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Relationship between stereopsis and vision-related quality of life in patients with branch retinal vein occlusion

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ABSTRACT

Background To investigate the relationship between stereopsis and vision-related quality of life (VR-QOL) in patients with branch retinal vein occlusion (BRVO) before and after treatment with intravitreal ranibizumab (IVR).

Methods This prospective multicentred observational study included 37 patients undergoing IVR treatment for unilateral BRVO and 24 age-matched healthy controls. Stereopsis was evaluated using the TNO stereo test (TNO) and Titmus stereo test (TST) every month, and the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25) was administered at baseline, then at 3, 6 and 12 months after treatment.

Results Time course of the changes in stereopsis and VR-QOL. IVR treatment significantly reduced central fovea thickness and improved both the TNO and the TST from 2 to 12 months (both $p<0.05$). Stereopsis before and after IVR injection in the eyes with BRVO were significantly worse than those in control subjects (TNO, $p<0.001$; TST, $p<0.001$). The VFQ-25 composite score significantly improved from 3 to 12 months after IVR treatment ($p<0.05$). Univariate analysis showed that the TNO score at baseline was significantly correlated with the VFQ-25 composite score at baseline and after treatment ($p<0.05$, $p<0.05$, respectively). TST score was not associated with the VFQ-25 composite score at baseline or after treatment.

Conclusions Treatment with IVR for BRVO improved cystoid macular oedema, which was correlated to improved stereopsis, although not to the control level. The TNO score at baseline was associated with VR-QOL in patients with BRVO.

Key messages

What is already known on this topic?

► Intravitreal ranibizumab improved vision-related quality of life (VR-QOL) in patients with branch retinal vein occlusion (BRVO).

What this study adds?

► Stereopsis at baseline was associated with VR-QOL in patients with BRVO.

How this study might affect research, practice or policy?

► We should pay attention not only to visual acuity but also to stereopsis. This is because stereopsis is related to quality of life.

INTRODUCTION

Branch retinal vein occlusion (BRVO) is a common retinal vascular condition that may result in significant loss of visual functions including visual acuity, contrast sensitivity, metamorphopsia and stereopsis.[1–4] Stereopsis is the perception of depth from disparity which is the difference in the position of features in the retinal images in the two eyes. Even in cases where visual acuity is improved after treatment, stereopsis in patients with BRVO is worse than in healthy subjects.[4]

The 25-item National Eye Institute Visual Function Questionnaire (VFQ-25) is a vision-specific health-related quality of life (QOL) instrument composed of 12 vision-targeted health-related QOL domains to assess patients' perception of their visual-related function and the influence of vision problems on performance of daily activities.[5] Suzukamo *et al* developed a Japanese version of the VFQ-25 and proposed a particular combination of subscales on the basis of the Japanese version's factor structure and other psychometric characteristics.[6] Prior studies have reported vision-related QOL (VR-QOL) results for various retinal diseases such as macular hole (MH),[7] epiretinal membrane (ERM),[8] diabetic macular oedema (DMO),[9] proliferative diabetic retinopathy (PDR),[10] retinal detachment (RD),[11] age-related macular degeneration and retinal vein occlusion (RVO).[12–17]

The impact of QOL is accurately reflected by assessing an individual's presenting binocular visual function, because individual use both eyes for functional vision.[18] When compared with a control group without ocular disease, statistically significant decreases in VR-QOL were found in patients with unilateral BRVO.[19] Stereopsis, which is one of the binocular visual functions, is improved by treatment for 6 months in patients with BRVO, but not to control levels.[4] Patients with

BRVO may have an increased risk of impaired stereopsis and reduced QOL, thus VR-QOL in patients with BRVO might be associated with stereopsis. Ng *et al* reported that stereopsis was associated with the VR-QOL, specially during driving, after RD surgery.[20]

However, no study has investigated the relationship between VR-QOL and stereopsis in patients with BRVO. In this study, we sought to elucidate the relationship between VR-QOL including subscales in detail and stereopsis, and reveal the time course of change in stereopsis for 12 months.

METHODS

This prospective study adhered to the tenets of the Declaration of Helsinki. Institutional Review Board approval was obtained. All participants were informed of their rights, and they provided written informed consent before undergoing the study procedures. Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research. This study included patients who had been diagnosed with BRVO at the University of Tsukuba Hospital and Mito Kyodo General Hospital between December 2016 and December 2019. All patients were treatment-naïve. Exclusion criteria included (1) previous history of vitreoretinal surgery; (2) previous history of ophthalmic disorders except mild refractive errors and mild cataract; (3) undergoing macular oedema treatment within the last 90 days (including subtenon triamcinolone acetonide, intravitreal bevacizumab, intravitreal ranibizumab (IVR), intravitreal aflibercept, topical steroid, carbonic anhydrase inhibitors); (4) undergoing intraocular surgery within the last 90 days; (5) contralateral eye of RVO; (6) poor control of hypertension and diabetes mellitus; (7) undergoing laser treatment within the last 30 days; and (8) anisometropia >2 D. We also included age-matched controls. Eligible patients with a diagnosis of BRVO were examined every month and treated with an IVR injection pro re nata for 12 months. During the treatment period (months 0–2), the patients received monthly IVR injections. During the observation period (months 3–12), all patients received monthly IVR injections if the central retinal thickness (CRT) was >300 µm, as measured by optical coherence tomography (OCT), or if serous RD or subretinal haemorrhage were present. IVR was performed by two ophthalmologists (TM and SM).

All patients were evaluated at baseline and monthly post-treatment using the TNO stereo test (TNO) and Titmus stereo test (TST); best-corrected visual acuity (BCVA) and OCT images were also obtained. The patients answered the VFQ-25 before treatment and at 3, 6 and 12 months after treatment.

We tested two indices of the stereopsis using the TNO and TST at a standard viewing distance of 40 cm with an appropriate spectacle correction. To ensure that patients did not use monocular clues on the TST, their responses were checked by inverting the stereo target and asking if the target appeared in front of or behind the page. TNO and TST were converted from seconds of arc to logarithm (log) value for analysis. The BCVA was measured using the Landolt chart and converted to the logarithm of the minimum angle of resolution units (logMAR) for analysis. The retinal microstructure was obtained using a spectral domain OCT (Cirrus; Carl Zeiss, Dublin, California, USA) and five-line raster cross scans and a macular cube were performed using Cirrus analysis software V.3.0, with more than 7/10 signal strength. We quantitated the CRT, central fovea thickness (CFT) and the presence of serous RD.

The research staff explained the VFQ-25 questionnaire to the patients, provided detailed instructions, helped if needed and checked the completed questionnaires. The VFQ-25 consists of 25 items where patients are expected to assess the level of difficulty of specific visual symptoms and daily activities. Each item applies to 1 of the 12 subscales, namely, 'general health', 'general vision', 'ocular pain', 'near activities', 'distance activities', 'social functioning', 'mental health', 'role difficulties', 'dependency', 'driving', 'colour vision' and 'peripheral vision'. These subscales range from 0 to 100 points, with 100 indicating the highest function. The VFQ-25 composite score is the average score for all subscales, without questions regarding 'general health'. In this study, a Japanese version of the VFQ-25 was used, which was modified to accommodate the Japanese lifestyle and culture and which has been validated for ocular diseases.[6]

The mean and SD were calculated for age, the TNO score, the TST score, BCVA, VFQ-25 composite score and duration of disease. The TNO, TST, BCVA, CFT and VFQ-25 composite scores were analysed using a repeated-measures analysis of variance to assess the time course of the changes. If significant differences were found, a Bonferroni test was performed. The Mann-Whitney U test was used to compare the VFQ-25 composite score between patients with BRVO at baseline and 12 months after IVR and the control subjects. The relationship between the stereopsis and VFQ-25 composite score and 12 subscales at baseline and 12 months was assessed by means of the Spearman's rank correlation coefficient test. The relationship between the stereopsis and the number of injections was assessed by means of the Spearman's rank correlation coefficient test. Statistical analysis was performed using SPSS Statistics for Mac software (V.25, IBM Corp.). All statistical tests were two-sided and the level of significance was set at $p<0.05$.

RESULTS

We analysed 37 patients (17 male, 20 female) who were diagnosed with BRVO. Their ages averaged 67.5±10.3 years (mean±SD). Twenty-four age-matched healthy control subjects (11 male, 13 female) were included in the study. The baseline characteristics of patients with BRVO and control subjects are shown in table 1. The mean duration of disease was 2.7±2.8 months. BCVA and stereopsis (assessed with the TNO and the TST) were

Table 1 Clinical characteristics in patients with branch retinal vein occlusion at baseline and control subjects

	Patients with branch retinal vein occlusion	Control subjects	P values
Cases, n	37	24	–
Age (years)	67.5±10.3	64.7±6.0	0.053
Sex (male/female)	17/20	11/13	0.99
TNO stereo test (log)	2.90±0.64	1.79±0.21	<0.001*
Titmus stereo test (log)	2.63±0.79	1.70±0.16	<0.001*
Best-corrected visual acuity (logMAR)	0.40±0.30	−0.08±0.07	<0.001*
VFQ-25 composite score	76.9±10.9	–	–
Duration (months)	2.7±2.8	–	–

The values are shown as the mean±SD.
*Significant between-group difference (Mann-Whitney U test, χ^2 test).
logMAR, logarithm of the minimum angle of resolution; VFQ-25, The National Eye Institute 25-item Visual Function Questionnaire.

significantly worse in the patients with BRVO than in the control subjects (p<0.001 and p<0.001, respectively).

The time course of changes in the TNO and TST scores in patients with BRVO are charted in figure 1. IVR injections significantly improved the TNO score from 2 months after treatment (p<0.05) (figure 1A) and the TST score from 2 months after treatment (p<0.05) (figure 1B) during the follow-up period from baseline. At baseline, TNO and TST values (second of arc) in patients with BRVO were 794 and 427 which corresponded to circle 1 and 2. At 12 months, these values were 219 and 95, which corresponded to circle 3 and 5. Even after treatment, the TNO and TST scores in patients with BRVO at 12 months were significantly worse than those of the control subjects

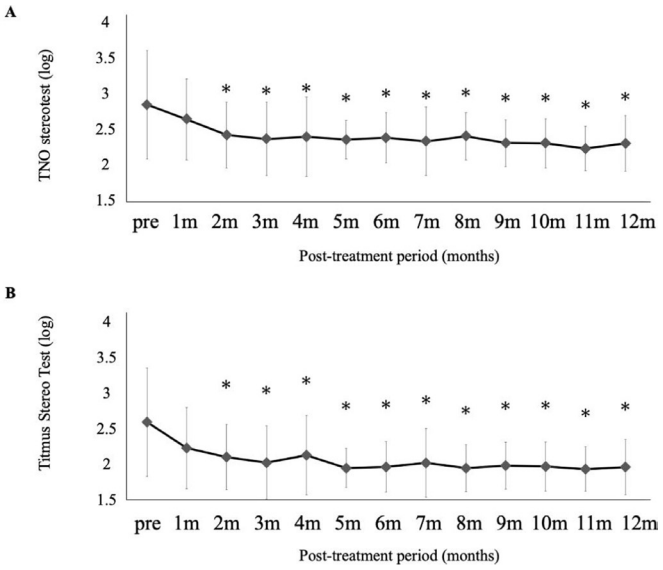

Figure 1 The time course of changes in stereopsis in patients with branch retinal vein occlusion before and after treatment for 12 months with intravitreal ranibizumab. (A) The TNO stereo test score improved significantly from 2 months after treatment. (B) The Titmus stereo test score improved significantly from 2 months after treatment. *One-way repeated measures analysis of variance with a Bonferroni test.

(p<0.001 and p<0.001, respectively). The TNO and TST scores were not correlated with the number of injections.

Changes from baseline BCVA and CFT are shown in figure 2. There was a significant improvement in BCVA (online supplemental figure A) and CFT (online supplemental figure B) after 1 month in the BRVO group. At 12 months, the BCVA of patients who received IVR treatment increased by 0.35 logMAR, while CFT reduced by 281 µm. IVR injections also resulted in significant improvements in the VFQ-25 composite scores from baseline (76.9±10.9, 84.9±7.9, 84.6±7.5 and 86.6±7.7 at baseline, 3, 6 and 12 months, respectively, p<0.05).

Scatter plots of stereopsis and the VFQ-25 composite scores at baseline and after treatment are shown in figure 2. The TNO score at baseline significantly correlated with VFQ-25 composite score at baseline (r=−0.38, p<0.05, figure 2A) and at 12 months (r=−0.34, p<0.05, figure 2C). In contrast, TST scores were not correlated with VFQ-25 composite score at baseline and 12 months (figure 2D–F).

Tables 2 and 3 display the relationship between stereopsis and each VFQ-25 subscale in patients with BRVO at baseline (table 2) and at 12 months (table 3). There were significant associations between the TNO scores and 'general health', 'general vision', 'distance activities', 'social functioning', 'colour vision' and 'peripheral vision' at baseline. The TST scores showed a significant correlation with 'ocular pain' at baseline (table 2). At 12 months after treatment, there was only a significant association between the TNO scores and 'distance activities' (table 3).

DISCUSSION

We found that patients with BRVO had worse stereopsis and BCVA at baseline than control subjects and the mean VFQ-25 composite score for patients with BRVO was 76.9±10.9 points. Several studies have provided impairment of stereopsis and BCVA in patients with retinal diseases such as MH,[21 22] ERM[23] and RD[24] when compared with control subjects. Previous studies have

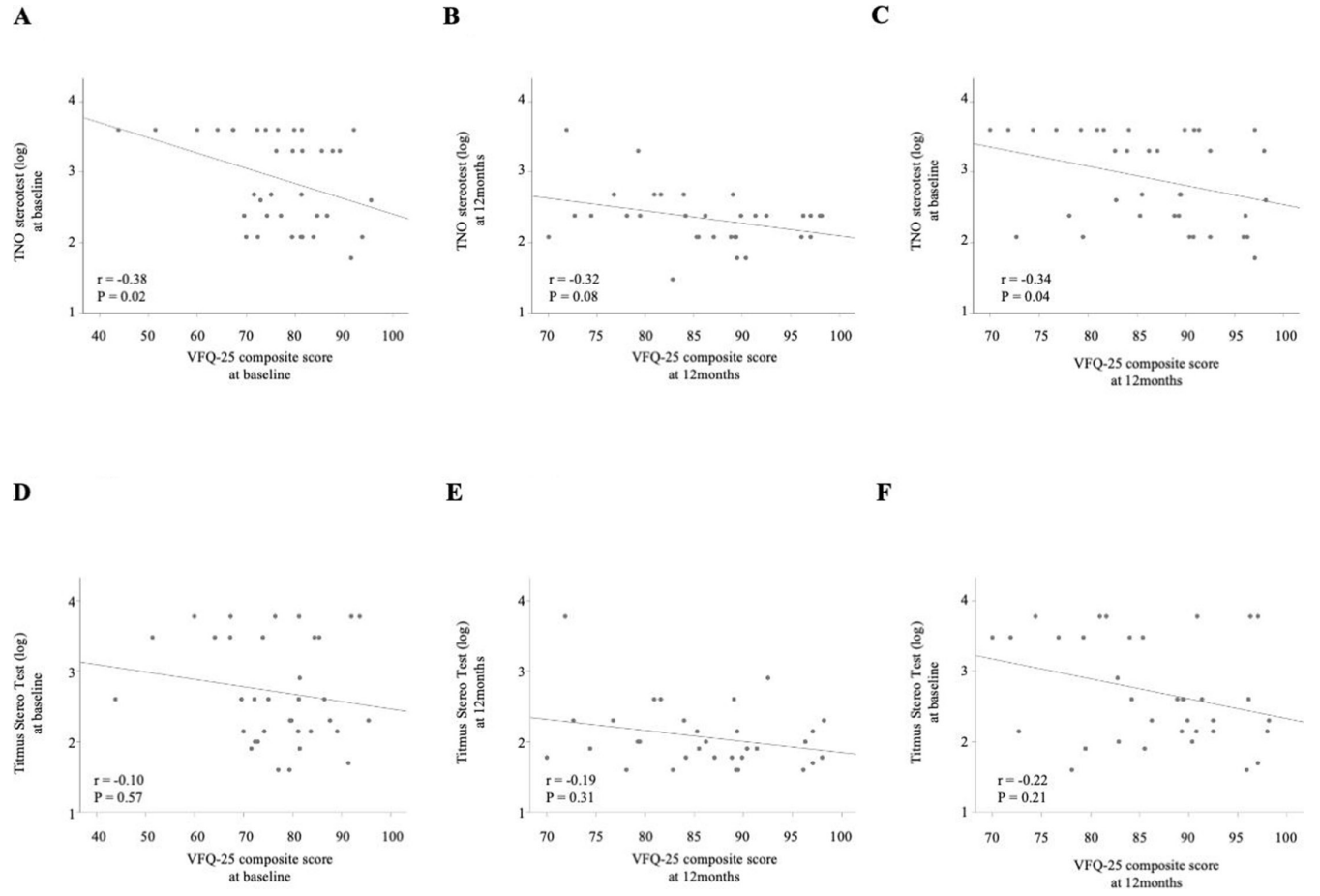

Figure 2 Scatter plots of stereopsis and the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25) composite score at baseline and after treatment. (A) TNO stereo test at baseline versus VFQ-25 composite score at baseline. (A) TNO stereo test at 12 months after treatment versus VFQ-25 composite score at 12 months after treatment. (C) TNO stereo test at baseline versus VFQ-25 composite score at 12 months after treatment. (D) Titmus stereo test at baseline versus VFQ-25 composite score at baseline. (E) Titmus stereo test at 12 months after treatment versus VFQ-25 composite score at 12 months after treatment. (F) Titmus stereo test at baseline versus VFQ-25 composite score at 12 months after treatment.

described that the mean VFQ-25 composite scores at baseline in patients with MH,[7] ERM,[8] DMO[9] and PDR[10] were 70.5, 66.2, 63.1 and 56.3, respectively. Okamoto *et al* reported that the mean VFQ-25 composite score was 89.4 in healthy controls.[8] Disturbance in stereopsis in patients with BRVO compared with control subjects was similar to that in patients with other unilateral retinal disorders. The mean VFQ-25 composite score in patients with BRVO was relatively smaller than that of healthy controls, and higher than that of patients with other retinal diseases.

The present study represents the 1-year course of changes in stereopsis in patients with BRVO who underwent IVR treatment. Okamoto *et al* revealed that vitrectomy for ERM and MH significantly improved stereopsis.[22 23] Taken together, these findings indicate that stereopsis induced by retinal diseases is improved with adequate therapy. IVR treatment has been proven to be effective for the BCVA, stereopsis and contrast sensitivity in patients with BRVO for 6 months.[3 4] By contrast, Sugiura *et al* reported that IVR did not improve metamorphopsia.[2] For the purposes of evidence-based counselling of patients and their families, clinicians should be aware that not all visual functions in patients with BRVO have been improved. In this study, the number of injections was not correlated with stereopsis. Treatment with an IVR injection pro re nata for 12 months like this study protocol improved stereopsis, although not to the control level. The other protocol such as treat and extend might be better for stereopsis in patients with BRVO.

Although the IVR treatment for BRVO improved stereopsis, stereopsis of BRVO after treatment was significantly worse than that of control subjects in this study. It is known that vitrectomy for MH and ERM significantly improved stereopsis, although not in control subjects.[22 23] Watanabe *et al* reported that even after successful RD, stereopsis of RD has markedly deteriorated compared with that of control subjects.[24] Even after treatment, patients with BRVO had stereopsis that was as poor as that in patients with other retinal disorders. BRVO is a vascular occlusive disease that results in macular oedema (MO) or serous RD (SRD). Patients with central serous chorioretinopathy with SRD have micropsia due to the compression of photoreceptors, which can result in stretching of the photoreceptors, which can then result

Table 2 The correlation between National Eye Institute 25-Item Visual Function Questionnaire subscales and stereopsis in patients with branch retinal vein occlusion at baseline

	Stereopsis at baseline			
	TNO stereo test		Titmus stereo test	
VFQ-25 subscales at baseline	r	P values	r	P values
General health	−0.36	<0.05*	−0.22	0.20
General vision	−0.39	<0.05*	−0.28	0.11
Ocular pain	0.03	0.85	−0.44	<0.01*
Near activities	−0.28	0.10	−0.20	0.25
Distance activities	−0.39	<0.05*	−0.24	0.17
Social functioning	−0.45	<0.01*	−0.26	0.14
Mental health	−0.21	0.23	−0.06	0.74
Role difficulties	−0.26	0.13	−0.05	0.80
Dependency	−0.30	0.08	−0.26	0.14
Driving	−0.16	0.44	0.08	0.70
Colour vision	−0.52	<0.01*	−0.32	0.06
Peripheral vision	−0.38	<0.05*	−0.16	0.37

*Significant correlation between VFQ-25 subscales at baseline and stereopsis at baseline (Spearman's correlation coefficient).
VFQ-25, 25-item National Eye Institute Visual Function Questionnaire.

in micropsia.[25 26] Lovasik *et al* reported that loss of stereopsis with increasing amounts of aniseikonia.[27] Based on this information, it is possible that aniseikonia may cause stereopsis deficits in patients with BRVO. However, the exact cause of this loss in stereopsis even after treatment remains unknown. Further studies are required to elucidate the mechanisms of stereopsis.

The TNO score was significantly associated with the VFQ-25 composite score before and after treatment, whereas the TST score was not associated with the VFQ-25 composite score in this study. The difference in the size of the two devices may help to explain the difference between the associations of TNO and TST with the VFQ-25 composite score. The objective of the TNO was 60 mm, and that of the TST was 5 mm. The viewing distance was 400 mm, the viewing angle of the TNO was 8.5°, that of the TST was 0.7°22; stereopsis was categorised as 'local' or 'global'. In clinical practice,

Table 3 The correlation between National Eye Institute 25-Item Visual Function Questionnaire subscales and stereopsis in patients with branch retinal vein occlusion at 12 months after treatment

	Stereopsis at 12 months after treatment			
	TNO stereo test		Titmus stereo test	
VFQ-25 subscales at 12 months after treatment	r	P values	r	P values
General health	−0.18	0.31	−0.11	0.54
General vision	−0.05	0.81	−0.05	0.77
Ocular pain	−0.01	0.94	0.07	0.69
Near activities	−0.35	0.053	−0.26	0.15
Distance activities	−0.41	<0.05*	−0.15	0.41
Social functioning	−0.20	0.27	−0.18	0.33
Mental health	−0.27	0.14	−0.24	0.20
Role difficulties	−0.20	0.28	−0.10	0.58
Dependency	−0.22	0.22	−0.29	0.11
Driving	−0.20	0.35	−0.04	0.85
Colour vision	−0.21	0.26	−0.24	0.18
Peripheral vision	−0.21	0.24	−0.04	0.84

VFQ-25=25 Item Visual Function Questionnaire.
*Significant correlation between VFQ-25 subscales at 12 months after treatment and stereopsis at 12 months after treatment (Spearman's correlation coefficient).
VFQ-25, 25-item National Eye Institute Visual Function Questionnaire.

stereopsis used to detect a contour-based stereo target such as the TST is considered to be 'local', while the stereopsis to detect a random dot-based stereo target such as the TNO is considered to be 'global'.[28–31] For calculating the viewing angle, the length of the TNO on the ocular fundus was 2.5 mm and that of the TST was 0.2 mm. Since the BRVO lesion size was larger than length of the TST on the ocular fundus, TNO, which is a type of 'global' stereopsis, might be associated. To the best of our knowledge, this is the first study to examine the association between stereopsis and VR-QOL. Potic *et al* reported that stereopsis was associated with the VR-QOL, especially during driving, in patients with RD.[32] Therefore, stereopsis is important for VR-QOL in patients with retinal disease, and our data may help improve the patient's adherence to become willing to actively and continuously receive care.

In our study, there were no correlations between the TST score and any of the VFQ-25 subscales except for 'ocular pain', whereas the TNO was significantly correlated with quality of vision subscales such as 'general vision', 'distance activities', 'colour vision',and 'peripheral vision' at baseline. In addition, 'distance activities' were also significantly correlated with the TNO at 12 months. It is noteworthy that impairment in 'distance activities' was seen in patients with BRVO due to unilateral retinal diseases. Although BCVA in patients with BRVO recovered to the level of control subjects after IVR treatment, recovery in 'distance activities' was poor, which may be explained by the impairment in stereopsis. The VFQ-25 composite score was not associated with stereopsis in patients with BRVO at 12 months after treatment in this study. This may be because that other visual functions such as contrast sensitivity and metamorphopsia were more relevant to the VFQ-25 composite score and further study is needed to determine the relationship between the VFQ and visual functions.

There are some limitations to this study, First, the small sample size reduced the probability of identifying statically significant associations. Second, the lack of examination affected stereopsis including eye dominance, pupil size and accommodation can be a limitation of this study.[33–36] Further, the placebo effect may have affected the VFQ-25 results. For example, it is possible that the patients recognised that they had received IVR treatment and answered the VFQ-25 questions more positively because of the expectation that they would benefit from the treatment, resulting in inflated VFQ-25 scores. In addition, the result of VFQ-25 was totally subjective and would vary between patients depending on many personal factors. This cannot be avoided by the study design, but could account for some of the improvements in the NEI VFQ-25.

In summary, our findings underscore the fact that IVR treatment for BRVO improved stereopsis and VR-QOL for 12 months. Stereopsis in unilateral BRVO was worse than in control subjects, even after treatment. The TNO score at baseline was associated with VR-QOL in patients with BRVO.

Contributors Design and conduct of the study: FO, TO. Data collection: SM, TM, YS, YO. Management, analysis and interpretation of data: TH, FO. Preparation of the manuscript: SM, FO. Review of the manuscript: FO, TO. Approval of the manuscript: FO, TO. The guarantor: SM

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Institutional Review Board of the Tsukuba University Hospital and Mito Kyodo General Hospital (number: H27-238, approved date: 26 February 2016) and was conducted in accordance with the tenets of the Declaration of Helsinki.

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