



Comparison of Optical Coherence Tomography Biomarkers in Nonproliferative and Proliferative Diabetic Retinopathy: Marmasia Study Group Report No. 2

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Abstract

Objectives: To compare structural optical coherence tomography (OCT) biomarkers and visual acuity between eyes with nonproliferative (NPDR) and proliferative diabetic retinopathy (PDR) in real-life clinical settings.

Materials and Methods: This retrospective, cross-sectional, multicentre study included 818 eyes of 534 patients with treatment-naïve diabetic macular oedema (DMO) from nine tertiary clinics. Evaluated parameters included central macular thickness (CMT), DMO morphology, disorganisation of the retinal inner layers, ellipsoid zone (EZ) integrity, vitreoretinal interface abnormality (VRIA), and posterior hyaloid status. Analyses used eye-level data with patient-clustered robust standard errors and study-centre fixed effects. A joint multivariable logistic model mutually adjusted EZ integrity, posterior hyaloid status and VRIA together with clinical covariates, with Holm correction across six structural-domain tests.

Results: Of the 818 eyes, 646 had NPDR and 172 PDR. Mean best-corrected visual acuity (BCVA) was worse in PDR (0.74 ± 0.54 versus 0.57 ± 0.42 logarithm of the minimum angle of resolution; $p < 0.001$). In univariable clustered comparisons, no biomarker survived false

Abstract

discovery rate correction across ten comparisons (lowest $q=0.095$, VRIA). In the joint model (636 eyes, 431 clusters), none survived Holm correction: posterior hyaloid detachment was nominally associated with PDR (odds ratio [OR] 2.03, 95% confidence interval [CI] 1.05-3.92; Holm $p=0.208$), the global EZ term was not significant ($p=0.221$), and VRIA was not significant after adjustment for posterior hyaloid status (OR 1.36, 95% CI 0.67-2.75; $p=0.388$). Centre-adjusted CMT did not differ ($p=0.890$). Secondly, PDR, disrupted EZ, higher CMT and VRIA were each associated with worse BCVA.

Conclusion: In treatment-naïve DMO, no structural OCT biomarker was independently associated with proliferative disease after accounting for fellow-eye correlation, centre effects, mutual adjustment, and multiplicity. Posterior hyaloid detachment gave the most consistent nominal signal, and the vitreoretinal interface variables carried overlapping rather than independent information. These findings do not establish prognosis.

Keywords: Diabetic retinopathy, diabetic macular oedema, ellipsoid zone, OCT biomarkers, vitreoretinal interface

Introduction

Diabetes mellitus affects about 460 million people worldwide, and diabetic retinopathy (DR) is its most common microvascular complication.¹ DR is classified as either nonproliferative (NPDR) or proliferative (PDR). PDR is characterised by new blood vessel growth caused by severe retinal ischaemia.² Vision loss in DR most frequently results from diabetic maculopathy, including diabetic macular oedema (DMO) and ischaemic maculopathy, as well as PDR-related complications such as vitreous haemorrhage and tractional retinal detachment.³ DMO can develop at any stage of DR, with the risk increasing as disease duration and severity increase.^{3,4}

The main imaging methods for DR are colour fundus photography, fundus fluorescein angiography (FFA), and optical coherence tomography (OCT). FFA shows leakage and blood flow, while OCT provides detailed cross-sectional images and retinal thickness measurements, which are important for making treatment decisions and monitoring progress.⁵

Studies of macular oedema structural features have shown links between DR stage and vision impairment.^{6,7,8} This has led to different DMO classification systems incorporating features such as diffuse retinal thickening, cystoid macular oedema, subretinal fluid (SRF), and disorganisation of the retinal inner layers (DRIL).^{6,9,10,11} Advances in technology have also improved our understanding of vitreoretinal interface disorders and the importance of the ellipsoid zone (EZ) and external limiting membrane (ELM) for prognosis.¹² In this study, we compared structural OCT biomarkers between NPDR and PDR eyes with untreated DMO in a large multicentre group, using methods that consider correlations between eyes, differences between centres, and adjustments for multiple biomarkers and comparisons.

Materials and Methods

This retrospective, cross-sectional, multicentre study was conducted within the MARMASIA Study Group, a

network of retina specialists at nine tertiary ophthalmology departments in İstanbul, Kocaeli, and Sakarya, Türkiye. The Institutional Review Board of Kocaeli University Faculty of Medicine approved the study protocol (no: GOKAEK-2022/07.19, date: 14.04.2022), which followed the ethical principles of the 1964 Declaration of Helsinki and later amendments. Written informed consent for the use of their medical data for research purposes was obtained from all patients at their initial presentation. The study is registered on ClinicalTrials.gov (number: NCT05472376).

Eligible patients were aged 18 years or older with type 1 or type 2 diabetes mellitus and treatment-naïve DMO at the index examination, defined as no previous intravitreal injection and no previous macular (focal, grid, or micropulse) laser. Panretinal photocoagulation (PRP) performed more than four months before the index visit was permitted. Of the included eyes, 115 (75 with NPDR and 40 with PDR) had previously received PRP. Therefore, the cohort was treatment-naïve for macular oedema but not globally naïve to photocoagulation. We excluded eyes with phacoemulsification within 1 month, any laser within 4 months of the index visit, or a history of intravitreal injection or vitrectomy.

Eyes with a coexisting ocular condition capable of affecting macular architecture or visual acuity, such as retinal vein occlusion, age-related macular degeneration, uveitis, advanced glaucoma, or high myopia (spherical equivalent worse than -6.00 dioptres) were also excluded. Other exclusion criteria were media opacity precluding adequate imaging, scans below the recommended signal strength, haemodialysis, and pregnancy. Both eyes were included when eligible; within-patient correlation was accounted for in the statistical analyses.

Baseline data comprised age, sex, and diabetes duration. In addition, each participant underwent a standardised assessment including best-corrected visual acuity (BCVA) with an electronic Snellen chart, slit-lamp biomicroscopy, dilated funduscopy, and OCT. Retinopathy

stage was assigned by the treating retina specialist on the basis of dilated fundus examination and colour fundus imaging, in accordance with the International Clinical Diabetic Retinopathy Disease Severity Scale.² FFA was obtained at the clinician's discretion during routine care, usually when neovascularisation was suspected, and, when available, was used to support staging. However, angiographic findings were not systematically recorded in the study dataset and were therefore unavailable for analysis.

Optical Coherence Tomography Assessment

OCT was performed using Spectralis (Heidelberg Engineering, Heidelberg, Germany), RS-3000 (Nidek, Gamagori, Japan), RTVue-100 (Optovue Inc., Fremont, CA, USA), or Triton (Topcon Corporation, Tokyo, Japan), depending on availability at each centre, with the macular cube or raster protocols on each device. We checked image quality and foveal centration before grading. Although acquisition protocols differed across devices, we graded biomarkers using shared predefined definitions.

The device software automatically calculated central macular thickness (CMT) after confirming foveal centration. Since platforms differ in the outer segmentation

boundary—Spectralis measures from the internal limiting membrane to Bruch's membrane, others to the retinal pigment epithelium—absolute CMT values are not interchangeable. The platform used was determined solely by the equipment at each centre and was unrelated to retinopathy stage, ensuring device allocation was independent of group assignment.

Before study initiation, investigators met to standardise the assessment procedures. They jointly reviewed sample images and resolved any uncertain cases by reaching a consensus with the coordinating investigators. Cases were graded at each centre by retina specialists or experienced ophthalmologists. Graders were aware of retinopathy stage, as this information was available in the clinical records.

DMO was classified into four types according to Panozzo et al.¹³ and the EURETINA guideline:¹⁴ diffuse/spongious oedema, defined as sponge-like retinal swelling with reduced intraretinal reflectivity; cystoid oedema, defined as low-reflective intraretinal cystoid spaces separated by highly reflective septa; and each of these with SRF, defined as an optically clear space between the retina and the retinal pigment epithelium ([Figure 1](#)). Where both patterns coexisted, the predominant one was selected. Largest cyst

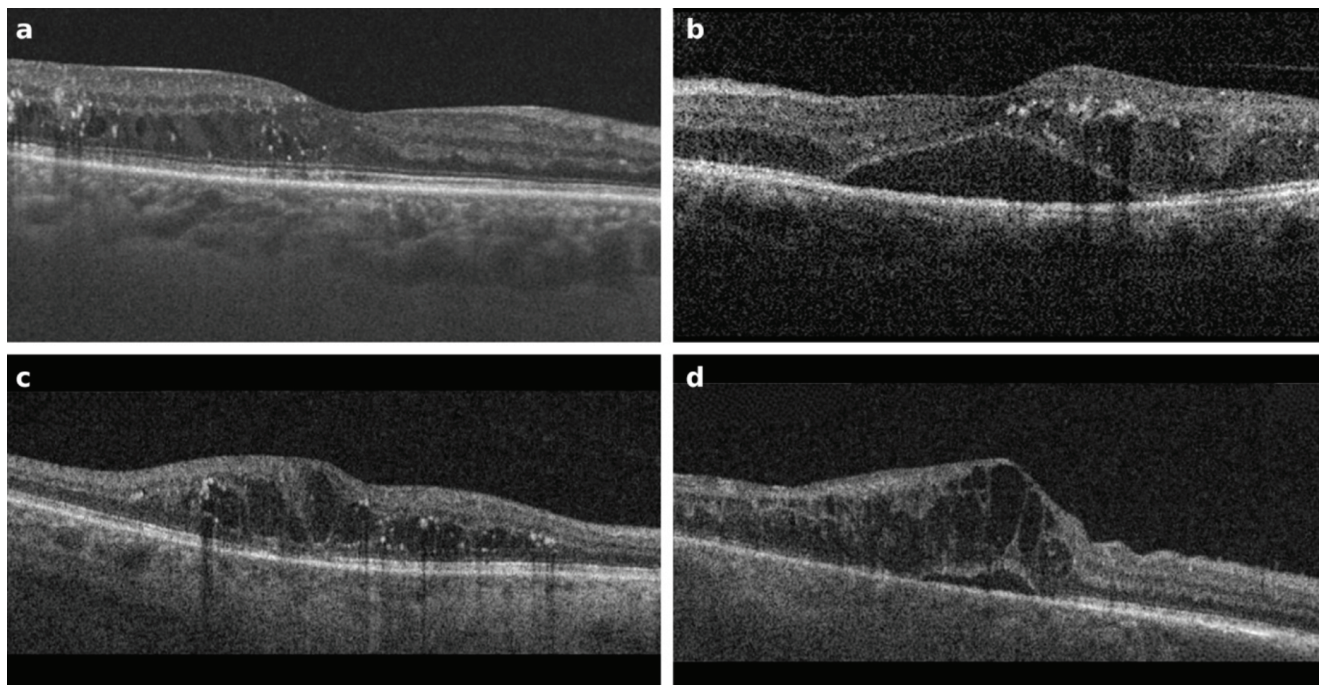


Figure 1. Representative spectral-domain optical coherence tomography B-scans of the four morphological types of diabetic macular oedema, obtained from eyes included in the present study. a) Diffuse/spongious oedema: sponge-like retinal swelling of the macula with reduced intraretinal reflectivity. b) Diffuse/spongious oedema with subretinal fluid: spongiform thickening accompanied by an optically clear space between the retina and the retinal pigment epithelium. c) Cystoid oedema: low-reflective intraretinal cystoid spaces with highly reflective septa. d) Cystoid oedema with subretinal fluid: cystoid oedema accompanied by an optically clear space between the retina and the retinal pigment epithelium

diameter and maximum vertical SRF height were measured with the calliper tool in the OCT software.

EZ and ELM integrity was assessed within a 500- μ m fovea-centred region on the central scan and graded as disrupted (complete loss of the band), partially intact (continuous but attenuated or irregular), or intact. Scans with shadowing that prevented band assessment were classified as not evaluable and excluded from analysis.

DRIL was defined, in accordance with Sun et al.¹⁵, as the inability to identify the boundaries between the ganglion cell-inner plexiform and inner nuclear-outer plexiform layer complexes over a minimum width of 500 μ m in the central foveal region. Areas in which these layers were displaced, thinned, or compressed by cystoid spaces but whose boundaries remained identifiable were not graded as DRIL.

Vitreoretinal interface abnormalities (VRIA) comprised epiretinal membrane, vitreomacular adhesion, vitreomacular traction, and other tractional abnormalities of the macula. Posterior hyaloid status was classified as attached or detached where reliably visualised, and as not evaluable otherwise.

Statistical Analysis

We used SPSS version 26.0 (IBM Corp., Armonk, NY, USA) for descriptive statistics and R version 4.6.0 for all inferential analyses. Continuous data are shown as mean $\pm$ standard deviation, and categorical data as counts and percentages. Snellen BCVA was converted to logarithm of the minimum angle of resolution (logMAR) following standard testing protocols,¹⁶ using 2.10 and 3.10 as equivalents for counting fingers and hand motions, respectively.

We analysed 818 eyes of 534 patients, including both eyes for 284 patients and one eye for the other 250. All eye-level comparisons and regression models used patient-clustered robust (sandwich) standard errors to account for correlation between fellow eyes. Retinopathy stage was concordant between fellow eyes in 93.7% of bilateral pairs ($\kappa=0.814$). For variables with more than two categories, we report a single global Wald test. Eyes where ELM integrity, EZ integrity, or posterior hyaloid status could not be graded were excluded from those comparisons. Differences in gradability between groups are discussed in the Study Limitations.

We compared ten OCT biomarkers between groups: CMT, SRF presence, SRF height, largest cyst diameter, DMO morphology, DRIL, ELM integrity, EZ integrity, posterior hyaloid status, and VRIA. These biomarkers were treated as one multiplicity family and adjusted using the Benjamini-Hochberg false discovery rate procedure, with

q values shown in [Table 1](#). Age, sex, BCVA, and lens status were not included in this analysis.

We used multivariable logistic regression with the same clustering to examine factors linked to proliferative disease. The joint model included age, sex, diabetes duration, within-centre standardised CMT, DMO morphology, DRIL, EZ integrity, posterior hyaloid status, VRIA, lens status, and study centre. This analysis included only eyes evaluable for both EZ integrity and posterior hyaloid status, allowing mutual adjustment. ELM was only examined in a substitution model because EZ and ELM grades were highly collinear (Spearman $\rho=0.932$). We controlled family-wise error using the Holm correction across the six structural-domain terms. These analyses were not prespecified and are reported as secondary.

Since imaging was done on four platforms and protocols could vary by site, we included study centre as a fixed effect in all multivariable models and standardised CMT within each centre. We examined centre-related variability in CMT using a linear model with retinopathy group, centre, and their interaction. Because the dataset does not include an eye-level device field, we could not estimate device effects. We used the same multivariable linear regression structure to estimate associations with BCVA in secondary analyses. To test robustness, we refitted the models using only one eye per patient and after excluding eyes with previous PRP. We considered p values < 0.05 significant.

Results

We analysed 818 eyes of 534 patients with treatment-naïve DMO, of which 646 eyes had NPDR and 172 had PDR ([Table 1](#)). Mean BCVA was significantly worse in PDR than NPDR eyes (0.74 ± 0.54 versus 0.57 ± 0.42 logMAR; $p<0.001$). Age was slightly lower in the PDR group ($p=0.035$).

In univariable clustered comparisons, VRIA and posterior hyaloid detachment were more common in the PDR group (21.5% and 35.7%, respectively) compared to the NPDR group (12.5% and 25.2%; $p=0.010$ and $p=0.047$, respectively). However, after false discovery rate correction across the ten comparisons, no biomarker remained significant. The lowest adjusted values were $q=0.095$ for VRIA and $q=0.235$ for posterior hyaloid status. All other results were non-significant before and after adjustment ([Table 1](#)).

The joint multivariable model included 636 eyes from 431 patient clusters that could be evaluated for both EZ integrity and posterior hyaloid status ([Table 2](#)). No structural term remained significant after Holm correction. Posterior hyaloid detachment showed a nominal association with PDR (odds ratio [OR] 2.03, 95% confidence interval

Table 1. Demographic, clinical, and OCT characteristics of eyes with NPDR and PDR				
Variable	NPDR (n=646 eyes)	PDR (n=172 eyes)	p*	q†
Age, years	62.36±8.90	60.43±8.55	0.035	
Sex			0.139	
Female	320 (49.5%)	99 (57.6%)		
Male	326 (50.5%)	73 (42.4%)		
BCVA, logMAR	0.57±0.42	0.74±0.54	<0.001	
Lens status			0.462	
Phakic	544 (84.2%)	140 (81.4%)		
Pseudophakic	102 (15.8%)	32 (18.6%)		
CMT, µm	470.60±171.02	472.54±171.84	0.912	0.912
SRF height, µm	145.50±82.87 (n=206)	152.36±92.54 (n=50)	0.662	0.827
Largest cyst diameter, µm	299.95±177.36 (n=420)	325.20±161.10 (n=113)	0.208	0.482
DMO morphology			0.759	0.844
Diffuse/spongious	100 (15.5%)	32 (18.6%)		
Cystoid	306 (47.4%)	84 (48.8%)		
Diffuse/spongious + SRF	75 (11.6%)	18 (10.5%)		
Cystoid + SRF	165 (25.5%)	38 (22.1%)		
SRF present	240 (37.2%)	56 (32.6%)	0.351	0.584
DRIL present	326 (50.5%)	82 (47.7%)	0.585	0.827
ELM integrity			0.241	0.482
Disrupted	87 (14.5%)	21 (14.8%)		
Partially intact	198 (33.1%)	58 (40.8%)		
Intact	314 (52.4%)	63 (44.4%)		
Not evaluable, n	47	30		
EZ integrity			0.142	0.473
Disrupted	97 (16.4%)	24 (17.1%)		
Partially intact	205 (34.7%)	61 (43.6%)		
Intact	289 (48.9%)	55 (39.3%)		
Not evaluable, n	55	32		
Posterior hyaloid status			0.047	0.235
Detached	139 (25.2%)	45 (35.7%)		
Attached	412 (74.8%)	81 (64.3%)		
Not evaluable, n	95	46		
VRIA present	81 (12.5%)	37 (21.5%)	0.010	0.095

Values are presented as mean ± SD or n (%) unless otherwise indicated. Percentages for ELM integrity, EZ integrity, and posterior hyaloid status are calculated among gradable eyes; numbers of non-evaluable eyes are shown separately. *p values from comparisons with patient-clustered robust (sandwich) standard errors; for variables with more than two categories, a single global Wald test is reported. †q values: Benjamini-Hochberg false discovery rate-adjusted p values across the ten OCT biomarker comparisons; not calculated for demographic and clinical variables

BCVA: Best-corrected visual acuity, CMT: Central macular thickness, DMO: Diabetic macular oedema, DRIL: Disorganisation of the retinal inner layers, ELM: External limiting membrane, EZ: Ellipsoid zone, NPDR: Nonproliferative diabetic retinopathy, OCT: Optical coherence tomography, PDR: Proliferative diabetic retinopathy, SD: Standard deviation, SRF: Subretinal fluid, VRIA: Vitreoretinal interface abnormality, logMAR: Logarithm of the minimum angle of resolution

Table 2. Joint multivariable model of structural OCT biomarkers associated with proliferative diabetic retinopathy

Variable	Adjusted OR (95% CI)	p	Holm-adjusted p
Posterior hyaloid status		0.035	0.208
Attached	Reference		
Detached	2.03 (1.05-3.92)		
Ellipsoid zone integrity (global test)		0.221	0.884
Intact	Reference		
Partially intact	1.62 (0.90-2.94)		
Disrupted	1.10 (0.43-2.82)		
Vitreoretinal interface abnormality		0.388	1.000
Absent	Reference		
Present	1.36 (0.67-2.75)		
DMO morphology (global test)	-	0.045	0.224
DRIL, present vs absent	1.02 (0.48-2.17)	0.966	1.000
CMT, per within-centre SD	1.02 (0.78-1.35)	0.862	1.000

CI: Confidence interval, CMT: Central macular thickness, DMO: Diabetic macular oedema, DRIL: Disorganisation of the retinal inner layers, OCT: Optical coherence tomography, OR: Odds ratio, SD: Standard deviation

[CI] 1.05-3.92; $p=0.035$; Holm-adjusted $p=0.208$), as did DMO morphology (global $p=0.045$; Holm $p=0.224$). The global EZ term was not associated with PDR ($p=0.221$), and the association for VRIA became weaker after adjusting for posterior hyaloid status (OR 1.36, 95% CI 0.67-2.75; $p=0.388$). These two factors were strongly related (OR 8.56, 95% CI 5.14-14.26). In a secondary model that did not include posterior hyaloid status, VRIA was associated with PDR (OR 2.19, 95% CI 1.27-3.78; $p=0.005$), but this is not considered an independent effect. CMT ($p=0.862$) and DRIL ($p=0.966$) were not associated with proliferative disease.

After adjusting for study centre, mean CMT was 1.99 μm greater in PDR than in NPDR eyes (95% CI -26.23 to 30.22; $p=0.890$), and the group-by-centre interaction was not significant ($p=0.250$). Imaging was more often ungradable in PDR eyes than in NPDR eyes for ELM integrity (17.4% compared to 7.3%; OR 2.45, 95% CI 1.16-5.16), EZ integrity (18.6% compared to 8.5%; OR 2.19, 95% CI 1.07-4.47), and posterior hyaloid status (26.7% compared to 14.7%; OR 2.13, 95% CI 1.22-3.72). All three differences remained significant after Holm correction.

In the secondary analysis of visual acuity, worse BCVA was linked to PDR (0.137 logMAR, 95% CI 0.037-0.237; $p=0.007$), higher within-centre standardised CMT (0.160 logMAR per standard deviation, 95% CI 0.115-0.205; $p<0.001$), complete EZ disruption versus an intact EZ (0.285 logMAR, 95% CI 0.121-0.450; $p<0.001$), and VRIA (0.168 logMAR, 95% CI 0.043-0.292; $p=0.008$). There was no association with partially intact EZ ($p=0.293$) or posterior hyaloid detachment ($p=0.581$).

Two sensitivity analyses supported these results. In the first, one eye per patient was analysed, using the index-eye designation recorded in the study database. After excluding 109 eyes with ungradable EZ integrity and/or posterior hyaloid status from the 523 index eyes, this analysis included 414 eyes of 414 patients. Posterior hyaloid detachment again showed a nominal association with PDR (OR 2.22, 95% CI 1.04-4.70; $p=0.038$), whereas VRIA (OR 1.35, 95% CI 0.55-3.31) and the global EZ term ($p=0.129$) did not. In the second, the 95 eyes with previous PRP within the 636-eye evaluable subset were excluded, leaving 541 eyes of 365 patients, and the pattern was unchanged: posterior hyaloid detachment (OR 2.50, 95% CI 1.18-5.28, $p=0.017$); VRIA (OR 1.68, 95% CI 0.75-3.78); EZ ($p=0.220$). All sensitivity p values are nominal.

Discussion

Interest in using OCT-based biomarkers for staging and predicting DR is increasing. Many studies now support OCT as a reliable way to assess both DR and DMO. New OCT biomarkers and oedema classification methods are expected to become more common in daily clinical practice.^{6,7,8,17,18}

We studied 818 eyes from 534 patients with untreated DMO, comparing key structural OCT biomarkers between nonproliferative and proliferative disease. Our analysis accounted for inter-eye correlations, centre effects, and multiple comparisons. No biomarker showed a clear independent association with PDR after adjusting for these factors. Posterior hyaloid detachment showed the most consistent association, but group differences involving

vitreoretinal interface observed in simpler analyses did not maintain their significance.

Vitreoretinal interface problems are known to be part of advanced DR. Vitreomacular adhesion and traction are more common in proliferative disease, likely due to higher levels of inflammatory mediators and vascular endothelial growth factor in the vitreous.^{19,20} Our findings are consistent with these reports, but our joint analysis shows that posterior hyaloid status and VRIA are closely linked. When we included posterior hyaloid status in the model, the link with VRIA mostly disappeared. This suggests that both markers reflect the same interface issue rather than separate problems. Studies on posterior vitreous detachment and DR stage have shown mixed results, with some finding it more common and others less common in advanced disease.^{21,22,23,24,25}

Many studies have examined the importance of EZ disruption. Szeto et al.¹⁷ found that when both the EZ and ELM are affected, visual outcomes in DMO are worse. Turkseven Kumral et al.²⁶ observed more EZ disruption in proliferative disease. In our simple analysis, EZ grade distributions differed descriptively between groups, but the global test was not significant. There are two possible explanations for this. First, we could not grade EZ integrity in more PDR eyes, often because of shadowing from bleeding or opacity. These eyes likely had more advanced disease, and their exclusion may have obscured a group difference. Second, both groups were restricted to eyes with DMO, making our results different from studies of all eyes. Importantly, disrupted EZ remained the strongest sign of worse vision in our secondary analysis, showing the importance of outer retinal health even without stage differences.²⁷

Wang et al.²⁸ recently compared NPDR and PDR eyes using spectral-domain OCT and fundus autofluorescence. They found that posterior vitreous detachment and epiretinal membrane were more common in PDR, consistent with our descriptive results. However, these associations did not persist after adjusting for multiple factors. Their findings for the outer retina were the opposite of our unadjusted results, possibly because our study included only eyes with DMO and because sample size and image quality differed. They also found hyperreflective foci to be the biomarker most strongly associated with proliferative disease. We did not measure this in our study, but including it in future research would make sense.

The main strength of this study is its multicentre analysis of DMO-related OCT features, using methods that consider inter-eye correlations, mutual adjustment, image quality, and multiple comparisons. We do not claim that these biomarkers differ independently by

retinopathy stage. Some associations reported in smaller studies, including ours, may not show true independent effects. DMO morphology, which has been associated with treatment response,²⁹ also did not distinguish between the two stages in our data, and reported subtypes vary widely between populations.³⁰ Our joint model was complex and used a smaller group of evaluable cases, so its accuracy is limited. The absence of multiplicity-adjusted significant associations means we did not show independent effects, but it does not prove they do not exist. For example, DMO morphology was not significant in simple analysis but was nominally significant in the joint model.

Study Limitations

This retrospective, cross-sectional study cannot determine causality or prognosis. The lack of standardised angiographic data and the optional use of FFA resulted in an inability to assess retinal ischaemia. This may have led to misclassification between severe NPDR and early PDR, which could have reduced observed differences. The role of ischaemia is only hypothesised and not tested. Furthermore, retinopathy stage was binary, limiting severity analysis.

Imaging was done on four platforms with different boundaries and resolutions. Devices were assigned without considering retinopathy stage, and missing eye-level identifiers prevented adjusting for device effects, risking confounding. Grading was performed at each centre without central review or duplicate grading, so interobserver agreement could not be assessed. Graders were also aware of the retinopathy stage, possibly causing bias and variability.

Image gradability varied across groups, meaning complete-case estimates reflect associations within a selected, fully evaluable subset. Assessing DRIL is more challenging with significant cystoid change, potentially leading to misclassification in eyes with severe oedema. Hyperreflective foci were not recorded. Finally, 115 eyes had prior PRP treatment over four months before the index examination, but excluding these eyes did not affect the results.

Conclusion

In this large multicentre cohort of eyes with treatment-naïve DMO, we found no structural OCT biomarker that was independently associated with proliferative disease after accounting for fellow-eye correlation, study centre, clinical factors, and the influence of other biomarkers. Posterior hyaloid detachment had the most consistent association and showed a similar pattern in sensitivity analyses. However, the association between VRIA and PDR observed in univariable tests did not persist after

adjustment for posterior hyaloid status. EZ integrity was not significantly associated with PDR in either analysis. In the secondary analysis, proliferative disease, greater macular thickness, EZ disruption, and VRIA were each associated with worse visual acuity. Future longitudinal studies using standardised multimodal imaging and central grading are needed to determine whether any of these features have prognostic value.

Ethics

Ethics Committee Approval: The Institutional Review Board of Kocaeli University Faculty of Medicine approved the study protocol (no: GOKAEK-2022/07.19, date: 14.04.2022), which followed the ethical principles of the 1964 Declaration of Helsinki and later amendments.

Informed Consent: Written informed consent for the use of their medical data for research purposes was obtained from all patients at their initial presentation.

Declarations

Authorship Contributions

Surgical and Medical Practices: I.Ö.S., E.K.T., F.B.K., M.O.S., T.A.G., E.Ö.T., H.S.S.K., I.K.K., U.Y., E.Ç., A.D.S., A.A., U.L., E.B., N.Y.E., Ö.A.Ö., E.B.E., A.Ö., B.A.Ö., M.N.Y., Ö.Ş., V.L.K., Concept: I.Ö.S., E.K.T., F.B.K., M.O.S., T.A.G., E.Ö.T., H.S.S.K., I.K.K., U.Y., E.Ç., A.D.S., A.A., U.L., E.B., N.Y.E., Ö.A.Ö., E.B.E., A.Ö., B.A.Ö., M.N.Y., Ö.Ş., V.L.K., Design: I.Ö.S., E.K.T., F.B.K., M.O.S., T.A.G., E.Ö.T., H.S.S.K., I.K.K., U.Y., E.Ç., A.D.S., A.A., U.L., E.B., N.Y.E., Ö.A.Ö., E.B.E., A.Ö., B.A.Ö., M.N.Y., Ö.Ş., V.L.K., Data Collection or Processing: I.Ö.S., E.K.T., F.B.K., M.O.S., T.A.G., E.Ö.T., H.S.S.K., I.K.K., U.Y., E.Ç., A.D.S., A.A., U.L., E.B., N.Y.E., Ö.A.Ö., E.B.E., A.Ö., B.A.Ö., M.N.Y., Ö.Ş., V.L.K., Analysis or Interpretation: I.Ö.S., E.K.T., F.B.K., M.O.S., Literature Search: I.Ö.S., E.K.T., F.B.K., Writing: I.Ö.S.

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