The Role of Serum Inflammation-Based Factors in Anti-Vascular Endothelial Growth Factor Treatment for Macular Edema Secondary to Retinal Vein Occlusion and Its Subtypes

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Keywords

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Platelet-to-lymphocyte ratio · Anti-vascular
endothelial growth factor treatment

Abstract

Objective: The aim of this work was to evaluate the association between pretreatment inflammation-based factors and outcomes in patients with macular edema (ME) secondary to retinal vein occlusion (RVO) and its subtypes after intravitreal ranibizumab or conbercept implant. **Methods:** This retrospective observational study included patients who were diagnosed with ME secondary to RVO at the First Affiliated Hospital of Nanchang University between January 2017 and January 2019, and who subsequently received intravitreal anti-vascular endothelial growth factor (VEGF) treatment. Blood-based parameters were measured before treatment, and correlations between best-corrected visual acuity (BCVA) and each of 3 parameters – neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) – were analyzed to identify predictors of effective intravitreal injection treatment

outcomes. **Results:** A total of 315 treatment-naïve eyes treated with anti-VEGF drugs for RVO-ME were retrospectively analyzed in this study. The mean PLR value was significantly different in the effective and ineffective group for RVO-ME (138.03 ± 48.61 vs. 106.79 ± 27.28), branch RVO (BRVO)-ME (216.47 ± 53.04 vs. 185.94 ± 51.47), and central RVO (CRVO)-ME (231.07 ± 66.05 vs. 196.20 ± 60.44). The cutoff value of the PLR was 97.92, the area under the curve was 0.70, and the sensitivity and specificity were 81.5 and 44.3%, respectively. The mean NLR value was significantly different in the effective and ineffective groups for RVO-ME (2.20 ± 1.40 vs. 1.92 ± 0.89), and BRVO-ME (2.01 ± 0.80 vs. 1.82 ± 0.84), but not in patients with CRVO-ME (2.51 ± 2.02 vs. 2.12 ± 0.95). There are no significant differences between BRVO-ME and its subtype groups in MLR values. But the mean MLR value was significantly higher in the conbercept group than in the ranibizumab group among patients in the effective group (0.27 ± 0.11 vs. 0.25 ± 0.14). **Conclusion:** Higher pretreatment PLR was associated with BCVA in patients with RVO-ME and its subtypes who were treated with anti-VEGF drugs. The PLR may be used as a predictive and prognostic tool for effective intravitreal injection treatment outcomes.

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Introduction

Retinal vein occlusion (RVO) is the second most common retinal vasculopathy after diabetic retinopathy. Depending on the location of obstruction, RVO can be differentiated into central RVO (CRVO) and branch RVO (BRVO) [1]. A multicenter study showed that the prevalence rates for BRVO and CRVO were 4.42 and 0.80 per 1,000 persons; these varied among ethnic groups and increased with age, but were not affected by sex [1, 2]. Vascular occlusion leads to retinal ischemia, which can increase vascular permeability and cause the accumulation of secondary intraretinal fluid and subretinal fluid in the outer plexiform layer and subretinal space. Macular edema (ME) easily occurs secondary to these pathophysiologic changes, typically producing secondary retinal pigment epithelial changes that lead to poor visual acuity.

Risk factors of RVO are known to include hypertension, systemic vascular disease, hyperlipidemia, pregnancy, oral contraceptive use, and hypercoagulability; however, the underlying pathogenesis of RVO remains unclear [3]. Interestingly, some studies have shown that local and systemic inflammation can induce both atherosclerosis and systemic hypercoagulability, which influence the development of ME secondary to RVO (RVO-ME) [4]. Several studies have shown that the levels of inflammatory factors (e.g., vascular endothelial growth factor [VEGF], interleukin-1 β , and interleukin-6) are associated with the severity of ME [5]. In addition, aqueous humor levels of proinflammatory cytokines are reduced after dexamethasone treatment in patients with RVO [6].

VEGF is an endothelial cell mitogen and vasopermeability factor that can cause conformational phosphorylation and changes in protein content in the tight junctions of retinal vascular endothelial cells [7]. The relatively recent introduction of anti-VEGF drugs has aided in the treatment of many retinal diseases, including age-related macular degeneration, radiation retinopathy, and diabetic ME, especially when pathological changes involve ME and neovascularization. In RVOs, elevated secretion of VEGF leads to elevated vascular permeability and vasodilation, which aggravates the severity of ME [8]. Thus, VEGF inhibitors have become the primary treatment approach for RVO-ME, which has significantly impacted the treatment and visual outcomes in RVO-ME [9]. In the past decade, clinical trials have increasingly shown that, compared with macular grid laser and panretinal photocoagulation, anti-VEGF therapy (e.g., intravitreal injections of ranibizumab [IVR] or conbercept [IVC]) could bring superior visual acuity [9].

There is growing evidence to support the relationship between the inflammatory response and RVO-ME [5]. Serum inflammation-based markers (e.g., neutrophil-to-lymphocyte ratio [NLR], monocyte-to-lymphocyte ratio [MLR], and platelet-to-lymphocyte ratio [PLR]) reportedly can be used as prognostic indicators for many conditions, including cancers [10], cardiovascular diseases [11], and inflammatory or infectious pathologies [12]. Recently, the level of serum NLR ratio was reported to be correlated with RVO [13]. However, the relationships between serum inflammation-based markers and RVO-ME, especially in patients receiving anti-VEGF therapy, have not been studied in detail. Therefore, this study was performed to investigate levels of serum inflammation-based factors and explore their relationship with effectiveness in patients with RVO-ME who were treated with ranibizumab or conbercept.

Materials and Methods

This retrospective study included 315 patients who were diagnosed with RVO-ME and received initial anti-VEGF therapy between January 2017 and January 2019 at the First Affiliated Hospital of Nanchang University. All patients underwent a complete ocular examination including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, and fundus biomicroscopy. Based on an ophthalmoscopic fundus examination, patients who had hemorrhages, cotton wool-spots, edema, and venous dilatation and tortuosity originating from arteriovenous crossing in a localized retinal area were diagnosed with BRVO, and patients who had pathologic changes in 4 retina quadrants accompanied by retinal vein dilatation were diagnosed with CRVO. In accordance with the American Academy of Ophthalmology guidelines, RVO-ME was detected using optical coherence tomography (Cirrus HD – OCT; Carl Zeiss Meditec Inc., Dublin, CA, USA) and fundus fluorescein angiography. All optical coherence tomography exams were performed by the same qualified physician who was blinded to the patients' vision parameters when analyzing the optical coherence tomography images.

Patients were excluded if they met any of the following conditions: (1) other treatments for RVO during the follow-up period, such as laser photocoagulation, intraocular steroid treatment, or periocular steroid treatment; (2) other concomitant ocular diseases such as posterior uveitis or age-related macular degeneration; (3) history of an acute coronary event or stroke in the previous 3 months; (4) presence of glaucoma, diabetes, systemic inflammatory diseases, cardiovascular, hepatic, and renal disorders, blood dyscrasias, and/or malignancy; (5) history of routine anti-inflammatory drug, oral contraceptive, and/or anticoagulants use; (6) history of smoking and/or alcohol consumption; (7) occurrence of vitreous hemorrhage and infection after surgery.

The specific anti-VEGF drug (ranibizumab or conbercept) used for therapy in this study was determined by the treating physician and patients. All included patients received intravitreal injections of 0.5 mg/0.05 mL ranibizumab or conbercept under aseptic

Table 1. Comparison of the ineffective group and the effective group with RVO-ME

	Ineffective group (<i>n</i> = 158)	Effective group (<i>n</i> = 157)	<i>p</i> value
Baseline characteristics			
Age, years	57.34±11.88	58.90±12.20	0.18
Male/female	79/79	76/81	0.78
BRVO/CRVO	103/55	99/58	0.69
Ranibizumab/conbercept	105/53	100/57	0.61
Preoperative BCVA, logMAR	0.75±0.40	0.79±0.40	0.41
Postoperative BCVA, logMAR	0.78±0.42	0.55±0.32	<0.01
Changes in BCVA, logMAR	0.02±0.08	0.26±0.19	<0.01
Preoperative IOP, mm Hg	14.11±2.60	14.04±2.91	0.87
Postoperative IOP, mm Hg	13.82±2.69	13.72±2.70	0.78
Changes in IOP, mm Hg	2.47±1.68	2.13±1.47	0.09
Laboratory findings			
White blood cells, ×10 ⁹ /L	5.79±1.95	5.72±1.50	0.97
Neutrophils, ×10 ⁹ /L	3.35±1.54	3.42±1.18	0.21
Monocytes, ×10 ⁹ /L	0.42±0.18	0.41±0.15	0.40
Platelets, ×10 ⁹ /L	189.51±54.78	221.87±58.59	<0.01
Lymphocytes, ×10 ⁹ /L	1.83±0.54	1.73±0.58	0.06
NLR	1.92±0.89	2.20±1.40	0.01
MLR	0.24±0.11	0.26±0.13	0.21
PLR	106.79±27.28	138.03±48.61	<0.01

RVO, retinal vein occlusion; ME, macular edema; BRVO, branch RVO; CRVO, central RVO; BCVA, best-corrected visual acuity; IOP, intraocular pressure; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

tic conditions. If the postoperative BCVA improved compared with preoperative BCVA, we considered the treatment effective; otherwise, we considered it to be ineffective. In patients who received treatment in both eyes, only the eye that first received treatment was analyzed. If patients had accepted more than one treatment, we just analyzed the first intervention. All patients provided written consent for IVR or IVC treatment and for the use of their data for research purposes. Patients returned for follow-up 1 week postoperatively, then were evaluated monthly and received injections as needed or pro re nata.

Patients' peripheral blood samples for complete blood counts were obtained between 5:00 and 6:00 a.m. from the antecubital vein before IVR or IVC treatment. Leukocyte subtypes were measured using an automated blood coagulation analyzer (XE-2100; Sysmex, Kobe, Japan). NLR, MLR, and PLR were calculated and recorded for all blood samples.

Statistical Analysis

All statistical analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Parametric data are reported as the mean ± SD and categorical data as percentages. Independent parameters were compared via the independent-sample *t* test or using the Mann-Whitney U test if there was no normal distribution. The χ^2 test was used to evaluate the categorical data and determine associations between dichotomous variables. The correlation was evaluated by Spearman correlation test. The optimal cutoff point

of NLR, PLR, and MLR was determined by receiver operator characteristic (ROC) curve analysis. The areas under the curve (AUC) were calculated to analyze the accuracy of the tests. A *p* value <0.05 was significant in all of the analyses.

Results

A total of 315 treated eyes of 315 patients diagnosed with any type of RVO-ME were included in this study; all patients had received intravitreal injections of anti-VEGF drugs. The mean age of the ineffective and effective groups were 57.34 ± 11.88 and 58.90 ± 12.2 years, respectively. The clinical features and laboratory characteristics of the patients are summarized in Table 1. There were no statistically significant differences in age, sex, diseases, drug species, preoperative BCVA, preoperative IOP, or postoperative IOP between the ineffective and effective groups (*p* > 0.05). Moreover, there were no statistically significant differences between the groups with respect to level of white blood cells, neutrophils, monocytes, or lymphocytes (*p* > 0.05).

Table 2. Comparison of the ineffective group and the effective group with BRVO-ME

	Ineffective group (<i>n</i> = 103)	Effective group (<i>n</i> = 99)	<i>p</i> value
Baseline characteristics			
Age, years	59.97±10.38	61.11±11.11	0.32
Male/female	42/61	41/58	0.97
Ranibizumab/conbercept	73/30	63/36	0.27
Preoperative BCVA, logMAR	0.70±0.39	0.72±0.36	0.60
Postoperative BCVA, logMAR	0.72±0.41	0.48±0.28	<0.01
Changes in BCVA, logMAR	0.02±0.07	0.26±0.18	<0.01
Preoperative IOP, mm Hg	14.31±2.42	14.00±2.92	0.51
Postoperative IOP, mm Hg	13.76±2.67	13.76±2.73	0.97
Changes in IOP, mm Hg	2.55±1.63	2.32±1.52	0.38
Laboratory findings			
White blood cells, ×10 ⁹ /L	5.38±1.53	5.53±1.25	0.23
Neutrophils, ×10 ⁹ /L	3.05±1.24	3.23±0.86	0.01
Monocytes, ×10 ⁹ /L	0.40±0.17	0.38±0.14	0.44
Platelets, ×10 ⁹ /L	185.94±51.47	216.47±53.04	<0.01
Lymphocytes, ×10 ⁹ /L	1.77±0.47	1.75±0.57	0.54
NLR	1.82±0.84	2.01±0.80	0.02
MLR	0.23±0.11	0.24±0.10	0.72
PLR	108.46±28.74	132.14±42.34	<0.01

BRVO, branch retinal vein occlusion; ME, macular edema; BCVA, best-corrected visual acuity; IOP, intraocular pressure; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Change in BCVA was regarded as the standard grouping of the patients, and this parameter showed significant differences between the ineffective and effective groups (0.02 ± 0.08 vs. 0.26 ± 0.19 , $p < 0.05$); however, the magnitude of changes in intraocular pressure was not significantly different between the groups (2.47 ± 1.68 vs. 2.13 ± 1.47 , $p > 0.05$). Platelet levels were higher in the effective group than in the ineffective group (221.87 ± 58.59 vs. 189.51 ± 54.78 , $p < 0.01$). A high PLR was correlated with a better prognosis of effective treatment (138.03 ± 48.61 for the effective group; 106.79 ± 27.28 for the ineffective group, $p < 0.01$). The mean NLR values were 1.92 ± 0.89 and 2.20 ± 1.40 in the ineffective and effective groups, respectively, and the difference between the 2 groups was statistically significant ($p = 0.01$, $p < 0.05$). The mean MLR values were 0.24 ± 0.11 and 0.26 ± 0.13 in the ineffective and effective groups, respectively; the difference between the 2 groups was not statistically significant ($p > 0.05$).

Regarding the subtypes of RVO-ME, including BRVO and CRVO (i.e., BRVO-ME and CRVO-ME), there were no statistically significant differences in age, sex, drug treatment, preoperative BCVA, preoperative IOP, postoperative IOP, or changes in IOP between the ineffective

and effective groups ($p > 0.05$; Tables 2, 3). Similarly, there were no significant differences in levels of white blood cells, neutrophils, monocytes, and lymphocytes between the ineffective and effective groups ($p > 0.05$). Platelet count was a significant factor, and was higher in the effective group than in the ineffective group (216.47 ± 53.04 vs. 185.94 ± 51.47 for BRVO-ME; 231.07 ± 66.05 vs. 196.20 ± 60.44 for CRVO-ME, $p < 0.05$). The mean NLR value was significantly different in patients with BRVO-ME (1.82 ± 0.84 for the ineffective group; 2.01 ± 0.80 for the effective group, $p < 0.05$), but not in patients with CRVO-ME (2.12 ± 0.95 for the ineffective group; 2.51 ± 2.02 for the effective group, $p > 0.05$). There was also a statistically significant difference in mean PLR values between the effective and ineffective groups for both RVO-ME subtypes (132.14 ± 42.34 vs. 108.46 ± 28.74 for BRVO-ME; 148.07 ± 56.76 vs. 103.66 ± 24.24 for CRVO-ME, $p < 0.05$). However, the mean MLR was not significantly different between the 2 groups ($p > 0.05$).

In RVO-ME and its subtypes, the levels of white blood cells, neutrophils, monocytes, and lymphocytes did not significantly differ between the ranibizumab and conbercept groups ($p > 0.05$; Table 4). Although the mean MLR

Table 3. Comparison of the ineffective group and the effective group with CRVO-ME

	Ineffective group (<i>n</i> = 55)	Effective group (<i>n</i> = 58)	<i>p</i> value
Baseline characteristics			
Age, years	52.40±13.00	55.14±13.12	0.27
Male/female	37/18	33/25	0.25
Ranibizumab/conbercept	32/23	37/21	0.54
Preoperative BCVA, logMAR	0.86±0.40	0.92±0.42	0.43
Postoperative BCVA, logMAR	0.86±0.44	0.67±0.33	0.02
Changes in BCVA, logMAR	0.04±0.10	0.25±0.19	<0.01
Preoperative IOP, mm Hg	13.73±2.89	14.12±2.90	0.52
Postoperative IOP, mm Hg	13.95±2.73	13.66±2.67	0.57
Changes in IOP, mm Hg	2.33±1.76	1.81±1.30	0.17
Laboratory findings			
White blood cells, ×10 ⁹ /L	6.57±2.38	6.05±1.82	0.28
Neutrophils, ×10 ⁹ /L	3.91±1.87	3.73±1.54	0.61
Monocytes, ×10 ⁹ /L	0.47±0.18	0.45±0.15	0.65
Platelets, ×10 ⁹ /L	196.20±60.44	231.07±66.05	<0.01
Lymphocytes, ×10 ⁹ /L	1.94±0.65	1.69±0.59	0.03
NLR	2.12±0.95	2.51±2.02	0.27
MLR	0.26±0.12	0.30±0.16	0.11
PLR	103.66±24.24	148.07±56.76	<0.01

CRVO, central retinal vein occlusion; ME, macular edema; BCVA, best-corrected visual acuity; IOP, intraocular pressure; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 4. Comparison of ME secondary to RVO and its subtypes in the effective group

	RVO group			BRVO group			CRVO group		
	ranibizumab (<i>n</i> = 100)	conbercept (<i>n</i> = 57)	<i>p</i> value	ranibizumab (<i>n</i> = 63)	conbercept (<i>n</i> = 36)	<i>p</i> value	ranibizumab (<i>n</i> = 37)	conbercept (<i>n</i> = 21)	<i>p</i> value
Male/female	49/51	27/30	0.84	28/35	15/21	0.79	21/16	12/9	0.98
White blood cells, ×10 ⁹ /L	5.84±1.56	5.52±1.38	0.20	5.63±1.19	5.35±1.35	0.10	6.17±2.01	5.81±1.43	0.48
Neutrophils, ×10 ⁹ /L	3.47±1.25	3.32±1.05	0.52	3.29±0.84	3.12±0.89	0.24	3.77±1.71	3.67±1.22	0.80
Monocytes, ×10 ⁹ /L	0.40±0.15	0.42±0.13	0.40	0.37±0.13	0.40±0.14	0.28	0.46±0.17	0.44±0.12	0.65
Platelets, ×10 ⁹ /L	223.78±60.53	218.51±55.39	0.57	220.13±53.68	210.08±52.02	0.26	230.00±71.06	232.95±59.24	0.72
Lymphocytes, ×10 ⁹ /L	1.77±0.55	1.66±0.62	0.10	1.78±0.52	1.68±0.66	0.14	1.73±0.62	1.62±0.56	0.41
NLR	2.21±1.63	2.18±0.85	0.31	1.99±0.79	2.05±0.83	0.91	2.58±2.46	2.40±0.85	0.10
MLR	0.25±0.14	0.27±0.11	0.045	0.22±0.89	0.26±0.12	0.076	0.30±0.18	0.29±0.10	0.33
PLR	135.96±50.01	141.66±46.26	0.34	130.21±38.54	135.53±48.69	0.96	145.74±64.52	152.17±40.73	0.15

RVO, retinal vein occlusion; ME, macular edema; BRVO, branch RVO; CRVO, central RVO; BCVA, best-corrected visual acuity; IOP, intraocular pressure; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

value was significantly higher in the conbercept group than in the ranibizumab group among all patients (0.27 ± 0.11 vs. 0.25 ± 0.14 , $p < 0.05$), this difference was not statistically significant in patients with BRVO-ME or in patients with CRVO-ME. In addition, the other 2 inflam-

matory predictors (NLR and PLR) did not significantly differ between the 2 treatment groups ($p > 0.05$).

ROC curve analysis showed that the optimal cutoff value of PLR for predicting an effective outcome was 97.92, with 81.5% sensitivity and 44.3% specificity (AUC 0.70;

Table 5. Comparison of ROC curves for NLR, PLR, and platelets in the prediction of effective treatment

	AUC	95% CI	Sensitivity, %	Specificity, %
NLR (>1.98)	0.58	0.518–0.643	50.3	63.3
PLR (>97.92)	0.70	0.643–0.756	81.5	44.3
Platelet count (>178.5 ×10 ⁹ /L)	0.65	0.593–0.713	81.5	42.4

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

Fig. 1. Comparison of ROC curves for NLR, PLR, and platelets in the prediction of effective treatment.

95% CI 0.643–0.756). Furthermore, the optimal cutoff value of NLR was 1.98, with 50.3% sensitivity and 63.3% specificity (AUC 0.58; 95% CI 0.518–0.643). The optimal cutoff value of platelets was 178.5, with 81.5% sensitivity and 42.4% specificity (AUC 0.65; 95% CI 0.593–0.713; Table 5; Fig. 1). The areas under the ROC curves of each of the 3 variables were compared.

Discussion

The present study showed that pretreatment platelets, PLR, and NLR were significantly associated with an effective visual outcome in patients with RVO-ME and its subtypes following anti-VEGF treatment. Furthermore,

compared with NLR and platelets, higher PLR may be a stronger and better predictor for anti-VEGF treatment. Notably, the level of MLR was related with the efficacy of ranibizumab or conbercept treatment among the broader subset of patients with RVO-ME, but this association was lost in the subgroup analysis.

As a common retinal vascular pathology, RVO is intractable after the development of ME or neovascular glaucoma, especially in older patients. ME is the most common cause of visual impairment and is always accompanied by high vascular permeability and an increased level of VEGF [14]. Although it can be easily diagnosed, the pathogenesis of RVO-ME is complicated and remains poorly understood. Systemic diseases such as hypertension and diabetes mellitus, as well as high homocysteine and thrombophilia diseases, are associated with RVO-ME [15, 16]. Moreover, intravitreal injection treatments targeting the reduction of inflammatory factors, especially VEGF, could increase visual acuity in patients with RVO-ME, suggesting that inflammation is a key aspect in the pathogenesis of RVO-ME [9].

White blood cells and their subtypes play crucial roles in modulating inflammation reflection in cardiovascular disease [17]. Highly activated neutrophils release an extensive mixture of chemical mediators, including VEGF, reactive oxygen species, and cytokines; these can impair the endothelial barrier, thereby increasing vascular permeability and aggravating ME [18]. In contrast, low levels of lymphocytes are associated with a poor prognosis in patients with coronary artery disease [19]. The NLR, which is calculated based on the neutrophil and lymphocyte count, is associated with inflammation and has been widely used as a marker to predict systemic inflammatory responses and outcomes. Previous studies have shown the prognostic value of NLR with respect to mortality in cardiovascular diseases [20], malignancies [21], and cerebrovascular disease [22]. In the present study we found that the pretreatment NLR was associated with treatment outcomes in patients with RVO-ME who received anti-VEGF therapy; high NLR (>1.98) was more likely to re-

sult in better visual acuity, suggesting effective treatment. Dursun et al. [13] demonstrated that higher NLR (>1.89) was associated with the progress of RVO and could be used as a tool for the prediction of systemic inflammation in patients with RVO. Therefore, NLR could be a significant prognostic factor for RVO-ME patients. However, among RVO subtypes, we found that NLR was related to the treatment outcome for patients with BRVO-ME, but not for patients with CRVO-ME. In contrast, Turkseven Kumral et al. [23] showed that NLR was not affected in patients with BRVO. Because of these conflicting results, it remains unclear whether NLR would be a significant prognostic factor for patients with ME secondary to RVO subtypes. The results in this study may have been influenced by the limitation of the study design (described later in this section); therefore, we will further explore this relationship in future studies.

In addition to their physiological or pathological functions in thrombosis and hemostasis, platelets can play an important role in inflammation and release of VEGF [24, 25]. Xu et al. [26] showed that platelets can serve as effectors of inflammation injury in a variety of pulmonary disorders and syndromes. In addition, Vinholt et al. [27] found that the platelet count could be useful for stratification of cardiovascular risk – a high platelet count was associated with an increased risk of cardiovascular disease. We found that the pretreatment platelet count was associated with outcomes in patients with RVO-ME and its subtypes when patients were treated with anti-VEGF drugs, and that a high platelet count (>178.5) was predictive of better postoperative BCVA outcomes. Furthermore, previous studies showed that the PLR were closely related to the progression and prognosis of cancers [28] and venous thrombosis [25]. Our results indicated that high PLR, which combines the predictive value of platelets and lymphocytes, could be a better prognostic factor for RVO-ME and its subtypes in patients treated with anti-VEGF drugs when platelet count was assessed based on ROC curve analysis. However, the potential mechanism underlying the association between elevated PLR and better outcomes is poorly understood. Seropian et al. [29] reported that higher PLR was positively correlated with cardiovascular diseases. In addition, some studies have shown relationships between RVO and various thrombotic diseases [30] and systemic inflammatory diseases [31]. Therefore, PLR may be a significant prognostic factor for RVO-ME and its subtypes in patients treated with anti-VEGF drugs.

The MLR is another inflammatory factor that is closely associated with progressive cardiovascular disease [32]

and retinal illness [33]. In this study, investigation of the relationship between IVR or IVC outcomes and MLR showed that MLR was associated with the efficacy of IVR or IVC treatment of patients with RVO-ME, which may be due to the pharmacological mechanisms underlying treatment with ranibizumab and conbercept. Ranibizumab is an anti-VEGF-A monoclonal antibody fragment that does not contain the Fc antibody region [34], whereas conbercept is a novel recombinant fusion protein that contains the Fc antibody region, which binds the second, third, and fourth Ig domains of the VEGF receptor [35]. The 2 anti-VEGF drugs prevent the combination between VEGF and receptor in different ways. However, our results indicated that the mean MLR value could not predict the outcome of treatment efficacy for RVO-ME and its subtypes' efficient group. Li et al. [36] suggested that IVR or IVC did not cause an obvious difference in the treatment in BRVO-ME. Thus, the MLR may be related to the prognosis of patients with RVO-ME who were treated with anti-VEGF in the effective group, but this relationship was not confirmed in the present study. Further studies are therefore required to reach a definitive conclusion.

We are aware of the limitations of this study. Firstly, changes in BCVA were used to judge whether the treatment was effective, which may have caused reporting bias. Next, other potential markers of inflammatory status (e.g., C-reactive protein and interleukin) and their associations with PLR, NLR, and MLR were not investigated. Lastly, the retrospective design and low patient number may limit the generalizability of our conclusions. Because of the convenience and low cost of the parameter, there may be value in determining whether PLR is predictive or prognostic in patients with RVO-ME who are receiving anti-VEGF drugs. Consequently, a high pretreatment PLR may be strongly correlated with effective visual improvement prognosis in patients with RVO-ME and its subtypes who are treated with anti-VEGF drugs. Further studies are needed to confirm the predictive and prognostic value of PLR for outcomes in patients with RVO-ME and its subtypes after anti-VEGF treatment.

Statement of Ethics

This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the First Affiliated Hospital of Nanchang University. All of the subjects signed informed consent forms.

Conflict of Interest Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. The authors declare that they have no competing interests.

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Author Contributions

X.W.: conceived and designed the experiments. J.R.: wrote the manuscript. N.W., X.Q., and Y.H.: perform the data analyses. Y.W., Y.C., L.Y., and H.H.: collect data and information. S.L. and L.S.: helped perform the analysis and follow-up patients.

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