*** *Mehmet İçöz, Mücella Arıkan Yorgun,Yelda Yıldız Taşçı, Yasin Toklu;* ***Data Collection and/or Processing:*** *Mehmet İçöz;* ***Analysis and/or Interpretation:*** *Mehmet İçöz, Mücella Arıkan Yorgun,Yelda Yıldız Taşçı;* ***Literature Review:*** *Mehmet İçöz, Mücella Arıkan Yorgun,Yelda Yıldız Taşçı;* ***Writing the Article:*** *Mehmet İçöz;* ***Critical Review:*** *Mücella Arıkan Yorgun,Yelda Yıldız Taşçı, Yasin Toklu;* ***References and Fundings:*** *Mehmet İçöz, Yasin Toklu;* ***Materials:*** *Mücella Arıkan Yorgun,Yelda Yıldız Taşçı, Yasin Toklu.*

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