The Systemic and Ocular Risk Factors for Retinal Vein Occlusion: A Retrospective Study

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Research article

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Abstract

BACKGROUND: We sought to evaluate the systemic and ocular risk factors for severity on visual acuity and central retinal thickness in macular edema secondary to retinal vein occlusion (RVO-ME).

METHODS: This retrospective study included 46 RVO-ME patients in The First Affiliated Hospital of Sun Yat-sen University from January 2015 to November 2019. Systemic examinations include blood pressure, blood glucose, blood lipids, vascular endothelial function, and carotid artery color ultrasound. Ocular examinations include the best-corrected visual acuity (BCVA) and the central retinal thickness (CRT). The integrity of the outer retina was evaluated as well. According to the baseline BCVA and CRT levels, the patients were divided into high vision group and low vision group, high CRT group, and low CRT group. Multivariate logistic regression analyses were performed to analyze the risk factors on baseline BCVA and CRT.

RESULTS: We enrolled 19 eyes of CRVO (central retinal vein occlusion) and 27 eyes of BRVO (branch retinal vein occlusion). We identified 31 (67.4%) as high CRT and 23 (50.0%) as poor VA of 46 patients on admission. There were 15 cases of BRVO in the high CRT group (48.4%) and 12 cases in the low CRT group (80.0%). The type of disease (BRVO/CRVO) was an independent factor of baseline CRT (P=0.017). Endothelial dysfunction correlates with baseline BCVA independently (P=0.038). Ellipsoidal zone (EZ) destruction was found in 19 cases (82.6%) in the low vision group and 6 cases (26.1%) in the high vision group. EZ integrity correlates with baseline BCVA independently (P=0.017).

CONCLUSION: The central retinal vein occlusion (CRVO) has markedly higher CRT than branch retinal vein occlusion (BRVO). Endothelial dysfunction and disrupted ellipsoidal zone were significantly associated with poor baseline VA on admission.

Key Message

- Recent publications showed systemic diseases such as hypertension, diabetes mellitus, and hyperlipidemia are risk factors with the occurrence of retinal vein occlusion (RVO).
- Our study reports that the endothelial dysfunction and disrupted ellipsoidal zone were significantly associated with poorer baseline best-corrected visual acuity (BCVA). However, the systemic risk factors are not related with to the extent of clinical manifestation.

Background

Retinal vein occlusion (RVO) is the second common retinal vascular disease, secondary to diabetic retinopathy. RVO causes sudden painless visual loss accompanied by retinal hemorrhages, retinal edema, and venous engorgement, and vascular tortuosity. The causes of visual loss in RVO include macular edema (ME), ischemia, and the presence of exudates and hemorrhages [1, 2]. RVO includes central RVO (CRVO), branch RVO (BRVO), and hemiretinal RVO (HRVO), which are a group of diseases caused by obstruction of venous flow. Because vascular endothelial growth factor (VEGF) has a significant role in

neovascularization of ME in RVO [3], the injection of anti-VEGF drugs is an effective way of treatment of ME secondary to RVO. Poor final visual acuity after treatment with anti-VEGF agents in RVOs is related to several predictive factors at baseline, including the presence of intraretinal fluid, cystoid type of macular edema among others [4]. In patients with CRVO, macular thickness and integrity of the ellipsoidal zone (EZ) have been observed to correlate with baseline visual acuity and prognosis [5]. Baseline visual acuity is also a predictor of visual outcome after the resolution of ME in CRVO [6].

RVO also has several systemic risk factors. From RVO's pathogenesis, Virchow's triad for thrombosis plays an important role, including hemodynamic change, degenerative vessel wall, and blood hypercoagulability. Besides, systemic diseases such as hypertension, diabetes mellitus, and hyperlipidemia are strongly associated with the occurrence of RVO [7]. Atherosclerotic-associated diseases are also linked to RVO, including carotid plaque, obesity, and cigarette smoking [8]. In Grave's disease, thyroid eye disease can be an unusual risk factor for RVO, so as in other retrobulbar compressive pathology [9].

However, the relationship between baseline CRT and VA in ME secondary to RVO and these well-known risk factors was not clear. These studies aimed to elucidate the impact of systemic and ocular risk factors on baseline visual acuity and OCT parameters.

Methods

We conducted a retrospective study including 46 patients with treatment-naive RVO-ME referred consecutively from January 2015 to November 2019 in the department of Ophthalmology, the First Affiliated Hospital of Sun Yat-sen University. The CRVO and BRVO diagnosis were based on the International Classification of Diseases, Tenth Revision (ICD-10) code H34.813 and H34.833, respectively [10]. This study was approved by the *Independent Ethics Committee for Clinical Research and Animal trials of the First Affiliated Hospital of Sun Yat-sen University*. This study followed the tenets of the Declaration of Helsinki.

The inclusion criteria included: Only patients with clinical findings consistent with a diagnosis of RVO (acute vision loss, diffuse intraretinal hemorrhage, venous tortuosity) and macular edema and age ≥ 18 years old were included in the studies. The exclusion criteria included: patients who received any form of surgical or medical treatment; patients who exhibit other complications such as neovascularization of the iris, neovascularization of the angle, and vitreous hemorrhage; patients who have other retinal diseases such as diabetic retinopathy, hypertensive retinopathy, and retinal detachment.

Patient charts were reviewed to collect the following data: age, sex, history of hypertension, diabetes, hyperlipemia, smoking, operation history, the date of presentation probable duration of RVO (as determined by subtracting the subjective symptom onset from the date of clinical presentation), Snellen best-corrected visual acuity (BCVA) based on subjective refraction on admission. Snellen BCVA was converted to logarithm of the minimum angle of resolution (log MAR): Log MAR = lg (1/Snellen BCVA). The log MAR value for counting fingers visual acuity was assigned as + 2.0 log MAR according to

methods published by Holladay [11]. We also recorded hematological examination (concentration of blood glucose and blood lipid) and results of carotid artery color ultrasound and brachial artery color ultrasound. The subjects were classified as hypertension when systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg according to the guidelines of The European Society of Hypertension/European Society of Cardiology or if they reported taking antihypertensive medication, as verified by the interviewer [12]. Diabetic subjects were defined in line with the American Diabetes Association [13] or based on self–reported data. Dyslipidemia was defined following the criteria of the ATP III Expert Panel of the US National Cholesterol Education Program, as total cholesterol > 240 mg/dL or triglyceride > 200 mg /dL [14], or has been diagnosed as hyperlipidemia and was currently taking hypolipidemic drugs. Smoking history was defined as smoking ≥ 5 packs per week for more than one year.

Brachial artery color ultrasound

We examined the endothelial function of the brachial artery using an established method [15]. In brief, subjects were instructed to rest in a supine position for 15 mins, after which flow-mediated vasodilation (FMD) was assessed in the right arm using high-resolution ultrasonography (Phillips HD15, USA), The brachial artery was scanned laterally, and its diameter at the diastole end (i.e. from the inner border of the adventitia to the inner border of the adventitia) was measured. The cuff was positioned 5 cm proximal to the antecubital fossa. A view of a 5-cm transverse section of the brachial artery was recorded for periods of 30 sec at baseline and during peak reactive hyperemia (up to 3 min after cuff release following deflation of the blood pressure cuff, which had been previously inflated around the forearm to 50mm Hg above systolic blood pressure for 5min). The vessel diameter was calculated automatically using built-in software. FMD was defined by the following formula: FMD (%) = {(maximal artery lumen diameter after cuff release-artery lumen diameter at baseline)/ artery lumen diameter at baseline} × 100 [16]. Endothelial dysfunction was defined as FMD (%)＜10% [17].

Carotid artery color ultrasound

All patients' tests were conducted by one physician from the Ultrasonography Department of The First Affiliated Hospital of Sun Yat-sen University using diagnostic ultrasound equipment (Phillips HD15, 50-MHz probe, USA). Ultrasound longitudinal images of the common carotid artery were acquired at the end of diastole, in which the far wall intima-media interface was clearly defined [18]. The leading edge of the intima and the media-adventitia interface were traced as continuous lines, and mean IMT values were calculated automatically. A carotid plaque was defined as a localized protruded lesion with a thickness of IMT of the carotid artery ≥ 1.5 mm [19].

OCT imaging protocol

SD-OCT (Spectralis, Heidelberg Engineering Inc, CA, USA) was performed on all patients during the initial examination. The integrity of the outer retinal layers was analyzed in the horizontal and vertical scans centered on the fovea, including the external limiting membrane (ELM), ellipsoid zone (EZ), and retinal

pigment epithelium (RPE). For example, ELM was graded as “disturbed” if we were unable to follow the hyperreflective zone of the ELM in an area measuring 200 μm or more, regardless of whether it was in the horizontal or vertical SD-OCT scan [20]. Similarly, the integrity of EZ and RPE was assessed (Fig. 1a-c). Experienced operators manually measured the central retinal thickness (CRT) as the distance between the inner limiting membrane (ILM) of the macular fovea and the hyperreflective inferior limit of retinal pigment epithelium (RPE) on B-scan through the fovea, using a caliper integrated into the device (Fig. 2).

According to the central retinal thickness of the macula, the enrolled eyes were classified into the high CRT group (CRT ≥ 440 μm) and the low CRT group (CRT < 440μm). According to the degree of impaired vision, the enrolled eyes were classified into the good VA group (BCVA ≥ 1.0 Log MAR) and the poor VA group(BCVA<1.0).

Statistical analysis

Statistical analysis was performed using SPSS for Windows software, version 20.0 (SPSS Inc, Chicago, Illinois USA). Analysis of Pearson χ2 test was used to compare the risk factors in different groups. Univariate analyses are followed by multivariate logistic regression analyses, modeling visual condition (BCVA) and morphological condition (CRT) as a binary variable which were performed to determine risk factors for visual loss and macular pathology. A *P* value of 0.05 or less was considered statistically significant.

Results

A total of 46 eyes from 46 patients met the inclusion criteria for this study. Table 1 describes the demographics and ocular characteristics of the total patient population. Twenty-eight (60.87%) patients were male. The mean age was 62.87 ± 12.69 years (range: 38-84 years). The mean duration was 3.77 ± 7.19 months (range: 0.20-36.00 months). Of this sample, 19(41.30%) had CRVO and 27(58.70%) had BRVO. Among patients with RVO, 29 (63.04%) had hypertension, 9 (19.57%) had diabetes, 18 (39.13%) had hyperlipidemia, 9 (19.57%) had smoking history, 24 (52.17%) had endothelial dysfunction, 13 (28.26%) had a carotid plaque. The OCT images showed disrupted ELM in 20 (43.48%) patients, disrupted EZ in 25 (54.35%) patients, and disrupted RPE in 2 (4.35%) patients. The mean BCVA was 1.00 ± 0.74 Log MAR (range: 0.00-3.00 Log MAR) and the mean CRT was 666.24 ± 332.80 μm (range: 293.00-1553.00 μm).

Association of macular edema with various factors and diseases

Univariate analysis for risk factors of macular edema is outlined in table 2. Between high CRT group and low CRT group, RVO type (CRVO) [16 (51.6%) versus 3(20.0%), *P*=0.041], disrupted ELM [17 (54.8%) vs 3 (20.0%), *p*=0.025] and disrupted EZ [21 (67.7%) vs 4 (26.7%), *p*=0.009] were risk factors for higher CRT. Logistic regression analysis demonstrated that RVO type (CRVO) was overall the strongest risk factor for higher CRT with an OR of 8.378 (95%CI 1.468 to 47.802, *p*=0.017) (table 3).

Association of visual acuity with various factors and diseases

Univariate analysis for BCVA in RVO patients is outlined in table 4. Between high poor VA group and good VA group, endothelial dysfunction [16 (69.6%) vs 8 (34.8%), p=0.018], CRT ≥440μm[20 (87.0%) vs 11 (47.8%), p=0.005], disrupted ELM [15 (65.2%) vs 5 (21.7%), p=0.003] and disrupted EZ [19 (82.6%) vs 6 (26.1%), p<0.001] were risk factors for poorer BCVA. Logistic regression analysis demonstrated that endothelial dysfunction and disrupted EZ were overall the strongest risk factors for poorer BCVA with an OR of 6.010 (95%CI 1.105 to 32.690, p=0.038) and 32.481 (95%CI 1.857 to 568.201, p=0.017) (table 5).

Discussion

In this study, we evaluated risk factors for macular edema secondary to RVO. RVO type was the strongest independent factor for higher CRT (CRT ≥ 440μm). Besides, disrupted ELM and EZ was found to be a significant risk factor by univariate analysis. There was no difference in gender, age, duration, systemic diseases, smoking habits, vascular endothelial function, carotid plaque and disrupted ELM, EZ, and RPE. These results indicate that patients with CRVO may potentially be more likely to suffer more serious macular edema than patients with BRVO.

Prior studies have shown that there are differences in pathological mechanisms between CRVO and BRVO. Rachel *et al.* reported visual acuity was generally poor at baseline (≤20/40) and decreased further over time in CRVO [21]. It has been demonstrated that CRVO eyes had a higher ischemic index and VEGF level compared with BRVO eyes [22]. Spaide *et al.* reported that increased VEGF would induce dilated macular capillaries and hyperpermeability [23], which may explain why patients with CRVO had a thicker central retina than BRVO.

Our study demonstrates that endothelial dysfunction and disrupted EZ associate with worse visual acuity in RVO patients. Spaide *et al.* reported that endothelial dysfunction is an independent risk factor for BRVO, however, CRVO and smoking patients were not included in their studies [23]. The endothelium plays an important role in vascular function and prior studies suggest that abnormal vascular endothelium and arteriosclerosis are risk factors for RVO [24, 25]. Generated from vascular endothelial cells, Nitric oxide (NO) is an important signal molecule, regulating local blood flow [26]. In RVO with endothelial dysfunction, decreased NO level might reduce the retinal blood flow and increase platelet aggregation, which may have negative effects on visual acuity [27]. In experimental BRVO eyes, decreased vitreous NO level and narrowing of retinal arteries can be observed, supporting that impairment in the release of NO may contribute to the development of hypoxia and necrosis in the affected retina [28]. However, further investigation is needed to demonstrate it.

Our studies also show that disruption of EZ correlated with poorer visual acuity. The EZ is referred to the hyperreflective band between ELM and RPE in OCT, which is used for the evaluation of photoreceptor health. Its disruption correlates with poor vision in various diseases including RVO. It is reported that photoreceptor loss and EZ loss are the predictive factors for poor visual outcome and a large extent of macular edema in RVO [5, 29]. Touka *et al.* evaluated quantitative EZ metrics and observed that baseline VA was inversely associated with EZ loss [30]. In long-term visits, Chatziralli *et al.* also reported the

association between poor final visual acuity and photoreceptor disruption [20]. Kanakis *et al.* removed shadowing from the OCT scans and demonstrated the relationship between disruption of EZ and the areas of capillary nonperfusion [31]. Therefore, the disruption of EZ is not only caused by photoreceptor loss, but also other interconnected factors, including optical and histologic effects of both edema and ischemia. The association of EZ integrity with baseline vision which is similar to the results of previous studies paves the way for studies using OCT analysis of EZ integrity to evaluate the baseline VA in RVO patients.

Previous studies have shown that hypertension, diabetes mellitus, hyperlipidemia, carotid plaque, and cigarette smoking are associated with an increased risk of RVO [7, 8]. However, our study has shown that they are not related to the extent of clinical manifestation. The reason for this marked variance from prior studies is uncertain. Evidence supporting the direct impact of systemic disease on visual function and retinal morphology is still not sufficient. As it is a retrospective study, potential bias cannot always be eliminated, but it can nevertheless provide important results.

As with any retrospective analysis, the limitations of this study must be considered. This study is small and the results should be considered preliminary. Further assessment and research are needed to better understand the underlying pathophysiology of these retinal changes. Although other risk factors were not associated with VA and CRT at baseline, long-term follow-up and assessment of retinal architecture changes are needed. Finally, the cause of the association between endothelial dysfunction and baseline visual changes remains unknown, and further prospective human studies are required to determine the true nature of these changes.

Despite these limitations, our results highlighted some baseline features in patients with RVO-ME, which should help inpatient counseling and planning preventive management. Measuring the FMD of the brachial artery and evaluating the integrity of EZ may help earlier recognition of eyes being prone to have poor vision. Patients with CRVO tend to have more significant ME than BRVO. Our study is limited by the small sample size, therefore larger studies are required to confirm these observations.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were following the ethical standards of the *Independent Ethics Committee for Clinical Research and Animal trials of the First Affiliated Hospital of Sun Yat-sen University.* The number of ethical approval is 2020 [362]. Informed consent was obtained from all individual participants included in the study. The Approval letter for Research Protocol is attached in supplemental files.

Consent for publication

This manuscript does not contain personal and/or medical information about an identifiable living individual.

Competing interests

The authors declare that they have no competing interests that are relevant to the content of this article.

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Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by P.W., JC.Y, M.Z, and C.W. The first draft of the manuscript was written by JC.Y and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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

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Tables

TABLE 1 Demographics and ocular characteristics in RVO eyes (n=46 patients, 46 eyes)

	$N / \bar{x} \pm s$	%
Gender		
Male	28	60.87
Female	18	39.13
Age (years)	62.87 ± 12.69	
Duration (months)	3.77 ± 7.19	
RVO type		
CRVO	19	41.30
BRVO	27	58.70
Hypertension	29	63.04
Diabetes	9	19.57
Hyperlipidemia	18	39.13
Smoking	9	19.57
Endothelial dysfunction	24	52.17
Carotid plaque	13	28.26
Disrupted ELM	20	43.48
Disrupted EZ	25	54.35
Disrupted RPE	2	4.35
BCVA (LogMAR)	1.00 ± 0.74	
CRT (μm)	666.24 ± 332.80	

RVO = retinal vein occlusion; CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion; ELM = external limiting membrane; EZ = ellipsoid zone; RPE = retinal pigment epithelium; BCVA = best corrected visual acuity; CRT = central retinal thickness

TABLE 2 Univariate analysis for factors of macular edema

Factor	High CRT group, n=31(67.4%)	Low CRT group, n=15(32.6%)	c2	*P*
Gender (male)	20(64.5%)	8(53.3%)	0.531	0.466
Age ≥ 60 years	21(67.7%)	6(40.0%)	3.209	0.073
RVO type (CRVO)	15(48.4%)	12(80.0%)	4.167	0.041*
Duration ≥ 3 months	25(80.6%)	10(66.7%)	1.086	0.297
Hypertension	19(61.3%)	10(66.7%)	0.125	0.723
Diabetes	8(25.8%)	1(6.7%)	2.353	0.125
Hyperlipidemia	13(41.9%)0	5(33.3%)	0.314	0.575
Smoking	7(22.6%)	2(13.3%)	0.549	0.459
Endothelial dysfunction	18(58.1%)	6(40.0%)	1.322	0.250
Carotid plaque	8(25.8%)	5(33.3%)	0.282	0.595
Disrupted ELM	17(54.8%)	3(20.0%)	4.993	0.025*
Disrupted EZ	21(67.7%)	4(26.7%)	6.874	0.009**
Disrupted RPE	2(6.5%)	0(0.0%)	1.012	0.314

CRT = central retinal thickness; CRVO = central retinal vein occlusion; ELM = external limiting membrane; EZ = ellipsoid zone; RPE = retinal pigment epithelium

*: *P*0.05

**: *P*0.01

TABLE 3 Logistic regression analysis for risk factors of macular edema

Risk factor	Regression coefficient	Standard error	Walds	*P*	OR	95% CI	
						Lower	Upper
RVO type (CRVO)	2.126	0.889	5.723	0.017*	8.378	1.468	47.802
Disrupted ELM	0.075	1.315	0.003	0.954	1.078	0.082	14.197
Disrupted EZ	2.275	1.308	3.024	0.082	0.103	0.008	1.335

OR = odds ratio; CI = confidence interval; CRVO = central retinal vein occlusion; ELM = external limiting membrane; EZ = ellipsoid zone

*: *P*0.05

TABLE 4 Univariate analysis for factors of visual acuity

Factor	Poor VA group, n=23(50.0%)	Good VA group, n=23(50.0%)	c2	*P*
Gender (male)	14(60.9%)	14(60.9%)	0.000	1.000
Age≥ 60 years	16(69.9%)	11(47.8%)	2.242	0.134
RVO type (CRVO)	11(47.8%)	8(34.8%)	0.807	0.369
Duration≥ 3 months	18(78.3%)	17(73.9%)	0.119	0.730
Hypertension	15(65.2%)	14(60.9%)	0.093	0.760
Diabetes	7(30.4%)	2(8.7%)	3.453	0.063
Hyperlipidemia	7(30.4%)	11(47.8%)	1.460	0.227
Smoking	6(26.1%)	3(13.0%)	1.243	0.265
Endothelial dysfunction	16(69.6%)	8(34.8%)	5.576	0.018*
Carotid plaque	8(34.8%)	5(21.7%)	0.965	0.326
CRT ≥ 440μm	20(87.0%)	11(47.8%)	8.013	0.005**
Disrupted ELM	15(65.2%)	5(21.7%)	8.846	0.003**
Disrupted EZ	19(82.6%)	6(26.1%)	14.808	0.001**
Disrupted RPE	2(8.7%)	0(0.0%)	2.091	0.148

VA = visual acuity; CRVO = central retinal vein occlusion; CRT = central retinal thickness; ELM = external limiting membrane; EZ = ellipsoid zone; RPE = retinal pigment epithelium

*: *P*0.05

**: *P*0.01

TABLE 5 Logistic regression analysis for risk factors of visual acuity

Risk factor	Regression coefficient	Standard error	Walds	*P*	OR	95%CI	
						Lower	Upper
Endothelial dysfunction	1.793	0.864	4.308	0.038*	6.010	1.105	32.690
CRT ≥ 440μm	1.462	0.907	2.598	0.107	4.316	0.729	25.550
Disrupted ELM	-1.336	1.404	0.905	0.341	0.263	0.017	4.120
Disrupted EZ	3.481	1.460	5.682	0.017*	32.481	1.857	568.201

OR = odds ratio; CI = confidence interval; CRT = central retinal thickness; ELM = external limiting membrane; EZ = ellipsoid zone

*: *P*0.05

Figures

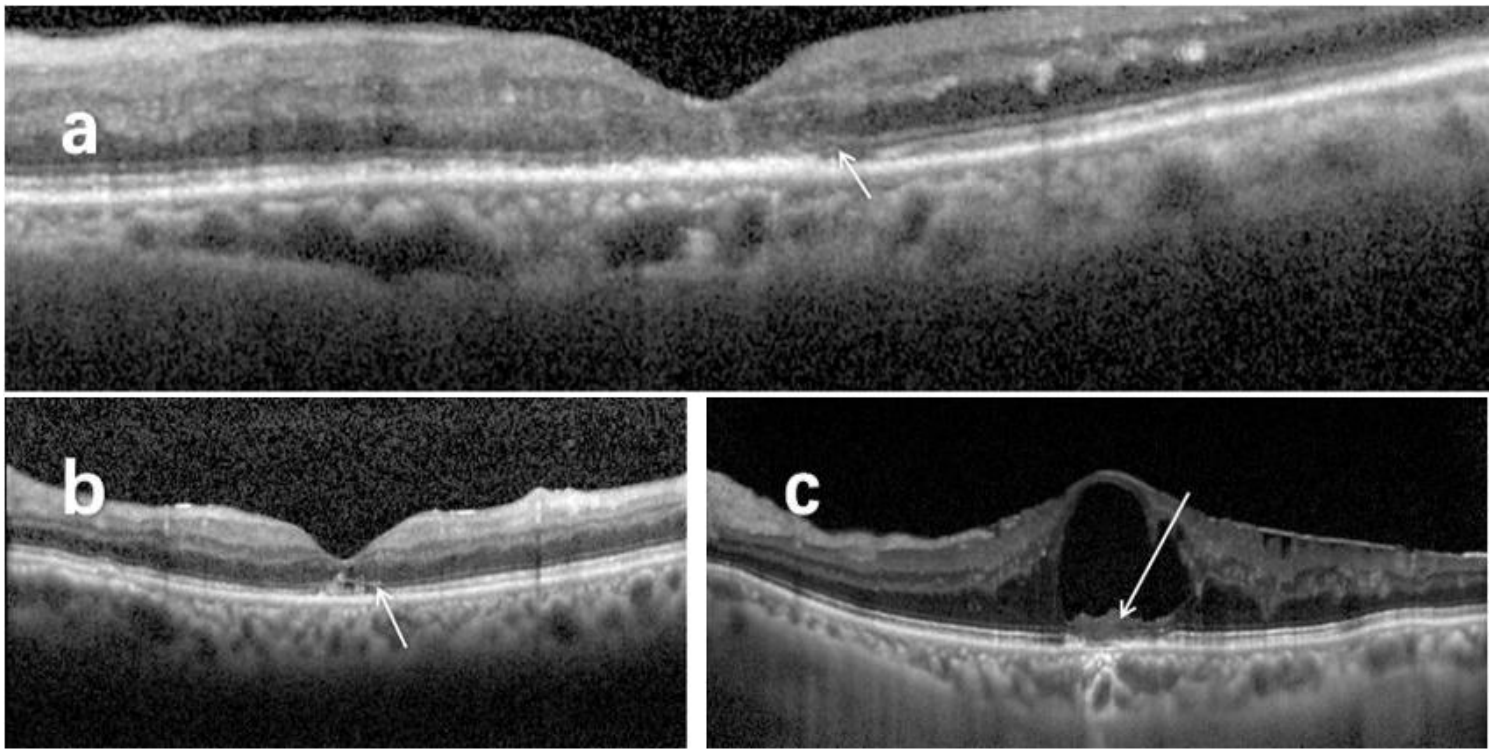

Figure 1

(a) A patient with BRVO of the left eye from our studies. The BCVA was 1.0 log MAR (20/200 Snellen equivalent), and the CRT was 294 μm. The integrity of ELM and EZ were disrupted. (b) A patient with CRVO of the right eye. The BCVA was 0.8 Log MAR (20/80 Snellen equivalent), and the CRT was 221μm. The integrity of EZ were disrupted. (c) A patient with BRVO of the left eye. The BCVA was 1.3 Log MAR (20/400 Snellen equivalent), and the CRT was 634 μm. The integrity of ELM, EZ and RPE were disrupted.

CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion; ELM = external limiting membrane; EZ = ellipsoid zone; RPE = retinal pigment epithelium; BCVA = best-corrected visual acuity; CRT = central retinal thickness

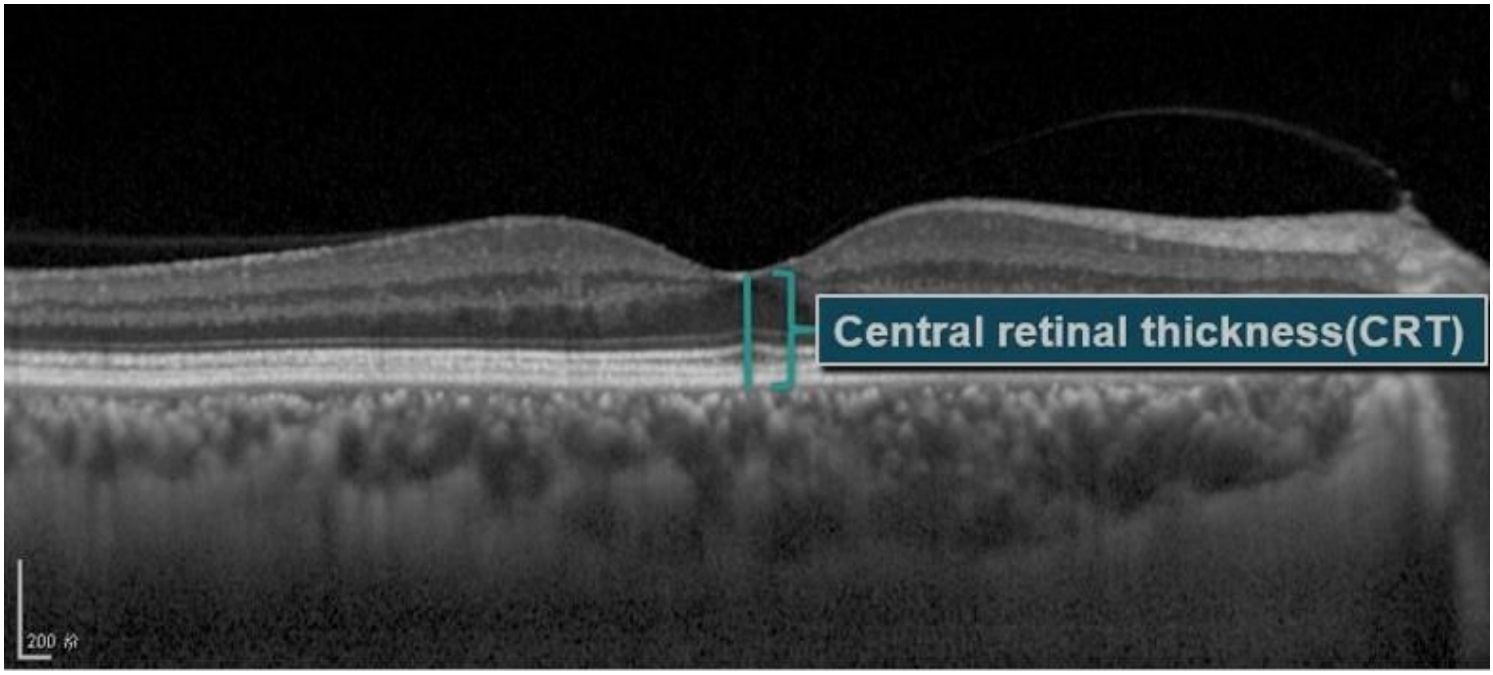

Figure 2

Measurement of CRT: B-scan though the fovea of the eye, the distance between the ILM of the macular fovea and the hyperreflective inferior limit of RPE was measured manually. CRT = central retinal thickness; ILM = internal limiting membrane; RPE = retinal pigment epithelium