Response of OCT Biomarkers Based on New Diabetic Macular Edema Classification TCED-HFV to Anti-VEGF Therapy and Its Prognostic Role in Vision Benefits

Meng Yan (✉ yankeyanmeng@126.com)

The Affiliated Hospital of Qingdao University <https://orcid.org/0000-0002-0890-6515>

Wenying Wang

The Affiliated Hospital of Qingdao University

Zhaoxia Zheng

The Affiliated Hospital of Qingdao University

Lu Li

The Affiliated Hospital of Qingdao University

Duo Zhang

The Affiliated Hospital of Qingdao University

Lina Zhang

The Affiliated Hospital of Qingdao University <https://orcid.org/0000-0002-3327-1160>

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Abstract

Introduction. To investigate the association between OCT biomarkers and visual prognosis, based on TCED-HFV, and to explore whether these biomarkers have predictive value in visual prognosis of DME patients.

Methods. The retrospective study included 166 eyes from 122 DME patients, who received 3 initial monthly intravitreal injections followed by PRN dosing.

Results. The significant improvement of BCVA, as well as statistical decrement of CMT and HF, could be observed ($p < 0.001$, $P = 0.023$, $P = 0.002$, respectively). The BCVA in early and advanced DME is significantly better than that in severe DME in baseline ($P = 0.027$, $P = 0.009$, respectively) and 1 year ($P = 0.017$, $P = 0.030$, respectively). The broken EZ/ELM was generally accompanied by the existence of SF ($P = 0.032$). The presence of DRIL and persistence SF were associated with negative visual effects ($P = 0.001$, $P = 0.045$, respectively). At month 12 the mean BCVA was significantly improved in both intact and disrupted EZ/ELM groups ($P = 0.023$, $P = 0.033$, respectively). The number of the DME patients with ERM increases after treatment ($P = 0.001$).

Conclusions. Intact EZ/ELM, the absence of DRIL and ERM might contribute to better response in patients. The persistence SF was a negative factor. Intravitreal anti-VEGF therapy was associated with ERM development and progression. It is not objective to consider only the OCT biomarkers but not the stages, and the indicators of different stages should be studied separately.

Introduction

Diabetic macular edema (DME) is the most common cause of vision impairment in patients with diabetic retinopathy (DR) and affects approximately 7% of all patients with diabetes [1, 2]. Approximately 50% of patients with DME lose two or more lines of visual acuity within 2 years if left untreated [3].

At present, fluorescein angiography (FFA) and optical coherence tomography (OCT) represent the techniques of choice for evaluating diabetic maculopathy, providing several quantitative and qualitative data points concerning DME [4]. Despite the fact that Early Treatment Diabetic Retinopathy Study (ETDRS) has traditionally been regarded the gold standard for classification and laser therapy planning in DR for many years, OCT is the most used modality today for anti-VEGF therapy management, evaluation and monitoring of individual treatment responses. New classification systems for DME were proposed in the past years, attempting to classify DME according to its extent (focal vs diffuse) [5], location (center- vs non-center-involving) [6], or nature (vasogenic vs non-vasogenic) [7, 8]. However, a morphological grading classification of DME, including all its relevant features visible on OCT is missing.

Recently, as a non-invasive diagnostic and quantitatively responsive method to reflect the therapeutic effect, a novel grading system of DM proposed by the European School of Advanced Studies in Ophthalmology (ESASO), classifying the phenotypes of macular involvement based on definitions, grading, and standard OCT figures, including also patients without retinal thickening. In particular, central macular thickness (CMT), the size of intraretinal cysts (IRC), the state of the ellipsoid zone (EZ) and the external limiting membrane (ELM), the occurrence of disorganization of the inner retinal layers (DRIL), the presence of hyperreflective intraretinal foci (HF), the presence of subfoveal fluid (SF), as well as the features of the vitreoretinal interface have been used to characterize DME [9].

Currently, the predominant treatments for DME are intravitreal injections of corticosteroids, or anti-vascular endothelial growth factor (VEGF) agents [10]. DME is characterized by increased vascular permeability and consequent leakage and lipid exudation in the macula, as a result of blood-retinal-barrier breakdown due to chronic hyperglycemia, while VEGF seems to play an essential role in the pathogenesis of DME [11]. Anti-VEGF therapy, compared with laser photocoagulation and steroid treatment, has been shown to lead to superior visual outcomes among the different treatments for DME [12, 13].

Based on the new grading system (TCED-HFV), the aim of this study was to investigate the relationship between OCT biomarkers, visual prognosis and classification, to observe the response of OCT biomarkers to anti-VEGF treatment, and to evaluate whether these biomarkers could predict visual prognosis of patients with DME.

Materials And Methods

Participants in this retrospective study were 166 eyes of 122 patients with DME, who were diagnosed and treated at Ophthalmology, the Affiliated Hospital of Qingdao University, between April 2018 and March 2021. All patients completed three consecutive monthly intravitreal injections of ranibizumab (Lucentis®) 0.5mg followed by pro re nata (PRN) dosing according to protocol-predefined retreatment criteria. The protocol required that monthly injections have to be continued if BCVA decreased or CMT was $\geq 300\mu\text{m}$ by OCT due to DME was observed investigator's opinion and was continued until stable visual acuity was reached [7].

Patients with other retinal diseases, vitreous hemorrhage, previous vitrectomy, ocular inflammation, macular ischemia on FFA, myopia $\geq 6D$, media opacities, uncontrolled glaucoma, ocular trauma surgery within the last 6 months and those whose OCT images were of poor quality were excluded from the study. The study was in accordance with the Tenets of Helsinki Declaration and was approved by the Institutional Review Board of the participating hospital. Written informed consents were obtained by all patients to use their data.

The following data were recorded: baseline demographics; previous treatments; ocular examination, FA, and OCT findings of the patients; the numbers of intravitreal injections; additional laser treatments; need for cataract surgery; and development of vitreous hemorrhage (VH). A venous blood sample was drawn from an antecubital vein in the morning after at least 8 hours of fasting. Determination of albumin, creatinine, blood ureanitrogen, total cholesterol, glycosylated albumin and concentrations of HbA1c were acquired. All measurements were performed at the department of diagnostic testing, the Affiliated Hospital of Qingdao University using commercially. Patients underwent a comprehensive ophthalmological examination in baseline and follow-up visits, which included slit lamp biomicroscopy, funduscopy, tonometry (intraocular pressure-IOP), FFA, and the spectral domain Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Dublin, CA, USA). Retinal analysis of the patients before the operation and at the earliest 1 year after the operation was performed using 6×6 mm images taken with the macular cube 512×128 protocol on the Cirrus HD-OCT device in our clinic. The grade was judged by scanning through a poorly formed fovea, or by the best visibility of the retinal structure in the case of middle layer opacification. A minimum signal strength ≥ 7 was required for the study.

The OCT images which were taken at baseline and follow-up visits were analyzed to determine the following: morphological characterization of DME (1) CMT calculated automatically by the instrument; (2) the size of IRC; (3) the visibility of ELM and/or EZ at the fovea; (4) the presence of DRIL; (5) the presence of SF; (6) the presence and the number of HF; and (7) the vitreoretinal relationship. SF was categorized as temporary if resolution was observed after intravitreal anti-VEGF injections; if SF existed during the whole treatment, usually defined as persistent SF. A manual count of the total number of HF, defined as small (<30 μm), punctiform discrete white lesions with reflectivity similar to the nerve fiber layer, absence of back-shadowing, and location in both inner and outer retina, was performed between the two vertical lines and calculated in the area of 3000 μm centered on the fovea[9].

Statistical analyses were performed using the SPSS 26.0 for Windows package. The numerical data are expressed as mean and standard deviation and the categorical variables as absolute frequency and percentage. For the analysis of best central visual acuity (BCVA), CMT, and the amount of HF, examined variables did not present a normal distribution as verified by the Shapiro-Wilk test and therefore, the Wilcoxon test has been used. We performed statistical comparisons between groups using the Chi Square test for categorical variables, Mann–Whitney test, ANOVA analysis, Kruskal-Wallis H test or paired Student's t test for numerical variables. The comparison of measurements between baseline and follow-up visits were performed with Cochran's tests. A P value lower than 0.05 was considered statistically significant.

Results

A total of 166 eyes (122 patients) were included in the study and were followed for 1 year. Descriptive characteristics of the enrolled patients were shown in Table 1. Overall, the average age was 60.72 ± 9.97 years and 48(39.34%) of the patients were male. The mean durations of diabetes was 12.61 ± 7.39 years. All patients received a mean of 6.24 ± 2.52 injections in a year. Before accepting anti-VEGF treatment, 94(56.63%) and 38(22.89%) eyes had undergone PRP and cataract surgery, respectively. SF was detected in 86(51.81%) eyes, DRIL in 30(18.07%) eyes. More than 40% of the eyes had vitreomacular interface abnormality (VMIA), and many are ungraded, which is likely to represent complete posterior vitreous detachment (PVD) where the posterior vitreous cannot be visualized on OCT images. Two (1.20%) eye had sign of vitreomacular traction (VMT), and 54(32.53%) eyes had epiretinal membrane (ERM). VH developed in 2(1.20%) eyes during the follow-up visits.

Table 1
Demographic and ocular characteristics

Baseline characteristics (166 eyes of 122 patients)	
Age (years)	60.72±9.97
Diabetes duration (years)	12.61±7.39
Gender (male)	
Male (%)	48(39.34)
Female (%)	74(60.66)
PRP status	
Yes (%)	94(56.63)
No (%)	72(43.37)
Lens status	
Phakic (%)	128(77.11)
Pseudophakia (%)	38(22.89)
Number of injections	6.24±2.52
Baseline BCVA (Log MAR)	0.68±0.38
Baseline CMT (μm)	478.96±140.62
Baseline HF	85.83±36.47
EZ/ELM status	
Intact (%)	48(28.91)
Disrupted (%)	106(63.86)
Absent (%)	12(7.23)
DRIL	
Absent (%)	136(81.93)
Present (%)	30(18.07)
SF	
Absent (%)	80(48.19)
Temporary (%)	72(43.37)
Persistent (%)	14(8.44)
DME stage	
Early DME (%)	10 (6.02)
Advanced DME (%)	144(86.75)
Severe DME (%)	12(7.23)
Atrophic maculopathy (%)	0.00
Legend: DR: diabetic retinopathy; PRP: panretinal photocoagulation; BCVA: best-corrected visual acuity; CMT: central macular thickness; HF: hyperreflective intraretinal foci; IRC: intra-retinal cysts; EZ: ellipsoid zone; ELM: external limiting membrane; DRIL: disorganization of the inner retinal layers; SRF: subretinal fluid; IVD: incomplete posterior vitreous detachment; PVD: posterior vitreous detachment; VMT: vitreomacular traction; ERM: epiretinal membrane.	

No significant differences were detected between BCVA in DME eyes with or without PRP and between phakic or pseudophakic eyes, as well as in men or women and right or left eyes (P values were 0.115, 0.747, 0.624 and 0.782, respectively). The number of HF was 57.00±7.78 in the early DME, 79.00±26.33 in the advanced DME and 119.00±38.55 in the severe stage (P=0.026). The average BCVA has been demonstrated a significant improvement at 3M and 6M, while the average CMT and HF decreased noticeably. An increased number of HF and thickness of CMT were generally accompanied by the recurrence of DME (Table 2).

Table 2
BCVA, CMT and HF of study eyes at baseline, 1, 3, 6, 12 months after intravitreal injections

	Baseline	1 month	p-value ^a	3 months	p-value ^a	6 months	p-value ^a	12 months	p-value ^a
BCVA	0.68±0.38	0.56 ±0.31	0.001	0.46 ±0.34	<0.001	0.51 ±0.35	<0.001	0.53±0.36	<0.001
CMT (μm)	478.96±140.62	349.94±86.15	<0.001	351.59±115.86	<0.001	408.77±142.14	0.032	415.77±118.63	0.023
HF	85.83±36.47	63.50±31.66	<0.001	53.35±25.76	<0.001	56.73±25.56	<0.001	62.20±29.90	0.002
Legend: a: Wilcoxon Test									

Based on the new DME classification given by ESASO, the visual acuity (Mean± SD) of the patients with early and advanced DME is significantly better than that in patients with severe DME in baseline (0.51±0.23 log MAR versus 0.67±0.38 log MAR versus 0.98±0.33 log MAR; P=0.027, P=0.009, respectively) and 1 year (0.24±0.17 log MAR versus 0.43±0.37 log MAR versus 0.81±0.18 log MAR; P=0.017, P=0.030, respectively). The best visual acuity outcome occurs in the patients with early DME (Table 3, P=0.042).

Table 3
BCVA at Baseline, 12 months of follow-up in eyes with DME treated with anti-VEGF agents

	Baseline	Month 12	Changes in BCVA	p-value ^a
DME stages				
Early DME	0.51±0.23	0.24±0.17	0.28±0.13	0.042
Advanced DME	0.67±0.38	0.43±0.37	0.24±0.26	<0.001
Severe DME	0.98±0.33	0.81±0.18	0.17±0.18	0.102
p-value ^b	0.009	0.012	0.834	
EZ/ELM status				
Intact	0.62±0.37	0.39±0.34	0.27±0.17	<0.001
Disrupted	0.71±0.41	0.42±0.36	0.21±0.29	0.004
Absent	0.98±0.33	0.81±0.18	0.17±0.18	0.102
p-value ^b	0.009	0.02	0.448	
DRIL				
Absent	0.65±0.38	0.41±0.30	0.22±0.23	<0.001
Present	0.87±0.36	0.85±0.16	0.01±0.40	0.513
p-value ^b	0.036	<0.001	0.004	
SF				
Absent	0.73±0.43	0.47±0.35	0.26±0.23	<0.001
Present				
Temporary	0.67±0.31	0.44±0.26	0.16±0.23	0.026
Persistent	0.48±0.29	0.43±0.30	0.05±0.11	0.341
p-value ^b	0.269	0.490	0.033	
Legend: a: Comparing baseline vs. Month 12 b: Comparing within groups				

SF presented in 86(51.81%) eyes including 4(40.00%) eyes in the early DME, 78(54.17%) eyes in the advanced stage and 4(33.33%) eyes in severe phase (P=0.311). The resolution of SF could be found after an average of 1.48±0.79 injections, while constant subretinal fluid has been seen in 14(8.44%) eyes during the whole treatment. With the recurrence of DME, SF reappeared in 14(22.22%) eyes and four SF-absent eyes in baseline developed SF, however. The better BCVA was related to the existence of baseline SF, although there was no statistically difference (Absent SF versus Temporary SF versus Persistent SF groups, 0.73±0.43 log MAR versus 0.67±0.31 log MAR versus 0.48±0.29 log MAR,

respectively, $P=0.269$). A persistence SF was a negative factor, meaning that the mean visual gain was less compared with SF-absent group (0.05 ± 0.11 log MAR versus 0.26 ± 0.23 log MAR, respectively, $P=0.045$).

In addition, a meaningless conclusion in the relationship between SF and serological indexes was drawn in our cohort, which includes albumin, creatinine, blood ureanitrogen, total cholesteral, glycosylated albumin and concentrations of HbA1c (Figure 1).

EZ/ELM was observed intact in 48(28.91%) eyes, disrupted in 106(63.86%) eyes and absent in 12(7.23%) eyes. The mean BCVA between the intact EZ/ELM, disrupted EZ/ELM and absent EZ/ELM group was compared, there was statically difference at the baseline (0.62 ± 0.37 versus 0.71 ± 0.41 versus 0.98 ± 0.33 , $P=0.009$). At month 12 the mean BCVA was significantly improved in both intact EZ/ELM group and disrupted EZ/ELM group with anti-VEGF treatment than that of absent EZ/ELM group(0.39 ± 0.34 log MAR versus 0.42 ± 0.36 log MAR versus 0.81 ± 0.18 log MAR, $P=0.023$, $P=0.033$, respectively).

Of the 106 eyes in the disrupted EZ/ELM group, 14 (13.21%) eyes restored integrity after intravitreal injections, of which 8 (7.55%) eyes had simultaneous occurrence and disappearance of SF and EZ interruptions, and 6 (5.66%) eyes had no SF throughout. The disruption of EZ/ELM was significantly related to the emergence of SF (Table 4, $P=0.032$).

Table 4
Relationship between the incidence of SF and the integrity of EZ/ELM

Relationship between the incidence of SRF and the integrity of EZ/ELM				
	EZ/ELM		c ²	P-value ^a
	Intact	Disrupted/Absent		
Absence of SRF	32	48	9.230	0.002
Presence of SRF	16	70		
a: Chi-square Test				

DRIL presented in 30(18.07%) eyes including 18(12.50%) eyes in the advanced DME and 12(100%) eyes in the severe stage($P<0.001$). The presence of DRIL had poor baseline vision and no significant difference was observed in BCVA after injections ($P=0.513$). A direct and statistically significant improvement in vision was found between the absence and the presence of DRIL(0.22 ± 0.23 versus 0.01 ± 0.40 , $P=0.004$).

ERM was identified in 54 (32.53%) eyes at baseline, 70 (42.17%) eyes at 1 month, 92 (55.42%) eyes at 3 months, 102 (61.45%) eyes at 6 months and 106 (63.86%) eyes at 1 year. The study showed that the incidence of ERM increased with an increasing number of injections (Table 5, $P<0.001$).

Table 5
Evolution of epiretinal membrane over time in all patients

	patients		c ²	P-value ^a
	Yes	No		
Baseline	54	112	144.471	<0.001
Month 1	70	96		
Month3	92	74		
Month6	102	64		
Month12	106	60		
Legend: a: Cochran's Q Test				

Discussion/conclusion

As the wide application of OCT in the diagnosis and monitoring of retinal diseases, we have discovered new pathologies related to retinal diseases, and researchers have begun to investigate the relationship between these pathologies and visual outcomes. Similar progress has been made in patients with DME because OCT has been able to identify various pathologies in these patients, such as CMT, HF, SF, EZ/ELM irregularity and DRIL, and these findings have begun to clarify the pathogenesis and prognosis of the disease. A large number of studies have been conducted on DME patients receiving anti-VEGF injections, and it has been confirmed that the microstructural changes seen at the

baseline by OCT scans can predict the treatment response[14, 10, 15]. The TCED-HFV classification, as a non-invasive diagnostic method, had shown its potential for early diagnosis of DME and could quantitatively response the therapeutic effect to anti-VEGF treatment.

Our findings suggested that the anti-VEGF treatment strategy significantly improved BCVA and reduced CMT. These observation indexes were associated with better results and higher patient's satisfactions rate after 3- and 6-months injections when compared with 1 year. Lam and Lai[16] reported that changes of BCVA and central foveal thickness in 48 eyes with DME treated with IVB during 6-month follow-up. The results showed significant improvements between baseline and 6-month mean BCVAs, as well as the reductions between baseline and 6-month mean central foveal thickness. They demonstrated the best treatment effect at 3 months, followed by 6 months, which had better results compared with the baseline. Similar conclusion can be drawn by Kumar and Sinha[17]. IVB resulted in a significant decrease in macular thickness and a significant improvement in visual acuity after 3 months, but this effect was weakened at the end of 6 months, although it was still statistically significant. The current findings compare favorably with those reported, and confirm their findings through longer follow-up and more patients.

In our study, a significantly decreased HF could be found under adequate anti-VEGF treatment. This result is consistent with the results observed in previous studies that hyperreflective foci or spots decreased after anti-VEGF treatment[18, 14, 10]. The exact formation mechanism of HF remains still unclear despite several theories have attempt to explain the special marker. Bolz et al.[19] reported that HF may represent tiny intraretinal protein and/or lipid deposits after inner blood-retinal destruction, playing as precursors of hard exudates. Additionally, some researchers suggested that HF might correspond to microglial cells, debris of photoreceptors, and RPE hyperplasia[20, 21]. All these studies stated that HF might be associated with retinal inflammatory response. With the aggravation of retinal inflammation, microglia cells are activated, increasing the number, changing morphology and gathering together, which act as HF on OCT[22–24]. Anti-VEGF therapy may inhibit the activation of VEGFR1-dependent microglia and restore structural damage[25]. The results suggested that a decreased number of HF may be connected with good response to anti-VEGF treatment for patients with DME. Additionally, the number of HF was associated with different stages of DME and especially high in severe DME. Thus, there may be a strong link between HF and exudative retinal disease and HF could be used as a predictive marker of visual function.

Previous studies have shown that the prevalence of SF in patients with DME ranges from 11.4–52.4%[26, 27]. Our finding shows that SF existed approximately 50.00% of the patients at baseline, which was consistent with the results reported in the previous literature. The high incidence rate of SF occurred in early and advanced DME, and the lowest in severe stage. With the advancement of OCT technology, higher quality images and neglected pathology can be easily and clearly obtained, which is also the reason for the increasing prevalence of SF. A great deal of literatures has reported positive, negative or no effects of SF on vision[28–31]. Zur et al.[30] suggested that better BCVA was related to the existence of baseline SF. On the contrary, Sophie et al.[28] proposed the presence of SF caused a poor visual acuity which improved significantly through aggressive and sustained suppression of VEGF. In addition, a post-hoc analysis of evaluating the effect of SF on treatment outcomes in patients with DME in the VIVID and VISTA studies indicated baseline SF status play an meaningless impact on treatment outcomes with IAI[31]. Similar findings were reported from Vujosevic et al.[29]. It is suggested that the effect of SF on the visual acuity is controversial for patients with DME. The degree of vision growth was greater in the absent SF group than that in the temporary SF and persistent SF groups, although baseline BCVA was mildly poorer compared with the other two groups. No significantly difference in BCVA was found in patients with persistent SF during treatment and follow-up, which means that the persistence SF may be a negative factor for visual outcome. Visual acuity after anti-VEGF therapy was greatly improved in both temporary SF and absent SF groups. In addition, SF reappeared in only 22.22% of patients in the present SF group, indicating that anti-VEGF therapy played an important role in the regression of SF.

Meanwhile, researchers explored the influence of systemic condition on SF, one of which is that poor renal function. De Benedetto et al.[32] and Melissa et al.[33] reported the cases of the hypoalbuminemia leading to subretinal fluid. Tsai et al.[34] reported that the presence of subretinal fluid before treatment was associated with lower EGFR stages and lower albumin levels. The reduction of serum albumin may decrease the intravascular osmotic pressure and increase the hydrostatic pressure, resulting in the retention of fluid in the subretinal space. All these findings suggested serum albumin is a sensitive marker of SF in chronic kidney disease. Conversely, we came to a meaningless conclusion in the relationship between SF and kidney markers. The discrepancy might be partly explained by the different population choices, different follow-up periods and different treatments. Interestingly, the persistent SF was observed in 14 patients with chronic kidney disease. As a result, larger sample sizes, more detailed imaging and longer follow-up periods are needed to confirm the clinical impact of SF.

The pathological mechanism underlying the formation of SF is not fully known, but one of the possible mechanisms is the EZ/ELM condition[29]. The apoptosis and proliferation of vascular endothelial cells may lead to vasodilation and increased vascular permeability[35]. Vascular endothelial growth factor may also influence the rupture and vasodilation of blood-retinal barrier (BRB)[36]. In addition, BRB destruction will also increase the osmotic pressure of intraocular fluid, which forces proteins moving in all directions[37]. However, it is difficult for proteins and cells to pass through intact EZ/ELM[37, 29]. Oncotic pressure will be created by this accumulation of protein, bind water and thus create a condition of retinal edema. Accumulated proteins, lipids and fluid may more easily enter the subretinal space as the EZ/ELM is

interrupted[29], resulting in the accumulation of subretinal fluid. In our study, SF appeared more likely in eyes with disrupted or absent EZ/ELM. In 8 eyes of the disrupted EZ/ELM group, EZ interruption and SF appeared at the same time. With the recovery of EZ, SF disappeared, which also confirmed our point of view.

Our data showed that patients with severe DME had significantly worse vision than those with early and advanced DME. The EZ/ELM condition was the most decisive indicator to distinguish advanced DME and severe DME. The status of EZ/ELM was referred to photoreceptor integrity and is considered to predict the visual prognosis. A study by Uji et al.[21] reported the intact EZ/ELM was associated to better visual outcomes. Similar finding was found by Muftuoglu et al.[38]. The present study showed poorer visual acuity outcomes in the eyes with absent EZ/ELM, while the best visual gain was obtained in eyes with intact EZ. Therefore, anti-VEGF therapy could achieve better therapeutic effect in early DME stage, as EZ/ELM was complete.

The incidence of VMIA in our study, including incomplete posterior vitreous detachment (IVD), PVD, VMT and ERM, stays the similar range to the previously report. The prevalence of ERM has been shown to vary from 6.6–43%[39–42] and is 32.53% in our study. The relationship between anti-VEGF therapy and ERM formation was not fully known. Some researchers indicated intravitreal injection of anti-VEGF agent might suppress ERM formation[43]. On the contrary, Anti-VEGF injections have been reported to promote tissue fibrosis and ERM formation[44–46]. The present data confirmed this, where the increasing prevalence of ERM is correlated with frequent intravitreal anti-VEGF injections. Das et al.[9] suggested the presence of ERM has a negative influence on the anatomical structure of corresponding region and was associated with poorer final visual acuity. This means that the effect of anti-VEGF treatment was decreased after ERM formation and explains why the best therapeutic effect of anti-VEGF injections came in 3- and 6-months. This was consistent with previous reports that ERM might serve as a physical barrier and reduce drug permeability[47].

Another indicator emphasized in patients with DME was DRIL, which was defined as the unidentifiable boundaries separating the inner layers of the retina (the ganglion cell layer (GCL)—inner plexiform layer (IPL) complex, inner nuclear layer (INL), and outer plexiform layer (OPL), predicted worse visual outcomes in the DME patients[27, 48, 49]. Previous studies hypothesized that the formation of DRIL was connected with the disruption and loss of Müller cells, bipolar cells, horizontal cells, and amacrine cells within the retina. DRIL occurred when the bipolar axon damaged as the elasticity of cells disappeared because of severe edema[50–52]. Additionally, PDR may form a fibrous vascular membrane and produce traction on the macula. Therefore, a variety of mechanisms related to vascular abnormalities and mechanical stress may be involved in the formation of DRIL[49]. The present results, showing the statistically difference between the eyes with and without DRIL, supported the findings of previous literatures, and DRIL may act as a negative indicator forecasting treatment outcome in treatment-naïve diabetic eyes.

Our retrospective study was limited by the relatively small number of graded patients and its retrospective character. The impact of Periodization was usually ignored while the great majority of present studies focused on the relationship between OCT findings and final visual acuity in patients with DME. Consequently, the controversial impact on therapeutic effect of indicators, such as HF and SF were reported repeatedly by researchers. Further prospective studies with more patients and an appropriate control group are needed to determine the long-term effect of OCT biomarkers on visual prognosis of patients in the different stages based on the grading protocol TCED-HFV. Further studies are warranted to evaluate TCED-HFV's potential in a clinical and a study setting, and to correlate all graded morphological characteristics in different stages to retinal function and disease severity.

Declarations

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

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Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

Compliance with Ethical Standards:

Author Contributions

The author conceived the study, collected and analyzed the data and wrote the manuscript.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

Correlation analysis of systemic condition and baseline subretinal fluid

Legend: a: Independent Samples Test b: Mann-Whitney U Test