

Hemoglobin-to-Red Blood Cell Distribution Width Ratio With Risk of Retinal Vein Occlusion and Visual Outcomes After Anti-VEGF Therapy: A Retrospective Study

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Research Article

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Abstract

Background

Retinal vein occlusion (RVO) is the second most prevalent cause of retinal vascular disorders, yet readily accessible biomarkers for risk stratification and prognosis remain limited. The hemoglobin-to-red blood cell distribution width ratio (HRR) is an emerging composite index reflecting inflammation and oxygen-carrying capacity, but its role in RVO has not been investigated.

Methods

This was a retrospective study, including 146 CRVO, 245 BRVO patients, and matched controls. Clinical and laboratory parameters were collected and compared between CRVO/BRVO and matched controls. Multivariable logistic regression, quartile analysis, subgroup analyses were used to assess the relationship between HRR and CRVO. Among them, 161 RVO patients with visual acuity data after the second anti-VEGF treatment were included and divided into two groups based on visual acuity: the good group (≥ 0.4) and the poor group (< 0.4). Multivariable logistic regression and quartile analysis were used to evaluate the association between HRR and visual prognosis.

Results

The results showed that a higher HRR was independently associated with a reduced risk of CRVO (odds ratio [OR] = 0.772, 95% confidence interval [CI]: 0.656–0.909, $p = 0.002$) in fully adjusted models, with a significant dose-response trend across quartiles (p for trend = 0.03). This association remained stable across subgroups stratified by sex, age, diabetes, and BMI (p interaction > 0.05). Moreover, in RVO patients receiving anti-VEGF treatment, higher HRR correlated with better baseline vision ($p < 0.001$) and independently predicted a lower risk of poor visual outcome (OR = 0.747, 95% CI: 0.573–0.952, $p = 0.023$).

Conclusion

HRR is a novel, independent protective biomarker for CRVO and a significant predictor of favorable visual prognosis after anti-VEGF therapy, offering a simple and economical tool for risk assessment and clinical management.

Introduction

Retinal vein occlusion (RVO) is the second most prevalent cause of retinal vascular disorders after diabetic retinopathy. Clinically, RVO manifests in two distinct forms: central RVO (CRVO), which has an estimated prevalence of 0.1%–0.4%, and branch RVO (BRVO), which affects 0.6%–1.2% of the population

[1]. Both CRVO and BRVO significantly impair visual acuity and diminish vision-related quality of life [2]. Although a wide range of factors, such as socioeconomic risk factors (age and gender), ophthalmic risk factors (glaucoma and ocular hypertension), and systemic risk factors (hypertension, diabetes, and hyperlipidemia), have been identified as increasing the risk of RVO, the exact pathogenesis of RVO remains unclear [3–5]. Regarding the treatment of RVO, despite advances in anti-vascular endothelial growth factor (VEGF) therapies in recent years, significant challenges persist in predicting individual treatment responses and long-term visual outcomes [6]. As timely intervention is critical for alleviating irreversible retinal damage and preserving visual function, the absence of reliable biomarkers for early risk assessment highlights an unmet clinical need. Furthermore, the heterogeneous pathophysiology of RVO—including inflammatory, hemodynamic, and metabolic components—requires a multidimensional approach to biomarker discovery [1, 7–9].

In recent years, researchers have discovered that peripheral blood cell count and its combinations, such as the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII), which can assess inflammatory status, are related to the occurrence of RVO [15–18]. However, due to the heterogeneity of sample sizes, design methods, and populations [10], these studies had inconsistent conclusions [10]. Therefore, we need to further validate these conclusions and explore new, reliable biomarkers, such as the hemoglobin-to-red blood cell distribution width (RDW) ratio (HRR).

HRR may reflect an underlying microvascular dysfunction and systemic inflammation more comprehensively due to its dual representation of oxygen-carrying capacity (hemoglobin) and erythrocyte heterogeneity (RDW), both of which are implicated in endothelial stress and thrombogenesis [11, 12]. HRR has recently emerged as a composite biomarker reflecting both inflammatory and nutritional status, derived from routine complete blood counts. Recent evidence suggests that the HRR has emerged as a promising biomarker in various diseases, such as cancer [13], stroke [14], coronary artery disease [15], depression [16], and chronic kidney disease [17].

However, its role in retinal vascular occlusions remains unexplored, and no prior studies have established its diagnostic or prognostic relevance in RVO. Therefore, the purpose of this study is to validate HRR as an independent biomarker for CRVO/BRVO risk and to determine its correlation with vision outcome after anti-VEGF treatment. By elucidating these relationships, we aim to establish HRR as a practical tool for early diagnosis and prognosis, ultimately guiding targeted interventions.

Method

Patients and study design

A retrospective study was conducted among patients who were admitted to the Department of Ophthalmology of the First Affiliated Hospital of Wenzhou Medical University from June 2020 to May 2025. The study protocol was approved by the ethics committee of the First Affiliated Hospital of

Wenzhou Medical University(KY2025-R222) and adhered to the principles of the Declaration of Helsinki. The inclusion criteria for the study population were as follows: (1) for RVO group: patients who were firstly diagnosed as macular edema secondary to CRVO/BRVO by optical coherence tomography and fundus fluorescein angiography in the First Affiliated Hospital of Wenzhou Medical University; (2).for control group: patients who were scheduled for eyelid, pterygium, or cataract surgery matched with RVO patients by gender, age (± 2 years), and admission time (± 1 month). The exclusion criteria were as follows: (1) combination with other fundus diseases, such as age-related macular degeneration, diabetic retinopathy, retinal detachment, and retinitis pigmentosa; (3) history of ocular surgery within six months; (4) history of trauma within six months;(5) history of ocular tumor, glaucoma, uveitis. The sample size of the case-to-control ratio was set to 1:1.

Data collection

The medical records of eligible patients were collected retrospectively from the electronic medical record system, which included clinical and laboratory data. Clinical data included sex, age, body mass index (BMI), history of hypertension, diabetes, and other diseases. For RVO patients, data on symptom duration, baseline best-corrected visual acuity (hereafter referred to as baseline vision), and best-corrected visual acuity after a second anti-VEGF treatment (hereafter referred to as treated vision) were also collected. Laboratory data comprised white blood cells(WBC); eosinophil, neutrophil, monocyte, lymphocyte, and basophil counts; red blood cells(RBC); hemoglobin; mean corpuscular volume(MCV); red blood cell distribution width(RDW); platelet; mean platelet volume(MPV); alanine aminotransferase (ALT); aspartate aminotransferase (AST); carbamide; creatinine; estimated glomerular filtration rate(eGFR); uric acid(UA); total cholesterol(TC); triglyceride; high-density lipoprotein cholesterol (HDL-C); and low-density lipoprotein cholesterol(LDL-C). The derived ratios were NLR, PLR, MLR, SII, SIRI, and HRR. These were calculated as follows:

$NLR = \text{neutrophil} / \text{lymphocyte}$

$PLR = \text{platelet} / \text{lymphocyte}$

$MLR = \text{monocyte} / \text{lymphocyte}$

$SII = \text{platelet} * NLR$

$SIRI = \text{monocyte} * NLR$

$HRR = \text{Hemoglobin} / RDW$

Statistical analysis

Data normality was assessed using the Shapiro–Wilk test. Continuous variables were summarized as the mean $\pm$ standard deviation or as medians with interquartile ranges, while categorical variables were

expressed as numbers and percentages. Categorical data were assessed using the chi-square test, and the comparison of continuous variables between the two groups was performed using an independent sample test or the Mann–Whitney U test. Binary logistic regression analyses were carried out to identify the relationships between CRVO and HRR, as well as that between the treated vision and HRR. In addition, the patients were divided into subgroups based on gender, age (≤ 60 ; > 60), diabetes mellitus, and BMI (≤ 24 , > 24). Subgroup analysis was used to verify the stability of the results. The statistical analysis was conducted using the SPSS software program (version 24.0) and R software (version 4.3.3). A p-value of less than 0.05 was considered indicative of statistical significance.

Results

Baseline characteristics of patients with CRVO/BRVO and controls

The study included 146 CRVO cases and 146 controls, as well as 245 BRVO cases and 245 controls. Table 1 shows a comparison of general baseline data between CRVO and the control group. The HRR of patients in the CRVO group was significantly lower than that in the control group ($p = 0.001$). Compared with the control group, the proportion of hypertensive patients in the CRVO group was significantly higher ($p = 0.003$). In addition, hemoglobin, RDW, ALT, AST, urea, HDL-C, SII, NLR, and PLR showed statistically significant differences (all $p < 0.05$). Table 2 presents the general baseline data comparison between BRVO and the control group. Except for hypertension ($p < 0.001$), no significant differences in the other parameters between BRVO and the control group were observed (all $p > 0.05$).

Table 1
Baseline characteristics of patients with CRVO and controls

Characteristics	Control	CRVO	P value
	N = 146	N = 146	
Gender (%)			1
Male	91 (62.3)	91 (62.3)	
Female	55 (37.7)	55 (37.7)	
Age (mean (SD))	60.49 (12.45)	60.34 (12.55)	0.918
Hypertension (%)			0.003
NO	92 (63.0)	66 (45.2)	
Yes	54 (37.0)	80 (54.8)	
Diabetes mellitus (%)			0.159
NO	119 (81.5)	108 (74.0)	
Yes	27 (18.5)	38 (26.0)	
BMI (median [IQR])	23.55 [21.85, 25.70]	23.45 [21.80, 25.40]	0.667
WBC (median [IQR])	6.40 [5.27, 7.57]	6.53 [5.30, 7.82]	0.692
Eosinophil (median [IQR])	0.09 [0.06, 0.18]	0.10 [0.07, 0.16]	0.672
Neutrophil (median [IQR])	3.94 [3.07, 4.94]	4.10 [3.37, 5.09]	0.21
Monocyte (median [IQR])	0.40 [0.31, 0.50]	0.38 [0.29, 0.49]	0.499
Lymphocyte (median [IQR])	1.81 [1.47, 2.25]	1.75 [1.28, 2.21]	0.084
Basophil (median [IQR])	0.02 [0.02, 0.03]	0.02 [0.02, 0.04]	0.983
RBC (median [IQR])	4.56 [4.26, 4.94]	4.52 [4.19, 4.86]	0.285
Hemoglobin (median [IQR])	141.00 [131.00, 152.00]	135.50 [125.00, 146.00]	0.003
MCV (median [IQR])	92.00 [89.53, 94.38]	91.20 [87.80, 93.97]	0.051
RDW (median [IQR])	12.90 [12.50, 13.47]	13.10 [12.60, 13.70]	0.028
Platelet (median [IQR])	228.50 [188.00, 264.50]	226.00 [190.75, 272.75]	0.721

SD : standard deviation; IQR: interquartile ranges; BMI: body mass index; WBC: white blood cell; RBC: red blood cell; hemoglobin, MCV: mean corpuscular volume : RDW: red cell distribution width ; MPV: mean platelet volume; ALT: alanine aminotransferase, AST: aspartate aminotransferase ; UA: uric acid; TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C :low-density lipoprotein cholesterol; SII systemic immune-inflammation index, SIRI: systemic immune-response index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; HRR: hemoglobin-to-Red Cell Distribution Width Ratio.

Characteristics	Control	CRVO	P value
	N = 146	N = 146	
MPV (median [IQR])	10.10 [9.40, 10.90]	10.15 [9.22, 10.80]	0.659
ALT (median [IQR])	20.00 [15.00, 30.00]	17.00 [14.00, 25.00]	0.014
AST (median [IQR])	24.00 [21.00, 30.00]	23.00 [19.25, 28.00]	0.018
Urea (median [IQR])	5.75 [4.30, 6.90]	6.10 [4.90, 7.57]	0.036
Creatinine (median [IQR])	70.50 [60.00, 80.00]	71.50 [60.00, 86.75]	0.397
eGFR (median [IQR])	95.80 [82.50, 106.40]	93.35 [71.83, 104.02]	0.146
UA (median [IQR])	343.50 [295.50, 400.75]	339.00 [275.25, 415.25]	0.841
TC (median [IQR])	5.34 [4.58, 6.02]	5.23 [4.41, 5.93]	0.274
Triglyceride (median [IQR])	1.73 [1.23, 2.90]	1.79 [1.25, 2.50]	0.43
HDL-C (median [IQR])	1.28 [1.09, 1.51]	1.19 [1.03, 1.40]	0.036
LDL-C (mean (SD))	3.21(0.86)	3.16(0.79)	0.635
SII (median [IQR])	472.85 [316.22, 649.66]	532.59 [380.16, 755.55]	0.014
SIRI (median [IQR])	0.81 [0.57, 1.30]	0.88 [0.62, 1.30]	0.159
NLR (median [IQR])	2.05 [1.56, 2.72]	2.42 [1.79, 3.10]	0.011
PLR (median [IQR])	121.32 [96.24, 150.80]	130.73 [106.19, 170.67]	0.038
MLR (median [IQR])	0.22 [0.16, 0.27]	0.23 [0.18, 0.28]	0.202
HRR (median [IQR])	10.83 [10.02, 11.73]	10.38 [9.16, 11.39]	0.001
SD : standard deviation; IQR: interquartile ranges; BMI: body mass index; WBC: white blood cell; RBC: red blood cell; hemoglobin, MCV: mean corpuscular volume : RDW: red cell distribution width ; MPV: mean platelet volume; ALT: alanine aminotransferase, AST: aspartate aminotransferase ; UA: uric acid; TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C :low-density lipoprotein cholesterol;. SII systemic immune-inflammation index, SIRI: systemic immune-response index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; HRR: hemoglobin-to-Red Cell Distribution Width Ratio.			

Table 2
Baseline characteristics of patients with BRVO and controls

Characteristics	Control	BRVO	P value
	N = 245	N = 245	
Gender (%)			1
Male	124 (50.6)	124 (50.6)	
Female	121 (49.4)	121 (49.4)	
Age (mean (SD))	59.86 (10.92)	59.88 (11.02)	0.984
Hypertension (%)			< 0.001
NO	161 (65.7)	106 (43.3)	
Yes	84 (34.3)	139 (56.7)	
Diabetes mellitus (%)			0.795
NO	212 (86.5)	209 (85.3)	
Yes	33 (13.5)	36 (14.7)	
BMI (median [IQR])	24.10 [22.00, 26.00]	24.48 [22.10, 27.10]	0.3
WBC (median [IQR])	6.41 [5.49, 7.35]	6.43 [5.41, 7.56]	0.519
Eosinophil (median [IQR])	0.10 [0.06, 0.18]	0.11 [0.06, 0.17]	0.932
Neutrophil (median [IQR])	3.88 [3.11, 4.78]	3.88 [3.29, 4.92]	0.349
Monocyte (median [IQR])	0.39 [0.30, 0.50]	0.39 [0.29, 0.47]	0.373
Lymphocyte (median [IQR])	1.76 [1.49, 2.10]	1.81 [1.42, 2.29]	0.487
Basophil (median [IQR])	0.02 [0.02, 0.03]	0.02 [0.02, 0.04]	0.099
RBC (median [IQR])	4.59 [4.29, 4.91]	4.63 [4.30, 5.01]	0.288
Hemoglobin (median [IQR])	139.00 [129.00, 150.00]	141.00 [129.00, 152.00]	0.535
MCV (median [IQR])	91.30 [88.50, 94.00]	91.00 [88.00, 93.30]	0.143
RDW (median [IQR])	12.90 [12.60, 13.40]	13.00 [12.50, 13.40]	0.576
Platelet (median [IQR])	232.00 [191.00, 263.00]	229.00 [196.00, 267.00]	0.652
MPV (median [IQR])	10.10 [9.30, 10.90]	10.00 [9.30, 10.80]	0.696
ALT (median [IQR])	21.00 [15.00, 31.00]	21.00 [15.00, 31.00]	0.931
AST (median [IQR])	23.00 [21.00, 28.00]	24.00 [20.00, 29.00]	0.579
Urea (median [IQR])	5.80 [4.80, 6.80]	5.60 [4.70, 6.60]	0.441

Characteristics	Control	BRVO	P value
	N = 245	N = 245	
Creatinine (median [IQR])	69.00 [58.00, 80.00]	69.00 [60.00, 82.00]	0.459
eGFR (median [IQR])	96.50 [82.40, 106.10]	93.70 [80.80, 102.90]	0.079
UA (median [IQR])	333.00 [284.00, 392.00]	327.00 [276.00, 391.00]	0.474
TC (median [IQR])	5.36 [4.52, 6.29]	5.36 [4.63, 6.11]	0.484
Triglyceride (median [IQR])	1.88 [1.24, 2.70]	1.81 [1.32, 2.58]	0.867
HDL-C (median [IQR])	1.30 [1.08, 1.48]	1.27 [1.08, 1.47]	0.59
LDL-C (mean (SD))	3.32 (0.95)	3.22 (0.90)	0.274
SII (median [IQR])	491.18 [356.14, 654.12]	512.35 [372.29, 668.79]	0.463
SIRI (median [IQR])	0.84 [0.58, 1.24]	0.82 [0.56, 1.22]	0.77
NLR (median [IQR])	2.17 [1.67, 2.83]	2.30 [1.62, 2.88]	0.56
PLR (median [IQR])	127.68 [100.63, 158.24]	124.43 [100.46, 157.77]	0.865
MLR (median [IQR])	0.22 [0.17, 0.28]	0.21 [0.15, 0.27]	0.137
HRR (median [IQR])	10.77 [9.84, 11.65]	10.85 [9.92, 11.80]	0.612

Association between HRR and CRVO

Table 3 shows the association between HRR and CRVO. In Model 1, which did not control for any covariates, HRR was associated with markedly reduced odds of CRVO, resulting in an odds ratio (OR) of 0.755 (95% confidence interval [CI]: 0.653–0.872, $p < 0.001$). This result indicates that a higher HRR is strongly linked to a lower occurrence of CRVO. Model 2 introduced the adjustment for hypertension, and the association remained significant, with an OR of 0.755 (95% CI: 0.652–0.874, $p < 0.001$). Model 3 further introduced the adjustments for hypertension, ALT, AST, urea, HDL-C, and SII. As NLR and PLR are considered inflammation-related parameters similar to SII, here only SII was included in Model 3. The results maintained statistical significance, with an OR of 0.772 (95% CI: 0.656–0.909, $p = 0.002$). This finding highlights the robustness of the association between HRR and CRVO.

Table 3
Association between HRR and CRVO

	Model 1			Model 2			Model3		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
HRR	0.755	0.653–0.872	< 0.001	0.755	0.652–0.874	< 0.001	0.772	0.656–0.909	0.002
HRR(quartile)									
Q1 (≤ 9.60)	1		ref	1		ref	1		ref
Q2 (9.61–10.73)	0.538	0.277–1.045	0.067	0.566	0.289–1.111	0.098	0.669	0.329–1.362	0.268
Q3 (10.74–11.60)	0.432	0.222–0.84	0.013	0.442	0.225–0.869	0.018	0.504	0.247–1.026	0.059
Q4 (≥ 11.61)	0.408	0.21–0.796	0.008	0.405	0.206–0.797	0.009	0.482	0.233–0.996	0.049
P trend	0.005			0.005			0.03		
Model 1: no covariates adjusted;									
Model 2: adjusted for hypertension									
Model 3: adjusted for hypertension, ALT, AST, urea, HDL-C, SII									

To further evaluate the relationship between HRR stratification and CRVO, the patients were categorized into four subgroups according to HRR quartiles: Q1 (≤ 9.60), Q2 (9.61–10.73), Q3 (10.74–11.60), and Q4 (≥ 11.61). With the lowest quartile (Q1) of HRR as a reference, the patients in the second quartile (Q2) exhibited an OR of 0.538 (95% CI: 0.277–1.045, $p = 0.067$) in Model 1, an OR of 0.566 (95% CI: 0.289–1.111, $p = 0.098$) in Model 2, and an OR of 0.669 (95% CI: 0.329–1.362, $p = 0.268$) in Model 3. The patients in the third quartile (Q3) exhibited significantly lower odds of CRVO, with an OR of 0.432 (95% CI: 0.222–0.84, $p = 0.013$) in Model 1, an OR of 0.442 (95% CI: 0.225–0.869, $p = 0.018$) in Model 2, and an OR of 0.504 (95% CI: 0.247–1.026, $p = 0.059$) in Model 3. The patients in the fourth quartile (Q4) exhibited significantly lower odds of CRVO, with an OR of 0.408 (95% CI: 0.21–0.796, $p = 0.008$) in Model 1, an OR of 0.405 (95% CI: 0.206–0.797, $p = 0.009$) in Model 2, and an OR of 0.482 (95% CI: 0.233–0.996, $p = 0.049$) in Model 3. The trend analysis across the HRR quartiles was significant for all three models, with p -values of 0.005, 0.005, and 0.03, respectively. The results indicate that an increased HRR is linked to a diminished likelihood of CRVO.

Subgroup analysis of the association between HRR and CRVO

We further conducted a subgroup analysis to investigate the effects of various factors on the relationship between HRR and CRVO. As demonstrated in Table 4, there was no significant difference in

the association of HRR with CRVO between male and female ($p = 0.491$). The OR was 0.815 (95% CI: 0.655–1.014, $p = 0.067$) among males and 0.667 (95% CI: 0.489–0.911, $p = 0.011$) among females. The patients were also divided into two groups according to age: age ≤ 60 and age > 60 . The OR was 0.704 (95% CI: 0.551–0.901, $p = 0.005$) among the group aged ≤ 60 and 0.833 (95% CI: 0.658–1.053, $p = 0.127$) among the group aged > 60 . As the interaction test produced a p -value of 0.625, no significant difference was found in the association of HRR with CRVO between the two groups. For the subgroup analysis of diabetes mellitus, the OR was 0.771 (95% CI: 0.637–0.933, $p = 0.007$) among patients without diabetes and 0.874 (95% CI: 0.608–1.257, $p = 0.467$) among patients with diabetes. The p -value of the interaction test was 0.425, which indicates that the HRR–CRVO relationship did not differ significantly according to diabetes mellitus status.

Table 4
Subgroup analysis of the association between HRR and CRVO

	Control	CRVO	Model3			
	N	N	OR	95%CI	P value	P for interaction
Stratified by gender						
Male	91	91	0.815	0.655–1.014	0.067	0.491
Female	55	55	0.667	0.489–0.911	0.011	
Stratified by age						
≤ 60	64	65	0.704	0.551–0.901	0.005	0.625
> 60	82	81	0.833	0.658–1.053	0.127	
Stratified by diabetes mellitus						
NO	119	108	0.771	0.637–0.933	0.007	0.425
YES	27	38	0.874	0.608–1.257	0.467	
Stratified by BMI						
BMI ≤ 24	83	84	0.782	0.631–0.969	0.025	0.712
BMI > 24	63	62	0.758	0.575–1.000	0.05	
Model 3: adjusted for hypertension, ALT, AST, urea, HDL-C, SII						

No significant difference was found in the association of HRR with CRVO between the BMI ≤ 24 and the BMI > 24 ($p = 0.712$). Individuals with a BMI ≤ 24 had an OR of 0.782 (95% CI: 0.631–0.969, $p = 0.025$), while those with a BMI > 24 had an OR of 0.758 (95% CI: 0.575–1.000, $p = 0.05$). Thus, the subgroup analysis highlighted the stability of the relationship between HRR and CRVO and showed no significant interactions between HRR and potential effect modifiers (gender, age, BMI, and diabetes mellitus).

Correlation of HRR with The Baseline and Treated Vision in RVO Patients

To investigate the associations among HRR, baseline vision, and treated vision in patients with RVO, Spearman correlation analysis was performed. As shown in Fig. 1-A, HRR exhibited a significant positive correlation with baseline vision in the overall cohort of 391 RVO patients ($P < 0.001$). Subgroup analysis revealed that this correlation was significant in 245 patients with BRVO ($P < 0.05$), but not in 146 patients with CRVO ($P = 0.07$). Among the 391 RVO patients, 161 have the treated vision (55 with CRVO and 106 with BRVO). Figure 1-B demonstrates that HRR remained significantly positively correlated with treated vision in these 161 patients ($P < 0.001$); again, the correlation was significant in the 106 BRVO patients ($P < 0.001$), but not in the 55 CRVO patients ($P = 0.848$).

Baseline characteristics of patients with good/poor treated vision in RVO patients

To further explore the association between HRR and treated vision, RVO patients were divided into two groups based on median treated vision: good (vision ≥ 0.4) and poor (vision < 0.4). As shown in Table 5, there were 83 patients in the good group and 78 in the poor group. The HRR levels in the good group were significantly higher than that in the poor group ($p = 0.002$). Patients in the good group were significantly younger than those in the poor group ($p = 0.005$). The baseline vision in the good group was significantly higher than that in the poor group ($p < 0.001$). In addition, WBC, Neutrophil, hemoglobin, RDW, eGFR showed statistically significant differences (all $p < 0.05$).

Table 5
Baseline characteristics of patients with good/poor treated vision in RVO patients

	Good treated vision	Poor treated vision	P value
	(N = 83)	(N = 78)	
Gender (%)			1
Male	33(53.0)	20(52.6)	
Female	39 (47.0)	37 (47.4)	
Age (median [IQR])	57.00 [51.00, 63.00]	63.00 [54.00, 70.00]	0.002
Hypertension (%)			0.792
NO	28(44.4)	15(34.9)	
Yes	43 (51.8)	43 (55.1)	
Diabetes mellitus (%)			0.394
NO	72(86.7)	63(80.5)	
Yes	11 (13.3)	15 (19.5)	
Duration of RVO(Month) (median [IQR])	1.00 [0.33, 2.00]	1.00 [0.33, 2.00]	0.865
Baseline vision (median [IQR])	0.30 [0.10, 0.40]	0.05 [0.05, 0.14]	< 0.001
BMI (median [IQR])	24.60 [22.45, 26.65]	23.45 [22.10, 25.87]	0.141
WBC (median [IQR])	6.39 [5.56, 8.51]	6.12 [5.10, 7.17]	0.021
Eosinophil (median [IQR])	0.10 [0.05, 0.16]	0.09 [0.06, 0.15]	0.748
Neutrophil (median [IQR])	4.13 [3.35, 5.30]	3.70 [2.97, 4.74]	0.027
Monocyte (median [IQR])	0.36 [0.29, 0.49]	0.36 [0.28, 0.45]	0.439
Lymphocyte (median [IQR])	1.98 [1.40, 2.44]	1.73 [1.38, 2.14]	0.109
Basophil (median [IQR])	0.03 [0.02, 0.04]	0.02 [0.02, 0.04]	0.094
RBC (median [IQR])	4.56 [4.38, 4.89]	4.57 [4.26, 4.82]	0.416
Hemoglobin (median [IQR])	141.00 [132.00, 151.00]	136.00 [123.25, 149.00]	0.039
MCV (median [IQR])	91.20 [88.05, 93.95]	90.75 [88.05, 93.15]	0.606
RDW (median [IQR])	12.80 [12.35, 13.35]	13.20 [12.70, 13.70]	0.007

	Good treated vision	Poor treated vision	P value
	(N = 83)	(N = 78)	
Platelet (median [IQR])	231.00 [194.50, 273.00]	224.00 [191.00, 255.75]	0.27
MPV (median [IQR])	10.10 [9.30, 10.60]	10.25 [9.20, 10.80]	0.706
ALT (median [IQR])	20.00 [17.00, 33.00]	19.50 [14.00, 29.50]	0.06
AST (median [IQR])	24.00 [21.00, 29.50]	24.00 [20.00, 30.50]	0.786
Carbamide (median [IQR])	5.60 [4.50, 6.35]	5.80 [5.10, 7.00]	0.064
Creatinine (median [IQR])	68.00 [59.00, 81.50]	71.00 [61.00, 84.00]	0.422
eGFR (median [IQR])	96.30 [83.20, 105.40]	89.85 [75.82, 101.70]	0.034
UA (median [IQR])	325.00 [271.50, 391.50]	349.00 [276.00, 432.75]	0.298
TC (median [IQR])	5.52 [4.79, 6.20]	5.46 [4.61, 6.06]	0.58
Triglyceride (median [IQR])	1.83 [1.34, 2.53]	1.69 [1.24, 2.61]	0.801
HDL-C (median [IQR])	1.26 [1.09, 1.44]	1.25 [1.09, 1.46]	0.967
LDL-C (mean (SD))	3.41 [2.92, 3.93]	3.27 [2.68, 3.78]	0.38
SII (median [IQR])	549.27 [374.69, 719.67]	492.00 [341.20, 668.99]	0.189
SIRI (median [IQR])	0.80 [0.54, 1.33]	0.79 [0.54, 1.05]	0.296
NLR (median [IQR])	2.35 [1.71, 2.96]	2.17 [1.63, 2.87]	0.453
PLR (median [IQR])	117.65 [101.17, 156.19]	123.77 [97.25, 156.26]	0.735
MLR (median [IQR])	0.20 [0.15, 0.26]	0.21 [0.15, 0.26]	0.761
HRR (median [IQR])	10.95 [10.37, 11.86]	10.44 [9.56, 11.35]	0.005

Association between HRR and Treated Vision

Table 6 presents the association between HRR and treated vision. In Model 1, which was unadjusted for covariates, higher HRR was associated with significantly lower odds of poor treated vision (odds ratio [OR] = 0.759, 95% confidence interval [CI]: 0.613–0.918, $p = 0.007$). This indicates that a higher HRR is strongly linked to a better visual outcome in RVO patients. After adjusting for age, baseline vision, WBC, neutrophil count, and eGFR in Model 2, the association remained significant (OR = 0.747, 95% CI: 0.573–0.952, $p = 0.023$).

Table 6
Association between HRR and Treated Vision

	Model 1			Model 2		
	OR	95%CI	P value	OR	95%CI	P value
HRR	0.759	0.613–0.918	0.007	0.747	0.573–0.952	0.023
HRR(quartile)						
Q1 (≤ 9.92)	1		ref	1		ref
Q2 (9.93–10.81)	0.339	0.132–0.834	0.021	0.184	0.051–0.593	0.006
Q3 (10.82–11.64)	0.339	0.132–0.834	0.021	0.315	0.089–1.025	0.061
Q4 (≥ 11.65)	0.199	0.075–0.500	< 0.001	0.232	0.059–0.828	0.028
P trend	0.001			0.07		
Model 1;unadjusted						
Model 2: adjusted for age,vision_baseline,WBC,Neutrophil,eGFR						

To further evaluate the dose-response relationship, patients were stratified into four subgroups based on HRR quartiles: Q1 (≤ 9.60), Q2 (9.61–10.81), Q3 (10.82–11.64), and Q4 (≥ 11.65). With the lowest quartile (Q1) serving as the reference group, Q2 showed significantly lower odds of poor treated vision in both Model 1 (OR = 0.339, 95% CI: 0.132–0.834, $p = 0.021$) and Model 2 (OR = 0.184, 95% CI: 0.051–0.593, $p = 0.006$). Q3 also demonstrated lower odds in Model 1 (OR = 0.339, 95% CI: 0.132–0.834, $p = 0.021$), but the association approached statistical significance in Model 2 (OR = 0.315, 95% CI: 0.089–1.025, $p = 0.061$). Q4 exhibited consistently lower odds in both Model 1 (OR = 0.199, 95% CI: 0.075–0.500, $p < 0.001$) and Model 2 (OR = 0.232, 95% CI: 0.059–0.828, $p = 0.028$). These results suggest a graded inverse association between HRR and the risk of poor treated vision, with higher HRR levels being associated with a progressively reduced risk

Discussion

This retrospective study examined the relationship between HRR and RVO based on the hospitalized population of 146 CRVO and 245 BRVO patients with matched controls. By adjusting for a number of confounders, we still found that HRR was negatively associated with CRVO incidence, suggesting a protective role of HRR against CRVO. The quartile analysis confirmed a dose-dependent relationship between HRR and CRVO risk, and additional subgroup analyses confirmed the stability of these results. Thus, these results demonstrate that HRR is a novel and independent predictor of CRVO. Moreover, we discovered that RVO patients with a higher HRR had not only better baseline vision but also better treated vision after anti-VEGF therapy. Previous studies have reported that a better baseline vision is associated with more rapid vision gains after anti-VEGF treatment [18, 19]. To further explore whether HRR independently affects treated vision rather than through influencing baseline vision, we conducted a

multivariable logistic regression analysis. The results show that HRR was an independent predictor of a lower risk of poor visual outcome. Therefore, HRR can also serve as a potential prognostic factor for RVO treatment.

Unlike most previous studies that did not separate CRVO and BRVO for risk factor analysis [20–22], our study analyzed the clinical and laboratory characteristics of CRVO and BRVO with their respective matched controls. We found that several factors (including hypertension, hemoglobin, RDW, ALT, AST, urea, HDL-C, SII, NLR, PLR, and HRR) were significantly associated with CRVO, while only hypertension showed a significant difference in BRVO. The results are not surprising, as the pathophysiology of RVO is multifactorial and differs between CRVO and BRVO [1]. BRVO typically occurs in accordance with an arteriovenous crossing, and it explains why hypertension, which increases artery stiffness, is the main risk factor for BRVO [8]. CRVO mainly results from an obstruction or a significant deceleration of venous flow in the central retinal vein at the optic nerve head level caused by systemic vascular comorbidities and inflammation [8, 9]. As the laboratory parameters reflect the status of systemic vascular comorbidities and inflammation, they can serve as risk predictors for CRVO.

Therefore, the different results in our study between CRVO and BRVO further indicate the different risk factors involved in CRVO and BRVO. Our study identified significant differences in HDL-C, NLR, PLR, and SII between CRVO and control patients, and the results were somewhat consistent with previous studies [20–22]. As a biomarker of red cell dysfunction, RDW has been reported to be associated with high systemic inflammation [23]. Previous studies have reported that RDW was significantly higher in RVO patients than in control participants [24, 25], and this finding is consistent with our study. However, in Pinna et al.'s study, BRVO was significantly associated with RDW, while CRVO was not significantly associated with RDW. In their study, they found no statistically significant relationship between RVO and RDW through multivariate logistic regression analysis [26]. Therefore, although previous studies have discovered different RDW levels between RVO and control patients, a single RDW is insufficient as a reliable biomarker for RVO occurrence.

Hemoglobin mainly reflects the degree of anemia, which has also been reported as a risk factor for RVO [27]. However, some studies have found no significant difference in hemoglobin between RVO patients and the control group [21, 25], while our study found a significantly lower hemoglobin in CRVO patients. This may be due to the combined analysis of CRVO and BRVO, and the hemoglobin effect may depend on the percentage of CRVO in the RVO population.

When exploring the relationship between HRR and vision, we found that the positive correlation was statistically significant in BRVO, but not in CRVO. This may be attributed to the insufficient sample size for CRVO; therefore, we merged BRVO and CRVO for analysis, and further exploration will be conducted in the future.

This study has several limitations that need to be considered. First, its retrospective design could introduce selection bias, as existing data were used without randomization. Second, the single-center nature of the study limits the generalizability of the findings to broader populations, especially those with

diverse ethnic or geographic backgrounds. Third, unmeasured confounders, such as lifestyle factors (e.g., smoking and physical activity) and medication use (e.g., anticoagulants), could affect HRR levels and RVO risk, but they were not considered in the study. Future prospective multicenter studies incorporating longitudinal data and experimental validation are needed to fill these gaps.

Conclusion

HRR is a novel, independent protective biomarker for CRVO and a significant predictor of favorable visual prognosis after anti-VEGF therapy, offering a simple and economical tool for risk assessment and clinical management.

Abbreviations

RVO

Retinal vein occlusion

BRVO

Branch retinal vein occlusion

CRVO

Central retinal vein occlusion

HRR

Hemoglobin-to-red blood cell distribution width ratio

BCVA

Best-corrected visual acuity

RDW

Red blood cell distribution width

WBC

White blood cells

RBC

Red blood cells

MCV

Mean corpuscular volume

MPV

Mean platelet volume

ALT

Alanine aminotransferase

AST

Aspartate aminotransferase

eGFR

Estimated glomerular filtration rate

UA

Uric acid

TC
Total cholesterol
HDL-C
High-density lipoprotein cholesterol
LDL-C
Low-density lipoprotein cholesterol

Declarations

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity having financial interests (e.g., honoraria, grants, etc.) or non-financial interests (e.g., personal or professional relationships) in the subject matter or materials of this manuscript.

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Author Contribution Statement

Zhu Lin and Leru Zhu were responsible for designing the study, collecting data, analyzing the data, writing and revising the manuscript. All authors have seen and agrees with how their name is listed.

Ethics approval and consent to participate

All procedures in this study were in accordance with the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (Ethical approval number: KY2025-R222) and adhered to the principles of the Declaration of Helsinki. The need for informed consent was waived by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (approval number: KY2025-R222) due to the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors certify that they have no affiliations with or involvement in any organization or entity having financial interests (e.g., honoraria, grants, etc.) or non-financial interests (e.g., personal or professional

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Authors' contributions

Zhu Lin and Leru Zhu were responsible for designing the study, collecting data, analyzing the data, writing and revising the manuscript.

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Figures

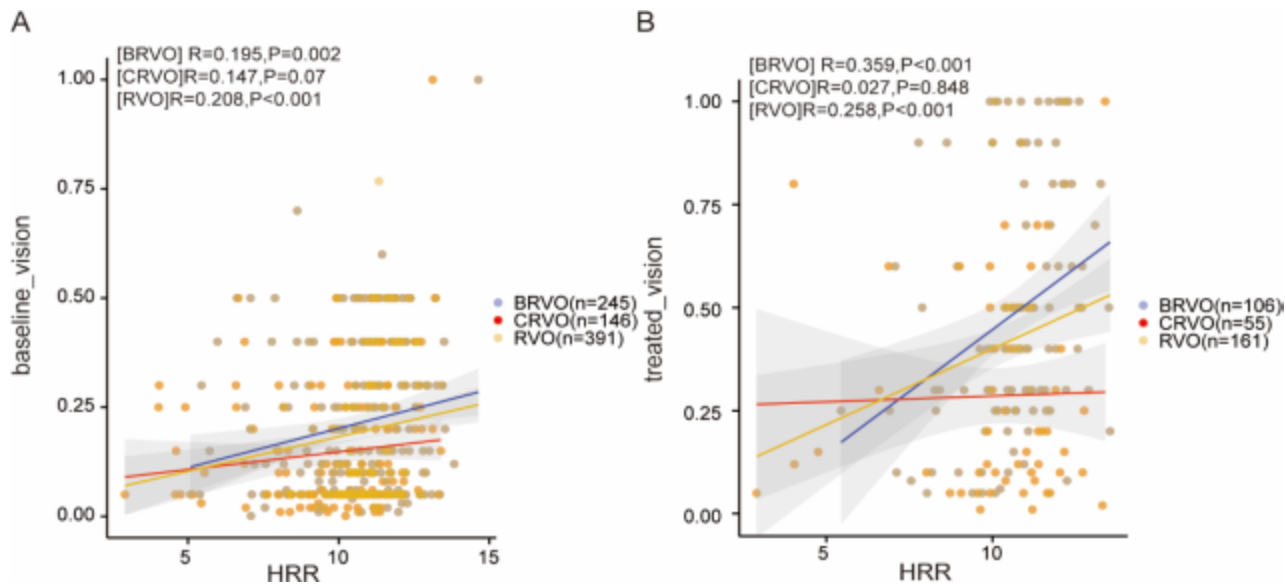


Figure 1

Correlation of HRR with baseline and treated vision in RVO patients A) the correlation analysis of HRR with baseline vision B) the correlation analysis of HRR with treated vision