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Optical Coherence Tomography-Based Grading of Diabetic Macular Edema Is Associated with Systemic Inflammatory Indices and Imaging Biomarkers

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Keywords
Diabetic macular edema · Optical coherence tomography · Inflammation · Grade · Stage · Biomarker

Abstract
Introduction: Objectives of the study were to investigate the correlation between optical coherence tomography (OCT)-based grading of diabetic macular edema (DME) and systemic inflammatory indices, imaging biomarkers, and early anti-vascular endothelial growth factor (VEGF) treatment response. ***Methods:*** A total of 111 eyes from 111 patients with DME treated with intravitreous anti-VEGF therapy for 3 consecutive months every month were enrolled in this retrospective study. According to a protocol termed "TCED," DME was divided into early, advanced, severe, and atrophic stages. The best-corrected visual acuity (BCVA), subretinal fluid (SRF), and the number of hyperreflective foci (HRF) in the whole retinal layers were analyzed at baseline and 3 months after the first injection. Peripheral blood inflammatory indices were calculated, including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet (PLT)-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and C-reactive protein (CRP). Statistical analysis was performed to compare the visual and anatomical results and evaluate HRF and SRF in different stages of DME before and after treatment. ***Results:*** There were significant differences in systemic inflammatory indices among the four groups, including NLR, PLR, MLR, SII, and CRP (all $p < 0.05$). The CRP, NLR, PLR, MLR, and SII were significantly higher in the atrophic stage compared to the advanced stage (all $p < 0.05$). Conversely, the CRP, NLR, PLR, MLR, and SII were significantly lower in the advanced stage compared to the early stage (all $p < 0.05$). Except for the atrophic stage, BCVA and central retinal thickness (CRT) were significantly improved after treatment in early, advanced and severe stages (all $p < 0.05$), especially in the severe stage. The decline in the proportion of SRF and HRF ≥20 was the most significant in the advanced stage after anti-VEGF treatment ($p < 0.001$, $p = 0.016$), but not in the early and severe stages (all $p > 0.05$). ***Conclusion:*** Systemic inflammatory indices and the decline in the proportion of SRF and HRF ≥20 were closely associated with different stages of DME based on "TCED." Meanwhile, the "TCED" grading system can predict visual and anatomical prognosis of DME after anti-VEGF treatment, which may be a biomarker for identifying risk stratification and management of DME.

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Introduction

Diabetes mellitus (DM) is a chronic disease that threatens human health. According to the latest epidemiological evidence, 4.63 million people had diabetes worldwide in 2019, which is expected to increase to 5.78 million by 2030 and to 7 million in 2045 [1]. Up to 40.3% of these patients presented with diabetic retinopathy (DR), including clinically significant diabetic macular edema (DME, 9.6%) and DME with visual impairment (2.75%) [2]. It has been reported that about 200,000 DME patients in China receive anti-vascular endothelial growth factor (VEGF) drugs as the first-line treatment every year, but a poor response is observed in 30–50% of cases [3–5]. Hence, it is essential to identify biomarkers that may predict and evaluate the efficacy of DME.

It has been established that VEGF and inflammation are involved in the pathogenesis of DME, and various mechanisms may lead to different responses to anti-VEGF treatment. Ample evidence suggests that the destruction of the blood-retinal barrier is the main reason for fluid accumulation in the retina, leading to retinal thickening and inflammatory changes [3, 6]. Inflammation, oxidative stress, and VEGF play a vital role in the pathophysiology of DME, but inflammation during the early or late stages has been largely understudied. Novel systemic inflammatory indices reflect body inflammation and immune cells' compensatory and procoagulant capabilities, which have been validated to be associated with multiple inflammatory diseases such as tumors, cardiovascular diseases, and DM and its complications [7–9]. There is a rich literature on the relationship between systemic inflammatory indices and DME [10–12]; however, the association with grade, stage, and severity of DME is yet to be further investigated.

DME assessment methods include ophthalmoscopy, fundus photography, fluorescein fundus angiography (FFA), and optical coherence tomography (OCT), among which OCT is the most sensitive method to identify retinal edema. DME can be divided into central or noninvolved fovea, angiogenic or non-angiogenic, and focal or diffuse edema [13–15]. However, the above classifications do not take into account DME morphology and clear edema area and hence have limited value to help design treatment plans. Growing evidence suggests differences in pathological mechanisms and responses to drugs in various microstructure changes on OCT [16, 17]. Importantly, based on the characteristics corresponding to different severity, treatment responses and visual prognosis of DME, the European Institute of Advanced Ophthalmology (ESASO) proposed a new DME classification based on the morphological features of OCT, including the central retinal thickness (CRT), the intraretinal cyst (IRC), the integrity of ellipsoid zone (EZ) and external limiting membrane (ELM) and the disorganization of the inner retinal layers (DRILs), established the "TCED" grading system, dividing the DME into early stage, advanced stage, severe stage, and atrophic stage [18]. OCT parameters, such as CRT, IRC, the integrity of EZ and ELM, and DRIL, have been substantiated as indicators of anti-VEGF or anti-inflammatory prognosis for DME [19–22]. To our knowledge, no study has hitherto applied the combination of the above four parameters to classify and evaluate the prognosis of DME.

In recent years, subretinal fluid (SRF) and hyperreflective foci (HRF) have aroused significant interest. In this respect, the presence of SRF and a large number of HRF are imaging biomarkers that can reflect the state of inflammatory activation in the retina. However, previous studies have mainly focused on evaluating baseline SRF and HRF, with little emphasis on their dynamic changes over time after treatment across different stages of DME. Herein, we explored the correlation between the "TCED" grading system and systemic inflammatory indices associated with DME, compared the visual and anatomical results, and evaluated HRF and SRF before and after treatment in different stages of DME.

Materials and Methods

Study Design

In this retrospective study, 111 patients with 111 eyes diagnosed with DME at the Ophthalmology Department of Zhujiang Hospital of Southern Medical University were recruited consecutively from January 2020 to August 2022. All patients were administered 0.05 mL of intravitreal anti-VEGF injections following a protocol of at least 3 monthly injections followed by pro re nata administration. This study was conducted following the Declaration of Helsinki and was approved by the Ethical Review Board of Zhujiang Hospital of Southern Medical University (ID:2022-KY-195). The need for written informed consent was waived by the Institutional Review Board due to the retrospective and anonymous nature of this study. The demographic data, ophthalmic examination results, and laboratory measurements were acquired from patients' records and hospital files.

Study Population

All patients underwent ophthalmic examinations at baseline and 1 month after the third injection, including the best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, color fundus photography, intraocular pressure (noncontact tonometer), OCT (Spectralis, Heidelberg, Germany) and FFA. The inclusion criteria were as follows: (1) patients were diagnosed with type 2 DM and DME following OCT and FFA; (2) patients were diagnosed with DME involving the fovea, which was defined as a retinal thickening

Table 1. SD-OCT grading system of DME

Characteristics	Grading	
T Central retinal thickness (CRT)	0	Less than 10% increase above upper normal values
	1	More than 10% but less than 30% increase above upper normal values
	2	More than 30% increase above upper normal values
C Intraretinal cysts (IRC)	0	Absent
	1	Mild
	2	Moderate
	3	Severe
E State of the ellipsoid zone (EZ) and the external limiting membrane (ELM)	0	Intact
	1	Disrupted
	2	Absent
D Disorganization of the inner retinal layers (DRIL)	0	Absent
	1	Present

in the central macular subregion (diameter 1 mm) in the OCT. The exclusion criteria were as follows: (1) patients with other diseases that can cause macular edema, such as retinal vein occlusion, age-related macular degeneration, polypoidal choroidal retinopathy, etc.; (2) patients with diseases that can affect visual function and fundus such as glaucoma, optic neuropathy, etc.; (3) patients who previously underwent laser photocoagulation, intravitreal injection of anti-VEGF drugs or steroid hormone, surgery on the vitreous and (or) retina, cataract surgery within 6 months; patients who underwent cataract surgery and retinal laser photocoagulation during the study period were not excluded; (4) patients with comorbidities (acute or chronic inflammation or infection, severe cardiovascular and cerebrovascular disease, autoimmune diseases, and malignancy) or given long-term steroid hormone and immunosuppressive medications; (5) patients with poor OCT imaging quality.

Biochemical and Hematologic Laboratory Indices

On the same day, after an overnight fast of 8 h, patients had a forearm venous puncture for blood extraction. Serum was separated prior to intravitreal anti-VEGF treatment. A Sysmex XE-2100 analyzer (Sysmex Corp., Kobe, Japan) measured full blood count, while biochemical analyses occurred on a Roche Cobas 8,000 system (Roche, Chicago, IL, USA) at ZhuJiang Hospital's Laboratory. Specifically, we analyzed lymphocytes, platelets (PLTs), monocytes, neutrophils, glycosylated hemoglobin (HbA1c), creatinine, cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Neutrophil-to-lymphocyte ratio (NLR), PLT-to-lymphocyte ratio (PLR), MLR, and systemic immune-inflammation index (SII) were calculated as ratios: neutrophils-to-lymphocytes, PLT-to-lymphocytes, monocytes-to-lymphocytes, and (neutrophils × PLT)-to-lymphocytes.

Analysis and Evaluation of OCT Parameters

OCT images were acquired using 6-mm vertical and horizontal scans centered on the fovea in high-resolution mode with spectral-domain OCT (SD-OCT, Heidelberg Spectralis OCT, Heidelberg Engineering, Germany). Horizontal images underwent qualitative and quantitative analysis using Image J version 1.53 (National Institutes of Health, USA). Recorded quantitative variables included: (1) CRT; (2) total number of HRF across retinal layers. Qualitative parameters were assessed for: (3) size of IRC; (4) integrity of ELM and EZ; (5) presence of DRIL; (6) presence of SRF. The same experienced ophthalmologist (Chen Yanxia) analyzed all OCT images twice and averages were used. And established the "TCED" grading system (Table 1), dividing the DME into early, advanced, severe, and atrophic stages (shown in Table 2, Fig. 1) [18]. We divided the HRF into two subgroups according to the number of HRF: HRF ≥20 and HRF <20 for analysis. The specific methods for quantifying OCT parameters are as follows:

CRT measured the distance from the internal limiting membrane to the outer border of the retinal pigment epithelium at the fovea.

HRF were distinct punctate foci with reflection intensity equal to or greater than the nerve fiber layer, distributed across retinal layers. HRF count was manual from inner limiting membrane to RPE.

IRC indicated oval low-reflection areas within the neurosensory layer. IRCs were qualitatively classified as absent, mild, moderate, or severe, with total area measured.

ELM and EZ integrity grading depended on the visibility and continuity of the outermost two reflective bands. Grades included recognizable integrity, disruption, and absence.

DRIL was characterized by indistinct boundaries between GCL-IPL complex, INL, and OPL. DRIL grading was categorized as absent or present.

SRF appeared as subretinal hypo-reflective spaces and was classified as absent or present.

Statistical Analysis

SPSS version 25.0 (IBM, New York, USA) and R version 4.0.3 (R, Vienna, Austria) were employed to conduct statistical analysis. To avoid the influence of binocular homogeneity and the overall systemic parameters on both eyes, data from the right eye were used for intergroup comparisons in patients with bilateral eye conditions. First, the BCVA is converted to the logarithm of the minimum resolution angle (logMAR). Continuous variables in the measurement data were expressed as mean ± SD, and differences between groups were analyzed using independent-sample *t* tests or

Table 2. SD-OCT staging of DME according to the different combinations of the four variables: thickening (T), cysts (C), EZ and ELM status (E), and DRIL (D)

Stage	T	C	E and/or D
Early DME (Fig. 1b)	T1	C1	E0 and D0
	T1	C2	E0 and D0
Advanced DME (Fig. 1c)	T1	C1	E1 and D0 or D1
	T1	C2	E1 and D0 or D1
	T2	C1	E0 and D0 or D1
	T2	C1	E1 and D0 or D1
	T2	C2	E0 and D0 or D1
	T2	C2	E1 and D0 or D1
	T2	C3	E0 and D0 or D1
	T2	C3	E1 and D0 or D1
Severe DME (Fig. 1d)	T1	C1	E2 and D0 or D1
	T1	C2	E2 and D0 or D1
	T2	C1	E2 and D0 or D1
	T2	C2	E2 and D0 or D1
	T2	C3	E2 and D0 or D1
Atrophic DME (Fig. 1e)	T0	C0	E2 and D0 or D1
	T0	C1	E2 and D0 or D1
	T0	C2	E2 and D0 or D1

F tests, and paired *t* tests were used for intra-group data before and after treatment. Non-normally distributed data were expressed as median, and differences between groups were examined by the Mann-Whitney U test or Kruskal-Wallis test, and Wilcoxon symbolic rank test was adopted for intra-group data before and after treatment. Categorical variables were described by percentages (%) and compared via χ^2 test or Fisher exact probability test. Wilcox test and Bonferroni correction method were used for further pairwise comparison between groups. *p* value of no more than 0.05 was interpreted to be statistically significant.

Results

Comparison of the Baseline Characteristics and Peripheral Blood Laboratory Indexes with Different Stages of DME

As shown in Table 3, according to the "TCED" classification system, the eyes were classified into early stage (n = 31), advanced stage (n = 38), severe stage (n = 35), and atrophic stage (n = 7). There were significant differences in HbA1c, C-reactive protein (CRP), NLR, PLR, MLR, and SII among the four groups. HbA1c in the early stage was higher compared to severe stage (p = 0.036). The CRP, NLR, PLR, MLR, and SII in the atrophic stage were significantly higher than in the advanced stage (p = 0.01, p = 0.013, p = 0.017, p = 0.040, p = 0.020, relatively); Conversely, the CRP, NLR, PLR, MLR, and SII in the advanced stage were significantly lower than in the early stage (p = 0.047, p = 0.02, p = 0.046, p = 0.022, p = 0.021, relatively). No significant difference in gender, age, duration of DM, history of hypertension and diabetic retinopathy grading, eGFR, Scr, TG, TC, HDL, and LDL among the four groups (p > 0.05).

Changes in BCVA (LogMAR) in Patients with Different Stages of DME after anti-VEGF Therapy

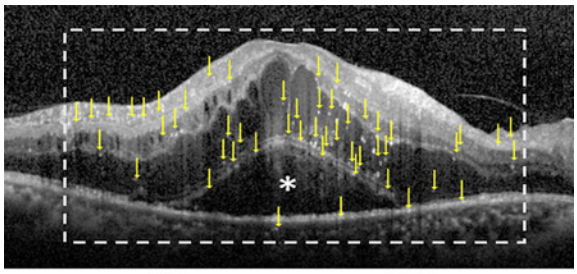
There were significant differences in BCVA (logMAR) at baseline and after treatment in different stages of DME (shown in Table 4, Fig. 2a). The baseline BCVA (logMAR) in the severe stage was significantly higher than in the early and advanced stages (p = 0.036, p = 0.004). The BCVA (logMAR) after treatment was significantly lower than before treatment in the early, advanced, and severe stages (p = 0.003, p = 0.01, p = 0.03, relatively), except for the atrophy stage (p = 0.293). Furthermore, there were considerable differences in the changes of BCVA (logMAR) before and after treatment among the four stages. In the post hoc test, there was a significant difference between the early stage and atrophic stage (p = 0.029).

Changes in CRT in Patients with Different Stages of DME after anti-VEGF Therapy

There were significant differences in CRT (um) at baseline and after treatment in different stages of DME (shown in Table 5, Fig. 2b). The baseline CRT was significantly lower in the early stage compared to the advanced and severe stages (p = 0.01, p = 0.002), and the baseline CRT in the atrophic stage was significantly lower than in the advanced and severe stages (p < 0.001, p = 0.001). The CRT during early, advanced, and severe stages after treatment was significantly lower than before treatment (p = 0.024, p = 0.001, p < 0.001, relatively), except for the atrophy stage (p = 0.578). Moreover, there were significant differences in the changes of CRT among the four stages. In the post hoc test, there was a significant difference between the severe stage and the early, advanced, and atrophic stages (p = 0.001, p = 0.008, p = 0.01, relatively).

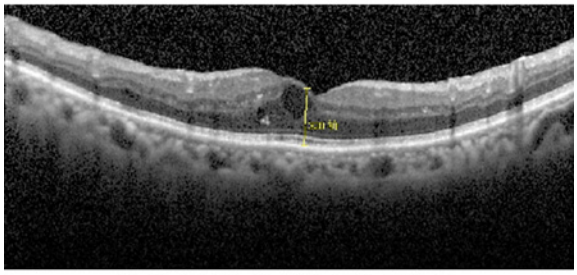
Changes in SRF and HRF in Patients with Different Stages of DME after anti-VEGF Therapy

The changes in SRF and HRF in patients with different stages of DME after anti-VEGF therapy are presented in Table 6 and Figure 3. SRF was observed in 30 (27.03%) eyes with DME, while 43 (38.74%) eyes had a large number of HRF (HRF ≥20). OCT-based grades of DME showed significant differences in the proportion of SRF and HRF ≥20 among the four groups at baseline and after anti-VEGF treatment, respectively (p < 0.05). The

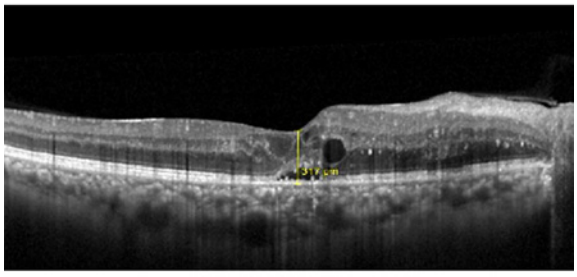


Yellow arrows represent HRF;

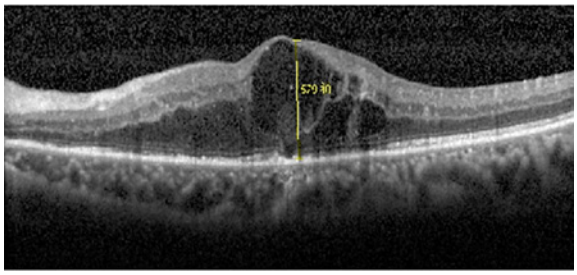
a White asterisk highlights SRF.



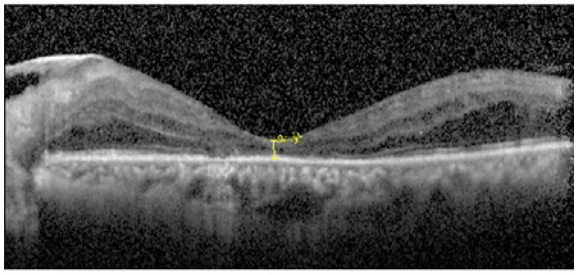
b Early DME: T=1;C=2;E=0;D=0.



c Advanced DME: T=1;C=2;E=1;D=1.



d Severe DME: T=2;C=3;E=2;D=1.



e Atrophic DME: T=0;C=1;E=2;D=0.

proportion of SRF and HRF ≥20 were higher in the advanced and severe stages at baseline, while the proportion of SRF in the atrophic stage was 0. We found that the proportion of SRF and HRF ≥20 decreased most significantly in the advanced stage after treatment ($p < 0.001$, $p = 0.016$), conversely, the proportion of HRF ≥20 was not significantly improved or even not improved in the early and severe stages.

Discussion

The heterogeneous manifestations of DME are very important in determining its severity and the choice of treatment. In the present study, systemic inflammatory indices were closely related to different stages of DME and may be used as prognostic indicators of visual and anatomical assessment after anti-VEGF treatment. Moreover, during the longitudinal analysis, inflammatory imaging biomarkers associated with different stages of DME changed over time, including the number of HRF in full-layer retinal and the state of SRF. These results reflected that DME is affected not only by local inflammation in the retina but also by systemic inflammation. Additionally, we observed that the DME staging was inconsistent with the DR grading; notwithstanding that some studies reported that the proportion of DME increased with the DR staging [23], so the relationship between DME and DR warrants further investigation. Taken together, our study further supports that systemic inflammation plays an important role in the occurrence and development of DME, suggesting that systemic inflammatory indices can indirectly indicate the severity of DME. Moreover, based on the OCT-based grading system, the combination of SRF and HRF represents a potential indicator for personalized DME therapy.

Systemic inflammatory indices are reported to be related to DR and DME. Kocbora et al. [24] documented an increase in serum CRP and TNF-α levels in patients with DME, suggesting that inflammation was involved in the pathogenesis of DME. Woo et al. [25] showed that the circulating neutrophil counts in DR patients were higher and related to the severity of DR, indicating that

Fig. 1. a Examples of OCT imaging biomarkers SRF and HRF. The number of HRF was evaluated over an area of 3,000 μm centered around the fovea. **d**, **e** Examples of OCT imaging biomarkers include T, C, E, and D with different stages of DME. SRF, subretinal fluid; HRF, hyperreflective foci; T, central retinal thickness; C, intraretinal cyst; E, external limiting membrane and ellipsoid zone; D, disorganization of retinal inner layers.

peripheral blood neutrophil-mediated inflammation played an important role in the pathogenesis of DR, no emphasis was placed on the presence of DME. There is no study has hitherto reported the relationship between inflammatory markers and different stages of DME [10, 26]. Our results revealed that the changes in systemic inflammatory indices including CRP, NLR, PLR, MLR, and SII, show a consistent trend among different stages of DME. These biomarkers were generally lower in the early stage and higher in the advanced stage compared to the atrophic stage, although the difference was not statistically significant in the severe stage. It may be attributed to the fact that hyperglycemia is one of the important risk factors for the occurrence and development of DR and DME [27], HbA1c increased significantly in the early group in our study, and hyperglycemia caused oxidative stress reactions. In turn, it leads to macular edema caused by increased systemic and ocular inflammatory levels. In addition, systemic inflammatory indices in severe and atrophic stages are higher than in the advanced stage, we make assumptions that this may be due to the fact that severe and atrophic stages are generally in the late stage of DME and the body is in a decompensated state, which resulted in the destruction of the retinal barrier. Indeed, it is highly conceivable that the inflammatory activation has already occurred in the early stage, and then the body is in a compensated state in the advanced stage and finally intensifies with the progression of the DME from severe to atrophic stages.

We found that anti-VEGF therapy was effective for early, advanced, and severe DME. Moreover, our results showed that the BCVA and CRT of these groups were much improved after treatment, except for the atrophy stage. In fact, the presence of DRIL and the destruction of EZ and (or) ELM in the atrophic stage may be linked to poor response. Additionally, macular ischemia and hypoxia bring about a series of microstructure linkage changes, such as severe IRC, higher CRT, and the destruction of retinal inner and outer structures, resulting in visual function damage. It should be noted that a more significant improvement in BCVA and CRT of DME was observed in the severe stage, consistent with previous reports that a worse BCVA and higher CRT at baseline can lead to better visual and anatomical improvement [28, 29]. This phenomenon may be explained by the "ceiling effect" that with poor baseline BCVA has more room for visual improvement and higher baseline CRT tends to be notably lower.

SRF indicates outer blood-retinal barrier disruption or retinal pigment epithelium (RPE) drainage dysfunction, and hydrops might be attributed to fluids leaked from the retina accumulated under the neurosensory retina layer via ELM or choroid capillary leakage [30]. It has been reported that SRF has a better response to VEGF [31, 32]. In this study, SRF partly regressed after treatment in early, advanced, and severe stages, and the proportion of regression in the early and advanced stages was higher, which suggests that this stage is sensitive to anti-VEGF treatment. It is widely thought that HRF is due to activated microglial cell migration, given that microglial cells are activated by inflammatory stimulation and migrate from the inner layer to the outer layer of the retina [33]. In the advanced stage, a more significant decrease in the proportion of HRF ≥20 was observed and the systemic inflammatory indices in the early, advanced, and atrophic stages were higher than in the advanced stage. Ye et al. [34] found that HRF of DME correlated with inflammatory blood markers, while Özata et al. [35] reported that NLR and SII levels were significantly higher in DME with SRF, which may indirectly reflect that the retinal microenvironment of the above three stages exhibited a highly inflammatory state.

More interestingly, a retrospective study found that poor visual function was associated with the incidence of recurrence of SRF and HRF throughout the follow-up period [36]. These results suggest that persistence and recurrence of SRF and HRF represent better indicators of visual prognosis than baseline SRF and HRF. Moreover, Ceravolo et al. [37] proposed that SRF and HRF represented a special inflammatory pattern, which may repeat over time, and is not conducive to long-term vision improvement. Therefore, the risk of recurrence of DME during the severe stage may be higher, and the significant correlation between SRF and HRF may be attributed to their inflammatory nature, while their combination may be a valuable indicator for the prediction and monitoring of anti-VEGF therapy in DME.

Although studies have proved that intraocular fluid examination can accurately evaluate the therapeutic effect of the disease, it is invasive by nature. Therefore, it is important to investigate noninvasive and cheap biomarkers such as OCT and systemic inflammatory indicators. Importantly, we focused on anti-VEGF therapies and evaluated the prognosis of different grades of DME by longitudinal analysis, which helps guide follow-up treatment. As mentioned above, in the advanced stage, the systemic inflammatory indices were lower, and the proportion of HRF and SRF regression was higher; thus, anti-VEGF treatment should be indicated as the first-line treatment for this stage. As for the early and severe stages, a combination of anti-inflammatory drugs may be required, or anti-inflammatory therapy should be set as the

Table 3. Comparison of the baseline characteristics and peripheral blood laboratory indexes with different stages of DME

Characteristics	Early DME (n = 31)	Advanced DME (n = 38)	Severe DME (n = 35)	Atrophic DME (n = 7)	p value
Gender, n (%)					0.887
Male	18 (58.06)	22 (57.89)	19 (54.29)	3 (42.86)	
Female	13 (41.94)	16 (42.11)	16 (45.71)	4 (57.14)	
Age, years, median (IQR)	59.06±11.74	60.34±9.65	61.37±8.59	61.71±13.11	0.809
Duration of DM, years, median (IQR)	10 (7, 13.5)	10.5 (7, 18)	11 (9.5, 20)	18 (11, 24)	0.264
Hypertension, n (%)					0.283
Yes	20 (64.52)	26 (68.42)	26 (74.29)	7 (100)	
No	11 (35.48)	12 (31.58)	9 (25.71)	0 (0)	
Diabetic retinopathy grading, n (%)					0.862
Mild or moderate NPDR	10 (32.26)	17 (44.74)	17 (48.57)	3 (42.86)	
Severe NPDR	17 (54.84)	18 (47.37)	15 (42.86)	4 (57.14)	
PDR	4 (12.9)	3 (7.89)	3 (8.57)	0 (0)	
Laboratory values, median (IQR)					
HbA1c, %	8.2 (7.15, 10.15)	7.55 (6.82, 9.4)	7.2 (6.5, 8.45)[a]	7.5 (6.55, 7.7)	**0.033**
Creatinine, μmol/mL	98 (69.5, 130.5)	90.15 (61.83, 140.75)	90.3 (66, 140)	121.49 (87.7, 164)	0.507
eGFR, mL/min	73.5 (41.85, 95.94)	72.35 (42.9, 88.6)	60.2 (39.75, 87.62)	46.82 (26.4, 59.8)	0.171
TC, mmol/L	4.75 (4.03, 5.85)	5.09 (4.1, 5.78)	4.97 (3.7, 5.73)	4.3 (4.03, 5.57)	0.929
TG, mmol/L	1.94 (1.44, 2.36)	1.43 (1.04, 2.11)	1.59 (1.17, 2.06)	1.54 (1.44, 2.93)	0.313
HDL, mmol/L	1.08 (0.96, 1.25)	1.06 (0.94, 1.27)	1.07 (0.86, 1.22)	1.04 (0.9, 1.12)	0.837
LDL, mmol/L	2.73 (2.37, 3.26)	2.91 (2.2, 3.67)	2.8 (2.15, 3.36)	2.51 (2.11, 3.94)	0.947
CRP, mg/L	1.52 (1.05, 4.81)	0.98 (0.78, 2.68)[a]	1.94 (0.97, 3.19)	3.87 (2.06, 6.24)[b]	**0.037**
NLR	2.7 (1.85, 5.13)	2.08 (1.57, 2.95)[a]	2.57 (1.75, 3.3)	4.02 (2.84, 7.53)[b]	**0.027**
MLR	0.33 (0.27, 1.73)	0.29 (0.22, 0.35)[a]	0.29 (0.23, 0.38)	0.51 (0.34, 2.3)[b]	**0.041**
PLR	150.47 (102.61, 354.72)	126.94 (98.66, 147.34)[a]	123.68 (105.7, 182.36)	211.04 (158.24, 480.54)[b]	**0.047**
SII	675.69 (457.52, 1511.16)	503.32 (333.8, 691.56)[a]	615.59 (384.63, 788.18)	1,608.51 (762.27, 1,900.18)[b]	**0.033**

DM, diabetes mellitus; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index. [a]$p < 0.05$ compared with early DME. [b]$p < 0.05$ compared with advanced DME.

Table 4. Changes in BCVA (LogMAR) in patients with different stages of DME after anti-VEGF therapy

Characteristics	Early DME (n = 31)	Advanced DME (n = 38)	Severe DME (n = 35)	Atrophic DME (n = 7)	p value
Baseline BCVA (logMAR)	0.52 (0.3, 0.7)	0.4 (0.3, 0.58)	1 (0.52, 1)[ab]	1 (0.4, 1.05)	**0.002**
BCVA after treatment (logMAR)	0.22 (0.12, 0.46)	0.3 (0.15, 0.65)	0.7 (0.4, 1)[ab]	1 (0.77, 1.11)[ac]	<**0.001**
Change of BCVA (logMAR)	−0.2 (−0.5, 0)	0 (−0.22, 0.14)	−0.22 (−0.4, 0)	0.3 (−0.2, 0.65)[a]	**0.044**
p value	**0.003**	**0.01**	**0.03**	0.293	–

BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution. [a]$p < 0.05$ compared with early DME. [b]$p < 0.05$ compared with advanced DME. [c]$p < 0.05$ compared with severe DME.

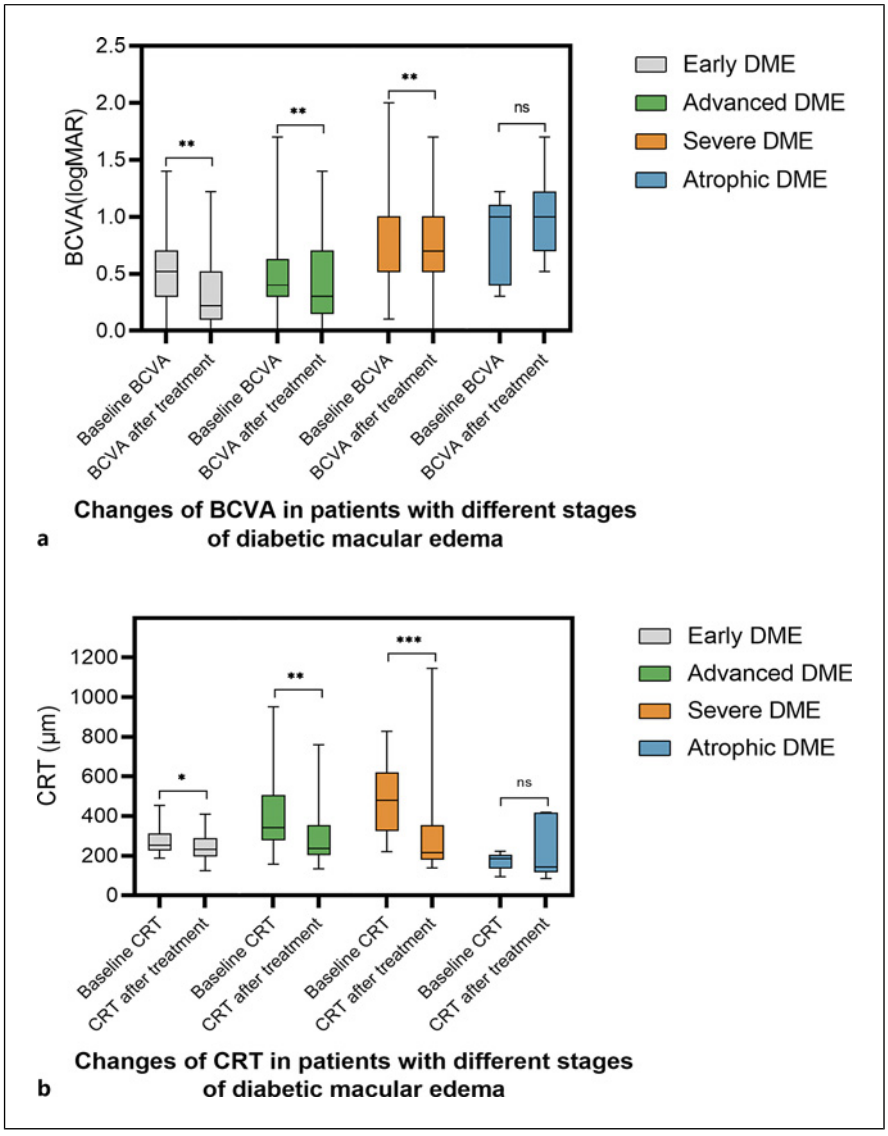


Fig. 2. a Changes of BCVA (LogMRA) in patients with different stages of diabetic macular edema; **b** Changes of CRT in patients with different stages of diabetic macular edema. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, and ns versus baseline BCVA (LogMRA) or baseline CRT.

Table 5. Changes in CRT in patients with different stages of DME after anti-VEGF therapy

Characteristics	Early DME ($n = 31$)	Advanced DME ($n = 38$)	Severe DME ($n = 35$)	Atrophic DME ($n = 7$)	p value
Baseline CRT, μm	254 (229, 303.5)	342 (285.75, 500.25)[a]	480 (337, 605)[a]	185 (158, 194.5)[bc]	<**0.001**
CRT after treatment, μm	222 (184.5, 273)	237 (206.25, 351.5)	215 (183.5, 341.5)	144 (130.5, 352.76)	**0.287**
Change of CRT, μm	−26 (−81, 22)	−84 (−223.5, 5.5)	−152 (−364.5, −78)[ab]	−25 (−172, 60.5)[c]	<**0.001**
p value	**0.025**	**0.001**	<**0.001**	0.578	–

CRT, central retinal thickness. [a]$p < 0.05$ compared with early DME. [b]$p < 0.05$ compared with advanced DME. [c]$p < 0.05$ compared with severe DME.

Table 6. Changes in SRF and HRF in patients with different stages of DME after anti-VEGF therapy

Characteristics	Early DME (n = 31)	Advanced DME (n = 38)	Severe DME (n = 35)	Atrophic DME (n = 7)	p value
SRF at baseline, n (%)					**<0.001**
Present	1 (3.23)	16 (42.11)	13 (37.14)	0 (0)	
Absent	30 (96.77)	22 (57.89)	22 (62.86)	7 (100)	
SRF after treatment, n (%)					**0.041**
Present	1 (3.23)	2 (5.26)	7 (20)	0 (0)	
Absent	30 (96.77)	36 (94.74)	28 (80)	7 (100)	
p value	1.0	**<0.001**	0.114	1.0	
HRF at baseline, n (%)					**0.025**
≥20	5 (16.13)	18 (47.37)	17 (48.57)	3 (42.86)	
<20	26 (83.87)	20 (52.63)	18 (51.43)	4 (57.14)	
HRF after treatment, n (%)					**0.017**
≥20	5 (16.13)	8 (21.05)	17 (48.57)	2 (28.57)	
<20	26 (83.87)	30 (78.95)	18 (51.43)	5 (71.43)	
p value	1.0	**0.016**	1.0	1.0	

SRF, subretinal fluid; HRF, hyperreflective retinal foci.

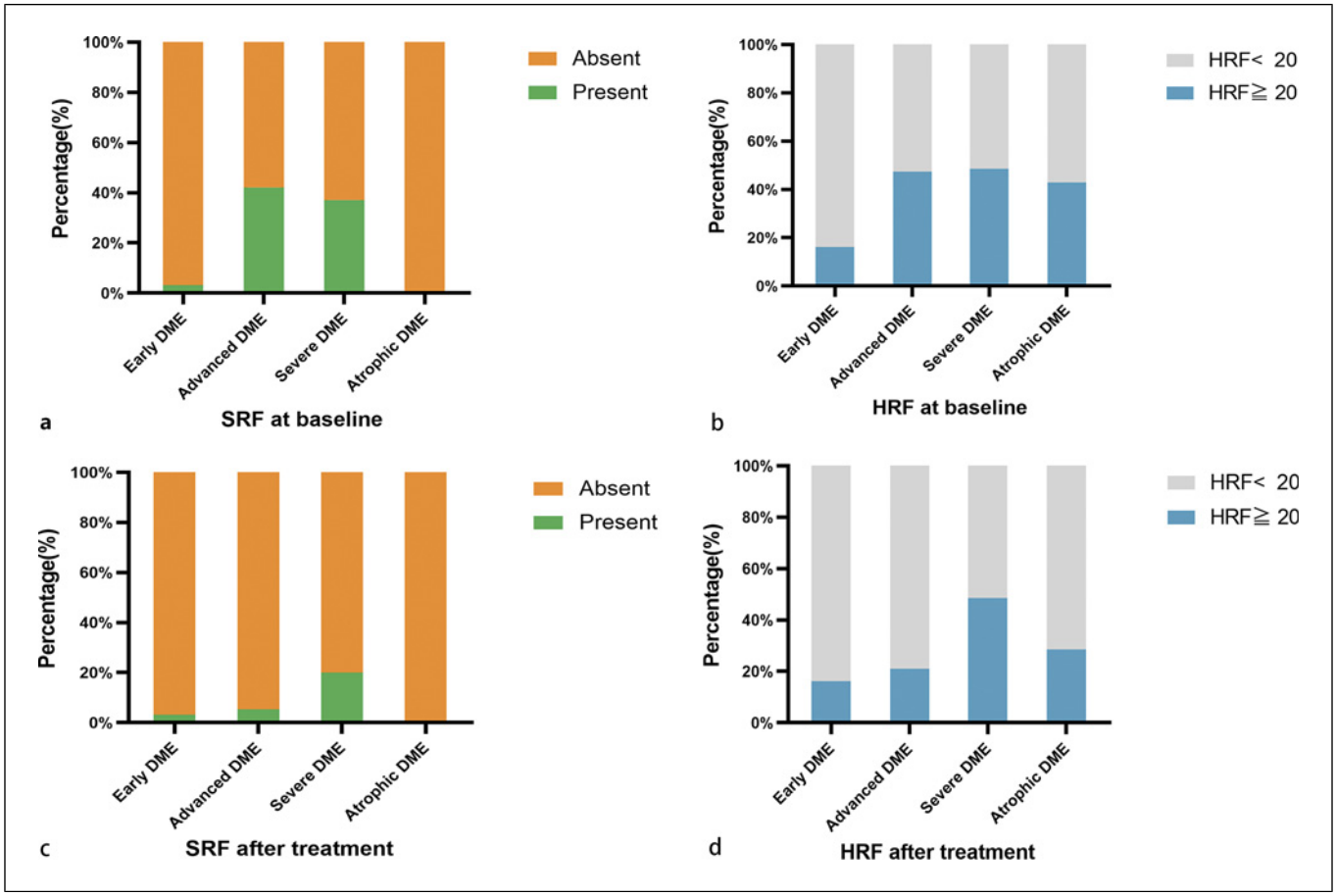


Fig. 3. a, **c** Percentage of presence or absence of SRF before and after anti-VEGF treatment with different stages of DME. **b**, **d** Percentage of the number of HRF ≥20 or <20 before and after anti-VEGF treatment with different stages of DME.

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first-line choice, which is consistent with dexamethasone implants being the first-line drug for DME [38]. To sum up, the "TCED" grading system can assist in the initial treatment selection of DME patients and help improve their compliance.

However, several limitations and shortcomings were present in this study. Indeed, this is a single-center, retrospective study and without the DR (no DME) control group. Moreover, three anti-VEGF drugs were analyzed in this study (Ranibizumab/Aflibercept/Conbercept), although their main target is VEGF-A, the latter two can also target VEFG-B and placental growth factor (PGF), which may lead to different therapeutic responses. Besides, OCT parameters were acquired manually; artificial intelligence is required to extract and analyze the images. Therefore, the significance of this study in clinical application is worthy of further exploration and validation in large sample-size studies.

Conclusion

In summary, systemic inflammatory indices were closely associated with different stages of DME based on "TCED," emphasizing the important role of systemic inflammation in the pathogenesis of DME. The "TCED" system grading is sensitive indicator for predicting the prognosis of DME post-anti-VEGF treatment. Meanwhile, it can reflect the decline in the proportion of SRF and HRF ≥20, which may be a biomarker for identifying risk stratification and management of DME patients.

Statement of Ethics

This study was performed in accordance with the tenets of the Declaration of Helsinki and approved by the Local Research Ethics Committee of Zhujiang Hospital of Southern Medical University (2022-KY-195). The need for written informed consent was waived by the Institutional Review Board due to the retrospective and anonymous nature of this study.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

C.Y.X. designed the study and collected the dataset. K.X.Y. and F.M. conceived the study, critically reviewed the intellectual content of the manuscript, and made substantive revisions to the important contents of the manuscript. C.Y.X. and Y.X.Y. were the major contributors to the analysis and the writing of the manuscript. All authors contributed to the article and approved the submitted version.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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