

Intravitreal Conbercept injection for different types of macular edema in retinal vein occlusion

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玻璃体腔注射康柏西普治疗视网膜静脉阻塞继发不同类型黄斑水肿

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摘要

目的: 采用光学相干断层扫描(OCT)图像分析康柏西普对视网膜静脉阻塞继发不同类型黄斑水肿的疗效。

方法: 回顾性研究。纳入2017年12月1日至2022年3月31日期间在皖南医学院弋矶山医院首次接受康柏西普注射治疗视网膜静脉阻塞继发黄斑水肿的患者。收集病程、年龄、高血压状况、治疗前及治疗后4-6 wk的OCT影像、黄斑中心凹厚度(CMT)及最佳矫正视力(BCVA)。根据不同黄斑水肿类型将患者分为4组: 黄斑囊样水肿(CME)、海绵状弥漫性视网膜增厚(SDRT)、浆液性视网膜脱离(SRD)以及混合型(FULL)。通过比较各组治疗前后CMT与视力的变化, 分析康柏西普治疗不同类型黄斑水肿的效果差异, 以及基线CMT和视力对治疗后视力的影响。

结果: 本研究共纳入139例139眼黄斑水肿患者, 平均年

龄为 58.9 ± 10.9 岁, 其中男62例(44.6%), 女77例(55.4%)。根据不同类型黄斑水肿分为4组, 其中CME组54例54眼, 平均年龄 59.6 ± 11.1 岁; SDRT组23例23眼, 平均年龄 56.6 ± 10.2 岁; SRD组22例22眼, 平均年龄 57.8 ± 12.0 岁; FULL组40例40眼, 平均年龄 60.0 ± 10.7 岁。组间在病程及年龄方面均无显著差异($P > 0.05$)。然而, 组间术前CMT存在显著差异($P = 0.01$, 单因素方差分析), 其中FULL组的CMT显著高于SDRT组($P = 0.03$)。四组间治疗前BCVA无显著差异($P = 0.26$)。康柏西普治疗后, 四组患者的CMT均降低, 视力均得到改善。其中, CME组和FULL组的CMT降低程度显著高于其他两组($P < 0.05$), CME组和SRD组的视力改善程度显著高于其他两组($P < 0.05$)。术后视力与术前CMT呈负相关($P = 0.044$), 与术前视力呈正相关($P < 0.01$)。

结论: 玻璃体腔内注射康柏西普治疗视网膜静脉阻塞继发黄斑水肿的疗效可能与OCT图像所观察到的水肿类型有关。其中, CME患者疗效最佳, 而SDRT患者疗效相对较差。

关键词: 视网膜静脉阻塞; 黄斑水肿; 康柏西普; 光学相干断层扫描

Abstract

• **AIM:** To analyze the effect of conbercept treatment on different types of macular edema secondary to retinal vein occlusion (RVO - ME) using optical coherence tomography (OCT) images.

• **METHODS:** This retrospective study included patients who first received conbercept injections for RVO - ME at Yijishan Hospital of Wannan Medical College from December 1, 2017, to March 31, 2022. Data on disease duration, age, hypertension, OCT images, central macular thickness (CMT), and best - corrected visual acuity (BCVA) were collected before and at 4-6 wk after treatment. Patients were divided into 4 groups according to different types of macular edema: cystoid macular edema (CME), sponge - like diffuse retinal thickening (SDRT), serous retinal detachment (SRD), and mixed type (FULL). Changes in CMT and visual acuity before and after treatment were compared among the groups to analyze differences in the effect of conbercept treatment on different ME types, and the effect of baseline CMT and visual acuity on post-treatment visual acuity.

• **RESULTS:** Totally 139 patients (139 eyes) were classified as having macular edema, including 62 males (44.6%) and 77 females (55.4%), with a mean age of 58.9 ± 10.9 years, and they were divided into 4 groups based on different types of macular edema, including 54 cases (54 eyes) (mean age 59.6 ± 11.1 years) in the CME

group, 23 cases (23 eyes; mean age 56.6 ± 10.2 years) in the SDRT group, 22 cases (22 eyes; mean age 57.8 ± 12.0 years) in the SDR group, and 40 cases (40 eyes; mean age 60.0 ± 10.7 years) in the FULL group. There were no significant differences in the duration of disease or age between groups ($P > 0.05$). There was a significant difference in preoperative CMT between groups ($P = 0.01$, one-way ANOVA), with the CMT in the FULL group being significantly greater than that in the SDRT group ($P = 0.03$). There were no significant differences in pre-treatment visual acuity between the four groups ($P = 0.26$). After conbercept treatment, the macular central recess thickness was reduced and visual acuity was improved in all four groups, among which the CMT in the CME and FULL groups was reduced significantly compared with the other two groups ($P < 0.05$), and the visual acuity in the CME and SRD groups was improved significantly compared with the other two groups ($P < 0.05$). Postoperative visual acuity was negatively correlated with preoperative CMT ($P = 0.044$) and positively correlated with preoperative visual acuity ($P < 0.01$).

• **CONCLUSION:** The efficacy of intravitreal conbercept in the treatment of RVO and macular edema may be related to the type of edema observed on OCT images, in which the efficacy is best in patients with CME but poor in patients with SDRT.

• **KEYWORDS:** retinal vein occlusion; macular edema; conbercept; coherent optical tomography

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INTRODUCTION

Retinal vein occlusion (RVO) is a retinal vascular disorder caused by thrombotic obstruction of the retinal venous system and is the second most prevalent cause of vision-threatening retinal vascular diseases^[1-2]. Macular edema is one of the most common complications associated with RVO. Chronic macular edema can damage the fundus structures, resulting in progressive vision loss and blindness^[3]. In recent years, intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents has become a widely adopted treatment for macular edema secondary to retinal vein occlusion (RVO-ME)^[4]. Conbercept, utilized in China for RVO treatment, has demonstrated satisfactory therapeutic outcomes. However, clinical experience has revealed that persistent edema and suboptimal visual improvement are occasionally observed. Similar suboptimal therapeutic responses have been observed with diabetic macular edema (DME) treatment. Optical coherence tomography (OCT) not only detects the presence of subretinal fluid but also enables precise classification of edema into distinct subtypes based on fluid localization and morphological patterns, including cystoid macular edema (CME), serous retinal detachment (SRD), sponge-like

diffuse retinal thickening (SDRT), and mixed edema (FULL)^[5]. These structural subtypes are not merely morphological variations but may reflect underlying differences in pathophysiology and blood-retinal barrier breakdown mechanisms. DME is categorized into four distinct types based on OCT characteristics, highlighting the variability in the efficacy of anti-VEGF and dexamethasone treatments across these types^[6-8]. Although conbercept has demonstrated overall efficacy in reducing central macular thickness (CMT) and improving vision in RVO, a detailed analysis of its effects across these specific OCT phenotypes is lacking. Therefore, this study aimed to investigate the efficacy of anti-VEGF therapy in four distinct types of RVO-ME, which could provide valuable insights for optimizing treatment strategies and predicting individual patient outcomes.

SUBJECTS AND METHODS

Ethical Approval Between December 1, 2017, and March 31, 2022, 139 patients (139 eyes) with RVO-ME were consecutively enrolled and retrospectively analyzed. This study was approved by the Medical Ethics Committee of the Yijishan Hospital of Wannan Medical College, and all participants provided signed informed consent for anti-VEGF treatment.

Patients All patients underwent comprehensive ophthalmic examinations prior to treatment, including measurement of best-corrected visual acuity (BCVA), spectral-domain OCT (Spectralis HRA OCT, Germany), intraocular pressure using NIDEK NT-530, slit-lamp biomicroscopy, and direct ophthalmoscopy. Including criteria: 1) diagnosed with RVO-ME by at least two retinal specialists; 2) intraocular pressure measured by tonometry within the normal range (10-21 mmHg); 3) undergoing anti-VEGF (conbercept) treatment for the first time; 4) collection of foveal images of the macula using the Heidelberg Spectralis OCT scanner both before and after treatment, with each pair of images using the Follow-up mode, and the two collection times spaced 4-6 wk apart. Excluding criteria: 1) prior retinal laser photocoagulation or intraocular injection of drugs other than anti-VEGF (conbercept) in the affected eye; 2) history of other eye diseases, including polypoidal choroidal vasculopathy, retinal detachment, diabetic retinopathy, age-related macular degeneration, high myopic retinopathy, glaucoma, cataract, retinal vasculitis, and other eye-involving diseases; 3) poor quality OCT images due to media opacity or abnormal signal strength index; 4) poor patient compliance, failure to follow up at the scheduled times.

Treatment All enrolled patients received a single initial intravitreal injection of conbercept (0.5 mg/0.05 mL) as their first-ever anti-VEGF treatment. Treatment response was assessed based on the anatomical and functional outcomes following the initial injection. All procedures were conducted with the patient's consent and informed consent forms were signed. All injections were administered by ophthalmologists at Yijishan Hospital of Wannan Medical College.

Measurement Indices Primary outcome measures were the changes in BCVA and CMT observed between baseline and 4-6 wk after post-treatment. The patient's BCVA was assessed

using an international standard vision chart, and visual acuity was statistically analyzed using the LogMAR scale. An experienced physician manually measured CMT using the caliper tool in the OCT software, averaging three measurements for accuracy. CMT was measured as the vertical distance from the retinal pigment epithelium at the macular center to the outer surface of the retinal nerve fiber layer. Improvement in CMT was quantified by the reduction in thickness, calculated as the difference between the pre- and post-treatment CMT. Improvement in visual acuity was calculated as the change from baseline to visual acuity measured at 4-6 wk after post-treatment.

Optical Coherence Tomography Imaging and Assessment

A total of 139 pretreatment OCT images were assigned to three retinal disease specialists for classification purposes. Classification criteria were derived from the macular edema categorization standards for DME patients using OCT, as established by Yassin *et al*^[7]. The classifications included CME, SDRT, SRD, and FULL. The CME pattern features intraretinal cystoid spaces with low reflectivity separated by highly reflective septa. The SDRT pattern showed low intraretinal reflectivity and sponge-like macular swelling. The SRD pattern was marked by shallow retinal detachment with a clear space between the retinal pigment epithelium (RPE) and retina. The FULL pattern combines the features of all aforementioned types (Figure 1).

Statistical Analysis Data were analyzed using SPSS version 26.0. BCVA was converted to LogMAR values using the Holladay method. Measurement data are reported as mean ± standard deviation. The Wilcoxon test was used to assess

statistical differences in clinical data before and after anti-VEGF treatment. Differences among the four groups were analyzed using one-way ANOVA when variances were equal and the Kruskal-Wallis test when they were not. The relationship between pre- and post-treatment visual acuity was assessed using the Pearson correlation coefficient (*r*) and *P* value.

RESULTS

Demographic and baseline characteristics of the patients are summarized in Table 1. A total of 139 patients (139 eyes) with RVO-ME were examined. No significant differences were found among the four groups in terms of baseline age, systemic disease, and disease duration.

Changes in Best-Corrected Visual Acuity and Central Macular Thickness in Each Group

Postoperative CMT significantly decreased across all groups (Figures 2 and 3A). Postoperative BCVA significantly improved in all groups (*P* < 0.001; Figure 3B).

The reduction in CMT after anti-VEGF treatment was statistically significant across all groups. The average CMT improvements in the CME group (436.96±152.73 μm) and the FULL group (454.43±210.60 μm) surpassed those in the remaining two groups (311.70±223.70 and 327.14±163.41 μm, *P* < 0.05; Figure 4A). LogMAR visual acuity improved significantly in all groups; however, significant differences were observed in the extent of improvement. The CME group (-0.40 ± 0.22) and the SRD group (-0.60 ± 0.40) demonstrated greater improvements than the SDRT group (-0.345±0.26) and the FULL group (-0.341±0.26, *P* < 0.05; Figure 4B).

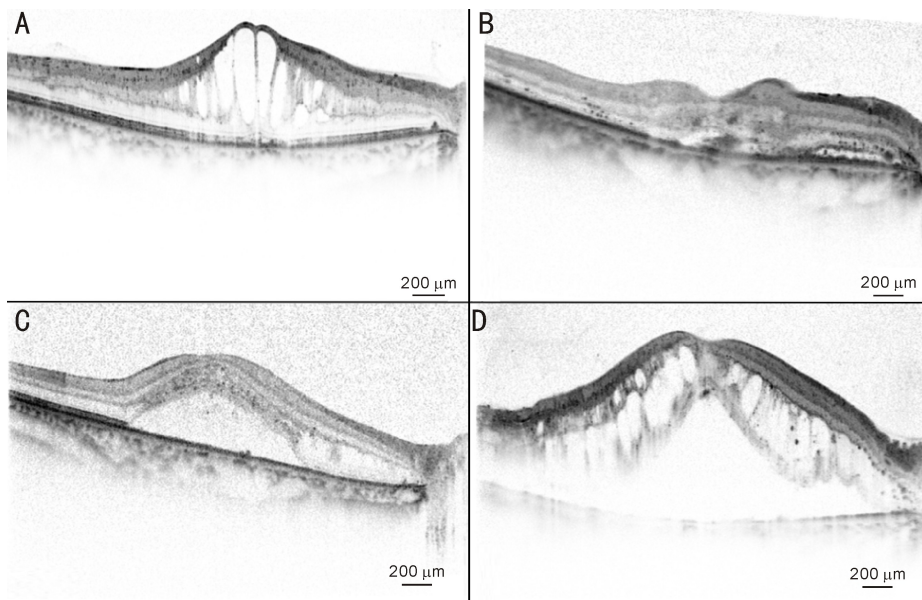


Figure 1 Examples of macular edema secondary to retinal vein occlusion classifications. A: Cystoid macular edema; B: Sponge-like diffuse retinal thickening; C: Serous retinal detachment; D: Mixed edema.

Table 1 Demographic and baseline characteristics of the patients

Parameters	CME (n=54)	SDRT (n=23)	SRD (n=22)	FULL (n=40)	<i>P</i>
Duration of disease ($\bar{x} \pm s$, d)	59.7±80.2	51.7±72.9	50.7±78.3	61.9±72.6	0.92
Age ($\bar{x} \pm s$, years)	59.6±11.1	56.6±10.2	57.8±12.0	60.0±10.7	0.61
Hypertension (n, %)	28 (52)	11 (48)	9 (41)	17 (43)	-

CME;Cystoid macular edema; SDRT; Sponge-like diffuse retinal thickening; SRD; Serous retinal detachment; FULL; Mixed edema.

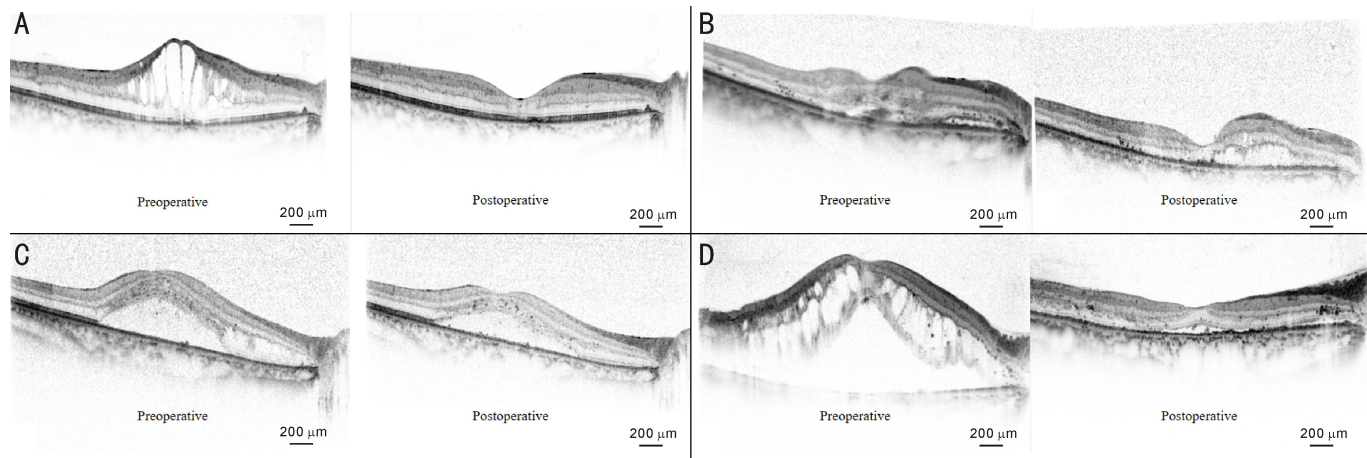


Figure 2 Representative pre- and post-treatment optical coherence tomography images. A: Cystoid macular edema; B: Sponge-like diffuse retinal thickening; C: Serous retinal detachment; D: Mixed edema.

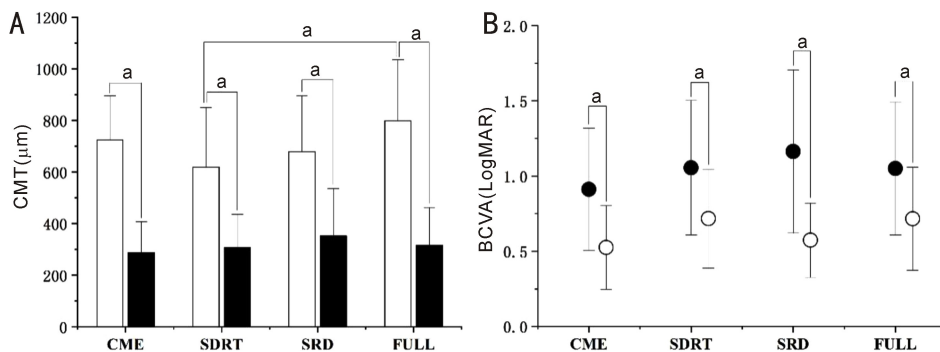


Figure 3 Treatment outcomes for different subtypes of macular edema. A: Changes in CMT before and after treatment across the four groups. White bars represent values before treatment, and black bars represent values after treatment; B: changes in BCVA before and after treatment across the four groups. Black circles denote values before treatment, white circles denote values after treatment, and vertical lines represent the standard deviation. ^a $P < 0.05$. CMT: Central macular thickness; BCVA: Best-corrected visual acuity; CME: Cystoid macular edema; SDRT: Sponge-like diffuse retinal thickening; SRD: Serous retinal detachment; FULL: Mixed edema.

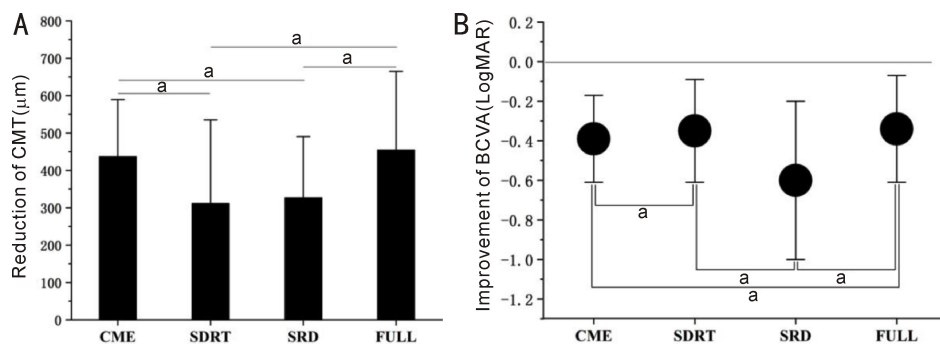


Figure 4 Comparison of anatomical and functional treatment outcomes across different macular edema subtypes. A: Comparison of the reduction in CMT before and after treatment across the four groups; B: Comparison of BCVA improvement before and after treatment across the four groups. Black circles represent the mean improvement in BCVA (LogMAR) for each group. Vertical lines indicate the standard deviation. ^a $P < 0.05$. CMT: Central macular thickness; BCVA: Best-corrected visual acuity; CME: Cystoid macular edema; SDRT: Sponge-like diffuse retinal thickening; SRD: Serous retinal detachment; FULL: Mixed edema.

Correlations of Preoperative Central Macular Thickness and Best-Corrected Visual Acuity with Postoperative Best-Corrected Visual Acuity

Preoperative CMT was negatively correlated with postoperative BCVA ($P = 0.04$, $r = 0.171$; Figure 5A). Preoperative BCVA was positively correlated with postoperative BCVA ($P < 0.001$, $r = 0.779$; Figure 5B).

Subgroup analysis showed no significant correlation between preoperative CMT and postoperative visual acuity across the groups. The correlation coefficients were as follows: CME ($P = 0.35$, $r = 0.13$), SDRT ($P = 0.40$, $r = 0.183$), SRD

($P = 0.34$, $r = 0.213$), and FULL ($P = 0.23$, $r = 0.195$; Figure 6 left). However, positive correlations between preoperative and postoperative visual acuity were observed within each subgroup: CME ($P < 0.001$, $r = 0.857$), SDRT ($P < 0.001$, $r = 0.815$), SRD ($P < 0.001$, $r = 0.727$), and FULL ($P < 0.001$, $r = 0.801$; Figure 6 right).

DISCUSSION

This study included 139 patients (139 eyes) diagnosed with macular edema secondary to RVO. Based on OCT imaging characteristics, the eyes were classified into four groups:

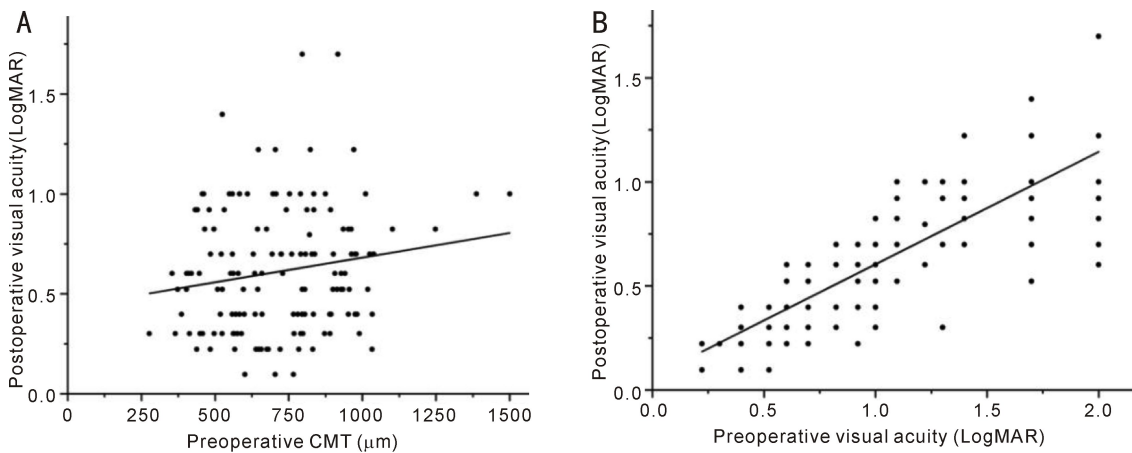


Figure 5 Predictive factors for postoperative visual acuity. A: Correlation between preoperative CMT and postoperative visual acuity; B: Correlation between preoperative visual acuity and postoperative visual acuity. CMT; Central macular thickness.

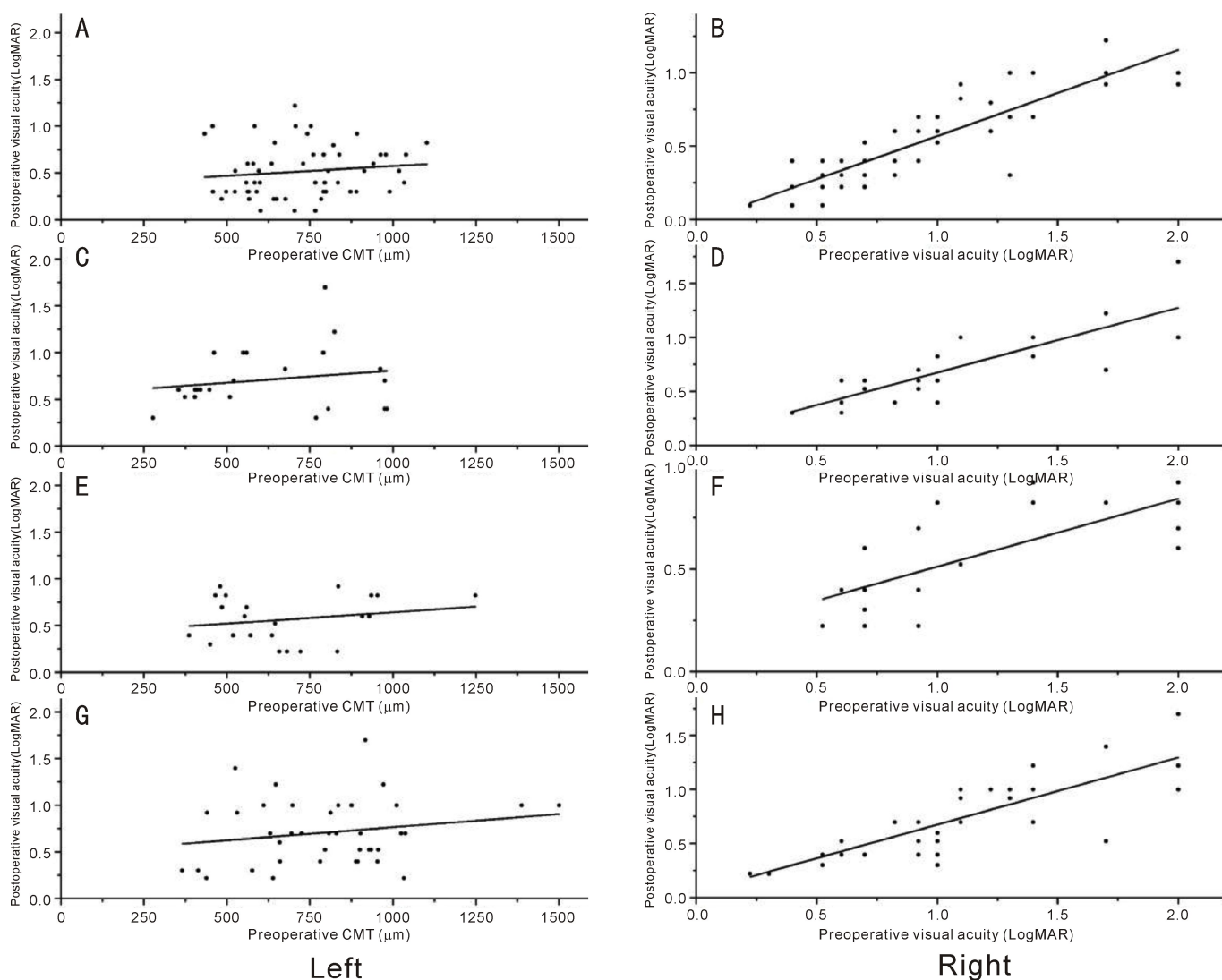


Figure 6 Correlations of preoperative factors with postoperative visual acuity. Left: Correlation between preoperative CMT and postoperative visual acuity in each group; Right: Correlation between preoperative visual acuity and postoperative visual acuity in each group. A and B; Cystoid macular edema; C and D; Sponge-like diffuse retinal thickening; E and F; Serous retinal detachment; G and H; Mixed edema. CMT; Central macular thickness.

CME (39%), SDRT (16%), SRD (16%), and FULL (29%). In previous DME studies, SDRT accounted for a larger proportion than CME. This distribution differs from that reported in previous studies on DME^[6-8], potentially revealing

differences in the mechanisms underlying the two types of macular edema. Our findings indicate that one month post-concept treatment, visual acuity significantly improved and CMT was markedly reduced across all groups, consistent with

previous findings^[9-10]. This further confirmed the efficacy of conbercept in the treatment of RVO-ME.

Treatment efficacy varied across the subgroups. The most significant reduction in ME was observed in the CME group, with moderate improvements in the FULL and SRD groups and minimal changes in the SDRT group. Consequently, conbercept injections were most effective in resolving CME. In eyes with BRVO, fluid leakage from the compromised retinal capillaries accumulates around the foveal pit, leading to extensive intracellular edema and Müller cell death. This process leads to the formation of cystic cavities that precede extracellular edema, thereby initiating CME^[11]. Anti-VEGF medications reduce vascular permeability and decrease retinal vascular leakage, thereby effectively diminishing CME.

SDRT is likely due to breakdown of the blood-retinal barrier. In RVO-ME, VEGF acts synergistically with ICAM-1, IL-6, and MCP-1, whereas the reduced expression of claudin-5 and claudin-19 further contributes to the disruption of the blood-retinal barrier^[12-14], thereby increasing extracellular fluid accumulation within the vascular lumen. SDRT is induced by multiple cytokines, which may partly explain why the reduction in CMT following anti-VEGF therapy was less pronounced than other subtypes. Although anti-VEGF agents effectively reduce VEGF-driven hyperpermeability, they may not be sufficient to fully restore the integrity of chronically damaged tight junction complexes. This compromised blood-retinal barrier allows for continuous low-level extravasation of fluid and proteins into the retinal parenchyma.

The incidence of major retinal vein branch occlusion was significantly higher in patients with SRD than patients with CME^[15]. Extensive venous congestion or significant capillary leakage causes the accumulation of fluid and proteins in the subretinal space, which induces traction of the foveal photoreceptor inner and outer segments. This leads to disruption of both the external limiting membrane and the photoreceptor inner segment/outer segment junction, ultimately resulting in neuroepithelial detachment^[16-17]. The reduction in CMT was less pronounced in this group than others^[18-19]. According to Kang *et al*^[20], compromised retinal pigment epithelium pump function impedes the resorption of subretinal fluid. Chronic serous detachment can lead to dysfunction and atrophy of the retinal pigment epithelium. RPE dysfunction appears to play a critical role in the pathogenesis of SRD^[21].

Patients in the FULL group displayed the highest baseline CMT, which decreased significantly after anti-VEGF treatment. The FULL group manifestations present considerable complexity, comprising cystoid edema, spongiform edema, and SRD. Compared with other subtypes, it may involve a broader spectrum of pathological changes, including disruption of the blood-retinal barrier and photoreceptor damage. Park *et al*^[22] noted that patients with branch BRVO-ME combined with SRD exhibited higher

VEGF levels in the aqueous humor than those without SRD. Although anti-VEGF therapy resulted in a significant reduction in CMT, the improvement in visual acuity was not clinically significant. Other contributing factors include delayed treatment initiation or irreversible retinal neurodegeneration secondary to chronic edema, which may account for the observed discrepancies.

This study demonstrated that baseline CMT in the RVO-ME group was negatively correlated with postoperative VA, whereas baseline VA was positively correlated with postoperative VA. Iida-Miwa *et al*^[23] previously reported a correlation between baseline foveal thickness and final VA. However, the relationship between CMT and final visual outcomes remains controversial, with some studies presenting conflicting results^[24-26]. In this study, no significant correlation was observed between baseline CMT and postoperative VA across subgroups, which may be attributed to the limited sample sizes within each subgroup. Further validation using a larger cohort is required to confirm these findings. Previous studies have identified baseline BCVA as a potential prognostic factor for visual outcomes in BRVO, indicating that patients with a better baseline BCVA are more likely to achieve favorable visual outcomes^[27-28], consistent with the findings of the present study.

This study has several limitations. First, the analysis was based on OCT images of various types of macular edema in RVO, without distinguishing between central RVO (CRVO) and branch RVO (BRVO), potentially overlooking differences in prognosis owing to varied etiologies. Additionally, the timelines of the study were set at 4-6 wk after a single intravitreal injection of anti-VEGF antibody, which represents the optimal period for assessing the effects of a single conbercept dose. However, considerable individual variations exist, and some patients may experience recurrent edema. Furthermore, our study did not compare conbercept and other anti-VEGF drugs. Future multicenter prospective randomized controlled trials are warranted to validate this hypothesis.

Based on OCT imaging, among the four types of RVO-ME, the CME group exhibited the best response to a single dose of anti-VEGF, the SDRT group displayed the poorest response, and the SRD and FULL groups showed moderate effects. In the FULL group, changes in CMT were the most pronounced; however, visual recovery was less significant than that in the SRD group. Our results demonstrated a differential response to conbercept among the four OCT-based subtypes of macular edema. This finding implies that a single treatment strategy may not be optimal for all patients. However, the pathophysiological mechanisms underlying these variable treatment responses warrant further investigation. Prospective randomized trials are required to validate whether a subtype-tailored treatment protocol ultimately leads to better long-term visual outcomes than a uniform treatment strategy.

Conflicts of Interest: Xue JR, None; Qian XP, None; Dong JH, None; Wu CF, None.

Authors' contributions: Wu CF conceived and designed the study; Xue JR and Qian XP performed data mining and statistical analyses; Xue JR and Dong JH interpreted the results of the statistical analyses; Dong JH prepared the figures and tables; Qian XP drafted the initial manuscript. Xue JR and Qian XP made critical comments and revised the initial manuscript; Xue JR and Wu CF have primary responsibility for the final content. All authors reviewed and approved the final manuscript.

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