• Clinical Research •

# Correlations between inflammatory biomarkers in peripheral blood and branch retinal vein occlusion

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## Abstract

● **AIM:** To investigate the possible relationship between inflammatory biomarkers in the peripheral blood of patients with branch retinal vein occlusion (BRVO).

● **METHODS:** A total of 63 BRVO patients were enrolled in this cross-sectional observational study. Meanwhile, 63 age- and gender-matched cataract patients were included as controls. Complete blood count and biochemical tests were performed, and inflammatory biomarkers including platelet to lymphocyte ratio (PLR), red blood cell distribution width to albumin ratio (RAR), neutrophil to lymphocyte ratio (NLR), systemic immune inflammation index (SII), and monocyte to high density lipoprotein cholesterol ratio (MHR) were compared between the two groups.

● **RESULTS:** There were no significant differences between the two groups in terms of age, sex, and prevalence of diabetes mellitus. Compared with the controls, patients with BRVO had a higher prevalence of hypertension and higher body mass index (BMI). Red blood cell distribution width (RDW), triglycerides, MHR, NLR, and RAR were elevated, whereas lymphocyte count and high-density lipoprotein were decreased in the BRVO group. Multivariate logistic regression analysis revealed that NLR (adjusted OR=1.686, 95%CI 1.075-2.646), RAR (adjusted OR=8.930, 95%CI 1.911-41.730), and body mass index (BMI; adjusted OR=1.174, 95%CI 1.010-1.365) were significantly associated with the risk of BRVO. In the receiver operating characteristic analysis, the area under the curve for NLR, RAR, and BMI were 0.602, 0.630, and 0.603, respectively. The sensitivity and specificity were 61.9% and 60.3%, 38.1% and 82.5%, and 61.9% and 57.1%, respectively.

● **CONCLUSION:** Peripheral blood inflammatory biomarkers are elevated in BRVO patients, suggesting systemic inflammation involvement. NLR, RAR, and BMI are positively correlated with BRVO. Monitoring NLR and RAR and strict weight control may be beneficial for the prevention and treatment of BRVO.

● **KEYWORDS:** branch retinal vein occlusion; peripheral blood; biomarker

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## INTRODUCTION

Retinal vein occlusion (RVO) is a common retinal vascular disease of which secondary macular edema, retinal neovascularization, and neovascular glaucoma can lead to irreversible visual loss[1]. According to the site of the occlusion, RVO is generally classified as central RVO and branch retinal vein occlusion (BRVO), and the latter is more prevalent[2]. The large population affected by this disease poses a great burden on healthcare systems[3]. The pathogenesis of RVO is multifactorial, with evident risk factors including hypertension, smoking, obesity, and oral contraceptives[4-5]. As reported, BRVO may be due to compression of the vein at the arteriovenous crossing[6], degenerative changes of the vessel wall[7], and abnormal hematological factors[8].

Although the pathogenesis of BRVO is not completely clear, inflammation is an important etiological factor for the disease[9]. Some studies suggested that RVO was strongly associated with inflammation, with intraocular inflammation playing an important role in macular edema secondary to RVO[10-11]. Inflammatory factors in the vitreous humor of RVO patients are significantly elevated and are positively correlated with the area of retinal nonperfusion and the severity of macular edema[12]. Studies also showed that the severity of macular ischemia in ischemic BRVO may influence the visual

prognosis[13]. Therefore, there may be possible relationship between inflammation and the prognosis of BRVO.

Accumulating evidence suggests that elevated levels of circulating inflammatory molecules are associated with BRVO[14-15]. Several studies have further investigated the level of different types of white blood cells and some novel inflammatory biomarkers including platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), and monocyte to high density lipoprotein cholesterol ratio (MHR) in BRVO patients, though the conclusions remained inconsistent[16-18]. Notably, other emerging inflammatory biomarkers including red blood cell distribution width to albumin ratio (RAR) and systemic immune inflammation index (SII), have yet to be investigated in the context of BRVO. Therefore, this study aims to elucidate the relationship between serum inflammatory biomarkers and BRVO, with the potential to identify novel risk factors, enhance pathophysiological understanding, and improve risk stratification and clinical management of the disease.

## PARTICIPANTS AND METHODS

**Ethical Approval** This cross-sectional observational study was approved by the Ethical Committee of West China Hospital, Sichuan University, and adhered to the tenets of the Declaration of Helsinki (No.2023662). Written informed consent was obtained from the all the subjects. No stipend was allocated to participants as no supplementary medical interventions or examinations were performed.

Patients diagnosed with BRVO at the ophthalmology clinic of West China Hospital of Sichuan University from June 2022 to December 2023 were enrolled as the BRVO group. All patients underwent a comprehensive ophthalmologic examination including best-corrected visual acuity, intraocular pressure, slit-lamp examination and dilated fundus examination. Patients with manifestation including arteriovenous nicking, venous dilation, and tortuosity with flame-shaped, dot-blot, superficial and deep retinal hemorrhages within a wedge-shaped retina region in dilated fundus examination were diagnosed as BRVO, and then fluorescein angiography [Heidelberg Spectralis high-resolution angiography (HRA)] and optical coherence tomography [Heidelberg Spectralis optical coherence tomography (OCT)] were performed to locate the occluded vein and detect macular edema. Meanwhile, age- and sex-matched controls were also enrolled as the control group. The inclusion and exclusion criteria were as follows.

Inclusion criteria for the BRVO group: 1) Patients aged ≥18y who were clinically diagnosed with BRVO on the basis of established diagnostic criteria. 2) Disease history ≤3mo. Exclusion criteria for the BRVO group: 1) Histories of other retinal diseases, such as diabetic retinopathy, age-related macular degeneration, uveitis, and glaucoma. 2) Refractive media opacity affects fundus observation. 3) Surgery, laser treatment, or intravitreal injection was performed within 3mo in the affected eye. 4) History of malignancies, autoimmune diseases, or other systemic inflammatory diseases. 5) History of specific medication use that could affect routine blood or biochemical test results.

Inclusion criteria for the control group: Cataract patients age and sex-matched with the BRVO group. Exclusion criteria for the control group: 1) History of retinal diseases, such as RVO, diabetic retinopathy, age-related macular degeneration, uveitis, and glaucoma. 2) Presence of malignancies, autoimmune diseases, or other systemic inflammatory conditions. 3) History of specific medication use that could affect routine blood or biochemical test results.

All subjects underwent fasting venous blood collection, as well as complete blood counts (Sysmex XN1000) and biochemical tests (Roche Cobas c701). Relevant laboratory indicators were recorded, and inflammatory biomarkers including PLR, RAR, NLR, SII, and MHR were calculated. The calculation method for these biomarkers is showed in Table 1.

**Table 1 Calculation method for inflammatory biomarkers**

| Parameters | Calculation method |
|---|---|
| PLR | Platelet/lymphocyte |
| NLR | Neutrophil/lymphocyte |
| MHR | Monocyte/high-density lipoprotein |
| RAR | Red blood cell distribution width/albumin |
| SII | Neutrophil×platelet/lymphocyte |

PLR: Platelet to lymphocyte ratio; NLR: Neutrophil to lymphocyte ratio; MHR: Monocyte to high density lipoprotein cholesterol ratio; RAR: Red blood cell distribution width to albumin ratio; SII: Systemic immune-inflammation index.

Data analysis was performed by IBM Statistical Package for the Social Sciences (SPSS) Statistics Version 25.0. Data that conformed to a normal distribution were compared using independent sample *t*-test. Data that did not conform to a normal distribution were compared using Mann–Whitney *U* test. Multivariate logistic regression was used to analyze the risk factors for BRVO. The receiver operating characteristics (ROC) curve was used to evaluate the predictive value. $P<0.05$ was considered statistically significant.

## RESULTS

A total of 63 patients with BRVO and 63 controls were enrolled in this study. The demographic characteristics of both groups were presented in Table 2. There were no significant differences between the two groups in terms of age, sex, and prevalence of diabetes mellitus. Compared with the controls, patients with BRVO had a higher prevalence of hypertension and higher body mass index (BMI). Higher red blood cell distribution width (RDW), triglycerides, MHR, NLR, RAR and lower lymphocyte counts and high-density lipoprotein (HDL) were found in patients with BRVO. There were no statistically

**Table 2 Demographic characteristics of the study participants**

| Parameters | BRVO, *n*=63 | Control, *n*=63 | *P* |
|---|---|---|---|
| Age, y | 60.17±11.53 | 60.67±8.88 | 0.789 |
| Sex (male/female) | 31/32 | 31/32 | 1.000 |
| DM, *n* (%) | 7 (11.1) | 3 (4.8) | 0.187 |
| HT, *n* (%) | 25 (39.7) | 10 (15.9) | 0.003[a] |
| BMI, kg/m$^2$ | 24.43±3.59 | 23.06±2.59 | 0.047[a] |

BRVO: Branch retinal vein occlusion; DM: Diabetes mellitus; HT: Hypertension; BMI: Body mass index. [a]*P*<0.05.

**Table 3 Comparison of laboratory findings between patients and controls**

| Parameters | BRVO | Control | *P* |
|---|---|---|---|
| Monocyte (×10$^9$/L) | 0.46±0.17 | 0.41±0.13 | 0.344 |
| Neutrophil (×10$^9$/L) | 3.67±1.24 | 3.43±1.06 | 0.351 |
| Lymphocyte | 1.88±0.70 | 1.99±0.50 | 0.048[a] |
| Platelet | 198.94±60.45 | 207.75±61.26 | 0.418 |
| RDW (%) | 13.50±1.51 | 12.99±0.94 | 0.020[a] |
| Albumin (g/L) | 46.47±2.96 | 47.25±2.33 | 0.110 |
| Glucose (mmol/L) | 5.85±1.18 | 5.49±0.75 | 0.131 |
| Cholesterol (mmol/L) | 5.21±0.87 | 5.17±0.96 | 0.779 |
| LDL (mmol/L) | 2.97±0.92 | 3.12±0.79 | 0.346 |
| Triglycerides (mmol/L) | 2.58±3.12 | 1.53±0.75 | 0.016[a] |
| HDL (mmol/L) | 1.31±0.41 | 1.57±0.38 | <0.001[a] |
| MHR (×10$^8$/mmol) | 3.78±1.79 | 2.84±1.30 | 0.003[a] |
| NLR | 2.23±1.21 | 1.80±0.92 | 0.049[a] |
| PLR | 115.10±44.24 | 108.25±34.93 | 0.527 |
| RAR (mL/g) | 2.92±0.37 | 2.76±0.23 | 0.005[a] |
| SII (×10$^9$/L) | 442.86±314.57 | 371.85±212.04 | 0.237 |

BRVO: Branch retinal vein occlusion; RDW: Red blood cell distribution width; LDL: Low density lipoprotein; HDL: High density lipoprotein; MHR: Monocyte to high density lipoprotein ratio; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; RAR: RDW to albumin ratio; SII: Systemic immune-inflammation index. [a]*P*<0.05.

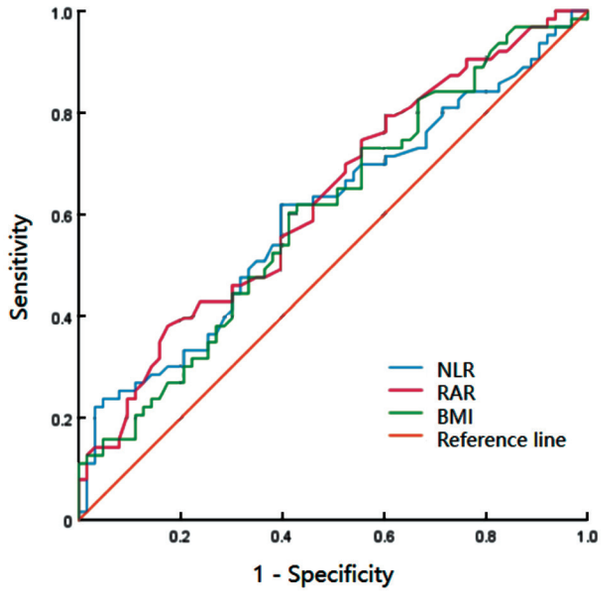


**Figure 1 ROC curve analysis of risk factors in predicting BRVO** BRVO: Branch retinal vein occlusion; NLR: Neutrophil to lymphocyte ratio; RAR: Red blood cell distribution width to albumin ratio; BMI: Body mass index; ROC: Receiver operating characteristics.

**Table 4 Multivariate logistic regression analysis of risk factors for BRVO**

| Risk factors | OR (95%CI) | *P* |
|---|---|---|
| Triglycerides | 1.548 (0.964-2.486) | 0.071 |
| MHR | 1.260 (0.902-1.760) | 0.175 |
| NLR | 1.686 (1.075-2.646) | 0.023[a] |
| RAR | 8.930 (1.911-41.730) | 0.005[a] |
| Hypertension | 2.070 (0.773-5.540) | 0.148 |
| BMI | 1.174 (1.010-1.365) | 0.036[a] |

BRVO: Branch retinal vein occlusion; MHR: Monocyte to high density lipoprotein ratio; NLR: Neutrophil to lymphocyte ratio; RAR: Red blood cell distribution width to albumin ratio; BMI: Body mass index; OR: Odds ratio; CI: Confidence interval. [a]*P*<0.05.

significant differences between the BRVO and control groups in terms of the neutrophil count, monocyte count, platelet count, LDL, cholesterol, albumin, blood glucose, PLR, or SII (Table 3).

Factors with statistically significant difference between two groups were further included in a multivariate logistic regression model. The results revealed that NLR [adjusted odds ratio (OR)=1.686, 95% confidence interval (CI) 1.075-2.646], RAR (adjusted OR=8.930, 95%CI 1.911-41.730), and BMI (adjusted OR=1.174, 95%CI 1.010-1.365) were independent risk factors of BRVO (Table 4).

The risk factors of BRVO were included in the ROC curve analysis to evaluate their predictive value. The area under curve (AUC) for NLR was 0.602, with a cutoff value of 1.715, sensitivity of 61.9%, specificity of 60.3%, and *P*=0.049; the AUC for RAR was 0.630, with a cutoff value of 2.945, sensitivity of 38.1%, specificity of 82.5%, and *P*=0.012; and the AUC for BMI was 0.603, with a cutoff value of 23.385, sensitivity of 61.9%, specificity of 57.1%, and *P*=0.047 (Figure 1; Table 5).

## DISCUSSION

The present study aimed to investigate the association between inflammation and BRVO by comprehensively evaluating various inflammatory biomarkers in the peripheral blood of BRVO patients. The results demonstrated significantly elevated levels of MHR, NLR, and RAR in BRVO patients. Further analysis revealed that RAR and NLR were positively correlated with the occurrence of BRVO.

In this study, the BRVO group exhibited a significantly higher level of NLR compared to controls. Neutrophils play a multifaceted role in inflammation, and elevated neutrophils levels indicate the activation of systemic inflammation.

**Table 5 ROC curve analysis of risk factors in predicting BRVO**

| Parameters | AUC | Cutoff value | Sensitivity (%) | Specificity (%) | 95%CI | *P* |
|---|---|---|---|---|---|---|
| NLR | 0.602 | 1.715 | 61.9 | 60.3 | 0.503-0.701 | 0.049[a] |
| RAR | 0.630 | 2.945 | 38.1 | 82.5 | 0.533-0.726 | 0.012[a] |
| BMI | 0.603 | 23.385 | 61.9 | 57.1 | 0.504-0.701 | 0.047[a] |

ROC: Receivers operating characteristics; AUC: Areas under the curve; CI: Confidence interval. [a]*P*<0.05.

Conversely, inflammation and oxidative stress can lead to decrease in lymphocyte numbers[19]. NLR is considered a reliable predictor for cardiovascular and cerebrovascular diseases[20] and has also been implicated in ocular vascular disorders. Zhang *et al*[21] identified NLR as a potential risk factor for neovascular glaucoma secondary to both RVO and diabetic retinopathy. Doğan *et al*[22] found NLR was elevated in eyes with SMD secondary to RVO. A Meta-analysis further confirmed that RVO patients had significantly higher NLR than controls[23]. Similarly, Şahin *et al*[24] reported elevated NLR in BRVO patients, suggesting its potential as an independent risk factor. Our findings align with these studies, supporting an association between increased NLR and higher BRVO risk. However, the AUC for NLR was only 0.602, indicating that its predictive value for BRVO remains relatively limited.

Beyond leukocyte-related biomarkers, dysregulated lipid metabolism has been linked to various pathological conditions. Abnormal lipid levels contribute to endothelial dysfunction, increased blood viscosity, and diminished antioxidant capacity, promoting thrombosis and inflammatory cascades[25]. Monocytes are responsible for secreting proinflammatory cytokines[26], while HDL not only facilitates reversing cholesterol transport but also exerts anti-inflammatory, antioxidant, and antithrombotic effects[27]. MHR has emerged as another novel systemic inflammatory biomarker investigated in lots of diseases. Pan *et al*[28] observed elevated MHR in both BRVO and CRVO, while Şatırtav *et al*[18] reported similar findings in BRVO cases, suggesting that MHR may be a risk factor for BRVO. The present study confirmed higher MHR levels in the BRVO group, yet the multivariate logistic regression analysis did not establish a statistically significant association with BRVO. Therefore, the evidence supporting MHR as a predictive marker for BRVO remains inconclusive. Given potential discrepancies due to variations in sample size and study populations, further validation through larger scale and longitudinal studies is warranted.

Recently, RAR has gained attention as a novel systemic inflammatory biomarker. Impaired red blood cells function can induce endothelial activation and vascular damage, contributing to cardiovascular disease[29]. Elevated RDW may reflect reduced erythrocyte adaptability and compromised antioxidant capacity. Pinna *et al*[30] reported higher RDW in the RVO patients compared to cataract control group, and Yang *et al*[31] found that elevated RDW correlated with poorer baseline and posttreatment visual outcomes in RVO. Given albumin's anti-inflammatory and antioxidant properties, RAR has emerged as a robust inflammatory biomarker in ocular diseases. Zhao *et al*[32] reported that RAR was elevated in diabetic retinopathy patients and served as an independent risk factor. However, no prior studies have examined RAR levels in RVO. Our study is the first to assess RAR in BRVO patients, revealing significantly higher RDW and RAR levels in this group. RAR exhibited a positive correlation with the risk of BRVO and may serve as a potential independent risk factor, suggesting its utility in identifying high-risk populations.

In addition to inflammatory biomarkers, we identified elevated BMI as another potential risk factor for BRVO. Obesity is a well-established risk factor for numerous systemic diseases. Our study found a positive correlation between BMI and BRVO incidence, possibly mediated by obesity-induced dyslipidemia and chronic inflammation. A nationwide cohort study in Korea reported that BMI reduction increased the risk of RVO in nondiabetic patients but had the opposite effect in diabetics[33], whereas another study observed a consistent positive association between BMI and RVO risk in both groups[34]. Although the precise relationship between BMI and BRVO remains unclear, maintaining a healthy weight is crucial for preventing a wide range of diseases.

This study has several limitations. First, it was a cross-sectional, single-center study and did not include a prospective cohort design with follow-up observations of the effects of inflammatory biomarkers on BRVO. Additionally, we did not control for the participants' dietary habits or lifestyle factors, which could also influence the results. Therefore, large-scale, prospective cohort studies with long-term follow-up of non-RVO populations are needed to validate the predictive utility of peripheral blood inflammatory markers for BRVO. Additionally, post-treatment biomarker monitoring in BRVO patients could help assess their prognostic significance.

In conclusion, the present study demonstrated elevated MHR, NLR, and RAR in BRVO patients, underscoring the role of inflammation in BRVO pathogenesis. NLR and RAR were positively associated with the risk of BRVO, and may serve as cost-effective screening biomarkers to identity high-risk

population. Furthermore, BMI is positively associated with the risk of BRVO, emphasizing the importance of weight management in BRVO prevention.

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