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Prognostics optical coherence tomography biomarker in macular oedema secondary to retinal vein occlusion

Authors:
Andrea R. Silitonga[1]
Hanna T.H. Silitonga[2]
Rova Virgana[3]
Iwan Sovani[3]
Arief Kartasasmita[3]
Erwin Iskandar[3]
Grimaldi Ihsan[3]
Made Indra[3]

Affiliations:
[1]SMEC Eye Hospital, Medan, Indonesia

[2]Department of Public Health, Preventive Medicine and Community Medicine, Faculty of Medicine, Ciputra University, Surabaya, Indonesia

[3]Vitreoretinal Department, Cicendo National Eye Hospital, Bandung, Indonesia

Corresponding author:
Hanna Silitonga,
hanna.silitonga@ciputra.ac.id

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Background: Identifying biomarkers predictive of future best-corrected visual acuity (BCVA) in macular oedema secondary to retinal vein occlusion (RVO-MO) is crucial for improving risk assessment, management strategies and patient consultations.

Aim: This study aimed to identify baseline optical coherence tomography (OCT) predictors of visual prognosis in RVO-MO following intravitreal bevacizumab (IVB) injection.

Setting: The study was conducted at Cicendo Eye Hospital, Bandung, Indonesia.

Methods: Retrospective study of 36 treatment-naïve eyes with RVO-MO (22 eyes with central retinal vein occlusion and 14 eyes with branch retinal vein occlusion). Each eye received at least three monthly IVB injections with a minimum follow-up of 4 months. Assessment of baseline OCT images focused on a 3-mm-wide retinal area centred on the fovea. Univariate and multivariate regression analyses were performed.

Result: There was a significant improvement in mean BCVA from 1.15 ± 0.42 logMAR to 0.80 ± 0.55 logMAR ($P < 0.001$) and a reduction in mean central macular thickness (CMT) from 732.2 μm ± 298.9 μm to 437.7 μm ± 352.9 μm ($P < 0.001$). Univariate regression analysis highlighted worse baseline BCVA and higher baseline CMT as factors correlating with poorer outcomes post-treatment. Several OCT biomarkers such as disorganisation of the retinal inner layer (DRIL) and disruption of the ellipsoid zone (EZ) and the external limiting membrane (ELM) were identified but did not show significant associations with final BCVA after multivariate analysis.

Conclusion: Baseline OCT biomarkers may elucidate the extent of vision loss; however, they may not be reliable in predicting treatment outcomes.

Keywords: branch retinal vein occlusion; central retinal vein occlusion; macular oedema; OCT Biomarker; bevacizumab intravitreal injection.

Introduction

Retinal vein occlusion (RVO) is a common cause of retinal vascular disease and both branch RVO (BRVO) and central RVO (CRVO) are associated with vision impairment.[1,2,3,4] Macular oedema (MO) is the most frequent cause of visual impairment in RVO.[5] It occurs secondary to damage or inflammation of the endothelium of retinal small blood vessels and interruption of the tight junctions because of upregulation of the vascular endothelial growth factor (VEGF), resulting in increased vascular permeability and pooling of fluid in the macula. Intravitreal anti-VEGF is considered a safe and effective treatment for RVO-MO.[1,2] Bevacizumab (off-label) is the most frequently used anti-VEGF drug because of its affordability.[2,3,4] However, frequent intravitreal injections and follow-up visits are required and not all patients are respondents; these considerations place a heavy burden on the patient and the physician. Therefore, biomarkers predicting future best-corrected visual acuity (BCVA) in eyes with RVO-MO may substantively improve risk assessment, management decisions and clinical consultation.[4]

Various demographic, clinical and imaging factors may predict visual acuity (VA) after treatment, such as patient age,[2] time to treatment initiation,[3,4] baseline VA,[2] ischaemic versus nonischemic disease[4] and central macular thickness (CMT).[2] Given the ease of identifying and obtaining CMT, it still demonstrates limitations in determining VA.[5] Therefore, other aspects of spectral-domain optical coherence tomography (SD-OCT) have been investigated to determine their viability as

biomarkers for VA and treatment outcomes, including intraretinal hyperreflective foci (HF)[6] disorganisation of the retinal inner layers (DRIL),[7,8,9,10] external limiting membrane (ELM) disruption,[11,12] ellipsoid zone (EZ) disruption[12,13] and choroidal thickness.[14]

Identifying patients who are likely to respond completely or only partially to long-term anti-VEGF therapy would enable physicians to help patients set realistic expectations for improvements with therapy. The goal of our study was to identify simple, clear predictors of visual outcomes using single SD-OCT B-scans that are used commonly in real-world clinical practice and could be adapted more easily to guide the medical management of RVO with MO.

Research methods and design

This was a retrospective study conducted in Cicendo National Eye Hospital and adhered to the tenets of the Declaration of Helsinki.

Study design

Medical records of patients with MO because of RVO from December 2018 to December 2019, were retrospectively reviewed. Out of 317 patients, only 22 eyes with CRVO and 14 eyes with BRVO met the inclusion and exclusion criteria.

Inclusion criteria were (1) patients older than 18 years old, (2) eyes with CRVO or BRVO and MO, (3) onset to presentation less than 90 days and (4) the involved eye must have had a minimum of 3 consecutive monthly intravitreal injection of bevacizumab (IVB) and minimum 4 months of follow-up. Exclusion criteria were: (1) the presence of ME because of other retinal diseases (diabetic retinopathy, vasculitis or uveitis and age-related macular degeneration), (2) evidence of anterior or posterior neovascularisation, (3) history of intravitreal anti-VEGF or retinal or macular laser, (4) prior ocular surgery (except for uneventful cataract surgery), (5) history of prior ocular trauma, (6) history of cerebral vascular accident or myocardial infarction, (7) signal strength on SD-OCT less than 6 and (8) incomplete medical record, examination or loss of follow-up. The initial assessment included the BCVA or pinhole VA, intraocular pressure measurement using non-contact tonometer, slit-lamp biomicroscopy, dilated binocular ophthalmoscopy and spectral-domain OCT of the macular area (Cirrus HD OCT, Carl Zeiss Meditec, Dublin, CA, USA).

Treatments

Macular oedema was defined as a CMT ≥ 300 µm. All patients initially received 3 monthly intravitreal injection of 1.25 mg/0.05 mL of bevacizumab and PRN thereafter. Patients were followed up monthly for at least 4 months after the initial injection. Re-treatments were performed if any intraretinal or subretinal fluid (SRF) was observed on SD-OCT.

Data collection

Patient charts were reviewed to collect the following data: age, sex, involved eye, RVO type, lens status, duration of RVO until the first injection, systemic comorbidities (e.g. hypertension) and BCVA at baseline and each follow-up visit. Best-corrected visual acuity was determined using the Snellen chart and converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analysis.

Image grading

The SD-OCT (Carl Zeiss Meditec, Dublin, CA) testing was performed through a dilated pupil. Only the scans of sufficient quality were used for image analysis. Each OCT scan of each visit was independently analysed by one grader who was masked to patient clinical data. Image analysis was conducted as previously described.

The scans were evaluated for (1) CMT, (2) presence of vitreomacular adhesion or traction and epiretinal membrane, (3) presence of intraretinal fluid or SRF, (4) presence and amount of hyperreflective spot, (5) disorganisation of retinal inner layers (DRIL) and (6) disruption of ELM and (7) EZ.

Vitreomacular adhesion was defined as an elevation of perifoveal vitreous cortex from the retinal surface with attachment of the vitreous cortex within 3 mm of the foveal centre, whereas vitreomacular traction was defined as vitreomacular adhesion accompanied by anatomic changes to the foveal contour, intraretinal pseudocyst formation, elevation of the fovea from the retinal pigment epithelium or a combination of these factors, as defined by the International Vitreomacular Traction Study group.[15] Vitreomacular adhesion status was considered ungradable if the posterior vitreous border could not be discerned as completely detached or completely attached.

Spectral-domain OCT images were also analysed for the presence, location and extent of macular fluid, including IRF and SRF (Figure 1). Eyes with IRF were graded for fluid location in the inner nuclear layer (INL) alone, the outer plexiform layer (OPL) plus outer nuclear layer (ONL) or both based on the International Nomenclature for OCT panel consensus.[16] The OPL and ONL were not analysed separately because OCT imaging incorporates Henle's fibre layer, which is histologically part of the OPL, within the hyporeflective ONL layer.[17] The size of the largest ganglion cell layer (GCL) cysts for each eye also was measured based on the horizontal diameter as described in previous studies of OCT biomarkers.[18] Eyes with SRF were quantified for SRF thickness based on the linear distance perpendicular to the retinal pigment epithelium. Subretinal fluid thickness was considered ungradable if signal attenuation, or 'shadowing', from overlying intraretinal fluid prevented accurate measurement of SRF thickness. Eyes also were graded for the presence, location and extent of vitreous or intraretinal HF, defined as discrete, dot-shaped lesions with similar or more reflectivity than the retinal pigment

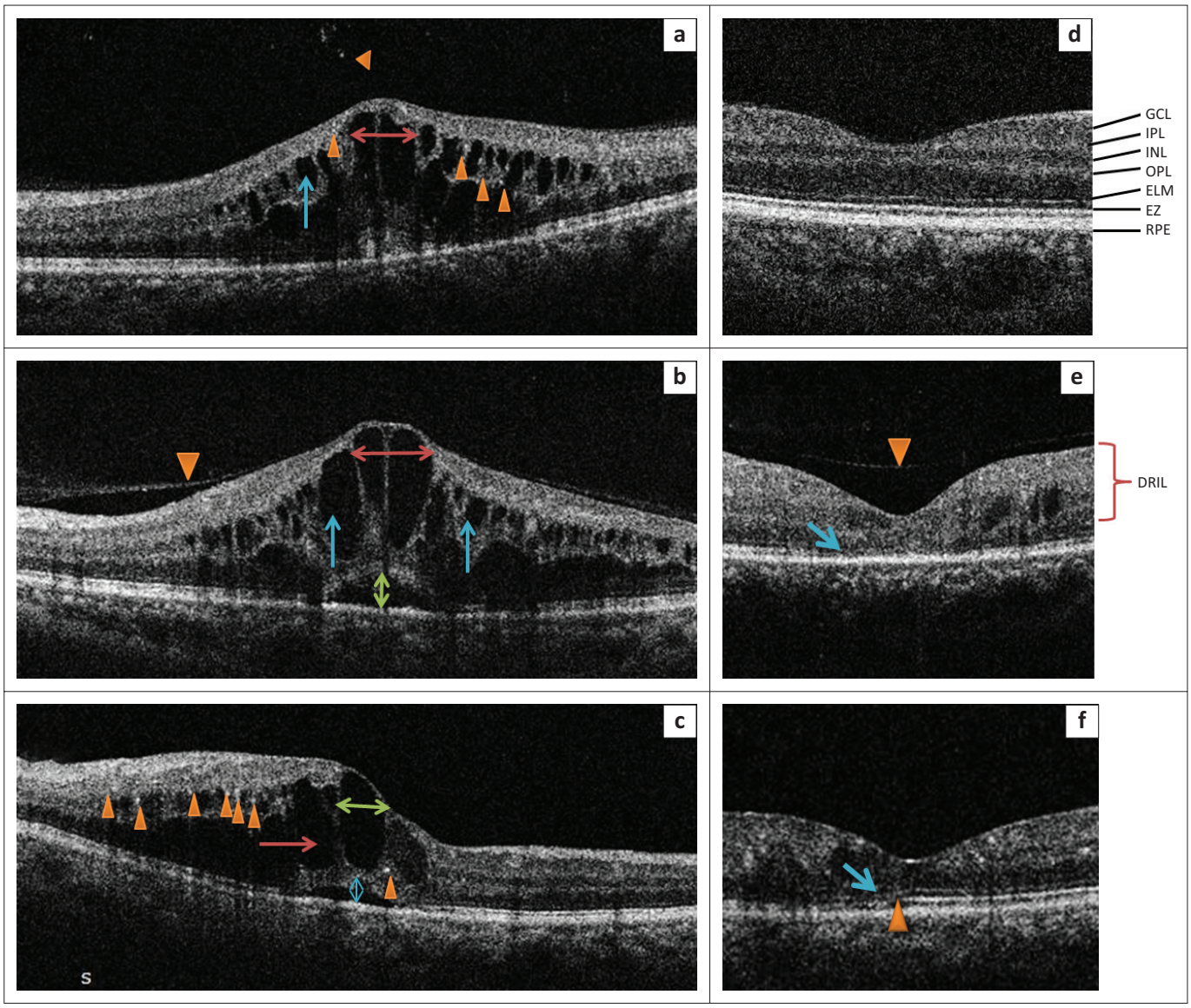


FIGURE 1: Spectral-domain optical coherence tomography features in eyes with macular oedema resulting from retinal vein occlusion (RVO). (a–f) Spectral-domain optical coherence tomography horizontal-line B-scans through the fovea of three patients with RVO in this study demonstrating the presence of vitreomacular adhesion (b, arrow), a posterior vitreous detachment (e, arrow), presence and amount of ganglion cell cyst measured using the horizontal diameter of the largest cyst (a–c, horizontal double arrow), presence of intraretinal fluid (a–c, arrow), presence and amount of subretinal fluid measured by vertical height (b,c, vertical double arrow) and presence and number of vitreous or intraretinal hyperreflective foci (a,c, arrowheads). (d) Magnified view of the central 1-mm region of a normal macula showing layers of inner and outer retina. (e, f) Magnified view of the central 1-mm region showing measurement of disorganisation of the retinal inner layers (DRIL) defined as loss of distinction between the ganglion cell and inner plexiform layer complex (GCL-IPL), inner nuclear layer (INL) and outer plexiform layer (OPL) and disruption or discontinuation of the ELM (e,f, arrow) and disruption of EZ (f, arrowhead).

epithelium band, with approximate diameters of 20 µm to 40 µm to avoid the inclusion of noise.[19]

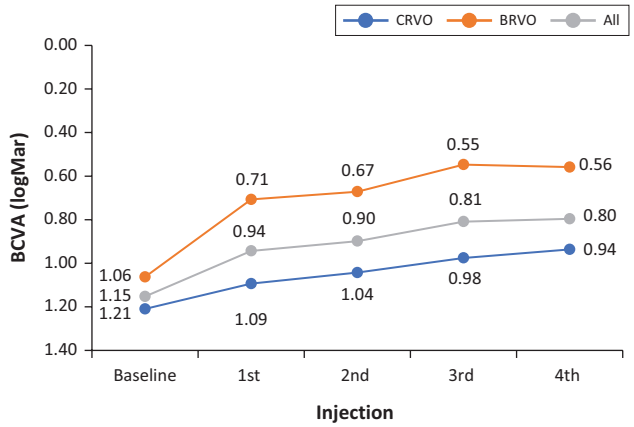
Disorganisation of the retinal inner layers was defined as the inability to identify any boundaries between the ganglion cell–inner plexiform layer complex, INL and OPL within the central 1000-µm region (per B-scan).[20] Disruption of ELM and EZ was defined as discontinuity in the respective hyperreflective bands within the central 1000-µm segment of the horizontal-line B-scan centred on the fovea.[21]

Statistical analysis

For the description of patients' characteristics at baseline, mean ± s.d. was used for continuous variables and counts with percentages for categorical variables. For the longitudinal comparisons of BCVA and CMT between baseline and at each follow-up visit, the Friedman *t*-test and Wilcoxon signed *t*-test were used, with the level of statistical significance set at 0.05. Univariate and multivariate linear regression analyses were used to examine the association between the baseline biomarkers and the final BCVA from baseline to last follow-up. Statistical analysis was performed using SPSS version 20.0. A $P < 0.05$ was considered statistically significant.

Ethical considerations

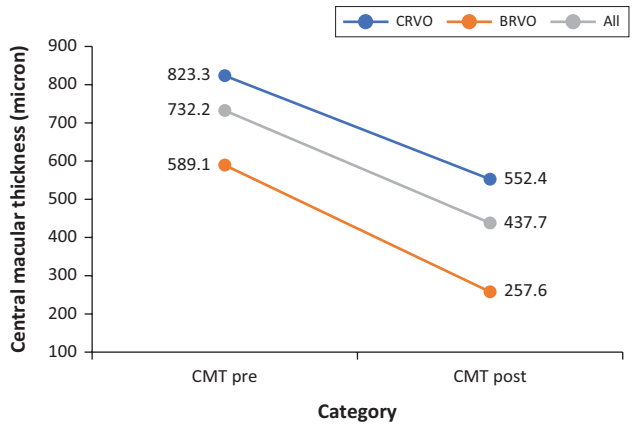
Ethical clearance to conduct this study was obtained from the Cicendo Eye Hospital Research Ethics Committee (No. LB.02.01/2.3/021/2021).



	Baseline	1st	2nd	3rd	4th	*P*
CRVO	1.21 ± 0.41	1.09 ± 0.51	1.04 ± 0.50	0.98 ± 0.52	0.94 ± 0.54	0.130
BRVO	1.06 ± 0.44	0.71 ± 0.46	0.67 ± 0.50	0.55 ± 0.49	0.56 ± 0.50	< 0.001*
All	1.15 ± 0.42	0.94 ± 0.52	0.90 ± 0.52	0.81 ±0.55	0.80 ± 0.55	< 0.001*

CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion.
*, Friedman *t*-test.

FIGURE 2: Evolution of visual acuity in patients with central retinal vein occlusion and branch retinal vein occlusion after treatment.



	CMT pre-treatment	CMT post-treatment	*P*
CRVO	823.3 ± 337.0	552.4 ± 412.6	< 0.002*
BRVO	589.1 ± 144.7	257.6 ± 56.3	< 0.001*
All	732.2 ± 298.9	437.7 ± 352.9	< 0.001*

CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; CMT, central macular thickness.
*, Wilcoxon *t*-test.

FIGURE 3: Central macula thickness in patients with central retinal vein occlusion and branch retinal vein occlusion after treatment.

Results

Patient characteristics

A total of 36 eyes from 36 patients were included in this study, consisting of 22 eyes with CRVO and 14 eyes with BRVO. Males comprised 16 patients (72.7%) of CRVO and women 10 patients (71.4%) of BRVO patients. The average age was 57.22 ± 12.0 years old for CRVO patients and 54.85 ± 11.29 years old for BRVO. Fifty per cent of patients in both groups had hypertension. Mean baseline BCVA was 1.20 ± 0.41 logMAR in CRVO patients and 1.06 ± 0.43 logMAR in BRVO patients. Mean CMT at baseline was 823.2 µm ± 336.9 µm in CRVO and 589.0 µm ± 144.6 µm in BRVO patients ($P = 0.03$).

Best-corrected visual acuity and central macular thickness changes after bevacizumab treatment

In the BRVO group, the mean baseline BCVA was 1.06 ± 0.43 logMAR. Figure 1 shows the evolution of BCVA over time, illustrating that there was a statistically significant improvement in BCVA at all time points and baseline (Friedman *t*-test, $P < 0.001$). Final BCVA after the fourth injection was 0.56 ± 0.50 logMAR. In the CRVO group, mean baseline BCVA was 1.21 ± 0.41 logMAR and although there was improvement of VA to 0.94 ± 0.54 logMAR after the fourth injection, the difference was not statistically significant (Friedman test, $P = 0.13$).

In the CRVO group, the mean CMT was 823.3 µm ± 337.0 µm at baseline and improved significantly to 552.4 µm ± 412.6 µm at the last follow-up (Wilcoxon *t*-test, $P = 0.002$). At the end of follow-up, the mean CMT had significantly decreased by 270.9 µm compared with baseline. In the BRVO group, the mean baseline CMT was 589.1 µm ± 144.7 µm. There was a statistically significant improvement in CMT after monthly IVB injections to 257.6 µm ± 56.3 µm (Wilcoxon *t*-test, $P = 0.001$) at the last visit. The mean CMT in the BRVO group had decreased by 331.5 µm compared with baseline.

Spectral-domain optical coherence tomography biomarkers in subjects with macular oedema following retinal vein occlusion

On baseline SD-OCT, mean CMT was 589.0 µm ± 144.6 µm in eyes with BRVO and 823.2 µm ± 336.9 µm in eyes with CRVO ($P = 0.03$; Table 1). There were 13.8% of the eyes that showed vitreomacular adhesion, with many of these being ungradable and likely representing a complete posterior vitreous detachment in which the posterior hyaloid could not be visualised on the OCT image. No eye showed signs of vitreomacular traction, and 11% demonstrated an ERM. All eyes demonstrated IRF, mostly located in both the inner nuclear layer, the OPL and ONL, whereas 25 patients (69.4%) of eyes also showed SRF (Table 2). The mean diameter of the largest intraretinal cyst was 302.5 µm ± 240.1 µm, and the mean SRF thickness was 194.5 µm ± 218.1 µm. Eyes of 25 (69.4%) patients demonstrated intraretinal hyperreflective spot (HS), with a mean of 4.25 ± 3.7 HS identified per eye (Table 2). At baseline, DRIL was present in 63.8% patients, and after treatment, DRIL persisted in 44.4% patients. Disruption of the outer retinal layers ranged from 52.8% to 55.6% of patients (Table 2). Overall, eyes with macular edema resulting from CRVO showed greater baseline CMT ($P = 0.03$).

Spectral-domain optical coherence tomography predictors of visual acuity after bevacizumab treatment

After bevacizumab treatment, the mean BCVA improved from a mean of 1.15 ± 0.42 logMAR at baseline to 0.80 ± 0.55 logMAR ($P < 0.001$). In univariate analyses, poor final BCVA was associated with lower baseline BCVA, higher CMT, presence of DRIL before and after treatment, EZ disruption and ELM disruption (Table 3). However, multivariate regression analyses showed that none of these biomarkers associated independently with BCVA gains after a minimum of 3 monthly injections of bevacizumab.

TABLE 1: Demographic and clinical characteristics at baseline.

Variables	CRVO (*n* = 22)			BRVO (*n* = 14)			*P*
	Mean ± s.d.	*n*	%	Mean ± s.d.	*n*	%	
Age (years)	57.22 ± 12.0	-	-	54.85 ± 11.29	-	-	> 0.05
Gender							
Male	-	16	72.7	-	4	71.40	> 0.05
Female	-	6	27.3	-	10	28.60	
Baseline BCVA (LogMAR)	1.20 ± 0.41	-	-	1.06 ± 0.43	-	-	0.22
CMT (μm)	823.2 ± 336.9	-	-	589.0 ± 144.6	-	-	0.03
Hypertension	-	11	50.0	-	7	50.00	> 0.05
Diabetes	-	2	0.1	-	1	0.07	> 0.05
Open angle glaucoma	-	0	0.0	-	2	0.14	> 0.05
Frequency of injection	3.86 ± 0.94	-	-	3.14 ± 0.36	-	-	> 0.05
Range	3–6	-	-	3–4	-	-	

BCVA, best-corrected visual acuity; CMT, central macular thickness; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; s.d., standard deviation.

TABLE 2: Summary of spectral-domain optical coherence tomography biomarkers in macular oedema following retinal vein occlusion.

Variables	All patients	CRVO (*n* = 22)	BRVO (*n* = 14)	*P**
Baseline visus (mean ± s.d.)	1.15 ± 0.42	1.20 ± 0.41	1.06 ± 0.43	0.220
Baseline CMT (mean ± s.d.)	732.1 ± 298.6	823.2 ± 336.9	589.0 ± 144.6	0.030*
Vitreomacular interface				
VMA (present/absent)	5/31	3/19	2/12	0.950
VMT (present/absent)	0/36	0/22	0/14	-
ERM (present/absent)	4/32	3/19	1/13	0.540
Macular fluid				
IRF (present/absent)	36/0	22/0	14/0	1.000
IRF location (INL/OPL-ONL/ both)	0/8/28	0/5/17	0/3/11	0.920
SRF (present/absent)	25/11	14/8	11/3	0.340
SRF thickness (μm), mean ± s.d.	194.5 ± 218.1	203.1 ± 256.0	181.0 ± 148.0	0.610
GCL cyst size (μm), mean ± s.d.	302.5 ± 240.1	321.3 ± 264.3	273.1 ± 202.1	0.550
Hyperreflective spot				
Hyperreflective spot (present/absent)	25/11	15/7	10/4	0.830
Hyperreflective spot (no.), mean ± s.d.	4.25 ± 3.7	3.77 ± 3.4	5.0 ± 4.29	0.450
Retinal layer disruption				
DRIL pre-treatment (present/absent)	23/13	15/7	8/6	0.501
DRIL post-treatment (present/absent)	16/20	9/13	7/7	0.590
IS/OS (EZ) disruption (present/absent)	20/16	14/8	6/8	0.220
ELM disruption (present/ absent)	19/17	14/8	5/9	0.102

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CMT, central macular thickness; DRIL, disorganisation of the retinal inner layers; ELM, external limiting membrane; ERM, epiretinal membrane; HS, hyperreflective spot; INL, inner nuclear layer; IRF, intraretinal fluid; IS/OS (EZ), photoreceptor inner/outer segment junction (ellipsoid zone); ONL, outer nuclear layer; OPL, outer plexiform layer; s.d., standard deviation; SRF, subretinal fluid; VMA, vitreomacular adhesion; VMT, vitreomacular traction.

*, $P < 0.05$, statistically significant.

Discussion

The relationship between retinal anatomic features and visual function is complex, with poor correlation between BCVA and CMT often noticed across different retinal conditions, including macular oedema resulting from RVO. In the Standard care versus Corticosteroid for Retinal vein occlusion (SCORE) 2 study comparing monthly aflibercept with bevacizumab for RVO-related macular oedema, baseline CMT was associated with 6-month BCVA outcomes on univariate regression, but only patient age and baseline BCVA were found to predict treatment response independently in multivariate models.[2] Our investigation showed the same result, whereas in univariate analysis, in macular oedema related to RVO, baseline BCVA and baseline CMT were associated with the final BCVA outcome. However, after multivariate analyses, none of these factors seem to be associated with the final BCVA. In our study, the initial CMT had no significant correlation with the final BCVA in the multivariate analysis, consistent with the results of Shin et al.[22] The CMT could have failed to represent the retinal integrity. Even after the complete resolution of MO, the visual outcome could be poor if the integrity of the

TABLE 3: Spectral-domain optical coherence tomography biomarkers associated with best-corrected visual acuity change after a minimum of three intravitreal bevacizumab injections in retinal vein occlusion (univariate regression analyses).

Spectral-domain OCT biomarker	Category	OR (95% confidence interval)	*P**
Age	10-year decrease	1.0 (-2.08 to 2.08)	1.000
Baseline BCVA	0.5 logMar decrease	12.03 (1.9 to 73.5)	0.007*
Baseline CMT	100 micron decrease	3.1 (1.5 to 6.50)	0.002*
Vitreomacular interface			
VMA presence	Present vs. Absent	1.39 (-7.6 to 14.3)	0.780
VMT presence	Present vs. Absent	-1.56 (-20 to 8.02)	0.590
ERM presence	Present vs. Absent	1.0 (-11.1 to 11.02)	1.000
Macular fluid			
IRF Location	OPL vs. Both	not available	0.060
SRF presence	Present vs. Absent	4.37 (-1.13 to 21.6)	0.060
GCL Cyst Size	200 increase	1.0 (-2.08 to 2.08)	1.000
Hyperreflective Spot			
Hyperreflective Spot presence	Present vs. Absent	-1.7 (-11.1 to 3.3)	0.530
Hyperreflective spot amount	5 spot increase	-2.08 (-7.4 to 1.7)	0.250
Retinal Layer Disruption			
DRIL before treatment presence	Present vs. Absent	-1.64 (-2.32 to -1.19)	0.009*
DRIL post-treatment presence	Present vs. Absent	-18.8 (-166 to -2.02)	0.002*
IS/OS (EZ) Disruption	Present vs. Absent	-10 (-90 to -1.09)	0.020*
ELM Disruption	Present vs. Absent	-12.5 (-111 to -1.28)	0.020*

OCT, optical coherence tomography; OR, odds ratio; CI, confidence interval; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CMT, central macular thickness; DRIL, disorganisation of the retinal inner layers; ELM, external limiting membrane; ERM, epiretinal membrane; GCL, ganglion cell cyst; HS, hyperreflective spot; INL, inner nuclear layer; IRF, intraretinal fluid; IS/OS (EZ), photoreceptor inner/outer segment junction (ellipsoid zone); ONL, outer nuclear layer; OPL, outer plexiform layer; SRF, subretinal fluid; VMA, vitreomacular adhesion; VMT, vitreomacular traction.

*, $P < 0.05$, statistically significant, univariate regression analysis.

retinal layer is disturbed. This finding shows the need to find other OCT biomarkers that significantly predict final BCVA.

Initial OCT biomarkers that correlated with visual outcomes included disorganisation of the retinal inner layers (DRIL), integrity of the EZ and ELM disruption on SD-OCT.[1,2,3] Sun et al. were the first to define DRIL and demonstrate a correlation between DRIL and VA in patients with diabetic macular oedema (DMO).[20] The pathogenesis of DRIL and its relationship to VA is not fully understood. The DRIL may represent an anatomical interruption in the visual transmission pathway secondary to the destruction of cells within the inner retinal layers possibly disrupting neural transmission from photoreceptors to the retinal ganglion cells.[9] It has also been hypothesised that ischaemia may instigate the development of DRIL and compromise the inner retinal circulation as it has been observed in DME, RVO, acute retinal necrosis and blunt ocular trauma. Inflammation also has been implicated in the development of DRIL.[9,8] The relative contribution of ischaemia and inflammation to the pathogenesis of DRIL is not clear, and further studies are needed to understand DRIL pathophysiology.[8,9,10]

The relationship between DRIL and VA in RVO has been analysed in many studies. Babiuch et al. in their study of 147 patients found DRIL in 62% of patients.[9] Persistence of DRIL was associated with decreased visual improvement in patients receiving anti-VEGF therapy. In our study, baseline DRIL was present in about 64% of patients, and after treatment, DRIL persisted in 44% of patients. Univariate regression analysis showed that the persistence of DRIL was also associated with poor final BCVA. Mimouni et al. similarly analysed the relationship between DRIL and VA in 136 eyes with BRVO and CRVO.[7] They found that an improvement in DRIL at 4 months following 3 monthly injections was a strong predictor of final VA outcomes at 8 months. Conversely, an increase of 100 µm of DRIL correlated with half line decrease of VA. Chan et al. evaluated the predictive value of various OCT parameters in MO secondary to CRVO.[10] In multivariate analysis, adjusting for baseline VA, worsening VA over 1 year was associated with 1-year increases in DRIL (point estimate, 0.06/100 µm, $P < 0.001$). A 3-month increase in DRIL (0.05/100 µm, $P = 0.003$) was the only factor predicting VA worsening over 1 year after controlling for baseline VA.

These findings, however, have not been uniformly replicated as subsequent studies looking at multivariate analysis to account for confounding variables have not found an association between extent of DRIL at baseline and final VA following treatment for macular oedema in RVO. Yiu et al. analysed OCT biomarker of 202 RVO patients enrolled in the prospective, multicentre Study Evaluating Dosing Regimens for Treatment with Intravitreal Ranibizumab Injections in Subjects with Macular Oedema following Retinal Vein Occlusion (SHORE), and after multivariate analysis found that none of the SD-OCT features they evaluated predicted visual gains after minimum of 3 monthly ranibizumab treatments.[23] Their results suggest that although outer retinal morphologic features may help to explain the extent of vision loss in RVO-related macular oedema before treatment, these imaging biomarkers do not predict treatment outcomes, and most eyes undergo substantial visual gains after ranibizumab therapy regardless of these baseline SD-OCT features. Berry et al. also did not demonstrate a correlation between baseline DRIL and final VA.[8] However, following 6 months of treatment, DRIL extent on OCT was predictive of VA up to 2 years of follow-up. Interestingly, baseline ischaemic index, measured as extent of nonperfusion on fluorescein angiography, was correlated with the extent of DRIL at final follow-up. In our study, after multivariate regression analyses, none of these biomarkers was associated independently with BCVA gains after a minimum of 3 monthly bevacizumab injections. Nakano et al. evaluated the association between DRIL and VA after anti-VEGF treatment for MO because of BRVO.[24] They determined that DRIL had a minor role in predicting VA after anti-VEGF treatment. It was not found to have a significant association on multivariable analysis.

The EZ, previously referred to as the third hyper reflective band, is a landmark in OCT commonly used for evaluation of photoreceptor health.[10] Its integrity has correlation with visual function in various diseases including RVO.[13] In the presence of severe oedema, quantification of EZ changes is very difficult or impossible manually. Measurement of EZ after resolution of macular oedema showed that a preserved EZ after resolution of macular oedema in eyes with CRVO was associated with better visual outcome as well as better initial vision and less oedema at presentation.[12]

The ELM, which is regarded as the zonula adherens between Müller cells and photoreceptors, seems to be a hallmark of photoreceptor function, and its status may directly reflect the potential for visual function and/or recovery.[10,12] Several studies attempted to elucidate the role of the ELM for visual function and preservation of the retinal structure: (1) The ELM acts as a barrier for macromolecules. A disrupted ELM fails to block the migration and deposits of extravasated lipoproteins in the outer retinal layers, and these migrated materials may damage the photoreceptor status and (2) Müller cells play an essential role in retinal function while regulating neuronal metabolism and interacting with photoreceptor cells. Moreover, Müller cells assume the role of natural optical fibres that guide light towards the photoreceptors, thus compensating for the 'inverse' layering of the retina. Therefore, structural damage to ELM would compromise both the structural barrier and the functional interaction between Müller cells and photoreceptors.[25,26]

The integrity of the EZ and the ELM was shown to be significantly associated with post-treatment BCVA after anti-VEGF agent injections in patients with RVO and AMD. Some studies demonstrated the integrity of the EZ was more highly associated with post-treatment BCVA than the ELM;[10,26] however, some studies reported the ELM was

more useful in the prediction of post-treatment BCVA.[26,27,28] One potential reason for the poor initial correlation and final VA involves the difficulty in quantifying DRIL, EZ and ELM disruption at initial presentation in RVO patients with DRIL. These patients may have massive macular oedema that obscures the boundaries. However, once the macular oedema had improved after initial treatment in the Berry et al. study, the correlation between DRIL and final VA became apparent and also in other studies considering EZ and ELM disruption.[8,24,25,27]

As mentioned earlier, the ELM reflects the integrity of both photoreceptor cell bodies and blood retinal barrier (BRB), whereas the EZ line may be correlated with the integrity of the photoreceptor outer segments.[10] The disappearance of the EZ on OCT may be linked to the structural change in the photoreceptor secondary to the disease process, which alters its refractive property and makes it invisible. However, the band reappears as the disease evolves, suggesting that the disruption is likely a reflection of altered refractive characteristics, which resolves as the inflammation resolves, rather than a permanent loss of cells or their function. Therefore, with treatment, the anatomical restoration of EZ may represent functional visual recovery.[10,12,27,28]

Although on univariate analysis we found correlation of baseline DRIL, EZ and ELM disruption to the post-treatment BCVA, after correcting for other variables in multivariate analysis, we found none of the baseline OCT features we evaluated predicted visual gains post treatment. This is coherent to the result of Yiu et al.[23] that suggests even though outer retinal morphologic features may help to explain the extent of vision loss in RVO-related macular oedema before treatment, these imaging biomarkers do not predict treatment outcomes, and most eyes undergo substantial visual gains after bevacizumab therapy regardless of these baseline SD-OCT features. In this study, most of the samples were from CRVO patients, and because of the greater likelihood of ischaemia and poorer baseline vision in eyes with CRVO, this further reduces the predictive value of imaging biomarkers in this study. In addition, it has been shown that DRIL, EZ and ELM disruption can resolve over time; so earlier and more precise detection might also yield improved clinical outcomes.[27,28]

Our study had some limitations, and this includes its retrospective nature, small sample size and using single baseline OCT images for each patient. Also, we focused on only a single horizontal-line B-scan, rather than more robust topographic mapping of OCT features outside the central region. Finally, our study did not incorporate other imaging methods such as fluorescein angiography or OCT angiography because SD-OCT biomarkers may have more predictive power, for example, if eyes with foveal ischaemia and limited visual potential were excluded. Future studies using multimodal imaging or artificial intelligence may improve the predictive power of SD-OCT biomarkers.

Conclusion

In summary, DRIL, EZ and ELM disruption could be useful as OCT biomarker for managing patients with RVO-related MO. They can be easily incorporated into daily clinical practice as a valuable tool for patient counselling. The development of DRIL, EZ and ELM disruption should be considered in the timing of therapeutic intervention given the reversibility potential of DRIL, EZ and ELM disruption.

Some of SD-OCT features may not predict visual gains after monthly bevacizumab treatments. Caution should be taken when making treatment decisions based on biomarkers that are not thoroughly validated. Greater focus on prospective clinical trial data and developing new artificial intelligence automated image analysis or machine learning algorithms may provide more objective support and may help to strengthen these findings in the future.

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Authors' contributions

A.R.S.: Conceptualisation, methodology, formal analysis, investigation, writing original draft, project administration, resources, funding acquisition; H.T.H.S.: Conceptualisation, methodology, formal analysis, investigation, validation, data curation, writing-review and editing and supervision; R.V.: Formal analysis, investigation, writing original draft, visualisation, project administration and software; I.S.: Validation, data curation, resource, writing-review and editing and supervision; A.K.: Validation, data curation, writing-review and editing and supervision; E.I.: Methodology, formal analysis, investigation and writing original draft; G.I.: Formal analysis, investigation, writing original draft; M.I.: Formal analysis, investigation and writing original draft.

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Data availability

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