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ORIGINAL RESEARCH

Analysis of OCT-Based Biomarkers and Recurrence in Eyes with Diabetic Macular Edema Following Anti-VEGF Therapy

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Objective: To identify pre-treatment optical coherence tomography (OCT) biomarkers predictive of recurrence in eyes with diabetic macular edema (DME) after anti-VEGF therapy.

Methods: This retrospective cohort study included 122 eyes with DME treated with anti-VEGF monotherapy (ranibizumab; Novartis Pharma Schweiz AG, Basel, Switzerland) at Pinghu First People's Hospital (January 2020 – December 2023). The treatment protocol consisted of 3 monthly loading doses followed by a pro re nata (PRN) regimen. Patients were stratified into recurrence (n=54) and non-recurrence (n=68) groups based on predefined criteria during 12 months of follow-up. Baseline OCT parameters were compared, and multivariate logistic regression was used to identify independent predictors. A combined model's predictive performance was assessed using receiver operating characteristic (ROC) curve analysis.

Results: The recurrence group had significantly higher baseline central retinal thickness (452.7±84.3 vs 391.5±70.2 μm, P=0.002), subretinal fluid (SRF) prevalence (63.0% vs 36.8%, P=0.008), proportion with ≥5 hyperreflective foci (HRF) (68.5% vs 35.3%, P<0.001), and ellipsoid zone (EZ) disruption rate (57.4% vs 30.9%, P=0.006), and required more injections (6.4±1.3 vs 4.8±1.2, P<0.001). Multivariate analysis confirmed HRF ≥5 (OR=3.52, P<0.001), SRF presence (OR=2.89, P=0.007), and EZ disruption (OR=2.41, P=0.023) as independent risk factors. Their combined model predicted recurrence with an AUC of 0.841.

Conclusion: HRF, SRF, and EZ integrity are key OCT biomarkers for DME recurrence. A combined model aids risk stratification for personalized management.

Keywords: diabetic macular edema, anti-VEGF therapy, optical coherence tomography, biomarker, recurrence, prediction

Introduction

Anti-vascular endothelial growth factor (VEGF) therapy has become the first-line treatment for diabetic macular edema (DME), demonstrating significant efficacy in reducing macular edema and improving visual acuity in the majority of treated eyes.[1] However, a substantial clinical challenge persists, as a considerable proportion of eyes experience recurrence or exhibit persistent edema following initial treatment, necessitating repeated injections to maintain therapeutic outcomes.[2] This variability in treatment response underscores the need for reliable predictive biomarkers to identify eyes at higher risk of recurrence and guide personalized management strategies.

Optical coherence tomography (OCT) provides high-resolution, non-invasive visualization of retinal microstructure and is integral to the management of DME.[3] Beyond central retinal thickness (CRT), various OCT-derived biomarkers—such as the presence of subretinal fluid (SRF), hyperreflective foci (HRF), cystoid macular edema (CME) morphology, and the integrity of the ellipsoid zone (EZ) and external limiting membrane (ELM)—have been investigated for their potential associations with treatment response and visual prognosis.[4,5] While these parameters offer insights into the underlying pathophysiological states, systematic analyses integrating multiple OCT biomarkers specifically to predict the risk of DME recurrence after anti-VEGF therapy remain limited.[6] Many existing studies focus on short-term anatomical

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or visual outcomes, with fewer employing multivariate models to evaluate the combined predictive value of pre-treatment OCT features for recurrence.[7,8]

The novelty of this study lies in its specific focus on identifying pre-treatment OCT biomarkers associated with recurrence in eyes with DME undergoing anti-VEGF monotherapy, utilizing a multivariate statistical approach to construct a predictive model. This research aims to bridge the gap between qualitative OCT observations and quantitative, clinically applicable risk assessment by systematically analyzing baseline structural characteristics and their correlation with recurrence during follow-up. We seek to identify independent OCT-based risk factors and evaluate their combined utility in predicting recurrence risk. The findings are expected to provide a practical, imaging-based tool to assist clinicians in stratifying recurrence risk, optimizing treatment intervals, and tailoring follow-up strategies, ultimately aiming to improve long-term visual outcomes for eyes with DME.

Materials and Methods

Study Design and Subjects

This single-center, retrospective cohort study investigated the association between pre-treatment OCT biomarkers and recurrence in eyes with DME undergoing anti-VEGF monotherapy. Patients were enrolled from the electronic medical record database of the Department of Ophthalmology at Pinghu First People's Hospital (Pinghu, China) between January 2020 and December 2023. Initially, 157 patients (157 eyes) with DME treated with intravitreal anti-VEGF were screened, of which 122 patients (122 eyes) met the inclusion criteria and completed follow-up. For patients with bilateral DME, only one eye per patient was randomly selected for inclusion to ensure statistical independence.

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) Age ≥ 18 years; (2) Diagnosis of DME confirmed by the presence of retinal thickening with or without cystoid spaces on OCT, supported by detectable leakage on fundus fluorescein angiography (FFA); (3) Treatment with a single anti-VEGF agent (ranibizumab) without concomitant corticosteroids, laser, or other therapies; (4) No intraocular injections or surgery within 3 months prior to baseline; (5) Ability to comply with follow-up, with complete and high-quality imaging data; (6) Central retinal thickness (CRT) ≥ 300 μm. The CRT threshold was selected to include eyes with definite edema requiring intervention, as per common clinical trial criteria. Exclusion criteria were: (1) Coexisting ocular pathologies affecting macular structure/function (eg, neovascular glaucoma, age-related macular degeneration, retinal vein occlusion, uveitis); (2) History of vitrectomy or laser photocoagulation; (3) OCT image signal strength ≤ 6 or poor quality precluding accurate assessment; (4) Unstable systemic conditions (eg, acute diabetic ketoacidosis, recent major cardiovascular event); (5) Pregnancy or lactation; (6) Severe hepatic/renal dysfunction or malignancy.

The study adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of Pinghu First People's Hospital ((Approval No.: Pinghu First People's Hospital Ethics Committee Research 2023 No. 012). Informed consent was obtained from all participants.

Sample Size Calculation

A priori sample size calculation was performed using G*Power software (version 3.1). Based on preliminary data, we assumed a recurrence rate of approximately 40%. To detect an odds ratio of 2.5 for a key OCT biomarker (eg, EZ disruption) with 80% power ($\alpha = 0.05$, two-sided) using logistic regression, a minimum sample size of 110 eyes was required. Our final sample of 122 eyes meets this requirement.

Treatment Protocol and Follow-up

Anti-VEGF Treatment Protocol

All patients received intravitreal ranibizumab (0.5 mg/0.05 mL; Novartis Pharma Schweiz AG, Basel, Switzerland; Approval No.: S20110085). The loading phase consisted of 3 monthly injections, followed by a pro re nata (PRN) regimen based on OCT and visual acuity criteria. All injections were administered by a single experienced retinal specialist to ensure consistency.

Follow-up and Recurrence Criteria

Follow-up visits were scheduled at baseline, 1, 3, 6, 9, and 12 months. Each visit included best-corrected visual acuity (BCVA) measurement, slit-lamp biomicroscopy, and OCT. Recurrence was defined as meeting any of the following: (1) Increase in CRT > 50 μm from the lowest previous value; (2) New or worsened cystoid macular edema (CME) or subretinal fluid (SRF); (3) Decrease in BCVA of ≥5 ETDRS letters.

OCT Examination and Parameter Assessment

All scans were acquired using the Spectralis SD-OCT system (Vision Micro Image (Henan) Technology Co., Ltd.) with a high-resolution macular cube protocol (20°×20°, 25 horizontal B-scans). Image analysis was independently performed by two ophthalmologists with 8 and 12 years of clinical experience in retina, respectively. Discrepancies were resolved by a third senior specialist. The following parameters were assessed: CRT: Automated measurement of the central 1 mm subfield thickness (μm). SRF: Presence of hyporeflective fluid between the retinal pigment epithelium and photoreceptor layer. CME: Presence of hyporeflective intraretinal cystoid spaces. Hyperreflective Foci (HRF): Discrete hyperreflective dots (>30 μm diameter) within the retinal layers. HRFs were manually counted on the central B-scan by the two independent graders, and the average count was used for analysis. EZ and ELM Integrity: Disruption of the ellipsoid zone or external limiting membrane bands was graded as present (discontinuous/irregular) or absent (continuous). Vitreomacular Interface (VMI): Presence of epiretinal membrane, vitreomacular traction, or macular hole.

Data Collection and Statistical Analysis

Data were collected using standardized forms. Systemic parameters, including HbA1c levels, duration of diabetes, and hypertension status, were recorded and included in the multivariate analysis. Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA). Normality was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation and compared using the independent samples *t*-test; categorical variables are presented as numbers (percentages) and compared using the Chi-square test. Variables with $p < 0.05$ in univariate analyses were entered into a multivariate binary logistic regression model (forward stepwise method) to identify independent predictors of recurrence, reported as odds ratios (OR) with 95% confidence intervals (CI). The predictive performance of significant OCT parameters was evaluated using receiver operating characteristic (ROC) curve analysis, calculating the area under the curve (AUC). A two-sided p-value < 0.05 was considered statistically significant.

Results

Comparison of Baseline Characteristics

A total of 122 eyes from 122 patients with DME were included in the final analysis. Based on the follow-up criteria, 54 eyes (44.3%) were categorized into the recurrence group and 68 eyes (55.7%) into the non-recurrence group. All patients completed the 12-month follow-up period without any reports of serious adverse events or treatment discontinuation. The comparison of demographic and clinical characteristics between the two groups is summarized in Table 1. There were no statistically significant differences in sex, age, duration of diabetes, glycated hemoglobin (HbA1c) level, history of hypertension, or baseline best-corrected visual acuity (BCVA) (all $P > 0.05$), indicating that the groups were well-matched at baseline.

Univariate Analysis of OCT Biomarkers

The comparison of pre-treatment OCT parameters between the recurrence and non-recurrence groups is presented in Table 2. At baseline, eyes that later experienced recurrence had a significantly greater central retinal thickness (CRT) (452.7 ± 84.3 μm vs 391.5 ± 70.2 μm, $P < 0.001$), a higher prevalence of subretinal fluid (SRF) (63.0% vs 36.8%, $P = 0.004$), and a higher proportion with an elevated number of hyperreflective foci (HRF) (68.5% vs 35.3%, $P < 0.001$). Furthermore, disruptions of the ellipsoid zone (EZ) (57.4% vs 30.9%, $P = 0.003$) and the external limiting membrane (ELM) (50.0% vs 29.4%, $P = 0.020$) were significantly more common in the recurrence group. No significant differences were observed in the prevalence of cystoid macular edema (CME) or vitreomacular interface abnormalities (VMA) between the two groups ($P > 0.05$).

Table 1 Comparison of Clinical Characteristics Between the Two Groups

Clinical Data	Recurrence Group (n=54)	Non-recurrence Group (n=68)	t/x^2	*P*
Sex	–	–	0.065	0.798
Male	33 (61.1%)	40 (58.8%)	–	–
Female	21 (38.9%)	28 (41.2%)	–	–
Age (years)	59.2±8.6	58.5±9.1	0.432	0.666
DM duration (years)	12.3±4.5	11.9±4.1	0.512	0.609
HbA1c (%)	8.15±1.23	7.96±1.17	0.870	0.385
Hypertension history	–	–	0.242	0.622
Yes	31 (57.4%)	36 (52.9%)	–	–
No	23 (42.6%)	32 (47.1%)	–	–
Baseline BCVA (ETDRS)	61.7±9.2	63.1±8.8	0.855	0.394

Table 2 Comparison of Baseline OCT Structural Parameters Between the Two Groups

OCT Parameter	Recurrence Group (n=54)	Non-recurrence Group (n=68)	t/x^2	*P*
CRT (μm)	452.7±84.3	391.5±70.2	4.374	<0.001
SRF presence, n (%)	34 (63.0%)	25 (36.8%)	8.272	0.004
HRF count ≥5, n (%)	37 (68.5%)	24 (35.3%)	13.289	<0.001
EZ disruption, n (%)	31 (57.4%)	21 (30.9%)	8.659	0.003
ELM disruption, n (%)	27 (50.0%)	20 (29.4%)	5.386	0.020
CME presence, n (%)	41 (75.9%)	46 (67.6%)	1.008	0.315
VMA presence, n (%)	13 (24.1%)	14 (20.6%)	0.212	0.645

Analysis of Injection Frequency and Recurrence Time

The treatment burden, measured by the number of anti-VEGF injections over the 12-month period, was significantly higher in the recurrence group (6.4 ± 1.3 injections) compared to the non-recurrence group (4.8 ± 1.2 injections, P < 0.001, Figure 1). Among the 54 eyes that experienced recurrence, the median time to the first recurrence event was 4.2 months (interquartile range [IQR]: 3.1–6.5 months).

Multivariate Logistic Regression Analysis

To identify independent predictors of DME recurrence, variables that showed significant differences in the univariate analysis (CRT, SRF, HRF count ≥5, EZ disruption, ELM disruption) were included in a multivariate binary logistic

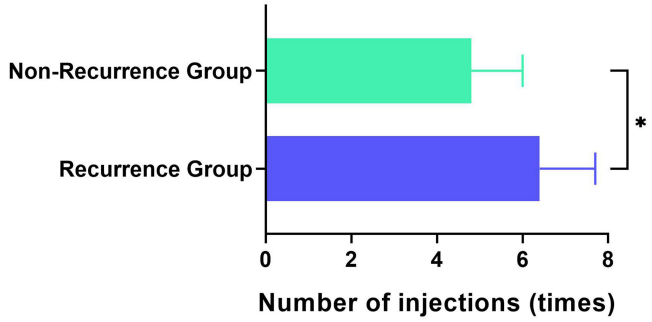

Figure 1 Comparison of the number of anti-VEGF injections between the recurrence and non-recurrence groups. P < 0.001.
Note: *P < 0.05 for intergroup comparison.

Table 3 Multivariate Logistic Regression Analysis of Factors Associated with DME Recurrence

Factor	*β*	*SE*	*Wald*	*P*	*OR*	*95% CI*
HRF count ≥5	1.26	0.35	12.89	<0.001	3.52	1.67–7.44
SRF presence	1.06	0.39	7.51	0.007	2.89	1.34–6.21
EZ disruption	0.88	0.39	5.15	0.023	2.41	1.13–5.13
Intact ELM structure	–0.76	0.38	3.95	0.047	0.47	0.22–0.99
CRT (per μm)	0.01	0.01	2.98	0.084	1.01	0.99–1.02

regression model. The model was adjusted for potential confounders, including age, diabetes duration, and baseline HbA1c level. The results demonstrated that an elevated HRF count (≥5) was the strongest independent risk factor for recurrence (Odds Ratio [OR] = 3.52, 95% Confidence Interval [CI]: 1.67–7.44, P < 0.001). The presence of SRF (OR = 2.89, 95% CI: 1.34–6.21, P = 0.007) and disruption of the EZ band (OR = 2.41, 95% CI: 1.13–5.13, P = 0.023) were also significant independent predictors. In contrast, an intact ELM structure was associated with a lower risk of recurrence (OR = 0.47, 95% CI: 0.22–0.99, P = 0.047). CRT, which was significant in the univariate analysis, did not retain independent predictive value in the multivariate model (P = 0.084). The results of the multivariate analysis are detailed in Table 3.

ROC Curve Analysis and Predictive Performance Evaluation

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of the significant OCT biomarkers (Figure 2). The presence of an elevated HRF count yielded the highest individual area under the curve (AUC) of 0.771. The presence of SRF and EZ disruption showed AUCs of 0.709 and 0.684, respectively. A combined predictive model incorporating these three independent predictors (HRF + SRF + EZ status) demonstrated superior predictive ability, with an AUC of 0.841 (95% CI: 0.767–0.914), a sensitivity of 82.6%, a specificity of 76.5%, and a Youden's index of 0.591. The detailed results of the ROC analysis are presented in Table 4.

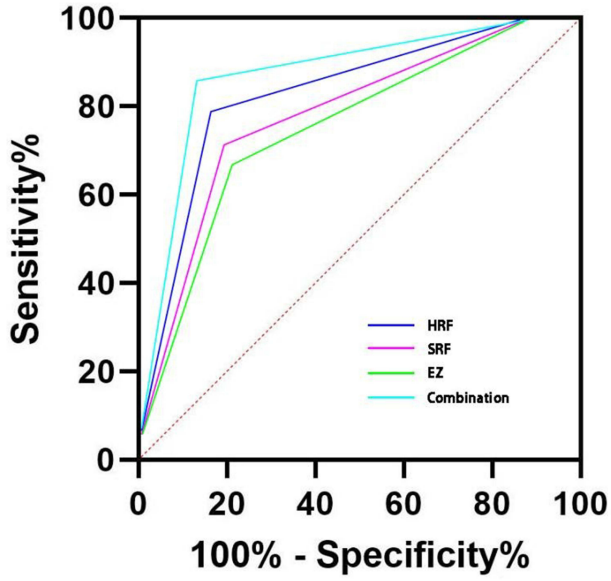

Figure 2 Receiver operating characteristic (ROC) curves of individual OCT biomarkers and the combined model for predicting DME recurrence.

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Table 4 Predictive Performance of OCT Biomarkers for DME Recurrence

Indicator	AUC	95% CI	Sensitivity (%)	Specificity (%)	Youden Index
HRF count ≥5	0.771	0.684–0.859	74.1	69.1	0.431
SRF presence	0.709	0.617–0.801	63.0	71.4	0.344
EZ disruption	0.684	0.588–0.780	57.4	69.1	0.265
Combined (HRF+SRF+EZ)	0.841	0.767–0.914	82.6	76.5	0.591

Discussion

As a retrospective investigation, this study sought to explore the potential of pre-treatment optical coherence tomography (OCT) biomarkers for preliminarily establishing a multi-parameter model to predict diabetic macular edema (DME) recurrence following anti-VEGF therapy. We identified that a high number of hyperreflective foci (HRF), the presence of subretinal fluid (SRF), and disruption of the ellipsoid zone (EZ) band were independent risk factors for recurrence, while an intact external limiting membrane (ELM) appeared protective. The combined predictive model incorporating these three core indicators demonstrated superior diagnostic efficacy, suggesting the potential clinical value of a multi-feature imaging approach for risk stratification and providing a basis for future validation.

Our findings align with and extend previous research on these biomarkers. HRF, recognized as indicators of intraretinal inflammatory activity, have been consistently linked to DME severity and treatment response. For instance, Viggiano et al[9] demonstrated that baseline HRF burden and ellipsoid zone integrity were among key OCT features predicting long-term outcomes in eyes with resolved DME treated with anti-VEGF therapy. Frizziero et al[10] in a systematic review similarly showed that high HRF counts correlate with worse anatomical and functional outcomes, and are reduced with effective therapy.Xu et al[11] additionally reported that greater disruption of the external limiting membrane (ELM) is associated with higher baseline HRF and worse prognosis. Our results confirm that a baseline HRF count ≥5 signifies a persistently pro-inflammatory microenvironment, likely contributing to incomplete response and recurrence despite anti-VEGF treatment.

The association between SRF and recurrence highlights the role of retinal pigment epithelium (RPE) dysfunction and profound blood-retinal barrier breakdown.[12,13] Zhou et al[14] found that the presence of SRF and disrupted ELM at baseline predicted refractory response in DME cases. This is consistent with our data, where SRF-positive eyes had a nearly threefold higher recurrence risk. Persistent SRF can impair photoreceptor-RPE interaction, leading to suboptimal visual outcomes.

Disruption of the EZ band, a key marker of photoreceptor integrity, was another significant predictor.[15,16] Suzuki et al[17] established that EZ disruption correlates with poor visual prognosis, and our study further indicates its value in predicting recurrence, consistent with findings from the narrative review by Sen et al,[18] which highlighted photoreceptor integrity (including EZ) among major OCT biomarkers associated with DME treatment response. This damage often coexists with other pathological features, such as HRF, reflecting a more advanced disease state.

Notably, central retinal thickness (CRT) did not retain independent predictive value in our multivariate model. While CRT remains a standard measure of edema, its variability and inability to distinguish the underlying pathophysiological drivers such as inflammation versus traction reduce its predictive utility. This limitation has also been discussed in recent literature (eg, Chondrozoumakis et al)[19] which argues for moving beyond thickness-based assessments toward more nuanced evaluation of specific microstructural changes (eg HRF, EZ, ELM).

The protective role of an intact ELM structure aligns with its function in maintaining retinal homeostasis. Pinto et al[20] suggested that ELM integrity is crucial for Müller cell support and photoreceptor survival. Its preservation might thus contribute to a more resilient retinal structure, less susceptible to recurrent fluid accumulation.Several limitations of our study must be acknowledged. The retrospective, single-center design from a Chinese population may introduce selection bias and limits the generalizability of our findings to other ethnicities. Furthermore, the use of a single anti-VEGF agent (ranibizumab) means the results may not be directly extrapolated to other anti-VEGF drugs or treatment regimens involving combination therapy. The manual quantification of OCT biomarkers, despite independent assessment by experienced graders, carries inherent subjectivity; future studies should employ automated or semi-automated algorithms for quantification of HRF and

other features to improve objectivity and reproducibility, as demonstrated by Okuwobi et al[21] in automated HRF quantification. We also did not incorporate systemic parameters like glycemic fluctuation or serum inflammatory markers, which could enhance predictive accuracy.

Conclusion

This study demonstrates that key pre-treatment OCT biomarkers, including hyperreflective foci (HRF), subretinal fluid (SRF), and ellipsoid zone (EZ) integrity, are independently associated with the recurrence of diabetic macular edema (DME) after anti-VEGF therapy. The integration of these parameters into a multi-feature model offers a valuable imaging-based tool for identifying high-risk eyes, facilitating personalized treatment and monitoring schedules. These findings underscore that DME recurrence involves multifaceted pathophysiology beyond mere edema, encompassing inflammation and photoreceptor damage. Future efforts should focus on validating this model in prospective cohorts and enriching it with automated analysis and clinical biomarkers to enhance predictive power.

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Disclosure

The authors report no conflicts of interest in this work.

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