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Assessment of systemic inflammatory response index and other inflammatory indicators in retinal vein occlusion

Mehmet Barış Üçer, MD[a,*], Selim Cevher, MD[b]

Abstract

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy. The study aimed to evaluate the association and the predictive value of inflammatory indicators in RVO. Sixty patients with RVO and 60 healthy individuals were enrolled in this retrospective study. Inflammatory indicators and other hematological parameters obtained from the peripheral venous sample were analyzed and compared among groups. White blood cell count ($P = .003$), neutrophil ($P < .001$), neutrophil-to-lymphocyte ratio (NLR) ($P < .001$), monocyte-to-lymphocyte ratio (MLR) ($P < .001$), platelet-to-lymphocyte ratio (PLR) ($P = .014$), systemic immune-inflammation index (SII) ($P < .001$), and systemic inflammatory response index (SIRI) ($P < .001$) were significantly higher; the lymphocyte count ($P < .001$) was significantly lower in patients with RVO. According to receiver operating characteristic analysis, NLR was significant at the good level (area under the curve [AUC] = 0.817, $P < .001$); SIRI, SII, and MLR were significant at the fair level (AUC = 0.774, $P < .001$; AUC = 0.733, $P < .001$, and AUC = 0.724, $P < .001$, respectively) and PLR (AUC = 0.630, $P = .014$) was significant at the weak level in terms of RVO prediction. SIRI was superior to other indicators, except NLR, to predict RVO. SIRI, NLR, SII, MLR, and PLR can be used as predictors for identifying the risk of RVO.

Abbreviations: ANOVA = analysis of variance, AUC = area under the curve, BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, DM = diabetes mellitus, HT = hypertension, MLR = monocyte-to-lymphocyte ratio, MPV = mean platelet volume, NET = neutrophil extracellular traps, NLR = neutrophil-to-lymphocyte ratio, OR = odds ratio, PDW = platelet distribution width, PLR = platelet-to-lymphocyte ratio, RDW = red cell distribution width, ROC = receiver operating characteristic, RVO = retinal vein occlusion, SII = systemic immune-inflammation index, SIRI = systemic inflammatory response index, SIRI = systemic inflammation response index, WBC = white blood cell.

Keywords: complete blood count, monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, retinal vein occlusion, systemic immune-inflammation index, systemic inflammatory response index

1. Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy. It causes visual dysfunction and vision loss due to complications such as macular edema, retinal ischemia, vitreous hemorrhage, and neovascularization. The prevalence of RVO is 0.42% for branch RVO (BRVO), 0.085 for central RVO (CRVO), and 0.52% for any RVO. Prevalence may vary by race and ethnicity, at a rate of 3.7 in whites, 5.7 in Asians, 3.9 in blacks, and 6.9 in Hispanics per 1000 individuals. It is estimated that around 16.4 (95% CI: 13.9–18.9) million people worldwide suffer from some type of RVO in at least 1 eye.[1] Several systemic and ocular risk factors, such as older age, systemic hypertension (HT), diabetes mellitus (DM), dyslipidemia, stroke, cerebrovascular event, chronic kidney disease, cardiovascular disease, atherosclerotic diseases, hypercoagulable situation, thrombophilia, oral contraceptives, smoking, systemic inflammatory diseases, glaucoma, high intraocular pressure, and increased cup-to-disc ratio are associated with RVO development.[2–4] RVO pathogenesis is multifactorial and not completely understood. Still, it follows the principles of Virchow triad: compression of the vein by the atherosclerotic artery, injury of the vessel wall, and hypercoagulability.

Local and systemic inflammation plays a role in RVO development by inducing atherosclerosis and hypercoagulability conditions.[5] Furthermore, atherosclerosis itself is a low-grade chronic inflammation. Recent data indicate that inflammation caused by the interaction between immune and inflammatory cells plays a crucial role in the development of RVO. The

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[a] *Department of Ophthalmology, Sincan Training and Research Hospital, Ankara, Turkey,* [b] *Department of Ophthalmology, Hitit University Erol Olçok Education and Research Hospital, Çorum, Turkey.*

**Correspondence: Mehmet Barış Üçer, Department of Ophthalmology, Sincan Training and Research Hospital, Gökçek, 250 Cad 2/A, 06949 Sincan/Ankara, Turkey (e-mail: dr.mbu@hotmail.com).*

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expression of inflammatory cytokines, growth factors, chemokines, and adhesion molecules, such as interleukin 8, interleukin 6, monocyte chemoattractant protein, platelet-derived growth factor, placental growth factor, intercellular adhesion molecule 1, interferon-inducible 10-kDa protein, pentraxin 3, erythropoietin, and vascular endothelial growth factor increase in patients with RVO.[6] The inflammatory response is the coordinated activation of signaling pathways that regulate inflammatory mediator levels in resident tissue cells and inflammatory cells, including neutrophils, macrophages, and lymphocytes recruited from the blood. As a simple, easy, and inexpensive examination, a complete blood count can reflect the inflammatory state. The absolute counts of white blood cells (WBC), neutrophils, monocytes, lymphocytes, and specific inflammation markers derived from those cells can be reliable indicators of systemic inflammatory status. In many pathologies based on inflammation, inflammatory indicators obtained from peripheral blood are now used as prognostic markers and progression predictors of many diseases, including RVO.[7–15]

This is the first study to evaluate systemic inflammation response index (SIRI) and monocyte-to-lymphocyte ratio (MLR) in elderly patients with RVO. The present study aims to determine the potential associations and the predictive value of inflammatory indicators such as the SIRI, neutrophil-to-lymphocyte ratio (NLR), MLR, platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and other hematologic parameter characteristics in patients with RVO.

2. Methods

This cross-sectional study was approved by the Ethical Committee of Hitit University School of Medicine (Date: 02/05/2023, Approval No: 2023-39) and conducted in accordance with the Declaration of Helsinki. The medical records of 60 patients diagnosed with any type of RVO between April 2022 and March 2023 were evaluated retrospectively. Sixty age- and gender-matched participants who had undergone cataract surgery were included in the control group. Patients with DM, malignancy, anemia, active smoking, acute/chronic infections, stroke, renal failure, chronic systemic inflammatory disease, connective tissue disease, renal failure, hepatic disorders, and chronic obstructive pulmonary disease were excluded from the study. Patients using anticoagulants or oral contraceptives were also excluded. The presence of systemic HT in the patients was also noted. All patients underwent a detailed ophthalmic examination. RVO was diagnosed according to the stereoscopic fundus examination. Patients with retinal hemorrhages in 4 retina quadrants accompanied by retinal vein dilation were diagnosed as CRVO, and patients with retinal venous dilation and tortuosity accompanied by flame-shaped and intraretinal hemorrhages in wedge-shaped regions were diagnosed as BRVO.

Venous blood samples were collected from all subjects at admission to the outpatient clinic to assess hematological parameters. All complete blood count parameters and inflammation indices were recorded. The ratio of neutrophil to lymphocyte count, platelet to lymphocyte count, and monocyte to lymphocyte count, determined as NLR, MLR, and PLR, respectively, were recorded. SII was calculated as neutrophil count × platelet count/lymphocyte count, and SIRI as monocyte count × neutrophil count/lymphocyte count.

2.1. Statistical methods

Statistical analyses were conducted using SPSS software (Version 22, SPSS Inc., Chicago, IL, USA). Descriptive statistics for categorical data were presented using frequencies (n) and percentages (%). Descriptive statistics for numerical data were presented as mean ± standard deviation or median (interquartile: Q1–Q3), based on the assumption of normal distribution. The Kolmogorov–Smirnov test, Shapiro–Wilk test, Histogram, and Q–Q plots were used together to assess the assumption of normal distribution for numerical data. Levene test was utilized to test the assumption of homogeneity of variances. When the assumptions for the parametric test were met, the Student *t* test was employed to compare continuous data between 2 independent groups; when the assumptions were not met, the Mann–Whitney *U* test was used. To compare numerical data among 3 independent groups, when the parametric test assumptions were met, analysis of variance (ANOVA) was used; when not met, the Kruskal–Wallis test was employed. post hoc tests, Tukey test after ANOVA, and the Dunn–Bonferroni test after the Kruskal–Wallis test were performed to determine the groups responsible for the significant differences in the comparisons. The impact of several of the patient prognostic scores on predicting RVO was investigated using receiver operating characteristic (ROC) analysis. Univariate and multivariate binary logistic regression analyses were performed to identify the risk factors affecting the prediction of RVO. Odds ratios (ORs) were calculated for each statistically significant parameter in the univariate and multivariate models, with 95% confidence intervals. A significance level of $P < .05$ was considered statistically significant for all comparisons.

3. Results

A total of 120 patients—60 (50%) RVO patients and 60 (50%) healthy controls—were included in the study. Of the patients with RVO, 63.3% (n = 38) were BRVO, and 36.7% (n = 22) were CRVO. Precisely 51.7% (n = 62) of all patients were female and 48.3% (n = 58) were male; the average age was 61.93 ± 5.44 (50–71) years. A comparison of demographic data, hematological parameters, and inflammatory indicators between the RVO and the control groups is presented in Table 1. Gender ($P = .273$), age ($P = .160$), and the presence of systemic HT ($P = .269$) were similar between both groups. WBC ($P = .003$), neutrophil ($P < .001$), NLR ($P < .001$), MLR ($P < .001$), PLR ($P = .014$), SII ($P < .001$), and SIRI ($P < .001$) values were significantly higher; the lymphocyte count ($P < .001$) was significantly lower in patients with RVO than in controls. Other hematological parameters were not significantly different between the groups ($P > .05$).

A comparison of demographic and hematological parameters between BRVO, CRVO, and the control groups is presented in Table 2. Age ($P = .353$), gender ($P = .262$), and the presence of systemic HT ($P = .207$) were similar among all 3 groups. WBC ($P = .010$), neutrophil ($P < .001$), lymphocyte ($P < .001$), NLR ($P < .001$), MLR ($P < .001$), SII ($P < .001$), and SIRI ($P < .001$) values were significantly different between the groups. In the post hoc analysis, WBC ($P = .025$), neutrophil ($P < .001$), NLR ($P < .001$), MLR ($P = .007$), SII ($P = .001$), and SIRI ($P < .001$) values were significantly higher; the lymphocyte ($P = .026$) count was significantly lower in patients with CRVO than in the control group. Similar to the CRVO group, neutrophil ($P = .001$), NLR ($P < .001$), MLR ($P < .001$), SII ($P = .001$), and SIRI ($P < .001$) values were significantly higher; the lymphocyte ($P = .002$) count was significantly lower in patient with BRVO than in controls. There were no significant differences in other hematological parameters between the BRVO and CRVO groups ($P > .05$). Although the PLR values were found to be significantly different between the groups according to the ANOVA test ($P = .044$), PLR values were not found to be significantly different in pairwise comparisons with the post hoc test ($P > .05$).

Sensitivity, selectivity, positive–negative predictive values, and likelihood ratio (+) values calculated using the ROC analysis findings and cutoff values determined by ROC analysis are presented in Table 3. In RVO prediction, NLR was significant at a good level, SIRI, SII, and MLR were significant at the fair level,

Table 1

Demographic characteristics and hematologic parameters for patients with RVO and a control group

	Control (n = 60)	RVO (n = 60)	*P* values
Gender (M/F)	26 (43.3%)/34 (56.7%)	32 (53.3%)/28 (46.7%)	.273*
Hypertension (yes/no)	31 (51.7%)/29 (48.3%)	37 (61.7%)/23 (38.3%)	.269*
Age (yr)	61.23 ± 4.77	62.63 ± 5.99	.160†
WBC	7.03 ± 1.54	8 ± 1.96	**.003**†
RBC	4.75 ± 0.44	4.79 ± 0.49	.649†
HB	13.6 ± 1.34	13.52 ± 2.01	.798†
HCT	41.09 ± 3.43	40.48 ± 5.51	.471†
MCV	86.75 (82.82–89.7)	86.25 (83–88.9)	.289‡
MCHC	33.07 ± 1.18	33.39 ± 1.66	.240†
MCH	28.66 ± 2.1	28.35 ± 3.03	.515†
RDW	13.7 (12.72–14.6)	13.4 (12.75–14.17)	.534‡
PLT	272.4 ± 66.74	259.2 ± 65.12	.277†
MPV	10.4 ± 0.89	10.19 ± 0.89	.204†
PCT	0.28 (0.24–0.31)	0.26 (0.22–0.31)	.167‡
PDW	12.32 ± 2.07	12.1 ± 2.15	.573†
NEU	3.94 ± 1.09	5.14 ± 1.59	**<.001**†
LYP	2.33 ± 0.55	1.95 ± 0.52	**<.001**†
MON	0.54 ± 0.16	0.59 ± 0.18	.141†
NLR	1.72 (1.34–2.08)	2.54 (1.92–3.26)	**<.001**‡
MLR	0.23 (0.19–0.26)	0.30 (0.24–0.38)	**<.001**‡
PLR	118.4 (94.27–137.5)	138.5 (106.2–165.3)	**.014**‡
SII	460.6 (337.8–602.9)	674.7 (489.7–872)	**<.001**‡
SIRI	0.826(0.662–1.223)	1.441 (1.01–2.044)	**<.001**‡

Values below $P < .05$ were shown bold.

HB = hemoglobin, HCT = hematocrit, LYP = lymphocyte, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MLR = monocyte-to-lymphocyte ratio, MON = monocyte, MPV = mean platelet volume, NEU = neutrophil, NLR = neutrophil-to-lymphocyte ratio, PCT = plateletcrit, PDW = platelet volume distribution width, PLR = platelet-to-lymphocyte ratio, PLT = platelets, RBC = red cell count, RDW = red cell distribution width, RVO = retinal vein occlusion, SII = systemic immune-inflammatory index, SIRI = systemic inflammation response index, WBC = white blood cell.

*Chi square test with n (%).

†Student's *t* test with mean ± standard deviation (SD).

‡Mann–Whitney *U* test with median (Q1–Q3).

and PLR was significant at the weak level. The optimal cutoff value of SIRI to predict RVO was ≥ 0.86, with an area under the curve (AUC) value of 0.774, with a 95% confidence interval (0.692–0.856), sensitivity 85%, and specificity 56.7%. The optimal cutoff value of SII to predict RVO was ≥ 655.2, with an AUC value of 0.733, with a 95% confidence interval (0.645–0.822), sensitivity of 56.7%, and specificity of 83.3%. The optimal cutoff value of NLR to predict RVO was ≥ 2.19, with an AUC value of 0.817, 95% confidence interval (0.743–0.891), sensitivity of 68.3%, and specificity of 81.7%. The optimal cutoff value of MLR to predict RVO was ≥ 0.265, with an AUC value of 0.724, 95% confidence interval (0.633–0.815), sensitivity of 63.3%, and specificity of 76.7%. The optimal cutoff value of PLR to predict RVO was ≥ 136.17, with an AUC value of 0.630, 95% confidence interval (0.529–0.731), sensitivity of 51.7%, and specificity of 75%. The ROC curve graph for NLR, MLR, PLR, SII, and SIRI is presented in Figure 1. The box plot showing the distributions and optimal cutoff points for NLR, MLR, and PLR is presented in Figure 2, and for SII and SIRI, these can be found in Figure 3.

The results of the univariate and multivariate binary logistic regression analysis are presented in Table 4. WBC, found to be significant as a result of basic statistical analyses, and PLR, NLR, MLR, SII, and SIRI categorical variables, created as a result of ROC analysis, were also significant in the univariate model ($P = .005$, $P = .003$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, respectively; Table 4). Neutrophils and lymphocytes, found to be significant in basic statistical analysis, were not included in the multivariate model because they were highly correlated with the NLR parameter. In addition, the PLR and NLR parameters were not included in the multivariate model because they were highly correlated with the SII index, and the MLR parameter was highly correlated with the SIRI index. In the multivariate model created with the WBC, MLR, and SII indexes, the effect of WBC was insignificant ($P = .794$). According to the multivariate model results, the effect of SIRI and SII indexes on RVO was significant ($P = .005$, $P = .002$, respectively). In the multivariate model, the OR (95% CI) was calculated as 3.7 (1.47–9.36) for SII and 4.45 (1.74–11.4) for SIRI (Table 4). The risk of developing RVO was 3.7 times higher in patients with SII values >655.2 and 4.45 times higher in patients with SIRI values >0.86.

4. Discussion

In the current study, the leukocyte and neutrophil counts were significantly higher, the lymphocyte count was significantly lower, and the monocyte count was similar in patients with RVO compared to controls. Many studies have found high neutrophil and low lymphocyte counts in patients with RVO. Neutrophils constitute 50% to 70% of all leukocytes. They are essential in acute damage and repair, cancer, autoimmunity, and chronic inflammatory processes and are the first cells recruited to an inflammatory site. Neutrophils can initiate atherosclerosis, accelerating and promoting atherosclerotic plaque instability.[16] High neutrophil and WBC counts promote vascular inflammation and significantly affect future cardiovascular events.[7,17] Neutrophils enhance their antimicrobial properties by releasing neutrophil extracellular traps (NETs), composed of extracellular chromatin decorated with histones and granular proteins. Responsive neutrophils generate NETs. They promote thrombus formation by acting as a scaffold for platelets and coagulation activation and are related to incidences of DM, HT, and cardiovascular events.[18] Wan et al[19] recently reported that plasma NET remnants, including cfDNA, MPO-DNA, and H3Cit, increased in RVO patients. The authors suggested that NET remnants may be related to inflammation and thrombus formation in RVO. Lymphocytes, unlike neutrophils, are immune cells that regulate the inflammatory response. They play a crucial

Table 2

Demographic characteristics and hematologic parameters of patients with BRVO, CRVO, and a control group.

	Control (n = 60)	BRVO (n = 38)	CRVO (n = 22)	*P* values	Post hoc *P* values
Gender (M/F)	26 (43.3%)/34 (56.7%)	18 (47.4%)/20 (52.6%)	14 (63.6%)/8 (36.4%)	.262*	–
Hypertension (Yes/No)	31 (51.7%)/29 (48.3%)	26 (68.4%)/12 (31.6%)	11 (50%)/11 (50%)	.207*	–
Age (yr)	61.23 ± 4.77	62.82 ± 5.77	62.32 ± 6.48	.353†	–
WBC	7.03 ± 1.54	7.89 ± 2.01	8.2 ± 1.91	**.010**‡	1–2:.053 **1–3:.025** 2–3:.796
PLT	272.4 ± 66.74	251.9 ± 61.89	271.9 ± 70	.294†	–
NEU	3.94 ± 1.09	5.01 ± 1.6	5.35 ± 1.58	**<.001**‡	**1–2:.001** **1–3:<.001** 2–3:.637
LYP	2.33 ± 0.55	1.93 ± 0.57	1.97 ± 0.44	**<.001**‡	**1–2:.002** **1–3:.026** 2–3:.956
MON	0.54 ± 0.16	0.57 ± 0.17	0.62 ± 0.2	.197†	–
NLR	1.72 (1.34–2.08)	2.56 (1.83–3.26)	2.47 (2.05–3.4)	**<.001**‡	**1–2:<.001** **1–3:<.001** 2–3:1.000
MLR	0.23 (0.19–0.26)	0.29 (0.24–0.39)	0.3 (0.21–0.35)	**<.001**‡	**1–2:<.001** **1–3:.007** 2–3:1.000
PLR	118.4 (94.27–137.5)	136.1 (98–164.8)	140.7 (108.4–166.9)	**.044**‡	1–2:.157 1–3:.102 2–3:1.000
SII	460.6 (337.8–602.9)	638.8 (450.1–844.4)	728.5 (517.4–1034)	**<.001**‡	**1–2:.001** **1–3:<.001** 2–3:1.000
SIRI	0.826 (0.662–1.223)	1.441 (1.043–1.808)	1.454 (0.984–2.324)	**<.001**‡	**1–2:<.001** **1–3:<.001** 2–3:1.000

Values below $P < .05$ were shown bold.

BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, F = female, LYP = lymphocyte, M = male, MLR = monocyte-to-lymphocyte ratio, MON = monocyte, NEU = neutrophil, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, PLT = platelets, SII = systemic immune-inflammatory index, SIRI = systemic inflammation response index, WBC = white blood cell.

*Chi square test with n (%).

†One way ANOVA with mean± SD. Kruskal-Wallis test with median (Q1–Q3).

‡One way ANOVA with Tukey post-hoc test (mean ± SD). Kruskal-Wallis test with Dunn-Bonferroni post-hoc test (median (Q1–Q3).

Table 3

The findings of the ROC analysis with sensitivity, specificity, positive-negative predictive and positive likelihood ratio values demonstrating the success of the indicators in predicting retinal vein occlusion (RVO).

	NLR	MLR	PLR	SII	SIRI
AUC (95% CI)	0.817 (0.743–0.891)	0.724 (0.633–0.815)	0.630 (0.529–0.731)	0.733 (0.645–0.822)	0.774 (0.692–0.856)
P values	<.001	<.001	.014	<.001	<.001
Cut off	≥2.19	≥0.265	≥136.17	≥655.2	≥0.86
Sensitivity (95% CI)	68.3% (54.9–79.4)	63.3% (49.8–75.1)	51.7% (38.5–64.6)	56.7% (43.3–69.2)	85% (72.9–92.5)
Specificity (95% CI)	81.7% (69.1–90.1)	76.7% (63.7–86.2)	75% (61.9–84.9)	83.3% (71.0–91.3)	56.7% (43.3–69.2)
PPV (95% CI)	78.8% (64.9–88.5)	73.1% (58.7–84)	67.4% (51.9–80)	77.3% (61.8–88)	66.2% (54.5–76.4)
NPV (95% CI)	72.1% (59.7–81.9)	67.6% (55.1–78.2)	60.8% (48.7–71.7)	65.8% (53.9–76)	79.1% (63.5–89.4)
LR + (95% CI)	3.73 (2.13–6.53)	2.71 (1.65–4.46)	2.07 (1.25–3.41)	3.4 (1.85–6.24)	1.96 (1.44–2.67)

AUC = area under the curve, CI = confidence interval, MLR = monocyte-to-lymphocyte ratio, NLR = neutrophil-to-lymphocyte ratio, NPV = negative predictive value, PLR = platelet-to-lymphocyte ratio, PPV = positive predictive value, ROC = receiver operating characteristic, SII = systemic immune-inflammatory index, SIRI = systemic inflammation response index.

role in inhibiting cell proliferation and migration. Low levels of lymphocytes are independently and significantly associated with cardiovascular disease.[20]

NLR, MLR, and PLR consist of the combination of 2 different inflammatory cells. In comparison, SII and SIRI are inflammatory complex biomarkers that combine 3 different inflammatory cells and are less affected by physiological conditions. Thus, these combinations may provide more information about inflammatory status in the pathogenesis of RVO than other cell counts alone. In the current study, all inflammatory indicators, including NLR, MLR, PLR, SII, and SIRI, were significantly higher in patients with RVO than in controls.

NLR has been proposed as a prognostic indicator in systemic inflammatory response and atherosclerosis.[21] NLR, one of the most studied inflammatory markers due to the close relationship between RVO and atherosclerosis, is high in patients with RVO in many studies, suggesting that it could be used as a predictive marker in identifying the risk of RVO.[8–10] Kazantzis et al[9] reported that NLR was superior to other inflammatory indicators in predicting the inflammatory status of RVO. In the current study, NLR has the highest AUC (0.817) according to ROC analysis. Therefore, NLR is assumed to be the best inflammatory indicator in predicting RVO development compared to other indicators. Furthermore, NLR is the second-highest

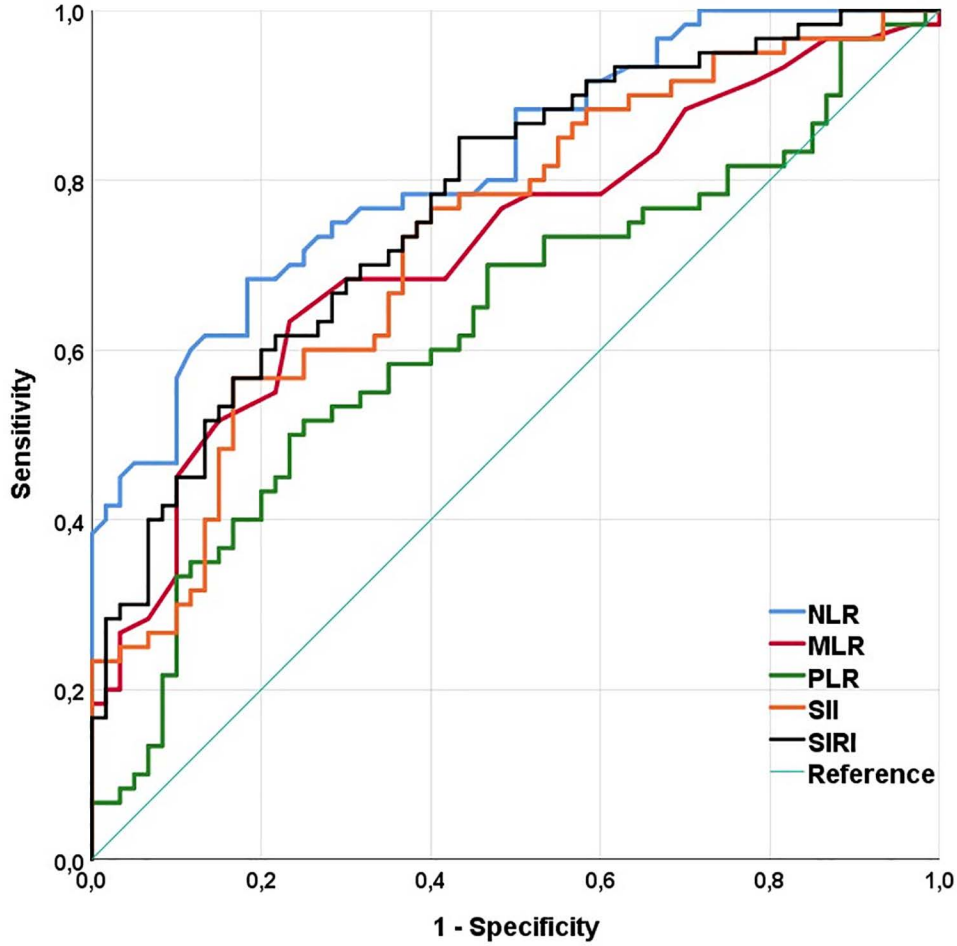

Figure1. ROCcurvesforneutrophil-to-lymphocyteratio(NLR),monocyte-to-lymphocyteratio(MLR),platelet-to-lymphocyteratio(PLR),Systemicimmune-inflammatory index (SII), and Systemic inflammation response index (SIRI) values to predict retinal vein occlusion (RVO). ROC = receiver operating characteristic.

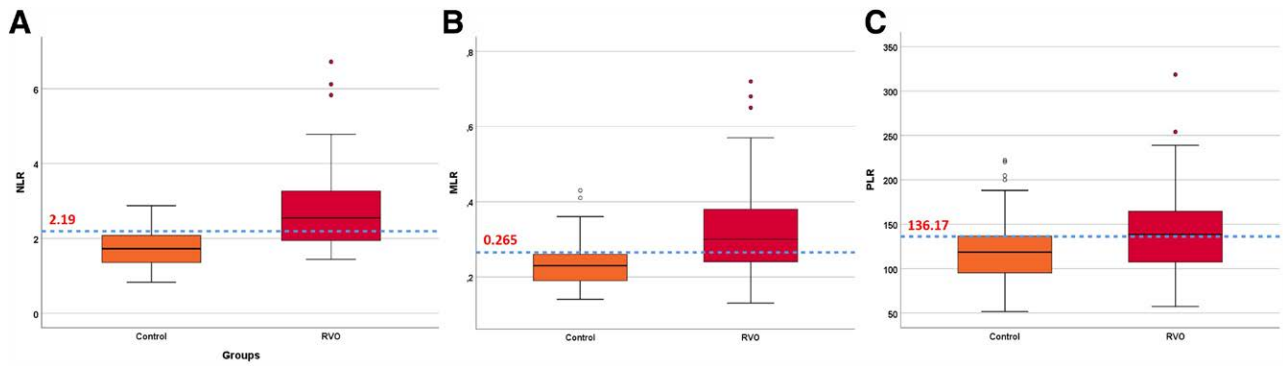

Figure 2. Box-plot showing the distribution of neutrophil-to-lymphocyte ratio (NLR) (A), monocyte-to-lymphocyte ratio (MLR) (B), platelet-to-lymphocyte ratio (PLR) (C) values among research groups.

sensitivity indicator after SIRI. The fact that neutrophils constitute the majority (50%–70%) of all circulating leukocytes in the peripheral blood and are at the center of inflammation as the first immune cell to quickly reach the inflammatory region in tissue damage may explain the superiority of NLR over other indicators in predicting the development of RVO.

During inflammation, blood monocytes migrate from peripheral blood to tissues. They phagocytose other cells and toxic molecules, produce inflammatory cytokines, and can differentiate into inflammatory dendritic cells, macrophages, or foam cells. Elevated monocyte count levels are positively associated with cardiovascular events and atherosclerosis.[11] MLR correlates more with the severity of coronary lesions and cardiovascular events than NLR and is a stronger predictor of cardiovascular mortality.[13] Elevated levels of MLR are found to be an independent predictor of treatment response in naive macular edema secondary to RVO treated with intravitreal anti-VEGF agents and associated with favorable treatment response.[22] In the current study, in predicting RVO, MLR was significant at the fair level (AUC = 0.724).

SII and SIRI are novel inflammatory indicators that use a combination of 3 peripheral blood inflammatory cells. Both

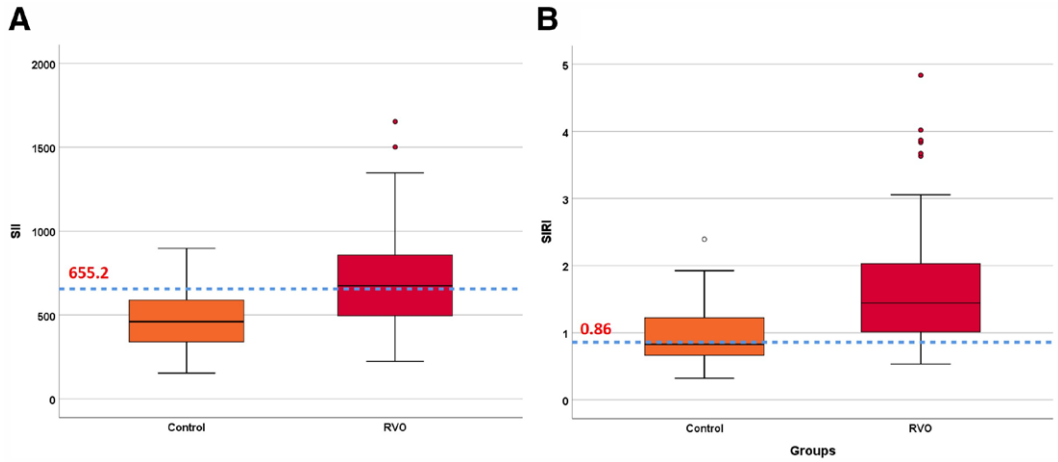

Figure 3. Box-plot showing the distribution of systemic immune-inflammatory index (SII) (A) and systemic inflammation response index (SIRI) (B) values among research groups.

Table 4

The results of univariate and multivariate binary logistic regression analysis conducted to determine the risk factors that are effective in the prediction of retinal vein occlusion (RVO).

	Univariate		Multivariate
	***P* values**	**OR (CI 95%)**	***P* values**
WBC	**.005**	1.38 (1.1–1.72)	Ns
PLR (≥136.17 & < 136.17)	**.003**	3.21 (1.48–6.95)	Ni
NLR (≥2.19 & < 2.19)	**<.001**	9.61 (4.11–22.5)	Ni
MLR (≥0.265 & < 0.265)	**<.001**	5.67 (2.56–12.58)	Ni
SII (≥655.2 & <655.2)	**<.001**	6.54 (2.8–15.3)	**.005**
SIRI (≥0.86 & < 0.86)	**<.001**	7.41 (3.1–17.7)	**.002**
Multivariate model: Nagelkerke R square = 0.311, classification accuracy: 70.8%			

Values below $P < .05$ were shown bold.

CI = confidence interval, MLR = monocyte-to-lymphocyte ratio, ni = not included, NLR = neutrophil-to-lymphocyte ratio, ns = not significant (P>0.05), OR = odds ratio, PLR = platelet-to-lymphocyte ratio, SII = systemic immune-inflammatory index, SIRI = systemic inflammation response index, WBC = white blood cell.

SIRI and SII have a common NLR component. Elevated SII is an independent risk factor for cerebrovascular events and associated with coronary artery disease severity.[14,23] A significant relationship between a higher SII and RVO was reported.[9] In another study, elevated SII was found to be correlated with high levels of IL-6 and VEGF in patients with RVO.[8] Zuo et al[10] found that the AUC of SII (0.666) was highest in patients with RVO. In their study, the optimal cut-off value of SII to predict RVO was > 326.46, with a sensitivity of 66.1% and specificity of 58.9%. In the current study, SII was significant at a fair level (AUC 0.733) in predicting RVO and has the highest specificity among the other inflammatory indicators.

SIRI is a more comprehensive marker for chronic low-grade inflammation based on monocyte, neutrophil, and lymphocyte counts. High SIRI levels have been identified as a prognostic and predictive factor for acute coronary syndrome, cerebrovascular events, and autoimmune inflammatory disease.[15,24,25] A study conducted in young patients with RVO reported that SIRI and other indicators, including NLR and SII, were significantly higher than controls, especially with ischemic RVO. SIRI showed no statistical difference between patients with BRVO and CRVO. The authors reported that the optimal cut-off value of SIRI to predict RVO was > 0.72, with an AUC value of 0.634, 95% confidence interval (0.536–0.732), sensitivity 56.25%, and specificity 73.44%.[13] In the current study, SIRI was significant at a fair level (AUC 0.774) in predicting RVO and has the highest sensitivity and lowest specificity among inflammatory indicators. According to the ROC analysis, SIRI is superior to SII, PLR, and MLR but not NLR in predicting RVO development. In the multivariate model, the OR (95% CI) was calculated as 3.7 (1.47–9.36) for SII and 4.45 (1.74–11.4) for SIRI. The probability of developing RVO was 3.7 times higher in patients with SII > 655.2 and 4.45 times higher in patients with SIRI > 0.86.

PLR may reflect both coagulation and inflammatory pathways. Some authors have reported a significant association between higher PLR and RVO, suggesting that it could be used as a prediction biomarker for identifying the risk of RVO.[12,26] Higher pretreatment PLR levels are a significant prognostic factor in patients with macular edema secondary to RVO following anti-VEGF treatment and significantly associated with an effective visual outcome.[27,28] In the current study, PLR has the lowest AUC value (0.630) in predicting RVO according to ROC curve analysis and showed the lowest sensitivity among inflammatory indicators.

Platelets are a source of inflammatory mediators that play an important role in the complex process of hemostasis and pathogenesis of thrombo-occlusive disease. The standard hemogram test has several platelet parameters, such as platelet count, mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit, and reticulated platelets. MPV indicates the average size of platelets. Larger platelets have higher metabolic and enzymatic activity and release more thromboxane-A2, thromboglobulin, and adhesion molecules. MPV is associated with higher platelet aggregation.[29] PDW is an indicator of changes in platelet size and a specific platelet activation indicator as MPV.[30] Plateletcrit indicates the quantitative abnormalities of platelets, and reticulated platelets are young forms of platelets. A previous meta-analysis reports that while MPV and PDW were significantly higher in patients with RVO, there is no significant relationship between platelet count and plateletcrit and RVO.[31] A recent study showed that although platelet count, MPV, PDW, plateletcrit, reticulated platelets, and platelet-lymphocyte ratio were similar to the control group in patients with RVO, the level of soluble P-selectin and concentration of platelet-derived procoagulant microvesicles was higher in patients with RVO in both BRVO and CRVO.[32] P-selectin is one of the best markers of platelet activation. Microvesicles are derived from membrane blebs of activated platelets and have

pro-coagulant, anti-coagulant, pro-inflammatory, and angiogenic properties. Platelet-derived microvesicles promote vascular inflammation, atherosclerosis plaque progression, and thrombus formation.[33] These findings indicate that platelets can contribute to the development of RVO by enhancing procoagulant activity even when the platelet parameters, such as platelet count and MPV, are within normal range. Red cell distribution width (RDW) shows the differences in the volume and size of erythrocytes. Pinna et al[34] reported that RDW levels were higher in RVO patients, but while RDW values were similar in CRVO patients, RDW was significantly higher in BRVO patients only. Ozkok et al[35] reported that high RDW levels in RVO patients were associated with lower initial and final vision. In the current study, the red cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, RDW, platelet count, MPV, plateletcrit, and PDW are not significantly different in the patients with RVO and the control group.

CRVO occurs due to the pressure of the atherosclerotic central retinal artery on the vein at the level of lamina cribrosa or further behind. BRVO occurs in the retina as a result of the compression of the overlying atherosclerotic arteriole on the venule within a common adventitial sheath. Although CRVO and BRVO have similar risk factors and pathophysiological mechanisms, they have different natural histories and prognoses. The current study showed that similar significant differences in neutrophil, lymphocyte, NLR, MLR, SII, and SIRI levels were also found when RVO was categorized as BRVO and CRVO; however, the WBC count was significantly higher only in patients with CRVO. Although PLR values were significantly different in the ANOVA ($P = .044$), no significant difference was found in pairwise comparisons, according to the post hoc test results. These results may indicate that inflammation plays a common and important role in the pathophysiology of both BRVO and CRVO.

The current study has some limitations. It has a retrospective design, and body mass index, C-reactive protein levels, serum lipid profile, and inflammation markers, such as cytokines, were not evaluated. Additionally, ischemic/non-ischemic subgroup analysis was not performed in patients with CRVO.

In conclusion, the current study revealed that SIRI and other inflammatory indicators, including NLR, SII, MLR, and PLR, are significantly elevated in elderly patients with RVO, even in BRVO versus CRVO. These results support the fact that inflammation plays a significant role in the pathogenesis of RVO. In RVO prediction, NLR was significant at the good level, SIRI, SII, and MLR were significant at the fair level, and PLR was significant at the weak level. SIRI was superior compared to other indicators, except NLR, in predicting RVO. The risk of developing RVO was 3.7 times higher in patients with SII values >655.2 and 4.45 times higher in patients with SIRI values >0.86. The SIRI, NLR, SII, MLR, and PLR can be used as predictors for identifying the risk of RVO.

Author Contributions

Conceptualization: Mehmet Barış Üçer, Selim Cevher.
Data curation: Mehmet Barış Üçer, Selim Cevher.
Formal analysis: Mehmet Barış Üçer.
Investigation: Mehmet Barış Üçer, Selim Cevher.
Methodology: Mehmet Barış Üçer.
Project administration: Mehmet Barış Üçer.
Supervision: Mehmet Barış Üçer, Selim Cevher.
Validation: Mehmet Barış Üçer.
Visualization: Mehmet Barış Üçer.
Writing – original draft: Mehmet Barış Üçer, Selim Cevher.
Writing – review & editing: Mehmet Barış Üçer, Selim Cevher.

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