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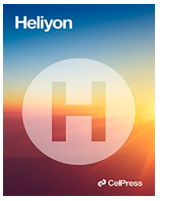

Biochemical and microstructural determinants of the development of serous retinal detachment secondary to retinal vein occlusion

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ABSTRACT

Purpose: To study the alteration of cytokine factors in aqueous humor and retinal microstructure in the formation of serous retinal detachment (SRD) secondary to retinal vein occlusion.
Methods: The subjects were 39 patients with RVO, of whom 31 patients had SRD (RVO-SRD). Spectral Domain Optical Coherence Tomography (SD-OCT) was used to measure the completeness of photoreceptor inner segment/outer segment (IS/OS) and the external limiting membrane (ELM) as well as the structure of RVO-SRD, including the height and shape of SRD. The aqueous humor was collected before intravitreal injection of Ranibizumab. The concentrations of VEGF, MCP-1, IL-8, IL-6, b-FGF and TNF-α in the aqueous humor were measured. All patients participated in the 6-month follow-up examinations, which included visual acuity, intraocular pressure, ophthalmologic examination, and SD-OCT. The time of recurrence of RVO-SRD was recorded.
Results: The formation of SRD was associated with the area of congested vein, disrupted IS/OS, ELM layers and high VEGF, MCP-1, IL-8, IL-6 levels. However, the height and shape of SRD were not relevant to any inflammatory factors. Moreover, high levels of MCP-1, IL-8 and IL-6 were found in large areas of congested veins. High levels of MCP-1 and IL-6 were observed in the patients with incomplete IS/OS and ELM. The recurrence of SRD was related to the high MCP-1 level.
Conclusion: High concentrations of cytokine factors in aqueous humor could induce vascular leakage, exacerbate the extent of macular edema, disrupt the structure of ELM and IS/OS, and develop SRD in RVO.

Key messages

What is already known on this topic

There are many hypotheses about the development of SRD, but it is still unclear. Few research has detected the change of cytokines in aqueous humor in SRD patients.

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What this study adds

We would investigate the relationship between cytokine factors and the formation of SRD, involving the height and shape of SRD, and measure the factors that affect SRD recurrence.

How this study might affect research, practice or policy

We could explore another hypothesis for the development of SRD and choose the best treatment according to the levels of cytokines.

Synopsis

The formation of serous retinal detachment was related to cytokines in aqueous humor. The development of serous retinal detachment was correlated with the incomplete photoreceptor inner segment/outer segment and the external limiting membrane.

1. Introduction

Retinal vein occlusion (RVO) causes unanticipated loss of visual acuity, especially in patients with risk factors of ageing, hypertension, or diabetes [1]. The clinical complications of RVO include macular edema, retinal ischemia, optic neuropathy, vitreous hemorrhage and serous retinal detachment (SRD) [2]. SRD is characterized by the leakage of fluid that accumulated under the neurosensory retina, which is a severer one that prone to recurrent and severely affect visual acuity [3]. Therefore, study of pathogenesis and treatment of SRD is arousing great attention. Optical coherence tomography (OCT) shows that SRD in RVO is mainly found beneath the macular fovea , which manifests fluid accumulation and the detachment between retinal neuroepithelium layer and retinal pigment epithelium [4]. Clogged retinal veins probably lead to vascular leakage that generates subretinal fluid and exerts traction force from the Müller cell cone to the photoreceptor inner segment/outer segment (IS/OS), disrupting the function of the external limiting membrane (ELM) [5]. In addition, retinal ischemia in RVO leads to hemodynamic overload and RPE barrier impairment, which may account for SRD [6]. However, the mechanism of SRD due to the RVO is still unclear.

Previous studies have shown that cytokines played an important role in the development of macular edema secondary to RVO and recurrence after anti-VEGF treatment, such as vascular endothelial growth factor (VEGF), monocyte chemotactic protein 1 (MCP-1), interleukin (IL)-8, IL-6, basic fibroblast growth factor (b-FGF), and tumor necrosis factor-α (TNF-α) [7,8,9]. Only a few research has detected the change of cytokines in intraocular fluid in patients with SRD in RVO [10,11]. In this study, we detected the changes of inflammatory cytokines (VEGF, MCP-1, IL-8, IL-6, b-FGF, and TNF-α) in aqueous humor and macular microstructure in RVO-SRD, aiming to explore the pathogenesis and recurrence mechanisms of SRD in RVO.

2. Methods

The research of 39 patients diagnosed with RVO in our ophthalmology department between January 2020 and September 2020 was approved by the Ethics Committee of the Second Hospital of Jilin University and was in accordance with the Helisinki Declaration. The inclusion criteria were as follows: (1) all three types of RVO based on the site of the occlusion were include in this study: central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), and hemiretinal vein occlusion (HRVO); (2) RVO patients accepted paracentesis for aqueous humor collection before intravitreal injection of Ranibizumab and participated in the 6-month follow-up. The exclusion criteria were as follows: (1) RVO patients with severe intraretinal and/or vitreous hemorrhage that prevented the accurate acquisition of OCT images; (2) retinal neovascularization or diabetic retinopathy; (3) glaucoma, or other ocular diseases that severely impaired vision; (4) history of other eye surgery.

Demographic characteristics, family history, surgical history, and clinical history of patients were collected. A comprehensive ophthalmologic examination, including best-corrected vision acuity (BCVA) test, slit-lamp microscopy, retinoscopy and intraocular pressure was applied for all participants before treatment and during follow-up period. Morphologic changes of the macular region retina were evaluated. SD-OCT (Spectralis HRA, Heildelberg Engineering, Heidelberg Germany) was used to measure the height, length, and area of the SRD with a calliper in the fovea. SD-OCT also assessed the integrity of the inner/outer photoreceptor segment (IS/OS) and the integrity of the external limiting membrane (ELM) using cross-sectional scans. These measurements were performed by 2 of the authors in a double-blind trail.

After RVO macular edema was occurred and diagnosed by SD-OCT, intravitreal injection of anti-VEGF was arranged within 5 days. Patients had signed informed consents before the aqueous humor was collected. Prior to the intravitreal injection of 0.05 ml Ranibizumab (10 mg/ml, Genentech, South San Francisco, CA, USA), paracentesis was performed and 50 μl aqueous humor was collected. The aqueous humor was stored in an Eppendorf tube and kept at −80 °C. A cytometric bead array (BD Co. Ltd., USA) was applied to measure the concentrations of VEGF, MCP-1, IL -8, IL -6, b-FGF, and TNF-α in the aqueous humor. Patients were followed up for 6 months and visual acuity, intraocular pressure, ophthalmic examination, and SD-OCT were measured.

SPSS 25.0 software (SPSS Inc, Chicago, IL, USA) was used to analyze data. The chi-square test was applied to observe frequencies in a contingency table. The Mann-Whitney *U* test was used to compare two samples from randomly selected values. The student's t-test was applied to hypotheses about the mean of a small sample drawn from a normally distributed population. A $p\text{-}value < 0.05$ was considered statistically significant.

3. Results

The average age of 39 patients (39 eyes) with RVO was 56.05 ± 8.92 years (Table 1), including 20 male patients (51.3 %) and 19 female patients (48.7 %). The number of three types of RVO is shown (Table 2) and the manifestation of RVO is below (Fig. 1): SRD is characterized by the leakage of fluid that accumulated under the neurosensory retina (Fig. 1A); cystoid macular edema causes leakage from perifoveal retinal capillaries and accumulation of fluid within the intracellular spaces of the retina, primarily in the outer plexiform layer (Fig. 1B); intact IS/OS and ELM and disrupted IS/OS are shown in Fig. 1C and D&1E.

3.1. The levels of cytokines in the aqueous humor in RVO with or without SRD

There were 31 patients (79.5 %) who had RVO combined with SRD (RVO-SRD). Compared with the RVO groups without SRD, the levels of VEGF, MCP-1, IL-8 and IL-6 were substantially increased in the RVO-SRD group ($p < 0.005$) (Fig. 2A, B, 2C, 2D). The concentrations of TNF and bFGF were not significantly different between these two groups (Fig. 2E and F). Thus, the patients with SRD produced high levels of VEGF, MCP-1, IL-8 and IL-6 in the aqueous humor.

3.2. The relationship between cytokine factors and the change of IS/OS and ELM in RVO

Cytokine factors in aqueous humor were analyzed. The decreased levels of MCP-1 and IL-6 were observed in completed IS/OS under the fovea ($p = 0.046$, $p = 0.019$, respectively) (Fig. 3A and C), and also occurred in undamaged ELM ($p = 0.03$, $p = 0.004$, respectively) (Fig. 3B and D). In the RVO-SRD group, a higher level of IL-6 was detected in the patients with broken ELM ($p = 0.025$). Thus, the defective IS/OS and ELM contributed to the high MCP-1 and IL-6 levels. Hence, the occurrence of SRD was connected with the high levels of MCP-1 and IL-6.

3.3. The height of SRD and the change of IS/OS and ELM in RVO

16 patients (41.0 %) with RVO had integrated IS/OS and ELM layers. Among them, 6 eyes (75.0 %) with integrated IS/OS and ELM occurred in the group without SRD, and 10 eyes (32.3 %) with integrated IS/OS and ELM occurred in the SRD group. There is a dramatic discrepancy between these two groups ($p = 0.028$). Hence, the formation of SRD was associated with intact IS/OS and ELM. Besides, we measured the height of SRD and found that the patients with undamaged IS/OS and ELM had a decreased level of SRD ($p = 0.002$, $p = 0.004$, respectively) (Fig. 4).

3.4. The relation between the formation of SRD and cytokines in three types of RVO

The larger area of congested veins contributed to the higher levels of MCP-1, IL-8 and IL-6 (Fig. 5). There are 14 eyes of CRVO (93.3 %) combined with SRD and 13 eyes of HRVO (81.3 %) combined with SRD. These two groups had a higher incidence of SRD than BRVO groups (4 eyes, 50.0 %) ($p = 0.048$). Thus, the development of SRD was highly in connection with the area of congested veins. Moreover, the large area of congested veins caused the high levels of cytokine factors. The highest levels of MCP-1, IL-8 and IL-6 were found in CRVO due to the largest area of clogged veins, which outperformed HRVO and BRVO groups ($p < 0.001$, $p = 0.003$, $p = 0.003$, respectively).

3.5. The relationship between the recurrence of SRD and cytokines

31 patients with RVO-SRD were injected with Ranibizumab and followed up for 6 months. We measured inflammatory factors and found that the patients who suffered SRD again possessed an increased level of MCP-1 in aqueous humor ($p = 0.015$) (Table 3).

4. Discussion

Our study revealed that the formation of SRD was not only related to the incompleteness of the ELM and IS/OS layers, but also to the high concentrations of cytokine factors: MCP-1, IL-6, and IL-8 in the RVO. We found that higher levels of MCP-1, IL-6 and IL-8 were detected in the larger area of the congested veins. Thus, the occurrence of SRD was associated with the area of the congested veins. In addition, the increased level of MCP-1 in our study might be related to the recurrence of SRD.

Table 1
Demographics of patients in the RVO.

	RVO group (n = 39)
Age	56.05 ± 8.92
SEX	
Male	20 (51.3 %)
Female	19 (48.7 %)
Hypertension	39

Table 2
The amount of disrupted IS/OS, disrupted ELM and SRD in 39 eyes with RVO.

	CRVO (15)	HRVO (16)	BRVO (8)
Disrupted IS/OS	9 (60.0 %)	12 (75.0 %)	2 (25.0 %)
Disrupted ELM	10 (66.6 %)	11 (68.6 %)	2 (25.0 %)
SRD	14 (93.3 %)	13 (81.3 %)	4 (50.0 %)

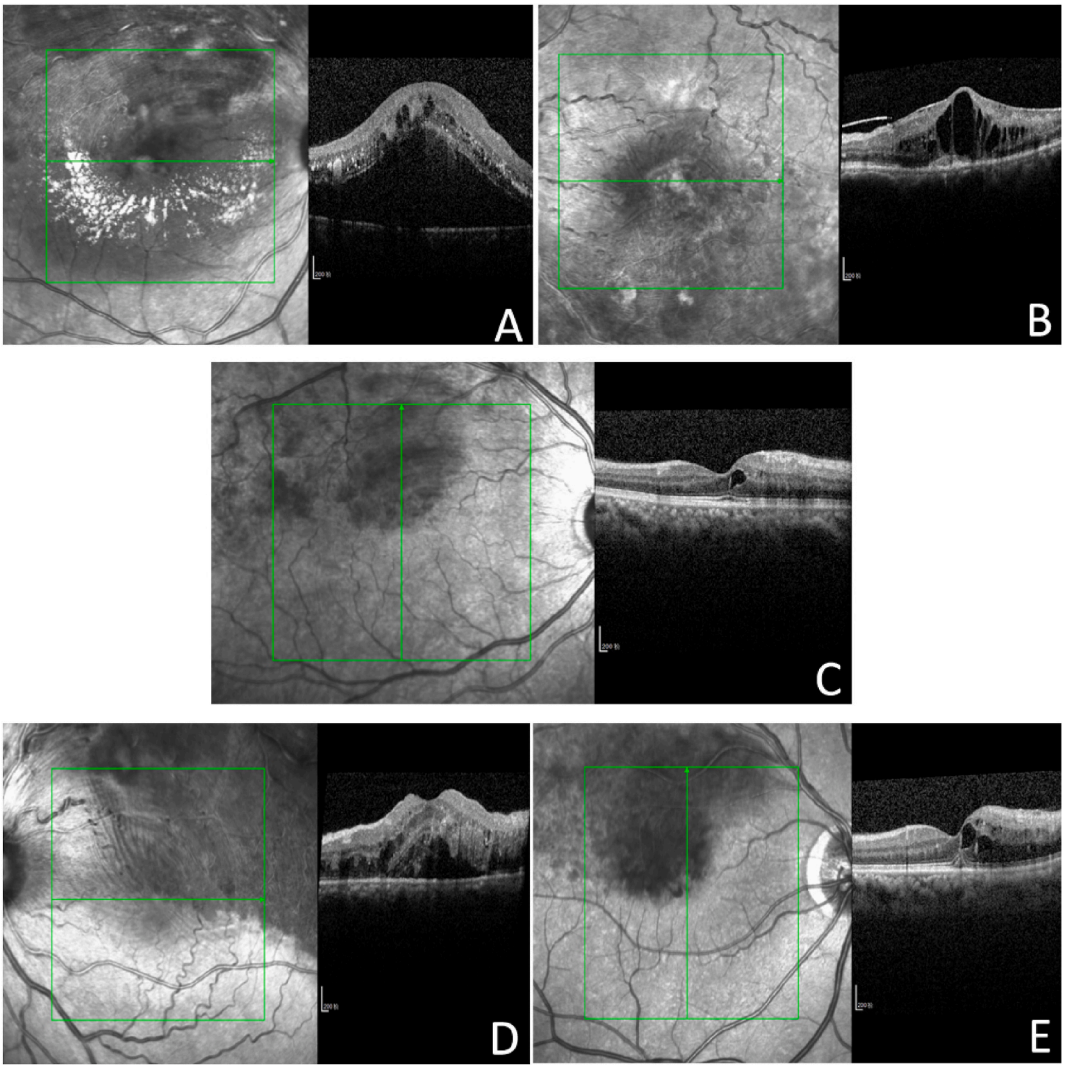

Fig. 1. The manifestations of RVO. A shows SRD in RVO and B is macular edema in RVO. C shows the intact IS/OS and ELM in RVO. D shows the disrupted IS/OS and E is disrupted ELM in RVO.

Serous retinal detachment usually occurs in retinal vein occlusion [12]. In our study, 31 eyes with RVO (79.50 %) suffered SRD, and the severity of SRD was determined by the incompleteness of the ELM and IS/OS layers. It has been reported that the formation of SRD was related to the interrupted ELM and IS/OS layers in BRVO, and the incomplete ELM and IS/OS layers caused SRD in macular edema [13–15]. The outer blood-retinal barrier (BRB) regulated the movement of solutes and nutrients from the choroid into the subretinal space, and the ELM layer had a partially similar function in blocking macromolecular proteins through the retina [16]. Moreover, the leakage from the vascular occlusion resulted in macular edema, and the macular edema exerted a pulling force from the Müller cell cone to the IS/OS layer, then damaged the barrier function of ELM [5]. Subsequently, macromolecular proteins passed through the ELM layer into the sub-retina, causing SRD. Koss et al. also suggested that the vascular leakage caused by CRVO produced the sub-retinal fluid which disturbed the structure of the fovea, particularly the Müller cell cone, forming SRD [14]. Ischemic RVOs caused major disruption in the ELM layer [17]. The integrity of ELM layer is critical for retinal microstructure. The integrity of the ELM

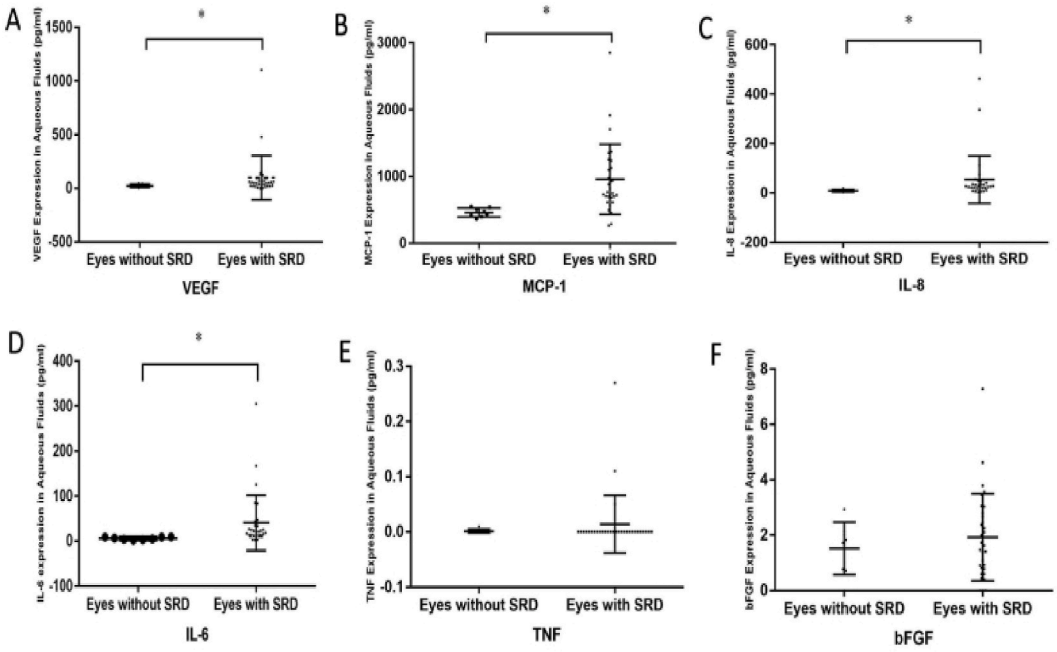

Fig. 2. The expression of cytokine factors in the aqueous fluids in patients with RVO. The concentrations of VEGF (A), MCP-1 (B), IL-8 (C) and IL-6 (D) were significantly increased in RVO eyes with SRD ($p < 0.05$). The expression of TNF (E) and bFGF (F) were not significantly different between RVO with SRD and RVO without SRD groups. Data were shown as mean ± SD. *: $p < 0.05$.

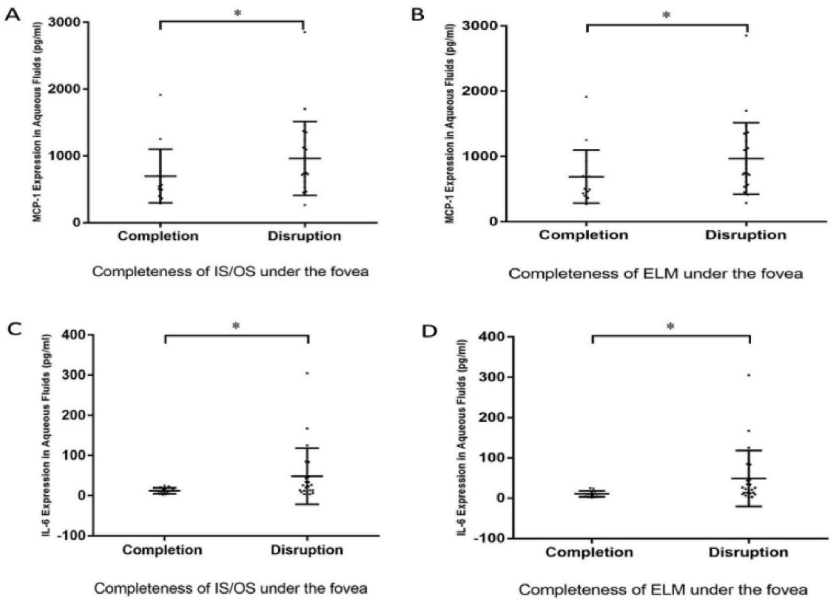

Fig. 3. The correlation between the expression of MCP-1 and IL-6 in aqueous fluids and the completeness of IS/OS or ELM under the fovea. The concentration of MCP-1(A&B) was increased significantly in RVO patients with disrupted IS/OS ($p = 0.046$) and ELM ($p = 0.03$). And the high level of IL-6 (C&D) was detected in RVO patients with disrupted IS/OS ($p = 0.019$) and ELM ($p = 0.004$). Data were shown as mean ± SD. *: $p < 0.05$.

indicated better visual outcomes in patients with RVO [18–21]. Besides, the incompleteness of the ELM and IS/OS layers was associated with the upregulation of MCP-1 and IL-6. Li et al. proposed the higher expression of MCP-1 and IL-6 in the aqueous humor of RVO eyes [8,22]. MCP-1 stimulated inflammatory cells to impair the vascular endothelium, leading to vascular leakage and exacerbating macular edema [23]. MCP-1 and IL -6 induced the expression of other inflammatory factors, especially VEGF, resulting in increased vascular permeability [24,25]. Therefore, the high concentrations of MCP-1 and IL-6 activate a portion of the inflammatory

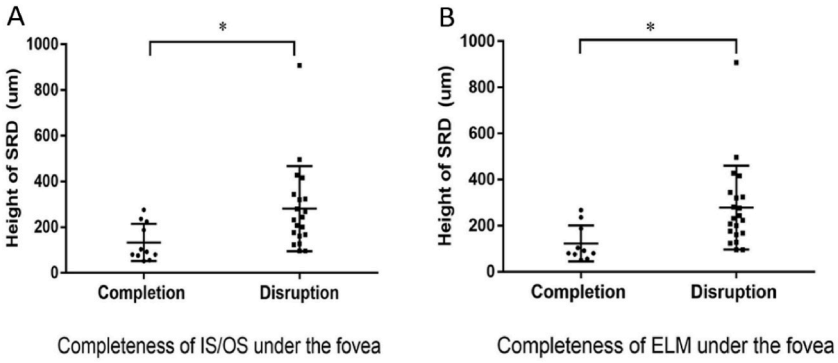

Fig. 4. The relationship between the height of SRD and the completeness of IS/OS (A) or ELM (B) under the fovea. The height of SRD was elevated due to the disruption of IS/OS ($p = 0.002$) or ELM ($p = 0.004$). Data were shown as mean ± SD. *: $p < 0.05$.

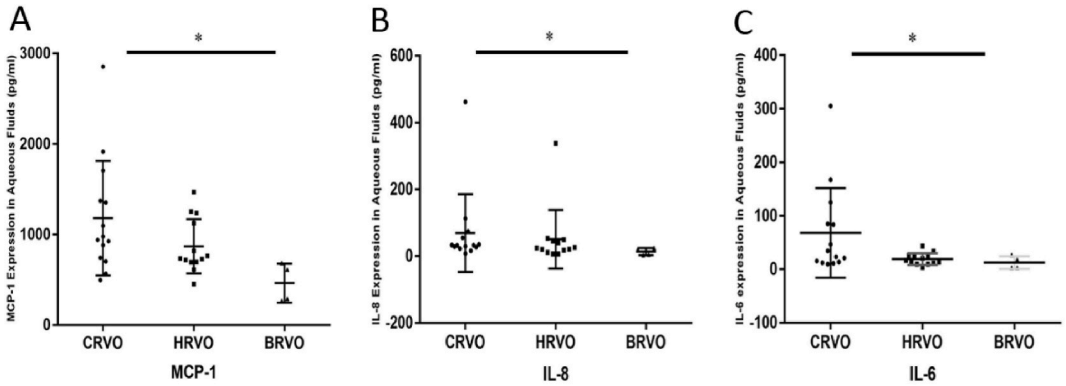

Fig. 5. The expression of cytokine factors in three different RVOs. The concentration of MCP-1 (A) was higher in CRVO than in HRVO and BRVO ($p < 0.001$). The levels of IL-8 and IL-6 were increased significantly in CRVO ($p = 0.003$, $p = 0.003$) (B&C). Data were shown as mean ± SD, one-way ANOVA. *: $p < 0.05$.

Table 3
The relation between SRD recurrence and cytokines in aqueous humor. The level of MCP-1 was increased in the SRD recurrence group ($p < 0.05$). The expression of VEGF, MCP-1, IL-6, IL-8, TNF and bFGF were not significantly changed between non-recurrence and recurrence groups. Data were shown as mean ± SD (No recurrence:n = 17, Recurrence: n = 14).

Cytokines(pg/ml)	Height of SRD(μm)		
	No recurrence	Recurrence	*P* value
VEGF	50.72 ± 43.50	157.54 ± 296.46	0.284
MCP-1	796.89 ± 418.49	1154.38 ± 582.67	0.015
IL-8	26.17 ± 17.26	88.68 ± 136.72	0.131
IL-6	29.42 ± 31.63	53.77 ± 84.14	0.973
TNF	0.06 ± 0.03	0.02 ± 0.07	0.439
bFGF	2.11 ± 1.70	1.69 ± 1.43	0.487

factors that exacerbate the extent of macular edema, which then disrupts the architecture of the ELM and IS/OS layers, triggering SRD.

Furthermore, the formation of SRD was correlated with the high expression of MCP-1, IL-6, IL-8, and VEGF. In previous studies, high levels of IL-6 and VEGF were detected in aqueous humor and vitreous when patients diagnosed with CRVO or BRVO with SRD [11, 26]. It showed that the high levels of IL-6 and VEGF promoted vascular permeability, which resulted in SRD [26]. IL-8 activates neutrophils and T lymphocytes, inducing angiogenesis and promoting vascular permeability [27]. In addition to vascular injury, the upregulated of MCP-1, IL-6, IL-8, and VEGF interfered with the outer barrier ability of the RPE, which then led to choroidal vessel leakage and promoted the formation of SRD [26]. Thus, the inflammatory pathway played an important role in the development of SRD. It has been suggested that dexamethasone implant may be more effective in the early stage of RVO-SRD patients because the morphology of the macula is soon recovered [28]. Anti-VEGF therapy preserved the macular structure and had the better visual outcome in the late stage [28–31]. Therefore, anti-inflammatory treatment combined with anti-VEGF therapy might be the best choice for RVO-SRD.

In our study, there are 14 eyes of CRVO (93.3 %) combined with SRD, 13 eyes of HRVO (81.3 %) combined with SRD, and 5 eyes of BRVO (50.0 %) combined with SRD. This is in line with the previous study that CRVO in combination with SRD occurred more frequently than BRVO combined with SRD [13]. Compared with macular BRVO, major BRVO was generally incorporated with SRD [11,12,32]. Comparably, CRVO and HRVO present more obviously a clogged area of veins [1]. Koss et al. found that inflammatory cytokines and VEGF were more highly expressed in undiluted vitreous samples with CRVO and HRVO than with BRVO [14]. We also detected higher concentrations of MCP-1, IL-8 and IL-6 in the larger area of the congested vein. Therefore, cytokine factors and vascular function are crucial for the development of SRD.

We also found that the height and shape of the SRD were not relevant to any inflammatory factors in the aqueous humor. In a study of BRVO, concentrations of cytokines (VEGFA, MCP-1, and IL-6) in the vitreous were also found to be rarely related to the height of SRD [15]. However, Koss et al. suggested that the high levels of MCP-1 and IL-6 in the vitreous influenced the height of SRD in CRVO [14]. With the development of RVO, the height of the SRD changed from a small point RD to a dome shaped RD [5]. There was no significant difference of cytokine factors between the RVO duration of less and more than 6 months [15]. Our study showed that cytokines were unrelated to the height of the SRD, probably because the levels of cytokines that we detected were within a short period of time after patients with SRD-RVO. Moreover, the high concentrations of cytokines and chemokines accelerated vascular permeability, causing or aggravating cystoid macular edema (CME) in diabetic retinopathy [33,34]. Nevertheless, Gaucher et al. proposed that the extension of SRD might not be associated with the severity of diabetic macular edema (DME) but depended on the reduction of the transport function of the RPE and hyperpermeability of the choroid [35]. Chen et al. found that thicker choroid appeared in RVO-SRD patients. The reason could be the dilatation of choroidal vessels and increased blood flow, which contribute to the increase of hydrostatic pressure in the choroid and thus choroidal leakage [36,37]. Overall, the severity of SRD could be affected by retinal edema and choroidal leakage. The function of cytokine factors in the progression of SRD should be further explored.

It was found that vision improved rapidly in patients with RVO-SRD, but BCVA had not improved in short-term follow-up after anti-VEGF therapy. Firat et al. suggested that considerable release of inflammatory factors and mechanical damage to photoreceptors due to SRD could result in low visual acuity [13]. Additionally, the persistence and recurrence of SRD in DME was another reason for a decrease in visual acuity [38]. We noticed that the recurrence of SRD occurred in RVO patients with high MCP-1 level before anti-VEGF injection. MCP-1 is generated from retinal endothelial cells and is associated with leukostasis in hypoxic retinas [39,40]. MCP-1 also participated in angiogenesis [41,42]. It has been reported that the expression of IL-6 and MCP-1 in aqueous humor in RVO were not affected after injected Ranibizumab [43]. Therefore, we proposed that the upregulation of MCP-1 might influence the development and recurrence of SRD. Anti-inflammatory therapies may be an important treatment for SRD and could prevent the recurrence of SRD in RVO [28,31]. To improve visual acuity, we recommend anti-inflammatory therapies in combination with the anti-VEGF injection when a high expression of MCP-1 is detected. A clinical trial which compares cytokines before and after anti-VEGF is advised to further help ophthalmologists draw a definitive clinical decision.

5. Conclusion

High concentrations of cytokine factors in aqueous humor could induce vascular leakage, exacerbate the extent of macular edema, disrupt the structure of ELM and IS/OS, and develop SRD in RVO.

Statement of ethnic

This study protocol was reviewed and approved by the Second Hospital of Jilin University, approval number 20200404109YY. All participants have signed the informed consent. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article. Raw data that support the findings of this study are available from the corresponding author, upon reasonable request. The data of this study has not been deposited into a publicly available repository, because it involves patients' information.

CRediT authorship contribution statement

Xin Liu: Writing – original draft, Methodology, Conceptualization. **Yahan Zhang:** Writing – review & editing, Writing – original draft. **Hongfang Yong:** Resources, Data curation. **Shun Zeng:** Resources, Data curation. **Ling Zuo:** Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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