

Evaluation of Plasma Inflammatory Markers in Patients with Nonarteritic Retinal Artery Occlusion

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ABSTRACT

Purpose: To examine the clinical characteristics, comorbid status and laboratory parameters of patients followed up with a diagnosis of retinal artery occlusion (RAO) and to compare blood inflammation parameters with control subjects.

Methods: The medical records of 49 patients who were followed up for RAO at Dicle University Medical Faculty between 2017 and 2020 were retrospectively analysed. The occlusion type was divided into two groups, central retinal artery occlusion (CRAO) and branch retinal artery occlusion (BRAO). The demographic characteristics and clinical and laboratory tests of the groups were compared. The blood WBC, neutrophil, lymphocyte, monocyte and platelet counts of the patients were also recorded, and the neutrophil/lymphocyte, monocyte/lymphocyte and platelet/lymphocyte counts were calculated by simple division and compared with 41 age- and gender-matched controls.

Results: There was no difference in age and gender between the CRAO and BRAO groups ($p = 0.220$ and $p = 0.303$ respectively). Heart disease was significantly more common in CRAO patients ($p = 0.004$), and hypertension was observed more often, although not significantly ($p = 0.084$). WBC, neutrophil and monocyte values were found to be significantly higher in those with RAO than in the controls ($p = 0.005$, $p < 0.001$, $p = 0.035$ respectively). The neutrophil-lymphocyte ratio (NLR) was found to be significantly higher in those with RAO ($p = 0.007$).

Conclusion: RAO is associated with significant elevation in WBC and NLR. The association of CRAO with cardiovascular disease is prominent.

Key words: retinal artery occlusion, blood inflammation marker, neutrophil-lymphocyte ratio.

INTRODUCTION

The central retinal artery, originating from the ophthalmic artery, supplies blood to the surface layer of all quadrants of the retina and to the optic disc. The outer retina is supplied by the choriocapillaris, which branches from the posterior ciliary artery¹. One important variation to this is the presence of a cilioretinal artery, which supplies the papillomacular bundle². Retinal artery occlusion is classified as either arteritic, due to giant cell arteritis, or nonarteritic. Nonarteritic retinal artery occlusion appears more frequently as central retinal artery occlusion (57%) and branch retinal artery occlusion (38%) and less frequently as cilioretinal artery occlusion (5%)³.

Occlusion may occur at the level of the ophthalmic artery, the central retinal artery, a branch retinal artery, or the cilioretinal artery³. While central retinal artery occlusion presents with painless and sudden-onset vision loss,

branch occlusion presents with sudden visual field loss⁴. Embolism is the most common cause of retinal artery occlusion, with the main source being atherosclerotic plaques, usually due to carotid artery disease. Cardiac embolism is another important cause, while an obstructive thrombus at the level just behind the lamina cribrosa is equally likely to cause retinal artery occlusion^{6,7}.

The development of atherosclerosis occurs through inflammation and oxidative stress, and lymphocytopenia is thought to play a role. Neutrophils also may accelerate the development of atherosclerosis^{8,9}, and the neutrophil-lymphocyte ratio (NLR), a marker of inflammation, has been associated with arterial stiffness and carotid intima-media wall thickness¹⁰. Several studies have also found a higher monocyte-to-lymphocyte ratio (MLR) and higher platelet-to-lymphocyte ratio (PLR) associated with clinical outcomes of systemic and ocular vascular disease^{11,12}. For

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these reasons, blood inflammation markers have clinical significance and can be used as simple, fast and easily accessible tests in retinal artery occlusion. The aim of the present study was to evaluate the clinical features, comorbid status, laboratory parameters and occlusion type in retinal artery occlusion patients followed up in our hospital and to compare their values for inflammation markers like the NLR, MLR and PLR with those of control subjects.

MATERIALS AND METHODS

In this retrospective study, 49 patients who were followed up with a diagnosis of retinal artery occlusion at Dicle University Faculty of Medicine between 2017 and 2020 were analysed. The tenets of the Declaration of Helsinki were adhered to. Ethics committee of Dicle University School of Medicine approved this study (Decision no: 122, date: 04.02.2021).

All patients' medical records were analysed in detail; age, gender, the application complaints and duration, all systemic diseases, such as diabetes mellitus (DM), hypertension (HT), heart disease and previous eye disease, the treatments the patients received and the drugs used were recorded. Hemogram, blood triglycerides, total cholesterol, LDL, HDL cholesterol, prothrombin, thrombin, protein C, protein S and methylenetetrahydrofolate reductase (MTHFR) enzyme analysis data were recorded from the hospital records. Carotid artery doppler ultrasound and echocardiography results were also recorded. The best corrected visual acuity of the patients at admission with Snellen, intraocular pressure with applanation tonometer, anterior segment evaluation with biomicroscopy and fundus examination were noted. The diagnosis of all patients was confirmed by fundus fluorescein angiography (FFA). In the study, in order to compare blood inflammation parameters with control subjects, hemogram and lipid profile records of 41 age- and sex-matched individuals who applied to the ophthalmology department for routine control were taken.

The neutrophil, lymphocyte, monocyte and platelet counts of the patients were recorded, and the NLR, the MLR and the PLR were calculated by simple division.

The retinal artery occlusion was divided into nonarteritic central retinal artery occlusion and branch retinal artery occlusion. Central retinal artery occlusion was defined by sudden vision loss and by central artery occlusion finding or by central artery occlusion in which the cilioretinal artery was sparing in FFA. Branch retinal artery occlusion was defined as a sudden loss in visual field, with branch retinal artery occlusion finding in FFA.

Statistical Analysis

The Windows statistical package programme (IBM SPSS; v21.0; Inc., Chicago, IL) was used for the statistical evaluation of our research data. The Fisher Exact test (for low sample size) and the Chi-square test were used to determine differences between proportions or relationships between categorical variables. Behavioural differences of group averages, in cases where normality and uniformity assumptions were met, were tested by analysis of variance (ANOVA). Parameters that were not normally distributed were assessed using nonparametric methods, such as the Kruskal-Wallis H Test (groups > 2) and the Mann-Whitney U Test (groups = 2). We evaluated the receiver operating characteristics (ROC) curve to specify the sensitivity and specificity of the NLR and white blood cell count (WBC) values with the optimal cut-off value for retinal artery occlusion. Differences were considered significant at $p < .05$.

RESULTS

When retinal artery occlusion was analysed in the two subgroups central retinal artery occlusion and branch retinal artery occlusion, no difference was observed in terms of age and gender ($p = .220$ and $p = .303$ respectively) (Table 1). Visual acuity was measured between light perception and 0.15 (max visual acuity with Snellen) in central retinal artery occlusion, while it was measured between counting fingers from 2 metres and 0.7 (with Snellen) in branch retinal artery occlusion. When the comorbid conditions of the patients were examined, it was found that heart disease was significantly more common in central retinal artery occlusion patients, and hypertension was observed more, although not significantly ($p = .004$ and $p = .084$).

Table 1: Age, gender and visual acuity of central retinal artery occlusion and branch retinal artery occlusion patients

	CRAO, N=28	BRAO, N=21	P value
Age (years) (mean \pm SD)	64.16 \pm 12.07	57.94 \pm 19.31	*0.220
Gender (female/male)	17/11	14/7	**0.303
Initial visual acuity	Light perception-0.15	2 meters finger counts -0.7	
*Anova t test was used, **Chi squared test, CRAO: central retinal artery occlusion, BRAO: branch retinal artery occlusion			

respectively). In terms of ocular disease association, two patients in the central retinal artery occlusion group had glaucoma; no additional ocular disease was found in the branch retinal artery occlusion group (p = .370). All accompanying diseases are given in Table 2.

In the control group 7 patients had DM, 11 had HT, 5 had heart diseases. The distribution of DM, HT and heart disease was similar in the retinal artery occlusion and control groups (p = .469, p = .165 and p = .226, respectively).

When blood inflammation parameters were compared

between retinal artery occlusion and the controls, WBC, neutrophil and monocyte values were found to be significantly higher in those with retinal artery occlusion (p = .005, p < .001, p = .035 respectively) (Table 3). NLR was found to be significantly higher in those with retinal artery occlusion (p = .007). There was no difference between the two groups in terms of MLR and PLR (p = .274 and p = .987 respectively) (Table 4). In the ROC analysis, the cut-off value of NLR was found to be 2.55 for retinal artery occlusion. The ROC analysis results of WBC and NLR are given in Table 5 and Figure 1.

Table 2: Distribution of comorbid diseases accompanying central retinal artery occlusion and branch retinal artery occlusion

	CRAO N=28 n (%)	BRAO N=21 n (%)	P value
Hypertension	15 (53%)	4 (19%)	**0.084
Diabetes mellitus	6 (21%)	1 (5%)	*0.225
Heart disease	10 (35%)	0 (0%)	*0.004
Serebrovascular disease	6 (21%)	1 (5%)	*0.155
Multipl systemic disease	5 (18%)	0 (0%)	*0.142
MTHFR polymorphisms	2 (7%)	1 (5%)	*0.669
Carotid plaque	5 (18%)	3 (14%)	*0.576
Glaucoma	2 (7%)	0 (0%)	*0.370

p* Pearson Chi-Squared Test, p** Fisher Exact Test, p<0.05 was statistically significant
 CRAO: central retinal artery occlusion, BRAO: branch retinal artery occlusion

Table 3: Comparison of blood parameters of retinal artery occlusion and control subjects

	RAO (n=49) mean ± SD (min-max)	Controls (n=41) mean ± SD (min-max)	P value
WBC (10 ³ µL)	8.55 ± 1.78 (5.77 - 13.03)	7.5 ± 1.33 (4.26 - 10.8)	*0.005
Neutrophil (10 ³ µL)	5.59 ± 1.83 (2.81 - 10.72)	4.18 ± 0.92 (2.3 - 6.11)	§<0.001
Monocyte (10 ³ µL)	0.65 ± 0.22 (0.18 - 1.13)	0.56 ± 0.15 (0.28 - 0.85)	*0.035
Lymphocyte (10 ³ µL)	2.37 ± 0.92 (0.7 - 4.6)	2.45 ± 0.65 (1.38 - 4.6)	**0.657
Platelet (10 ³ µL)	253.7 ± 78.65 (8.43 - 446)	265.49 ± 51.59 (152 - 368)	§0.309

**Anova T-test, *Welch T-test, §Mann Whitney U Test, p<0.05 was statistically significant
 RAO: retinal artery occlusion, WBC: White blood cell

Table 4: Comparison of inflammation markers of retinal artery occlusion and healthy controls

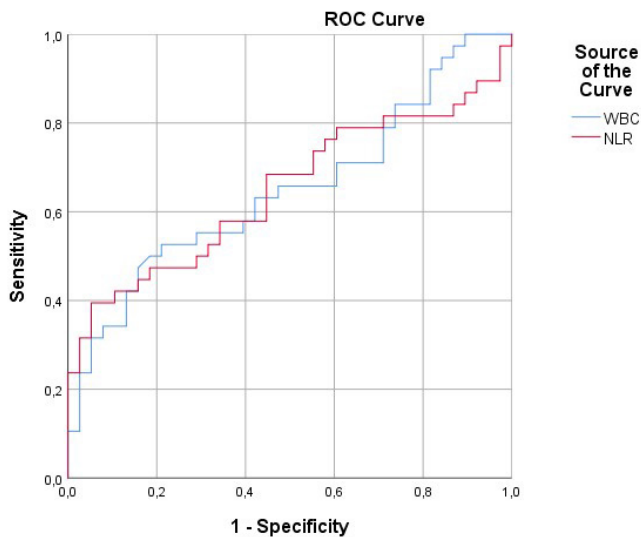
	RAO N=49 Mean ± SD	Controls N=41 Mean ± SD	*P value
Neutrophil-lymphocyte ratio	2.92 ± 2.06	1.81 ± 0.58	0.007
Monosit -lymphocyte ratio	0.31 ± 0.21	0.24 ± 0.06	0.274
Platelet-lymphocyte ratio	124.99 ± 61.98	114.92 ± 33.59	0.987

Mann Whitney U Test p<0.05 was statistically significant, RAO: retinal artery occlusion

Table 5: Receiver operating characteristics (ROC) analysis of neutrophil-lymphocyte ratio and white blood cell for prediction of retinal artery occlusion

Variable	AUC	P value	Sensitivity	Specificity	Threshold
NLR	0.665	0.025	0.95	0.40	2.55
WBC	0.649	0.026	0.81	0.50	8.27

NLR: neutrophil-lymphocyte ratio, WBC: White blood cell

**Figure 1:** Receiver operating characteristics (ROC) curve

DISCUSSION

In our study, 28 (59.1%) of the patients presenting with retinal artery occlusion had nonarteritic central retinal artery occlusion, and 21 (40.1%) had branch retinal artery occlusion. Retinal artery occlusion is associated with several systemic diseases, including heart disease and hypertension (HT), followed by diabetes (DM). Heart disease was also significantly higher in patients with central retinal artery occlusion. The NLR and WBC values, used as inflammation indicators, were significantly higher in patients with retinal artery occlusion.

Risk factors for nonarteritic retinal artery occlusion include diseases associated with an atherosclerotic condition, particularly in advanced age. These diseases include arterial HT, hyperlipidaemia, DM, carotid artery disease, coronary artery disease, and cerebral vascular events and can be exacerbated by tobacco use^{13, 14}. Patients under the age of fifty can have risk factors that include vasculitis, sickle cell anaemia, myeloproliferative disease, hypercoagulation conditions and the use of oral contraceptive pills^{15, 16, 17}. Here, we specified the risk factors of retinal artery occlusion in terms of the central retinal artery and branch occlusion.

In our study, we were able to show that nearly 18% of the patients with central retinal artery occlusion and 14% of patients with branch retinal artery occlusion had carotid plaques. Hayreh reported that the presence of plaque in the carotid artery is more prominent than the degree of stenosis in retinal artery occlusion. However, the embolism which causes most retinal artery occlusion may not be detected on examination because the embolus may have been displaced and is no longer apparent. In addition, the narrowest part of the central retinal artery, where the optic nerve sheath pierces the dura mater, can be occluded^{5, 6}.

In the absence of evident carotid stenosis or embolism, other risk factors must be investigated, including causes which may cause thrombophilia¹⁷. Some studies have reported a relationship between MTHFR C677T and A1298C polymorphisms and cerebrovascular diseases, venous thrombosis and retinal artery occlusion¹⁸. We found the MTHFR C677T heterozygote mutation in three of our cases, two of which were central retinal artery occlusion and one branch retinal artery occlusion.

In our study, approximately 21% of the patients had central retinal artery occlusion accompanied by cerebrovascular disease. The risk of development of stroke in patients with retinal artery occlusion, including nonarteritic central retinal artery occlusion and branch retinal artery occlusion, is well known^{19, 20}. One study showed significantly higher WBC, C-reactive protein (CRP), homocysteine and NLR values in patients with atherothrombotic acute ischaemic stroke compared to controls. In addition, the WBC and NLR values were significantly higher in patients who had died²¹. Similarly, in patients with acute ischaemic stroke, the prominent distinguishing value of WBC and NLR supports the equality of the two conditions, in accordance with our results.

Inflammation has been shown to play an important role in the development and progression of atherosclerosis, a major cause of carotid stenosis²². Circulating systemic immune system markers, such as CRP, interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF- α), are considered reliable indicators of atherosclerosis in carotid intima-media thickening²³. However, several biomarkers that

provide useful information about the immune system, such as IL-6 and TNF- α , cannot be easily assayed in routine clinical practice. By contrast, the stability of the NLR is less affected by physiological and pathological factors, so a high NLR may indicate the functional state of the immune system in the chronic inflammatory process²⁴. It is also a more accessible and reliable inflammation marker.

One study has reported that the NLR was a significant predictor of the degree of carotid stenosis in male patients with ischaemic stroke²⁵. NLR has been correlated with subclinical atherosclerosis and was also positively correlated with both maximal and accumulated extracranial carotid stenosis, an important cause of retinal artery occlusion.²² Platelets are known to play a role in the initiation of atherosclerotic lesions and associated disorders.²⁶ Hayreh et al. reported that the release of serotonin, a potent vasoconstrictor, by platelet aggregation on atherosclerotic plaques in the carotid artery in monkeys could cause temporary occlusion or impairment of blood flow in the central retinal artery²⁷. Şahin et al. demonstrated that mean the platelet volume values, which are indicators of platelet size and markers of platelet activity, were significantly higher in patients with retinal artery occlusion, indicating that larger platelets may be associated with the pathogenesis of retinal artery occlusions²⁸. Activated platelets have been reported to play a role in neutrophil uptake and activation. Activated neutrophils, in turn, may play a role in the development of the prothrombotic state by stimulating platelets, thereby providing the link between coagulation and inflammation pathways²⁹.

In our study, we compared the number of platelets and the PLR values between the groups, but we did not find a significant difference. However, a limitation of our study is that we did not analyse the mean platelet volume.

In previous studies, NLR showed significance for the existence of microvascular complications in subjects with type 2 diabetes³⁰. NLR was also a significant predictor for acute stroke or transient ischaemic episodes and blood pressure variability³¹. In our study, we found a cut-off value for NLR of 2.55, and this distinctive value had a 95% sensitivity and 40% specificity. The cut-off value for WBC was 8.25, and its sensitivity and specificity were 81% and 50%, respectively. Güven et al. reported a cut-off value for NLR of > 1.62 in central retinal artery occlusion patients and stated that this was a useful differential parameter.³² Our study included more patients, as well as both the central and branch occlusion of the retinal artery.

Studies are now focusing on physical exercise and some therapies to reduce cytokines (e.g. IL6), TNF- α , CRP and

neutrophilic inflammation, which all play roles in the development of atherosclerosis^{33, 34}. Physical exercise, in particular, is thought to reduce the level of inflammatory cytokines and CRP and may positively affect NLR by improving autonomic function^{26, 34, 35}. For this reason, we think that the role of inflammation in diseases should be investigated using easily measurable parameters. Similarly, this should also be considered for a condition such as retinal artery occlusion, which may result in severe vision loss and which does not yet have a salvage treatment.

One important limitation of our study is its retrospective design. Another limitation is the difficulty in determining the effect of drug use due to systemic disease on blood parameters in both groups. In addition, the blood parameters we examined are dynamic parameters, and the absence of preocclusion and follow-up values makes interpretation difficult.

In our study, we found that the NLR and WBC values may be predictive parameters that could distinguish patients with retinal artery occlusion from healthy controls. Overall, our findings support the view that controlling cardiac disease and hypertension, among prominent risk factors, will decrease the risk of occlusion of the central retinal artery.

Ethics approval : Ethics committee of Dicle University School of Medicine approved this study which adhered to the tenets of the Declaration of Helsinki (2021/122).

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

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