• Clinical Research •

Comparison of the effect of ranibizumab in retinal vein occlusion and macular edema with different optical coherence tomographic patterns

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Abstract

● **AIM:** To explore the morphological and functional parameters to evaluate the effectiveness of intravitreal injections of ranibizumab (IVR) in treating macular edema (ME) secondary to retinal vein occlusion (RVO).

● **METHODS:** This retrospective study involved 65 RVO patients (65 eyes) who received IVR and were followed-up for more than 3mo. ME was categorized into cystoid macular edema (CME), diffuse retinal thickening (DRT), and serous retinal detachment (SRD) according to optical coherence tomography (OCT) images. The comparison of best corrected visual acuity (BCVA; logMAR) and central macular thickness (CMT) among different follow-up points and those among 3 groups were performed by Kruskal-Wallis test. The correlation between BCVA and baseline parameters during treatment was analyzed using Spearman correlation analysis.

● **RESULTS:** BCVA tended to improve in all groups, with marked improvement in CME and DRT groups. CMT showed the greatest reduction after 1wk, and remained stable over the following 3mo. DRT patients had the worst BCVA and the highest CMT at baseline, but the differences became smaller after IVR treatment. CMT in SRD group was significantly better than in CME and DRT groups 3mo after IVR. Most patients of CME and SRD groups transitioned to a normal pattern at 3mo follow-up. DRT patients were most likely to transform into the other morphological groups, while SRD patients showed minimal transitions. BCVA at baseline was identified as the most important prognostic indicator in all 3 groups. Additionally, DRT patients with a longer clinical course, higher CMT and central retinal vein occlusion (CRVO) tend to exhibit worse BCVA after treatment. In addition, CRVO patients are more likely to have worse BCVA at 2 and 3mo follow-up compared with branch retinal vein occlusion (BRVO) patients in CME group. SRD patients with higher baseline CMT were prone to experiencing worse BCVA after treatment.

● **CONCLUSION:** The effectiveness of IVR is strongly correlated with baseline BCVA in all 3 groups. Baseline parameters including clinical course, CMT, and RVO position are also useful in predicting the BCVA at different time points after treatment.

● **KEYWORDS:** retinal vein occlusion; optical coherence tomography; serous retinal detachment; cystoid macular edema; diffuse retinal thickening

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INTRODUCTION

Retinal vein occlusion (RVO) stands as a prevalent cause of visual impairment and ranks as the second most common retinal vascular disorder[1]. RVO divides into two main types: central retinal vein occlusion (CRVO) with a prevalence ranging from 0.1% to 0.4% and branch retinal vein occlusion (BRVO) with a prevalence between 0.6% and 1.2%, depending on the thrombosis position[2]. Alongside RVO, macular edema (ME) and iris and/or retinal neovascularization emerge as common complications[3]. ME serves as the primary contributor to visual impairment in RVO patients, followed by foveal ischaemia. Despite the vision damage caused by RVO, some patients experience acute, painless vision loss in one eye and overlook the unilateral vision loss, leading to irreversible vision loss.

The exact pathogenesis of RVO remains unclear, although various risk factors have been investigated, including atherosclerosis, inflammation, compression, and vasospasm[4]. Associations have been identified between RVO and conditions

such as hypertension or glaucoma[5-6]. This study aims to explore the relationship between the prognosis of RVO and baseline characteristics, offering clinical observation targets and prognostic indicators for RVO patients.

Ranibizumab, an anti-vascular endothelial growth factor (anti-VEGF) agent, has been employed in treating ME secondary to RVO since 2010[7]. The elevation of VEGF levels in RVO patients is attributed to reduced blood flow in retinal capillaries and hypoxia. The upregulation of VEGF contributes to the disruption of blood-retinal barrier, and increased vascular permeability[8]. Anti-VEGF therapy prompted significant advancements in RVO treatment, with improved visual outcomes and fewer adverse events in multiple large randomized clinical trails[9-10].

ME has been suggested to be classified into cystoid macular edema (CME), diffuse retinal thickening (DRT), and serous retinal detachment (SRD) according to optical coherence tomography (OCT) images in diabetic ME patients[11-12]. While ME in RVO patients was previously dichotomized into two groups (CME with or without SRD), it has rarely been classified into more refined groups[13]. Thus, our study proposes that ME in RVO patients can also be categorized into three groups, aiming to elucidate the differences among these three groups. The retinal manifestations, pathogenesis and prognosis diverse across different morphological groups[14]. This research further analyzes the prognostic disparities and morphological changes among three groups after intravitreal injection treatment of ranibizumab. Accurate characterization of ME in RVO patients facilitates the diagnosis, classification of disease severity, and the development of personalized treatment approaches.

PARTICIPANTS AND METHODS

Ethical Approval This is a retrospective study performed on medical records of the RVO patients diagnosed in the Ophthalmology Department of the Fourth Affiliated Hospital of Soochow University, China. The ethics approval and consent to participate in the current study was approved and consented by the Ethics Committee of the Fourth Affiliated Hospital of Soochow University (ID: 241002).

Totally 65 patients (65 eyes) with ME and RVO were recruited in this study. Inclusion criteria for this study were as following: the ME was due to RVO, and the patients were treated with three intravitreal injections of ranibizumab at 3 timepoints (initial diagnosis, 1mo after first injection, and 2mo after first injection) and followed-up for more than 3mo. Patients were included only if the demographic and functional parameters before treatment and at least four examinations of best corrected visual acuity (BCVA; logMAR) and OCT scans at 1wk, 1, 2, and 3mo after the first intravitreal injection of ranibizumab were available. The exclusion criteria were as following: the OCT images were insufficient quality, patients had other eye diseases except refractive error or RVO, patients had hemi-central RVO, patients underwent ocular surgeries or retinal photocoagulation therapy, and patients had previous intravitreal injections. All the patients in this study were examined by the same OCT device (CIRRUS HD-OCT 5000, Carl Zeiss Meditech, Dublin, USA) and treated by the same ophthalmologic doctor according to the standard procedure at a dose of 0.5 mg.

Totally 26 of the patients (40%) were male and 39 of them were female (60%). All the patients were divided into three groups for further analyses based on different morphological ME according to OCT scans. The age, gender, clinical course, BCVA at baseline and each follow-up, intraocular pressure (IOP), central macular thickness (CMT), hypertension grade, and RVO position were recorded and analyzed among three groups.

The statistical analysis was performed by IBM SPSS Statistics version 25.0. Kolmogorov-Smirnov tests were firstly performed to check for normality. Data with normal distribution were expressed as mean±standard deviation, and data with abnormal distribution were expressed as median (1^{st} quartile, 3^{rd} quartile). Demographic and functional parameters at baseline were compared among three groups using variance analysis for normal distributed data, Kruskal-Wallis test for abnormal distributed data, and Chi-squared (χ^2) test for categorical variables. The correlation analysis was analyzed using Spearman correlation analysis. The comparison of BCVA and CMT among different follow-up points and those among three groups were performed by Kruskal-Wallis test. Statistical significance was set as $P<0.05$.

RESULTS

Demographic and Functional Parameters in Different Morphological Groups at Baseline To analyze the effects of different morphological ME groups on the efficacy of intravitreal injections of ranibizumab, RVO patients were divided into three groups based on the findings according to OCT scans. Type 1 was CME, those patients presented multiple intraretinal cyst-like areas of fluid but no subretinal fluid (Figure 1A). Type 2 was DRT, a sponge-like swelling of inner and outer layers of the retina (Figure 1B). Type 3 was SRD, those patients presented subretinal fluid between the neurosensory layer retina and retinal pigment epithelium (Figure 1C).

The comparative demographic and functional parameters among different morphological groups were presented at baseline in detail (Table 1). The distribution of age, gender, clinical course, IOP, hypertension grade and RVO position was similar among different morphological groups. All the patients had poor BCVA (logMAR) and elevated CMT at baseline,

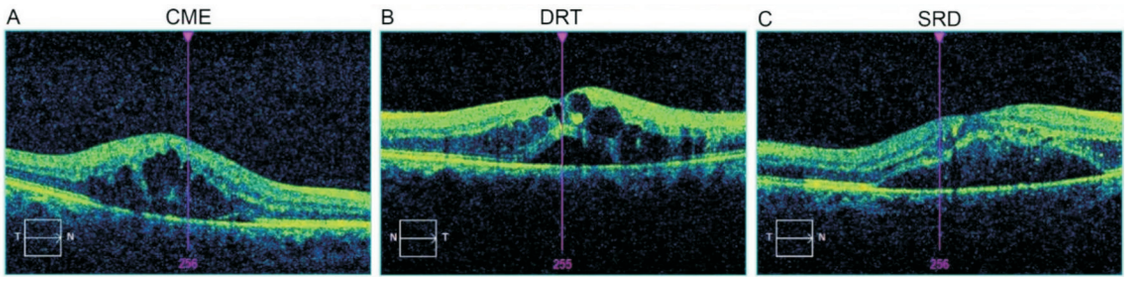

Figure 1 Typical optical coherence tomographic patterns of cystoid macular edema (CME), diffuse retinal thickening (DRT), and serous retinal detachment (SRD).

Table 1 Comparative demographic and functional parameters in the study groups at baseline

Parameters	CME	DRT	SRD	χ^2/F	*P*
Number (eyes)	19	37	9		
Age (y)	59.53±9.22	57.84±10.16	57.11±4.23	0.281	0.756
Gender (male:female)	7:12	17:20	2:7	1.809	0.405
Clinical course (mo)	2.00 (0.50, 3.00)	1.00 (0.49, 2.00)	1.00 (0.47, 3.00)		0.876
BCVA (logMAR)	0.67±0.35	1.02±0.60	0.68±0.44	3.611	0.033
IOP (mm Hg)	15.00 (13.00, 15.00)	14.54±1.95	14.78±2.68		0.940
CMT (μm)	404.00 (376.00, 539.00)	755.54±267.00	489.56±193.76		<0.001
Hypertension					0.478
Without	5	13	4		
Grade 1	8	18	3		
Grade 2	6	6	2		
RVO position				6.06	0.195
CRVO	4	17	1		
ST-BRVO	9	11	5		
IT-BRVO	6	9	3		

CME: Cystoid macular edema; DRT: Diffuse retinal thickening; SRD: Serous retinal detachment; BCVA: Best corrected visual acuity; IOP: Intraocular pressure; CMT: Central macular thickness; RVO: Retinal vein occlusion; CRVO: Central retinal vein occlusion; ST-BRVO: Superior temporal branch retinal vein occlusion; IT-BRVO: Inferior temporal branch retinal vein occlusion.

nevertheless, DRT patients had the worst BCVA and the highest CMT among three groups.

Changes of BCVA and CMT after Intravitreal Injections of Ranibizumab in Different Morphological Groups BCVA was prone to improve in CME, DRT, and SRD, especially significant in CME and DRT groups (Figure 2A-2C). BCVA after 1, 2 or 3mo treatment was significantly improved compared with baseline in CME patients. BCVA after 3mo treatment was also significantly improved compared with baseline in DRT patients. In addition, CMT was prone to reduce in each morphological group during the follow-up (Figure 2D-2F). CMT reduced most after 1-week treatment, and kept stable in the following 3mo.

Comparison of BCVA and CMT Among Different Groups at Different Time Points Compared with BCVA of DRT group at each time point, BCVA of CME group was significantly better at baseline, in 1wk, 1, 2, and 3mo after ranibizumab treatment (Figure 3A-3E). The CMT of DRT group was significantly higher than that of CME and SRD group, but the differences became smaller after ranibizumab treatment (Figure 3F-3J). Interestingly, CMT of SRD group was significantly better than that of CME and DRT groups after 3-month treatment.

Morphological Transformation Among Three Groups During Treatment The morphological types sometimes transformed during the treatment (Figure 4). Most patients of CME and SRD groups turned into normal pattern after 3-month treatment of ranibizumab. DRT patients were most likely to transform into the other morphological groups, while SRD patients seldom changed into other morphological groups. The representative case with morphological types, BCVA, CMT and OCT images in each group was illustrated in Figure 5.

Correlation Analysis Between BCVA and Baseline Parameters During Treatment In order to explore the influence factors of BCVA after intravitreal injections of ranibizumab, correlation analysis between BCVA and baseline parameters during treatment was performed (Table 2). BCVA after 1wk, 1, 2, and 3mo treatment significantly correlated with BCVA at baseline in all three groups. The relationship showed

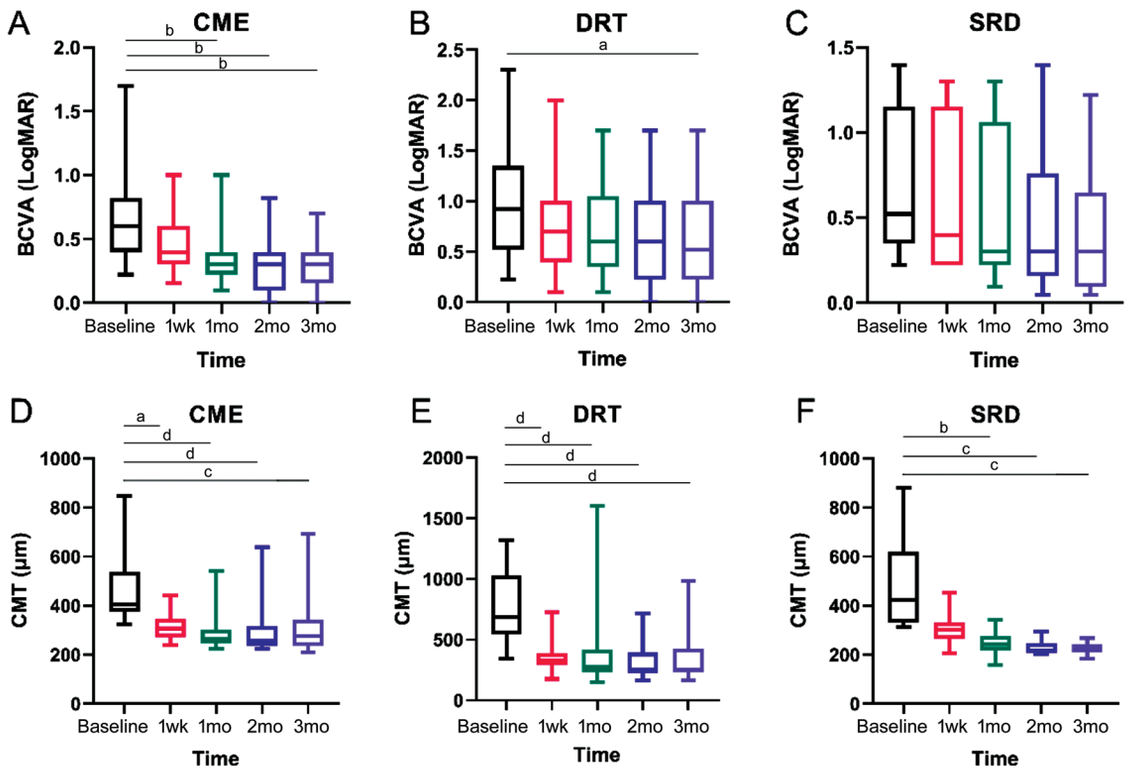

Figure 2 Changes of best corrected visual acuity (BCVA; logMAR) and central macular thickness (CMT) in different morphological groups BCVA was prone to improve in cystoid macular edema (CME), diffuse retinal thickening (DRT), and serous retinal detachment (SRD), especially significant in CME and DRT groups. CMT reduced most after 1-week, and kept stable in the following 3mo. [a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001, [d]*P*<0.0001, significant difference between the groups.

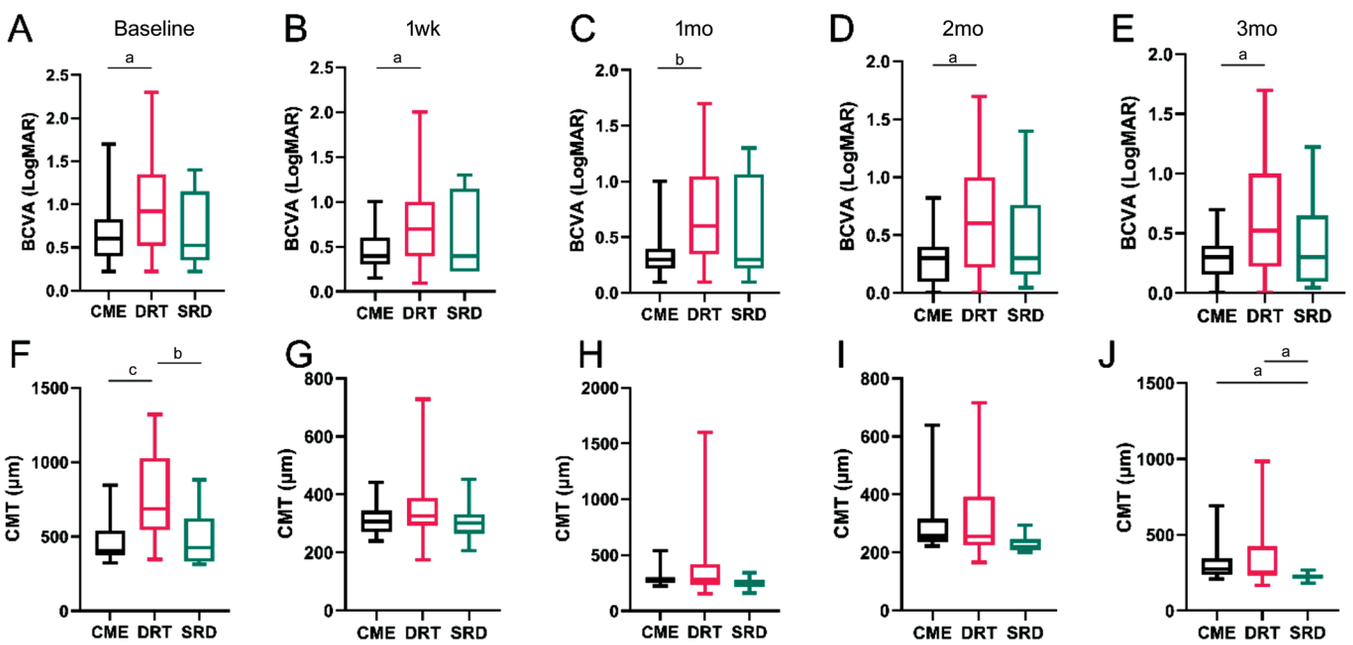

Figure 3 Comparison of best corrected visual acuity (BCVA; logMAR) and central macular thickness (CMT) among different groups at different time points Compared with BCVA of diffuse retinal thickening (DRT) group at each time point, BCVA of cystoid macular edema (CME) group was significantly better at baseline, in 1wk, 1, 2, and 3mo after ranibizumab treatment. The CMT of DRT group was significantly higher than that of CME and SRD group, but the differences became smaller after ranibizumab treatment. After 3-month treatment, CMT of SRD group was significantly better than that of CME and DRT groups. [a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001, significant difference between the groups.

the highest correlation after 1wk treatment, and turned lower during the follow-up. In DRT patients, BCVA after 1wk, 1, 2, and 3mo treatment significantly correlated with clinical course, CMT and RVO position. In CME patients, BCVA after 2 and 3mo treatment was significantly correlated with RVO position and BCVA after 3mo treatment was significantly correlated

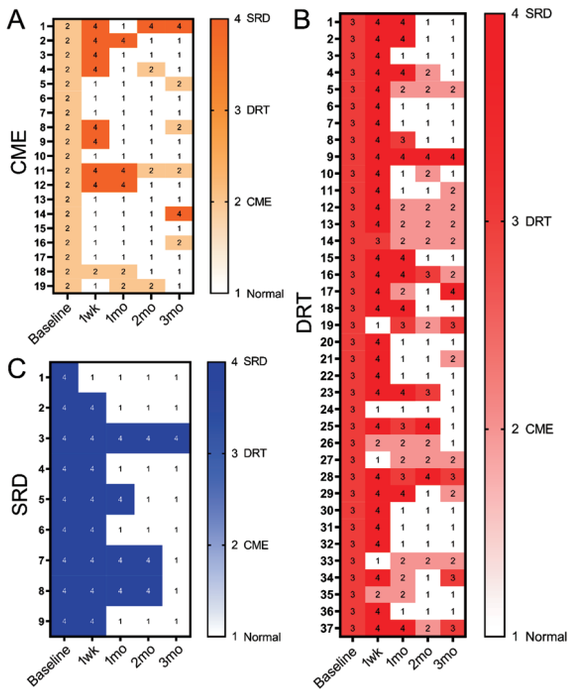

Figure 4 The morphological transformation among cystoid macular edema (CME), diffuse retinal thickening (DRT), and serous retinal detachment (SRD) groups during treatment Most patients of CME and SRD groups turned into normal pattern after 3-month treatment of ranibizumab. DRT patients were most likely to transform into the other morphological groups, while SRD patients seldom changed into other morphological groups (1: Normal group; 2: CME group; 3: DRT group; 4: SRD group).

with hypertension grade. In SRD patients, BCVA after 1wk and 1mo treatment was significantly correlated with CMT. Apparently, BCVA after treatment had the tightest relationship with BCVA at baseline in the three groups during the follow-up. DRT patients with longer clinical course, higher CMT and CRVO tends to have worse BCVA after treatment. In addition, CRVO patients were probably to have worse BCVA after 2 and 3mo treatment compared with BRVO patients in CME group. SRD patients with higher baseline CMT tended to have worse BCVA after treatment.

DISCUSSION

The primary outcome of this study was to identify predictive baseline indicators of the effectiveness of ranibizumab treatment for ME secondary to RVO. Many previous studies have examined baseline parameters in RVO patients[15-18]. For instance, Jaissle *et al*[19] proposed that baseline BCVA, age and duration of BRVO were crucial prognostic indicators for visual improvement. Nevertheless, due to the lack of consensus on the issue and the simplicity of previous RVO groups, we conducted detailed analyses in our patients, comparing among three distinct morphological groups. Consistently, BCVA at baseline emerged as the most significant prognostic indicator across all three groups in this study. Furthermore, we discovered that clinical course, CMT, and RVO position served as potential indicators for visual improvement in DRT patients. DRT patients exhibited the worst baseline BCVA and the highest CMT among three groups, making the predictive baseline parameters more complex in this subgroup. Baseline CMT also appeared to be another prognostic indicator for SRD patients. It has been reported that CRVO patients had higher vitreous levels of inflammatory factors such as soluble vascular endothelial growth factor receptor-2 and lower anti-inflammatory factors[20]. Consequently, CRVO patients were more likely to have worse BCVA after 2 and 3mo treatment compared to BRVO patients in CME group.

Chen *et al*[21] discovered that the morphologic characteristics in OCT reflected intraocular inflammatory factors and VEGF levels, thereby influencing the prognosis in diabetic ME patients. DRT was considered as the earliest form of diabetic ME, and showed a favorable response compared to other types after anti-VEGF treatment[22]. Similarly, in this study, DRT patients exhibited the worst BCVA and the highest CMT at baseline. Most patients of CME and SRD groups transitioned into normal pattern after 3mo treatment of ranibizumab. DRT patients were most likely to transform into the other morphological groups, while SRD patients seldom changed into other morphological groups. In addition, 42.11% of CME patients and 81.08% of DRT patients transitioned into SRD after 1wk treatment in this study. Meanwhile, 88.88% of SRD patients remained SRD type after 1wk treatment. Increased IOP and vascular permeability in RVO patients were considered as the main causes of ME secondary to RVO. Nevertheless, the pathogenesis of SRD is not solely associated with these causes, but also associated with more damage factors[20,23]. Central retinal artery is responsible to supply the 2/3, internal part of the retina, and choroidal vein network is responsible for the remaining 1/3 external part, so SRD patients had more damage factors associated with choroidal blood flow. Similarly, intravitreal anti-VEGF agents were more effective for the resolution of cystoid formation than serous detachment in diabetic ME patients[24]. SRD is thought to be caused by the movement of fluid from the edematous retina to the subretinal or the breakdown of the outer blood-retinal barrier in retinal pigment epithelial (RPE). Hypoxic settings decreases the ability of RPE to pump fluid and RPE impairment seems to play a key role in the pathogenesis of SRD[24]. Consequently, while ranibizumab, an anti-VEGF agent, efficiently improves CME, residual SRD may require more additional injections, combination therapy and recovery duration. These findings also suggested that in the presence of both intraretinal and subretinal fluid in the macula, DRT patients had more damage factors, which needed more additional injections and longer recovery duration.

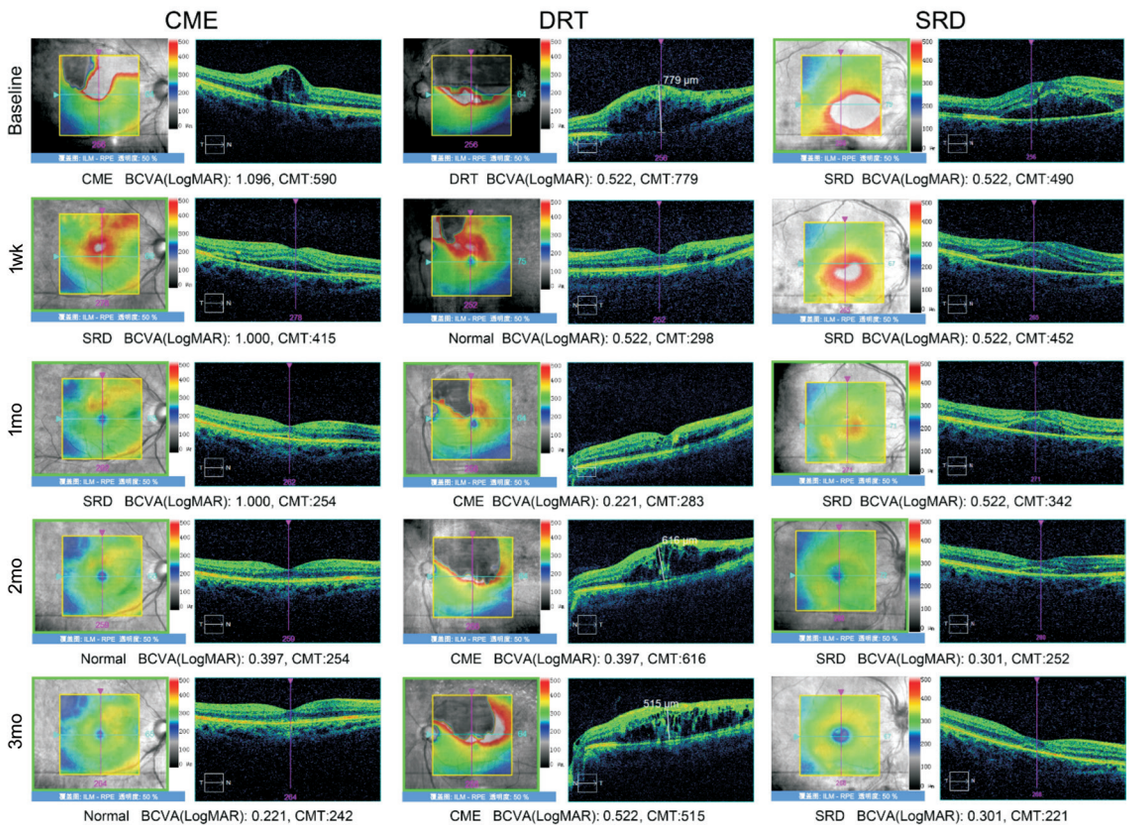

Figure 5 The representative cases with morphological types, best corrected visual acuity (BCVA; logMAR), central macular thickness (CMT) and optical coherence tomography (OCT) images in cystoid macular edema (CME), diffuse retinal thickening (DRT), and serous retinal detachment (SRD) groups.

Table 2 Relationship between BCVA and baseline parameters during treatment

Baseline parameters	BCVA after treatment (logMAR), spearman correlation coefficient, *r* (*P*)			
	1wk	1mo	2mo	3mo
Clinical course (mo)				
CME	-0.22 (0.36)	-0.31 (0.20)	-0.14 (0.58)	-0.04 (0.88)
DRT	0.35 (0.03)	0.29 (0.08)	0.47 (<0.01)	0.48 (<0.01)
SRD	-0.49 (0.18)	-0.25 (0.50)	-0.13 (0.74)	-0.01 (0.98)
BCVA at baseline (logMAR)				
CME	0.76 (<0.001)	0.70 (<0.001)	0.53 (0.02)	0.47 (0.04)
DRT	0.91 (<0.0001)	0.80 (<0.0001)	0.79 (<0.0001)	0.76 (<0.0001)
SRD	0.91 (<0.01)	0.75 (0.02)	0.70 (0.04)	0.64 (0.07)
IOP (mm Hg)				
CME	-0.15 (0.55)	-0.06 (0.82)	-0.10 (0.70)	-0.08 (0.75)
DRT	-0.17 (0.33)	<0.01 (0.99)	-0.08 (0.62)	-0.08 (0.65)
SRD	-0.55 (0.13)	-0.35 (0.35)	-0.36 (0.34)	-0.14 (0.71)
CMT (μm)				
CME	0.18 (0.45)	0.06 (0.82)	0.32 (0.19)	0.39 (0.10)
DRT	0.43 (<0.01)	0.37 (0.02)	0.41 (0.01)	0.44 (<0.01)
SRD	0.92 (<0.01)	0.78 (0.02)	0.59 (0.10)	0.54 (0.14)
Hypertension (without *vs* Grade 1 *vs* Grade 2)				
CME	-0.37 (0.12)	-0.24 (0.33)	-0.28 (0.25)	-0.53 (0.02)
DRT	0.15 (0.37)	0.13 (0.43)	0.06 (0.72)	0.06 (0.71)
SRD	0.36 (0.33)	0.42 (0.25)	0.61 (0.09)	0.41 (0.27)
RVO position (CRVO *vs* BRVO)				
CME	-0.17 (0.49)	-0.38 (0.11)	-0.57 (0.01)	-0.64 (<0.01)
DRT	-0.59 (<0.001)	-0.70 (<0.0001)	-0.64 (<0.0001)	-0.59 (<0.001)
SRD	-0.49 (0.22)	-0.49 (0.33)	-0.55 (0.22)	-0.55 (0.22)

BCVA: Best corrected visual acuity; CME: Cystoid macular edema; DRT: Diffuse retinal thickening; SRD: Serous retinal detachment; IOP: Intraocular pressure; CMT: Central macular thickness; RVO: Retinal vein occlusion; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion.

More and more studies have focused on the varied outcomes among different morphological groups. Dogan *et al*[25] discovered BRVO patients with SRD showed more marked morphological improvement than those without SRD. The enhanced anatomic outcomes in BRVO patients with SRD may be attributed to the association of the inflammatory factors and extensive morphological changes with the present of SRD. Chen *et al*[26] also suggested SRD might signal better anatomical improvement of RVO patients after anti-VEGF therapy due to the thicker central subfoveal choroid thickness in SRD patients. In this study, we further divided RVO patients into 3 groups. The 88.89% of SRD patients achieved anatomical recovery after 3-month treatment, the highest among three groups (CME: 68.42% and DRT: 56.76%). Remarkably, despite DRT patients having the highest CMT at baseline, there was no significant difference among three groups after 1wk, 1, 2mo treatment. However, SRD patients achieved lowest CMT after 3mo treatment. In summary, compared to CME or DRT patients, SRD patients are more probably to achieve anatomical recovery, and this difference becomes evident after 3mo treatment.

This study had several limitations, with the primary one being its retrospective design. Additionally, the small number of patients and imbalance among three groups were also major limitations that may have influenced the generalizability of the findings. Furthermore, OCT angiography data were not collected for evaluating ischemia and the state of microcirculation in this study. Parameters analyzed in this study were accessible basic data of RVO patients in clinical practice. These limitations should be considered when interpreting the results, and future studies could address these shortcomings to provide more comprehensive insights into the topic.

In conclusion, the effectiveness of intravitreal injections of ranibizumab is closely associated with baseline BCVA in all three groups. DRT patients with a longer clinical course, higher CMT and CRVO tend to exhibit worse BCVA after treatment. In addition, CRVO patients are more likely to have worse BCVA after 2-month and 3-month treatment compared with BRVO patients in CME group. SRD patients with higher baseline CMT were prone to experiencing worse BCVA after treatment. Moreover, SRD patients are more likely to achieve anatomical recovery, whereas DRT patients may require more additional injections and a longer recovery duration. It's imperative to differentiate morphological types of ME patients secondary to RVO in terms of diagnosis, personalized treatment and prognosis.

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Authors' contributions: The work presented here was carried out in collaboration among all authors. Liang J defined the research theme, discussed analyses, interpretation, and presentation. Xu Y drafted the manuscript, analyzed the data, developed the algorithm and interpreted the results. Yin YC and Song ZY helped to perform the statistical analysis and figure interpretation. Zhou XY and Zhang JJ helped to interpreted the results. All authors read and approved the final manuscript.

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