• Clinical Research •

Serologic parameters in young patients with retinal vein occlusion treated with anti-vascular endothelial growth factor

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Abstract

● **AIM:** To assess the relationship between serological parameters and the prognosis of young patients with retinal vein occlusion (RVO) after intravitreal conbercept injection (IVC).

● **METHODS:** This study enrolled 100 young patients (≤50 years old) diagnosed with RVO-related macular edema (RVO-ME) who had been undergoing IVC at the 474 Hospital in Xinjiang between January 2022 and October 2023. Patients were categorized into two groups: 70 eyes in the effective group and 30 eyes in the ineffective group. The effective group comprised patients exhibiting a visual acuity improvement of ≥2 lines at the last follow-up, with resolved ME and central macular thickness (CMT) <300 μm. Conversely, the ineffective group included patients with visual acuity improvement of <1 line, persistent ME, and CMT ≥300 μm at the last follow-up. Serological parameters, including white blood cell count, neutrophil count, lymphocyte count, monocyte count, and mean platelet volume were assessed before treatment. The correlation between best-corrected visual acuity (BCVA) and neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), and systemic immune response index (SIRI) was analyzed. Additionally, the association between these serological parameters and the efficacy of IVC was explored.

● **RESULTS:** Three months after treatment, the effective group demonstrated a significant improvement in BCVA from 0.82±0.20 to 0.36±0.10, with a concurrent decrease in CMT from 661.28±163.90 to 200.61±82.45 μm (P<0.001). Conversely, the ineffective group exhibited minimal changes in BCVA (0.86±0.25 to 0.82±0.14) and CMT (669.84±164.95 to 492.13±138.67 μm, P<0.001). The differences in BCVA and CMT between the two groups were statistically significant (P<0.001). According to subgroup analysis, in patients with central RVO (CRVO), BCVA improved from 0.82±0.23 to 0.49±0.12 in the effective group and from 0.80±0.18 to 0.76±0.22 in the ineffective group (P<0.001). The CMT changes followed a similar pattern. In patients with branch RVO (BRVO), comparable trends in BCVA and CMT changes were observed between the effective and ineffective groups (P<0.001). Additionally, the effective group exhibited higher PLR and SII values than the ineffective group (P<0.05). Further CRVO and BRVO subgroups analysis exhibited consistent PLR and SII value trends.

● **CONCLUSION:** Compared to other inflammatory factors, elevated PLR and SII levels before treatment are better predictors of outcomes in young RVO-ME patients undergoing IVC treatment.

● **KEYWORDS:** retinal vein occlusion; anti-vascular endothelial growth factor; systemic immune-inflammatory index; neutrophil-to-lymphocyte ratio

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INTRODUCTION

Constriction and relaxation limitations within the retinal vein lumen lead to retinal vein occlusion (RVO), obstructing blood circulation or vascular thrombosis[1]. This obstruction can manifest as central RVO (CRVO) or branch RVO (BRVO). RVO ranks as the second most common retinal vascular disease causing visual impairment, following diabetic retinopathy. Although RVO can occur at any age, it is typically diagnosed in 90% of patients over 50, with 10% under 40[2]. Various factors contribute to RVO pathogenesis. Common systemic diseases in middle-aged and elderly patients include cardiovascular disease, atherosclerosis, hypercoagulable

states, and thrombophilia[3]. While cardiovascular factors are pivotal in younger RVO patients, other mechanisms, such as hyperglobulinemia, multiple myeloma, iron deficiency anemia, acute lymphocytic leukemia, and hereditary spherocytosis, should be considered when CRVO occurs in patients under 40. These conditions, termed secondary hyperviscosity syndrome, can trigger CRVO in younger patients. Additionally, intense exercise-induced dehydration in young individuals can elevate blood viscosity, facilitating CRVO development. Elevated homocysteine levels impair endothelial function and promote vascular smooth muscle cell proliferation, contributing to CRVO. Deficiencies in protein C, protein S, and anticoagulant factors also contribute to RVO in young patients[4-6]. Moreover, extensive research suggests that systemic diseases such as systemic lupus erythematosus, sarcoidosis, systemic vasculitis, and rheumatoid arthritis are linked to CRVO development in young patients[1,7]. Secondary macular edema (ME), causing significant visual impairment, heavily influences the prognosis of young RVO patients. Prompt intervention and treatment are essential for young RVO-related macular edema (RVO-ME) patients because ME often persists despite 12mo of treatment, that this refractory ME may be associated with Müller cells, which induce increased VEGF expression related to traction, leading to disruption of the blood-retinal barrier and persistent ME. RVO patients exhibit elevated intravitreal vascular endothelial growth factor (VEGF) levels, and anti-VEGF therapy can mitigate retinal leakage, prevent vascular remodeling, alleviate ME, and enhance vision[8]. Anti-VEGF therapy is the recommended first-line treatment for RVO-ME[9]. Laser treatment is also a method for treating RVO. Damage to the retinal pigment epithelium tissue, which has a high metabolic rate, can occur due to laser exposure, resulting in scar tissue formation. This involves enhancing retinal ischemia, decreasing the production of VEGF, weakening the outer barrier of the retina, and boosting oxygen supply from the choroid to the retina, thereby improving the oxygen supply pathway. Nevertheless, laser intervention has the potential to cause peripheral visual field defects, irreversible visual impairment, and even color vision abnormalities. The dexamethasone intravitreal implant, functioning as an extended-release corticosteroid formulation, efficiently reduces inflammation, alleviates ME, and improves visual acuity. However, there are potential adverse outcomes associated with it, such the development of secondary cataracts and glaucoma. Complications are more prone to manifest if the treatment extends beyond 6mo, possibly leading to the need for additional intraocular surgery[10]. In some cases of RVO-ME, patients may suffer from persistent ME due to epiretinal membrane or vitreous traction. Therefore, carrying out careful monitoring is crucial with optical coherence tomography (OCT) during subsequent follow-ups. In the event of this situation arising, it is advisable to promptly carry out a vitrectomy procedure. It is also worth noting that some researchers suggest vitrectomy for patients with recurrent or persistent ME after treatment, as it improves retinal oxygenation[11]. However, some young patients respond poorly to anti-VEGF therapy and have a poor prognosis. It must also be emphasized that repeated administrations of the medication also pose a financial strain on the individual. Prolonged administration of various drugs through multiple injections heightens the likelihood of ocular complications, including endophthalmitis, increased intraocular pressure (IOP), and other side effects. Hence, healthcare providers must opt for more precise treatment modalities and individualized treatment strategies to offer prognostic support and alleviate the burden on patients with RVO-ME. In the current scenario, is essential to analyze emerging prognostic indicators to establish if they can predict the onset and progression of RVO, allowing for timely adjustments to the treatment plan.

Individuals with RVO demonstrate higher inflammatory factors in their aqueous humor or vitreous cavity, suggesting their involvement in RVO development[12]. In recent years, researchers have identified peripheral blood cell count and its combination as potentially relevant to ocular vascular diseases, using it to assess the inflammatory response status of these diseases[13]. Inflammatory biomarkers such as the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are believed to contribute to RVO development[14-16]. However, studies on these biomarkers have predominantly focused on patients over 50, with fewer investigating changes in serological parameters in young RVO patients. Therefore, this study aims to examine changes in peripheral blood inflammatory markers before and after anti-VEGF treatment in young RVO patients and assess the correlation between these hematological indicators and RVO-ME, thereby offering insights for personalized prognosis prediction in young RVO patients.

PARTICIPANTS AND METHODS

Ethical Approval This study was conducted retrospectively with approval from the Xinjiang 474 Hospital Ethics Committee, approval number 202310006, adhering to the principles of the Helsinki Declaration

Participants Medical records of 100 patients (100 eyes) diagnosed with RVO and treated at the Vitreous Injection Center of Xinjiang 474 Hospital between January 2021 and October 2023 were reviewed. Venous blood samples were collected for analysis before the initial vitreous cavity injection, with all patient data analyzed one month after the third injection. RVO is classified according to the site of the venous obstruction, with CRVO denoting obstruction

occurring posterior to the optic disc, and BRVO indicating blockage in the branch vessels. Hemi-lateral RVO (HRVO) is also recognized. This research study aims to simplify the classification of RVO by grouping it into two main types, CRVO, and BRVO, due to the challenges in distinguishing between HRVO and hemi-CRVO in clinical settings. Additionally, we have included the diagnostic criteria for RVO. Inclusion criteria comprised: 1) age <50y; 2) RVO diagnosis confirmed by OCT and fundus fluorescein angiography (FFA), CRVO: Upon fundus examination, findings reveal optic disc congestion with mild swelling, blurred borders, retinal venous blood flow stasis, and hemorrhage radiating from the optic disc. The retina displays superficial flame-shaped hemorrhages and yellowish-white exudates, along with ME. OCT: Central foveal bulging, retinal thickening in the macular region, observable retinal edema in the central fovea and the retina underneath it, exudation, presence of multiple cystic cavities in the outer plexiform layer and inner nuclear layer, and fluid in the cystic cavities. FFA: In the advanced phase, there is a presence of significant areas of capillary non-perfusion, compensatory dilatation of superficial and deep residual capillaries around the occluded area, microangioma formation, and petal-like fluorescein accumulation in the macula. BRVO: Localized venous dilation, hemorrhage, and exudation are observed in a triangular distribution during fundus examination, with the apex pointing toward the obstructed area. OCT: We witness the changes in the fovea profile, absence of the foveal contour, evident edema and exudation in the fovea and the retina below it, and cyst formation. FFA: In the region of retinal blockage, there is a detectable leakage of fluorescein, resulting in the staining of the vessel walls and surrounding tissues. In cases where the macula is affected, the presence of macular cystoid edema may become apparent in the later stages. 3) IOP within normal limits. 4) complete follow-up data.

Exclusion criteria encompassed: 1) presence of other ocular pathologies such as uveitis, age-related macular degeneration, glaucoma, diabetic retinopathy, and severe refractive opacities; 2) comorbidities including diabetes, systemic inflammatory disorders, cardiovascular diseases, sepsis, malignant tumors, or others; 3) history of intraocular surgery, vitreous hemorrhage, intraocular inflammation, ocular trauma, or prior laser treatments.

All participants underwent comprehensive ophthalmic assessments, including best-corrected visual acuity (BCVA, logMAR), slit-lamp biomicroscopy, color fundus photography, FFA, and OCT. Parameters such as IOP, BCVA, and central macular thickness (CMT) were documented. A diagnosis of ischemic CRVO was made following an FFA examination when the non-perfusion area in the retinal capillaries comprised ≥75% of the disc area, or the ischemic index was ≥35%.

Drawing Peripheral Blood The fasting period before blood collection lasted for 12h. Samples were drawn from the antecubital vein at 10:00 Beijing time. Hematological analysis was conducted using an automated coagulation analyzer (Sysmex XN-L-550, Japan), ensuring accurate measurement of white blood cells, neutrophils, lymphocytes, monocytes, and mean platelet volume. Subsequently, calculations and documentation were made for NLR, PLR, platelet count multiplied by neutrophil count divided by lymphocyte count (systemic immune inflammation index, SII), monocyte count multiplied by neutrophil count divided by lymphocyte count (systemic immune response index, SIRI), and other pertinent parameters. NLR is derived by dividing the neutrophil count by the lymphocyte count. PLR is obtained by dividing the platelet count by the lymphocyte count. SII is computed as the product of the platelet and neutrophil counts divided by the lymphocyte count. SIRI is calculated as the product of the monocyte count and the neutrophil count divided by the lymphocyte count.

Vitreous Cavity Injection of Anti-VEGF Drugs The conjunctival sac underwent thorough cleaning and disinfection after administering ocular surface anesthesia to all patients in the vitreous drug injection center's operating room. An eyelid speculum was employed to facilitate eyelid opening, and injections were administered 3.5–4 mm from the corneal edge, targeting the flattened part of the ciliary body. Conbercept (Chengdu Kanghong Biotech Co., Ltd., Sichuan Province, China) was then introduced into the vitreous cavity at a 0.5 mg/0.05 mL concentration. Participants adhered to a 3+*pro re nata* (PRN) pattern, receiving injections at weekly intervals.

The analytical parameters encompassed treatment serum parameters and pre- and post-treatment BCVA, IOP, CMT, and other patient conditions. One injection per month was initially administered for the first three months, transitioning to monthly follow-ups after the third injection. The decision to continue medication was contingent upon the severity of ME and BCVA. After the third injection, patients were categorized into effective and ineffective groups based on their BCVA, resolution of ME, and CMT levels one month after treatment. The effective group comprised patients exhibiting improved vision by two lines or more, resolution of ME, and CMT <300 μm at the final follow-up. Conversely, the ineffective group included patients with vision improvement of less than one line, persistent ME, and CMT ≥300 μm at the final follow-up.

Statistical Analysis Statistical analysis was conducted using SPSS 20.0 software. Measurement data with a normal distribution were expressed as mean and standard deviation. The independent samples *t*-test and Chi-square test were employed for group comparisons, with count data presented as percentages. Statistical significance was set at a *P*-value<0.05.

It is important to note that data not conforming to normal distribution were deemed unsuitable for statistical analysis.

RESULTS

Baseline Characteristics This study comprised 100 RVO patients under 50, including 53 males (53.0%) and 47 females (47.0%), with an average age of 39.47±7.22y. Among them, 39 patients (39.0%) presented with BRVO, while 61 (61.0%) had CRVO. The mean duration from baseline to final follow-up was 110.18±11.23d. A comprehensive medical examination of the enrolled patients revealed comorbidities: 4 patients had hypertension, 1 had diabetes, 2 had hyperlipidemia, 5 were obese [body mass index (BMI)>28], 2 had sleep apnea syndrome, 3 had hyperhomocysteinemia, 2 had systemic lupus erythematosus, 1 had nephrotic syndrome, and the specific etiology remained unidentified in 80 cases (Table 1).

Table 1 Characteristics of the enrolled patients

Characteristics	Data
Eye (*n*)	100
Gender (M/F)	53/47
Age (y)	39.47±7.22
BRVO (*n*)	39
CRVO (*n*)	61
IOP, mm Hg	17.68±3.84
BCVA, logMAR	0.84±0.21
Hypertensive disease	4
Diabetes	1
Hyperlipidemia	2
Obese (BMI>28)	5
Sleep apnea syndrome	2
Hyperhomocysteinemia	3
Systemic lupus erythematosus	2
Nephrotic syndrome	1
Unspecified reasons	81
Duration of symptoms (d)	10.12±5.75

CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion; IOP: Intraocular pressure; BCVA: Best-corrected visual acuity; BMI: Body mass index.

Comparison of General Information and Serologic Parameters Between Effective and Ineffective Groups After Anti-VEGF Therapy The effective group encompassed 70 eyes (70.0%) of the enrolled patients, while the ineffective group comprised 30 (30.0%). Baseline CMT did not exhibit significant differences between the two groups (661.28±163.90 *vs* 669.84±164.95). Intravitreal anti-VEGF treatment reduced CMT in both groups (200.61±82.45 *vs* 492.13±138.67). Comparing CMT changes before and after anti-VEGF treatment revealed a notable decrease in the effective group (t=26.12, P<0.001) compared to the ineffective group. Baseline BCVA showed no significant difference between the two groups (0.82±0.20 *vs* 0.86±0.25). Intravitreal anti-VEGF treatment enhanced BCVA in both groups (0.36±0.10 *vs* 0.82±0.14, P<0.001). Hematological parameters, including white blood cell count, red blood cell count, neutrophil count, monocyte count, lymphocyte count, platelet count, and mean platelet volume, did not display significant differences between the two groups. However, the effective group exhibited significantly higher PLR and SII compared to the ineffective group (P<0.001). At the same time, no significant difference was observed in NLR or SIRI between the two groups. Table 2 presents the detailed results. In BRVO patients with low PLR and SII, after three intravitreal injections, we observed a slight reduction in retinal edema, partial improvement in morphology, but with a CMT >300 μm.

Comparison of General Information and Hematological Parameters Between Effective and Ineffective Groups in CRVO Patients Among the enrolled CRVO patients, 41 eyes (67.21%) belonged to the effective group, while 20 eyes (32.79%) were in the ineffective group. Four eyes exhibited ischemic CRVO in the effective group, whereas 37 presented with nonischemic CRVO. In contrast, the ineffective group comprised 18 eyes with ischemic CRVO and two with non-ischemic CRVO. Baseline CMT did not show significant differences between the two groups (681.82±150.10 *vs* 691.88±140.38). Intravitreal anti-VEGF treatment reduced CMT in both groups (264.91±58.11 *vs* 581.32±86.54). Comparing CMT changes before and after anti-VEGF treatment revealed a notable decrease in the effective group (t=-17.08, P<0.001) compared to the ineffective group. Baseline BCVA did not significantly differ between the two groups (0.82±0.23 *vs* 0.80±0.18). Intravitreal anti-VEGF treatment improved BCVA for both groups (0.49±0.12 *vs* 0.76±0.22). However, when comparing BCVA changes between the two groups, the effective group demonstrated a more substantial improvement (t=5.32, P<0.001). Hematological parameters, including white blood cell count, red blood cell count, neutrophil count, monocyte count, lymphocyte count, platelet count, and mean platelet volume, did not significantly differ between the two groups. However, the effective group exhibited higher PLR and SII compared to the ineffective group (P=0.03, 0.02), while no significant difference was observed in NLR or SIRI between the two groups. Table 3 presented the detailed results. We selected a representative RVO-ME patient with high PLR and SII in the OCT (Figure 1). After three intravitreal injections in a CRVO patient with high PLR and SII, we observed the resolution of retinal edema, a decrease in CMT, and improvement in retinal morphology.

Comparison of General Information and Hematological Parameters Between Effective and Ineffective Groups in BRVO Patients The effective group comprised 29 eyes (74.4%) of the enrolled BRVO patients, while the ineffective group included ten eyes (25.6%). Baseline CMT did not differ

Table 2 Analysis of demographic characteristics and serological parameters of RVO patients in the effective and ineffective groups

Parameters	Efficient group	Inefficient group	Statistic index (t/χ^2)	*P*
n	70	30		
Age (y)	39.57±7.16	41.02±9.12	-0.32	1.12
CRVO/BRVO	41/29	20/10	0.10	0.74
IOP at baseline (mm Hg)	16.78±3.45	16.36±4.30	0.46	0.64
IOP after treatment (mm Hg)	16.83±4.02	16.19±4.40	0.63	0.52
BCVA at baseline (logMAR)	0.82±0.20	0.86±0.25	-1.21	0.96
BCVA after treatment (logMAR)	0.36±0.10	0.82±0.14	-2.12	<0.001
Change in BCVA (logMAR)	0.50±0.16	0.06±0.03	12.12	<0.001
CMT at baseline (μm)	661.28±163.90	669.84±164.95	-0.24	0.80
CMT after treatment (μm)	200.61±82.45	492.13±138.67	-17.42	<0.001
Change in CMT (μm)	450.12±135.88	195.0±101.13	26.12	<0.001
White blood cell (10^9/L)	7.07±3.20	7.44±3.12	-1.52	1.01
Red blood cell (10^{12}/L)	6.12±1.48	6.76±1.81	-1.66	0.10
Neutrophil (10^9/L)	3.06±0.45	3.03±0.56	0.25	0.79
Lymphocytes (10^9/L)	2.04±0.41	2.20±0.17	-1.60	0.11
Monocytes (10^9/L)	0.40±0.18	0.45±0.15	-1.05	0.29
Platelets (10^9/L)	300.27±44.05	282.48±41.22	1.70	0.09
Mean platelet volume (fL)	9.23±1.76	9.48±1.62	−0.60	0.54
NLR	1.56±0.40	1.38±0.29	1.30	0.14
PLR	152.27±37.26	129.11±22.30	2.12	0.02
SII	469.02±139.02	390.09±115.42	2.77	<0.001
SIRI	0.62±0.27	0.60±0.14	0.34	0.72

RVO: Retinal vein occlusion; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion; IOP: Intraocular pressure; BCVA: Best-corrected visual acuity; CMT: Central macular thickness; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune inflammation index; SIRI: Systemic inflammatory response index.

Table 3 Analysis of demographic characteristics and serological parameters of the effective and ineffective groups in the CRVO subgroup

Parameters	Efficient group	Inefficient group	Statistic index (t/χ^2)	*P*
n	41	20		
Age (y)	40.12±8.12	41.57±6.54	0.96	0.29
IOP at baseline (mm Hg)	17.08±3.44	17.05±4.33	0.02	0.97
IOP after treatment (mm Hg)	17.50±4.25	16.35±3.63	0.95	0.34
BCVA at baseline (logMAR)	0.82±0.23	0.80±0.18	-0.97	0.33
BCVA after treatment (logMAR)	0.49±0.12	0.76±0.22	-11.64	<0.001
Change in BCVA (logMAR)	0.34±0.23	0.06±0.05	7.21	<0.001
CMT at baseline (μm)	681.82±150.10	691.88±140.38	-0.67	0.50
CMT after treatment (μm)	264.91±58.11	581.32±86.54	-17.08	<0.001
Change in CMT (μm)	425.15±115.22	129.15±86.30	5.12	<0.001
White blood cell (10^9/L)	6.88±2.32	6.41±2.66	1.11	0.27
Red blood cell (10^{12}/L)	5.99±1.32	6.66±1.62	-1.57	0.12
Neutrophil (10^9/L)	3.08±0.36	2.93±0.55	1.21	0.23
Lymphocytes (10^9/L)	1.98±0.46	2.25±0.45	-1.61	0.95
Monocytes (10^9/L)	0.42±0.19	0.44±0.15	-0.44	0.65
Platelets (10^9/L)	292.76±46.61	278.05±45.22	1.10	0.27
Mean platelet volume (fL)	9.02±1.92	9.81±1.51	-1.47	0.14
NLR	1.64±0.41	1.56±0.44	1.65	0.09
PLR	155.84±44.73	130.83±44.24	2.20	0.03
SII	481.16±147.68	338.03±137.19	2.40	0.02
SIRI	0.66±0.26	0.61±0.29	0.67	0.50

RVO: Retinal vein occlusion; CRVO: Central retinal vein occlusion; IOP: Intraocular pressure; BCVA: Best-corrected visual acuity; CMT: Central macular thickness; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune inflammation index; SIRI: Systemic inflammatory response index.

significantly between the effective and ineffective groups (553.25±166.92 *vs* 541.86±214.49). Intravitreal anti-VEGF therapy decreased CMT in both groups (219.44±121.58 *vs* 446.12±105.15). Comparing changes in CMT before and after treatment revealed a statistically significant decrease in the effective group (t=5.21, P<0.01) compared to the ineffective group. Baseline BCVA did not significantly differ between the two groups (0.62±0.18 *vs* 0.63±0.24). After intravitreal anti-VEGF therapy, both groups demonstrated improved BCVA (0.31±0.12 *vs* 0.57±0.19). However, when comparing changes in BCVA between the two groups, the effective group displayed a more significant improvement (t=7.28, P<0.001). Hematological parameter analysis revealed no significant differences between the two groups in terms of platelet volume, neutrophil count, lymphocyte count, monocyte count, platelet count, or mean platelet volume. Nonetheless, the effective group exhibited a higher PLR than the ineffective group (P<0.001), while no significant differences were observed between the two groups regarding NLR, SII, or SIRI. Table 4 presented the detailed results. We selected a representative BRVO-ME patient OCT image (Figure 2) of a BRVO patient with low PLR and SII. After three intravitreal injections, we observed a slight reduction in retinal edema, partial improvement in morphology, but with a CMT >300 μm, the visual acuity improvement was less than one line.

Receiver Operator Characteristic Curve Analysis This study employed receiver operator characteristic curve (ROC) curve analysis to ascertain the predictive values of NLR, PLR, SII, and SIRI. The area under the curve (AUC) for NLR was 0.665 (95%CI: 0.557–0.773), with an optimal cutoff value of 1.72 and a sensitivity of 70.1%. For PLR, the AUC was 0.827 (95%CI: 0.745–0.909), indicating the best cutoff value of 121.22, a sensitivity of 80.2%, and a specificity of 68.3%. SII demonstrated an AUC of 0.776 (95%CI: 0.682–0.870), with a best cutoff value of 436.3, a sensitivity of 77.5%, and a specificity of 50.2%. The AUC for SIRI was 0.625 (95%CI: 0.513–0.737), with an optimal cutoff value of 0.75, a sensitivity of 51.7%, and a specificity of 72.3%. Table 5 and Figure 3 presented the detailed results.

DISCUSSION

RVO is the predominant retinal vascular disease among adults, trailing only diabetic retinopathy in prevalence. The etiology of RVO-ME is complex and exhibits variations between younger and older RVO patients. Younger RVO patients often manifest pronounced hemodynamic changes, inflammatory responses, and vascular lesions[5,8,16]. Studies also highlight the impact of platelet activation parameters, neutrophils, lymphocytes, and other mediators on the pathogenesis of ischemic vascular conditions, including acute pulmonary embolism and ongoing renal impairment[17-18]. Inflammatory markers' role in ocular

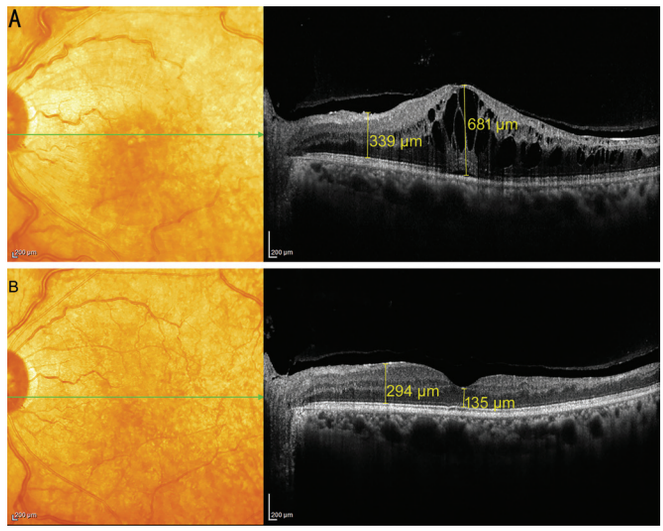

Figure 1 OCT image of a typical patient who responded well to IV injection therapy A: OCT image of a young CRVO patient before treatment; B: Image after 3 IVC this patient has high PLR and SII. The contact between the posterior hyaloid and the foveal has been released following 3 IVC. OCT: Optical coherence tomography; CRVO: Central retinal vein occlusion; PLR: Platelet-lymphocyte ratio; SII: Systemic immune inflammation index; IVC: Intravitreal conbercept injection.

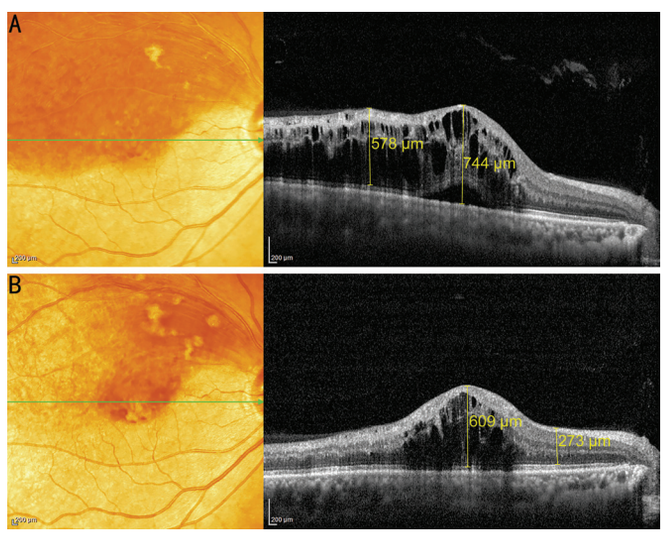

Figure 2 OCT image of a typical patient who responded poorly to IVC therapy A: OCT image of a young BRVO patient before treatment, B: Image after 3 IVC; this patient has low PLR and SII. OCT: Optical coherence tomography; BRVO: Branch retinal vein occlusion; PLR: Platelet-lymphocyte ratio; SII: Systemic immune inflammation index; IVC: Intravitreal conbercept injection.

diseases, particularly their correlation with retinal vascular occlusive disorders, has attracted considerable attention among researchers[19-20]. When retinal ischemia and hypoxia occur in RVO, VEGF levels increase, triggering overexpression of inflammatory factors and activating inflammatory pathways. Consequently, the blood-retinal barrier's integrity is compromised, rendering retinal vessels more permeable, facilitating fluid leakage, and culminating in ME, thereby

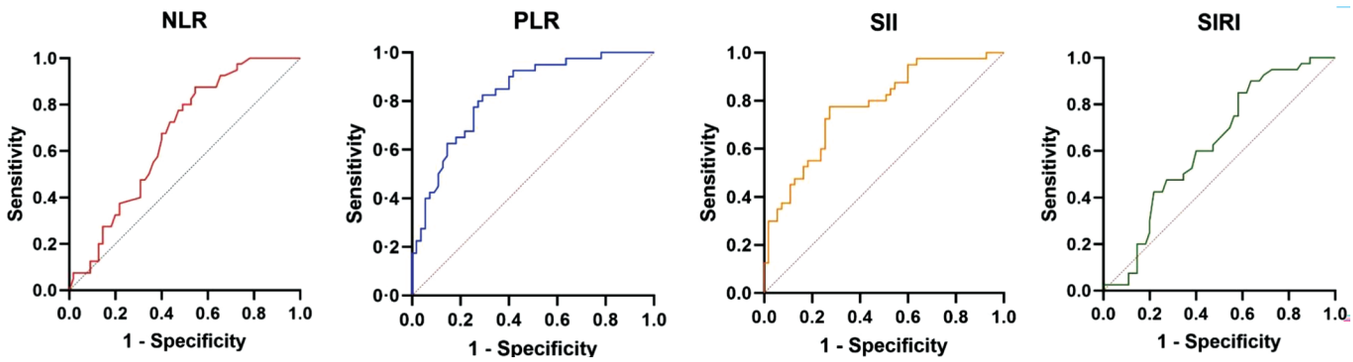

Figure 3 Receiver operator characteristic curve analysis of hematologic parameters identified as potential biomarkers NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune inflammation index; SIRI: systemic inflammatory response index.

Table 4 Comparison of demographic characteristics and serological parameters between the effective and ineffective groups of patients with BRVO

Parameters	Efficient group	Inefficient group	Statistic index (t/χ^2)	*P*
n	29	10		
Age (y)	36.45±10.05	38.33±9.61	-0.67	0.50
IOP at baseline (mm Hg)	16.96±3.10	16.16±4.30	-0.16	0.86
IOP after treatment (mm Hg)	16.11±3.52	17.00±3.21	-1.58	0.12
BCVA at baseline (logMAR)	0.62±0.18	0.63±0.24	-0.48	0.67
BCVA after treatment (logMAR)	0.31±0.12	0.57±0.19	-12.23	<0.001
Change in BCVA (logMAR)	0.34±0.22	0.08±0.07	7.28	<0.001
CMT at baseline (μm)	553.25±166.92	541.86±214.49	0.36	0.71
CMT after treatment (μm)	219.44±121.58	446.12±105.15	2.96	<0.001
Change in CMT (μm)	320.55±141.22	101.25±121.22	7.21	<0.001
White blood cell (10^9/L)	7.15±2.81	7.62±1.99	-0.63	0.52
Red blood cell (10^{12}/L)	6.21±1.23	6.42±1.65	-1.19	0.24
Neutrophil (10^9/L)	3.04±0.60	2.91±0.48	0.32	0.74
Lymphocytes (10^9/L)	2.01±0.37	2.04±0.24	-0.25	0.80
Monocytes (10^9/L)	0.38±0.15	0.39±0.19	-0.59	0.95
Platelets (10^9/L)	316.18±37.65	308.91±43.17	0.25	0.80
Mean platelet volume (fL)	9.56±1.41	9.53±1.55	0.52	0.59
NLR	1.58±0.52	1.48±0.30	0.67	0.50
PLR	163.39±42.63	143.94±32.33	2.64	<0.001
SII	470.04±183.19	459.79±159.11	1.23	0.22
SIRI	0.60±0.28	0.57±0.23	0.80	0.42

BRVO: Branch retinal vein occlusion; IOP: Intraocular pressure; BCVA: Best-corrected visual acuity; CMT: Central macular thickness; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune inflammation index; SIRI: Systemic inflammatory response index.

Table 5 ROC curve analysis results

Parameters	AUC	95%CI	*P*	Sensitivity, %	Specificity, %
NLR	0.665	0.557–0.773	0.006	70.1	55.6
PLR	0.827	0.745–0.909	0.001	80.2	68.3
SII	0.776	0.682–0.870	0.001	77.5	50.2
SIRI	0.625	0.513–0.737	0.003	51.7	72.3

ROC: Receiver operator characteristic curve; AUC: Area under the curve; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune inflammation index; SIRI: systemic inflammatory response index.

impairing visual acuity. Anti-VEGF therapy has become the most common treatment for RVO-ME. Conbercept, an anti-VEGF fusion protein, inhibits the binding of multiple VEGF family members to endogenous VEGF receptors. It

has a higher affinity for VEGF-A compared to monoclonal antibodies or endogenous VEGF receptors, making it a safe and effective treatment for RVO-ME[21-22]. After anti-VEGF intervention, significant improvements in BCVA and reduced CMT have been observed in younger RVO-ME patients. However, some individuals exhibit inadequate response to anti-VEGF therapy, attributable to various factors such as prolonged disease duration, extensive retinal ischemia, and systemic comorbidities[23]. The focus of current research is on providing personalized treatment plans. Studies have shown that increased expression of various inflammatory factors is related to the pathogenesis of RVO. Multiple cytokines, such as interleukin (IL)-6 and IL-8, detected in the aqueous humor or vitreous body have been shown to be significantly elevated in RVO-ME patients[24-25]. However, obtaining these samples is challenging owing to the high cost and the increased risk of infection from eye entry procedures. Therefore, identifying simple, convenient, and cost-effective inflammatory markers is especially important. The current research focuses on developing personalized treatment strategies[26-27]. Recent studies have extensively explored platelet activation parameters and peripheral inflammatory markers in RVO. However, investigations into these indicators, especially among younger RVO patients, remain scarce. Therefore, this study aims to elucidate platelet activation parameters and peripheral inflammation in young patients with RVO-ME.

The peripheral blood inflammatory markers include various factors, such as white blood cell count, platelet count, neutrophil count, and lymphocyte count. Elevated white blood cell counts have been associated with cardiovascular conditions such as coronary heart disease and stroke[28]. These cells adhere to and accumulate in retinal blood vessels, leading to occlusions in the retinal capillary network and temporary areas of reduced blood flow, thereby disrupting retinal microcirculation. The inflammatory cascade in RVO is facilitated by interleukins, with IL-1, IL-6, IL-8, IL-12, and others being more prevalent in RVO and correlating with future retinal ischemia[29]. An elevation in white blood cell count indicates inflammatory diseases in the body[28]. However, because a significant increase in white blood cells indicates increased systemic inflammation, intravitreal drug administration during this period increases the risk of post-surgical infection. Consequently, intravitreal drug therapy is withheld until white blood cell counts return to normal levels. Accordingly, our study observed no significant differences in white blood cell counts between the effective and ineffective treatment groups. Mean platelet volume (MPV) is a measure of platelet production rate and size, reflecting platelet size, responsiveness, and function. Platelets with high MPV exhibit heightened metabolism, enzyme activity, and stronger pro-inflammatory and pro-thrombotic effects. Studies have shown that MPV levels increase in both BRVO and CRVO patients, serving as an independent predictor of RVO and accelerating the progression of RVO-ME. However, our investigation identified no significant differences in MPV between the effective and ineffective treatment groups. Further analysis revealed no correlation between MPV and RVO subtype, suggesting that MPV cannot reliably predict anti-VEGF treatment outcomes in young RVO-ME patients.

The peripheral blood inflammatory markers can yield different parameters for analysis and comparison based on various calculation methods. NLR and PLR are indicative ratios of inflammatory cell activity associated with RVO. NLR stands for NLR, while PLR stands for the PLR. Elevated neutrophil levels can trigger the release of chemotactic factors such as matrix metalloproteinase-9 and VEGF, which significantly affect retinal vasculature, increasing vascular permeability and leading to ME. In young RVO patients, NLR, SII, and SIRI are significantly elevated, especially in young ischemic RVO patients. NLR and SII are positively correlated with IL-6 levels in aqueous humor, suggesting that systemic inflammation plays an important role in the pathogenesis of RVO in young patients[30]. NLR represents the balance between inflammatory and immune responses in the body. It has been associated with thrombotic conditions such as venous thrombosis and pulmonary embolism, suggesting its potential as a predictive marker for acute venous thrombotic events[31]. SII is calculated as the platelet count multiplied by the neutrophil count divided by the lymphocyte count. Levels of NLR and SII markedly increase in RVO-ME patients, indicating heightened inflammation and oxidative stress owing to the breakdown of the blood-retinal barrier[27]. While some studies have observed elevated NLR in young RVO patients compared to controls, others have found no significant association between NLR and RVO[15-16]. Discrepancies in findings may arise from variations in study populations and inclusion criteria. Our analysis did not reveal significant differences in NLR between effective and ineffective treatment groups, suggesting that while NLR may contribute to RVO pathogenesis, its role as a prognostic factor for RVO-ME patients remains uncertain and requires further investigation.

An important component of peripheral blood inflammatory markers is the platelet and lymphocyte counts, and PLR is the ratio of platelets to lymphocytes, which can reflects systemic inflammation and has been implicated in predicting treatment outcomes in RVO patients undergoing anti-VEGF therapy. Platelets participate in inflammatory responses, while lymphocytes are vital immune system components with anti-inflammatory properties. Rao *et al*[17] demonstrated that patients with higher PLR showed better responses to anti-VEGF

treatment, consistent with findings reported by Wang *et al*[29] and our research. Moreover, our study revealed that higher PLR correlated with improved treatment responses in CRVO and BRVO patients, characterized by enhanced BCVA and reduced CMT. This suggests that PLR is a valuable prognostic indicator for anti-VEGF treatment outcomes in RVO patients. However, further elucidation of the underlying mechanisms of PLR in RVO progression is warranted. Wang *et al*[29] also believes that in RVO-ME patients and their subtypes receiving anti-VEGF drug therapy, a higher platelet count before treatment suggests a better prognosis. However, this relationship was not found in this study, possibly due to the relatively young age of the patients included in our study. SII, reflecting the systemic inflammatory state and predicting cardiovascular risk, is determined by neutrophils, platelets, and lymphocytes[32]. SII has been linked to several ophthalmological conditions[33]. In our study, the effective group exhibited higher SII compared to the ineffective group, suggesting the influence of inflammatory factors on the prognosis of young RVO patients. However, further investigation revealed a correlation between SII and treatment outcomes in CRVO-ME patients, with no significant association observed in BRVO-ME patients. However, further research is needed to investigate the mechanistic impact of PLR and SII on the treatment outcomes of RVO-ME patients and to elucidate their specific mechanisms of action. SIRI, another indicator of systemic inflammatory balance, is linked to monocyte, neutrophil, and lymphocyte counts, SIRI is calculated as the monocyte count multiplied by the neutrophil count divided by the lymphocyte count. Numerous studies have identified it as a biomarker for chronic low-grade inflammation in various diseases, including angina and acute myocardial infarction[34-35]. Ophthalmology researchers have extensively investigated SIRI as an independent risk factor for diabetic retinopathy[36]. While some studies have reported higher SIRI levels in young RVO patients, our study found no significant difference in SIRI expression between effective and ineffective treatment groups. Additional research is needed to fully understand the role of SIRI in RVO progression[37]. PLR and SII may be able to rapidly identify patients in clinical practice who respond poorly to anti-VEGF treatment, enabling more precise design of treatment plans and the development of personalized communication strategies. Our study found no difference in SIRI expression between the effective and treatment groups.

Our study used ROC curves to evaluate the predictive performance of NLR, PLR, SII, and SIRI. The AUC for NLR was 0.665, with an optimal cutoff value of 1.72 and a sensitivity of 70.1%. For PLR, the AUC was 0.827, with an optimal cutoff value of 121.22, a sensitivity of 80.2% and a specificity of 68.3%. SII exhibited an AUC of 0.776, with an optimal cutoff value of 436.3, a sensitivity of 77.5% and a specificity of 50.2%. The AUC for SIRI was 0.625, with an optimal cutoff value of 0.75, a sensitivity of 51.7%, and a specificity of 72.3%. Notably, PLR and SII demonstrated high specificity but relatively lower sensitivity, suggesting their potential as useful diagnostic and predictive tools for identifying RVO-ME in young patients.

In summary, young RVO patients who exhibited favorable responses to anti-VEGF treatment displayed elevated levels of PLR and SII before intervention. These markers are promising in aiding clinicians in real-world assessments of young RVO-ME patients. Moreover, given the simplicity and accessibility of peripheral inflammatory markers, monitoring them may facilitate the prediction of treatment responses in RVO patients undergoing anti-VEGF therapy. In this study, we placed excessive emphasis on changes in macular thickness and resolution of ME, to the extent that we somewhat overlooked the traction exerted by the vitreous outside the macular area on the retinal structure. Traction from the vitreous on the retina can also affect the therapeutic efficacy of anti-VEGF treatment and BCVA. Some patients with RVO may require further treatment with vitrectomy. In future studies, we will utilize Widefield OCT to more extensively investigate the traction exerted by the vitreous, both within and outside the macular area, on the retina, as well as changes in retinal structure in RVO patients. This study is a retrospective study with a relatively small sample size, which presents certain limitations. It lacks analysis of other inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate, and there is a lack of large multicenter, prospective studies. Additionally, we only used BCVA and CMT as indicators, lacking an analysis of changes in retinal structure. Furthermore, this study also lacks a specific investigation into the role of inflammatory markers in the mechanisms underlying the occurrence and progression of RVO, making it impossible to reveal how peripheral blood inflammatory markers influence the development of RVO. Therefore, more research is needed in future clinical work, including increasing the sample size, conducting high-quality prospective clinical studies, and analyzing these markers in other retinal vascular diseases. Further research is needed to identify universally applicable indicators that can accurately predict the responsiveness of young RVO-ME patients to anti-VEGF treatment and enable the development of personalized treatment strategies for these individuals.

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