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"Neutrophil: Lymphocyte Ratio And Platelet: Lymphocyte Ratio In Retinal Vein Occlusion – A Comparative Observational Study"

Kiu Mondal, Somen Misra
(Senior Resident, Department Of Ophthalmology, AIIMS Raipur, India)
(Professor, Department Of Ophthalmology, AIIMS Raipur, India)

Abstract:
Context*: Retinal vein occlusion (RVO) is the second most common retinal vascular disease following diabetic retinopathy. Neutrophil: Lymphocyte ratio (NLR) and Platelet: Lymphocyte ratio (PLR) as inflammatory markers, recently become popular because of their simplicity, cost effectivity, and advantage in predicting clinical outcomes.*
Aims: *To find possible association of NLR and PLR values in patients diagnosed with RVO as compared to age and sex-matched controls.*
Settings and Design*: Hospital-based Cross-sectional Comparative Observational study*
Methods and Material: *This study included 38 patients with retinal vein occlusion (RVO group) and 38 age and sex-matched subjects (control group). A diagnosis of retinal vein occlusion was clinically made using a fundus examination. For haematological analysis, a blood sample was collected from the antecubital vein of all participants. NLR and PLR values were compared between groups.*
Results: *The mean NLR values were 2.18 ± 1.31 in the RVO group and 1.83 ± 0.79 in the control group. The mean PLR was 112.25 ± 70.03 and 101.52 ± 43.53 in RVO and control groups respectively. The difference between the two groups regarding NLR and PLR was not statistically significant. From the ROC curve, it seems that NLR and PLR are not good indicators ($p>0.05$) to predict RVO.*
Conclusions: *NLR and PLR may not be effective standalone markers for predicting RVO, emphasizing the multifactorial nature of RVO pathogenesis.*
Key-Words*: Neutrophil: Lymphocyte ratio (NLR), Platelet: Lymphocyte ratio (PLR), Retinal vein occlusion (RVO)*

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I. Introduction:

Retinal vein occlusion (RVO) is the second most common retinal vascular disease following diabetic retinopathy[1]. If RVO is not treated, it may lead to loss of vision due to macular oedema and retinal ischemia. The global impact of retinal vein occlusion is significant, with an estimated 16.4 million people affected worldwide[2]. RVO can be subdivided into branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). BRVO occurs due to distal venous obstruction resulting in localized haemorrhage, while CRVO occurs with obstruction at the lamina cribrosa leading to extensive retinal involvement. There are many risk factors like hypertension, diabetes mellitus, hyperlipidaemia, cigarette smoking, cardiovascular diseases, and renal diseases. Pathogenesis of RVO is multifactorial and is believed to follow the principle of Virchow's triad: venous stasis, injury of vessel wall and hypercoagulability[3]. Inflammation may also play an important role in RVO development by increasing hypercoagulability. Inflammatory processes play a critical role in the development of macular oedema related to retinal vascular disorders[4]. Neutrophils play a role in the inflammatory process and cytokines released by neutrophils affect various biochemical mechanisms that may lead to tissue damage[5]. Low levels of lymphocytes have been associated with physiologic stress[6]. The Neutrophil: Lymphocyte ratio (NLR) indicates the balance of the neutrophils (the active component of inflammation) with the lymphocytes (the regulatory and protective component)[7]. Platelets play a crucial role in the pathogenesis of thrombo-occlusive diseases[8]. Platelet hyperaggregability might be an important factor in the RVO development process. The Platelet: Lymphocyte ratio (PLR) indicates the balance of the platelets with the lymphocytes. NLR and PLR calculated from hemogram are emerging haematological inflammatory biomarkers[9] indicative of systemic inflammation. Their association with diseases like some cancers, diabetes, cardiovascular diseases and atherosclerosis has been well documented in literature[10].NLR and PLR as inflammatory markers, recently became popular because of their simplicity, cost effectivity, and advantage in

predicting clinical outcome[11]. Currently, there are few studies in the literature that have documented the association of NLR and PLR with RVO. In this study, we have aimed to measure NLR and PLR in RVOs and determine whether these ratios could be used as a predictive marker for RVO.

II. Material And Methods:

Over 18 months, a comparative observational study was conducted at AIIMS Raipur in the Department of Ophthalmology, involving 38 patients diagnosed with RVO and 38 age- and sex-matched healthy controls.

Study design: Hospital-based Cross-sectional Comparative Observational study.

Study duration: 18 months.

Study settings: Department of Ophthalmology, AIIMS Raipur

Operational definition:
Branch retinal vein occlusion: Occlusion of a branch of the retinal vein.
Key feature: Retinal haemorrhage in distribution of obstructed vein.
: Dilated and tortuous retinal vein in the distribution of obstructed branch.
Central retinal vein occlusion: Occlusion of central retinal vein.
Key feature: Retinal haemorrhage in all four quadrants
: Dilated and tortuous retinal vein in all four quadrants.

Inclusion criteria for cases:
All patients diagnosed with Retinal vein occlusion (BRVO, CRVO) presented to Ophthalmology OPD during the study period.

Exclusion criteria for cases:
1. Patients with documented preexisting systemic inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, Sjogren's syndrome, giant cell arteritis, inflammatory bowel disease, tuberculosis), renal diseases, hepatic disorders
2. Patients with documented blood dyscrasias like sickle cell disease, and malignancy.
3. Patients currently using oral contraceptive pills, anticoagulants, anti-inflammatory drugs
4. Pre-existing glaucoma, globe injury.

Control group:
Age and sex-matched individuals who visited the eye OPD with refractive error.

Study variables:
1. Neutrophil: Lymphocyte ratio
2. Platelet: Lymphocyte ratio
3. Type of retinal vein occlusion
4. Central macular thickness

Sample size: 76 (Case= 38, Control=38)

Methods
This study will involve patients clinically diagnosed with Retinal Vein Occlusion (RVO) and an age- and sex-matched healthy control group. 38 patients with retinal vein occlusion and 38 age and sex-matched controls were enrolled. Written informed consent following the Declaration of Helsinki was obtained from each participant, and the study was approved by the institute's ethics committee. A comprehensive medical history will be obtained from each participant. Visual acuity will be assessed using a Snellen chart and converted to ETDRS letters. The better eye of the control group will be evaluated for comparison with cases. The anterior segment of the eye will be examined using slit lamp biomicroscopy, and intraocular pressure will be measured with an Applanation tonometer. Pupil dilation will be achieved using Tropicamide 0.8% and Phenylephrine 5% drops, administered once every 15 minutes for a total of three times. Fundus examination will be conducted using an indirect ophthalmoscope, providing a thorough evaluation of the retina. The central macular thickness will be measured through Optical Coherence Tomography, specifically utilizing the CIRRUS 5000SD-OCT. For haematological analysis, a blood sample will be collected from the antecubital vein of all participants. The complete blood count (CBC) analysis will be performed at the haematology laboratory centre of AIIMS Raipur.

Subsequently, the obtained results for both haematological and ocular parameters will be compared between the Retinal Vein Occlusion patients and the control group to assess potential differences and correlations.

Statistical analysis

Statistical analysis was done using software packages for IBM SPSS vs 22 for Windows. Continuous and categorical variables were expressed as mean ± SD and percentages. Descriptive statistics were done for age distribution, gender, eye side, hypertension, diabetes, and Retinal Vein Occlusion. Independent t-test was used to compare BCVA, central macular thickness, Hemoglobin, Total Leukocyte Count, Neutrophil, Lymphocyte, Platelet, NLR and PLR. ROC curve of NLR and PLR was made to predict the development of RVO. Two-sided p values were considered statistically significant at $p<0.05$.

III. Results

The baseline characteristics of the study participants (Table 1) in the RVO and Control groups were compared. Both groups had similar average ages (55.18 ± 9.07 years for RVO and 55.15 ± 9.18 years for Control) (p=0.96). Gender distribution was also equal in both groups, with 21 males and 17 females (p=1.00). In terms of hypertension, 52.6% of the RVO group had hypertension compared to 42.1% in the Control group (p=0.73). The RVO group had significantly lower best corrected visual acuity (48.82 ± 23.02 ETDRS) compared to the Control group (80.66 ± 5.94 ETDRS) (p <0.001). Additionally, central macular thickness (μ) was significantly higher in the RVO group (412.89 ± 161.00) compared to the Control group (237.23 ± 21.99) (p <0.001)

Table 1. Baseline characteristics of study participants.

Characteristic	RVO (n=38)	Control (n=38)	*p*-value
Age (yrs)	55.18 + 9.07	55.15 + 9.18	0.96
Gender (M/F)	21/17	21/17	1.00
Hypertension (%)	20 (52.6%)	16 (42.1%)	0.73
BCVA (ETDRS)	48.82 ± 23.02	80.66 ± 5.94	<0.001
CMT (μ)	412.89 ± 161.00	237.23 ± 21.99	<0.001

The laboratory findings (Table 2) of the study participants, consisting of individuals with RVO and a Control group, were compared across various characteristics. Firstly, there was no significant difference in Haemoglobin levels between the two groups (RVO: 12.60 ± 1.64 g/dL, Control: 13.01 ± 1.34 g/dL; p=0.23). Similarly, Total Leukocyte Count (TLC), Neutrophil count, Lymphocyte count, and Platelet count did not exhibit statistically significant differences between the RVO and Control groups (p>0.05). The mean NLR values were 2.18 ± 1.31 in the RVO group and 1.83 ± 0.79 in the control group. The mean PLR was 112.25 ± 70.03 and 101.52 ± 43.53 in RVO and control groups respectively. NLR and PLR did not demonstrate significant differences between the two groups (NLR: p=0.165, PLR: p=0.426).

Table 2. Laboratory findings of study participants.

Characteristic	RVO (*n* = 38)	Control (*n* = 38)	*p*-value
Hemoglobin (g/dL)	12.60 ± 1.64	13.01 ± 1.34	0.23
TLC (/μ*L*)	7909.21 ± 1805.70	7948.42 ± 2277.35	0.934
Neutrophil (/μ*L*)	4710.00 ± 1516.30	4591.31 ± 1613.66	0.742
Lymphocyte (/μ*L*)	2530.78 ± 895.06	2731.84 ± 909.36	0.335
Platelet (/μ*L*)	251342.10 ± 80951.19	253210.52 ± 87563.77	0.923
NLR	2.18 ± 1.31	1.83 ± 0.79	0.165
PLR	112.25 ± 70.03	101.52 ± 43.53	0.426

The area under the ROC curve (Receiver Operating Characteristic Curve) (Figure 1) was C = 0.743 with Standard error (SE)

= 0.095 and 95% Confidence interval (CI) from 0.556 to 0.929 for NLR. The area under the ROC curve was C = 0.537 with SE = 0.109 and 95% CI from 0.322 to 0.751 for PLR. From the ROC curve, it seems that NLR and PLR are not good indicators (p>0.05) to predict Retinal vein Occlusion.

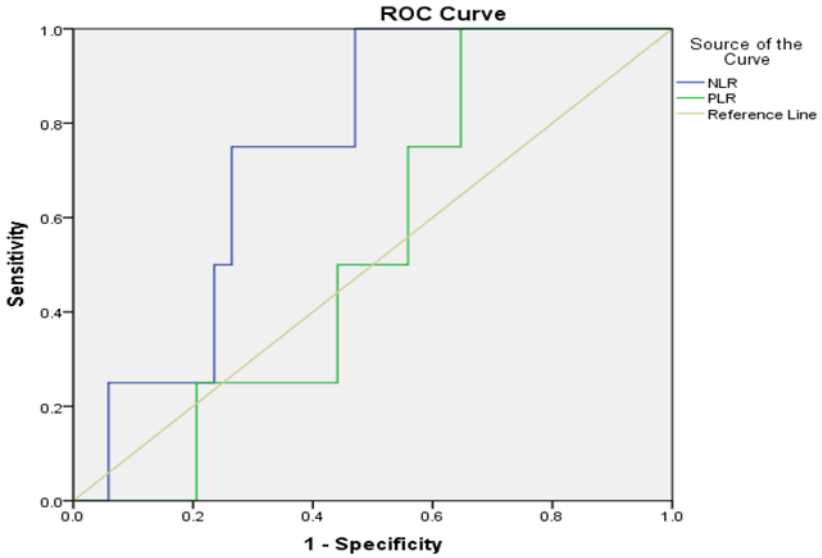

Figure 1: ROC Curve Analysis of NLR and PLR

IV. Discussion

The central focus of this study was to investigate the potential associations between NLR and PLR and RVO. We aimed to determine whether these ratios could serve as predictive markers for RVO. RVO is an important cause of visual impairment. Within RVO, BRVO prevails over CRVO, affecting an estimated 5.6 times more individuals[2]. The pathogenesis of RVO is complicated and multifactorial. Increased concentrations of various inflammatory cytokines in aqueous humor and serum have been found in patients with RVO and be related to the severity of the disease, which suggests that local and systemic inflammation is involved in the pathogenesis of RVO[12]. Thrombosis and inflammatory processes are central to the mechanisms underlying RVO. Some studies have highlighted the association between RVO and thrombotic conditions such as hyperhomocysteinemia, factor V Leiden mutation, protein C or S deficiency, and anticardiolipin antibodies[13]. Notably, both NLR and PLR serve as valuable inflammatory markers in diseases associated with thrombosis and inflammation. NLR has gained widespread acceptance as a cost effective and dependable marker of immune response in various medical disciplines. It reflects the dynamic relationship between innate (neutrophils) and adaptive (lymphocytes) immune responses during illnesses and pathological conditions. NLR is a versatile and widely utilized biomarker that aids in monitoring immune responses and predicting outcomes across diverse medical conditions like cardiovascular diseases, hypertension, cancers etc. Platelets serve as a source of inflammatory mediators, and increased platelet activation is a key factor in triggering and advancing atherosclerosis. Platelets directly modulate the activation of vascular endothelium[14]. PLR a newly recognized and cost-effective inflammatory marker calculated from platelet and lymphocyte counts, reflects both hyperactive coagulation and inflammatory pathways. Our study included 38 cases of diagnosed RVO patients and an age- and sex-matched control group of 38 individuals. We found that NLR and PLR were not significantly different between the RVO group and the control group (2.18 ± 1.31 vs 1.83 ± 0.79 p 0.165, 112.25 ± 70.03 vs 101.52 ± 43.53, p 0.426 respectively). NLR and PLR may not be strong indicators for predicting the occurrence of RVO. It seems from the ROC curve that NLR and PLR are not good indicators (p>0.05) to predict RVO. This suggests that these ratios may not be effective predictors of RVO.

To gain a deeper understanding of the significance of these results, it is essential to compare them with findings from similar articles. This comparative analysis reveals some variability in the relationship between NLR, PLR, and RVO across different studies.

Our findings align with some previous studies (Table 3), such as the work by Kumral et al[15] (2016) and Pinna et al[16] (2020), which did not find significant differences in NLR and PLR between RVO patients and controls. However, they contrast with other studies like Dursun et al[17] (2015), and Atum et al[18] (2019), which reported elevated NLR and PLR in RVO patients.

Table 3. Different Studies evaluating NLR and PLR in RVO

Study	Sample size	Study Variable	RVO	Results
Our Study	RVO cases - 38 Controls - 38	NLR PLR	RVO	The mean NLR values were 2.18 ± 1.31 in the RVO group and 1.83 ± 0.79 in the control group. The mean PLR was 112.25 ± 70.03 and 101.52 ± 43.53 in RVO and control groups respectively. The difference between the two groups in terms of NLR and PLR was not statistically significant.
Dursun et al[17]	RVO cases - 40 Controls - 40	NLR	RVO	NLR was notably higher in RVO patients than in the control subjects (3.0 ± 2.7 vs 1.5 ± 0.3, p<0.001)
Atum et al[18]	BRVO Cases- 77 Controls - 69	NLR PLR	BRVO	NLR was significantly elevated in individuals with BRVOs compared to the control group (2.60±2.05 vs. 1.74±0.70, p=0.001). PLR was also significantly higher in BRVO cases compared to controls (129.70±68.77 vs. 107.96±40.65, p=0.023)
Kumral et al[15]	BRVO cases – 30 Controls- 27	NLR	BRVO	NLR values were 2.24 ± 0.79 in the BRVO group and 1.89 ± 0.64 in the control group, with no statistically significant difference found between them (p = 0.30, p > 0.05)
Pinna et al[16]	RVO cases – 127 Controls - 127	NLR PLR	RVO	No statistically significant disparities between RVO patients and the control group

The variability in findings across these studies highlights the complex and multifactorial nature of RVO. While some studies suggest that NLR and PLR may be valuable markers for RVO, others do not find significant associations.

Several factors may contribute to these differing results. Firstly, the heterogeneity of the RVO population, which includes both BRVO and CRVO cases, could lead to different findings. Secondly, the small sample sizes in some studies, including ours, may limit the statistical power to detect subtle differences in these biomarkers. Thirdly, variations in patient demographics, comorbidities, and genetic predispositions could contribute to the variability in study outcomes.

It highlights the need for further research to clarify the relationship between these ratios and RVO. Our study results suggest that NLR and PLR alone may not be reliable indicators for the presence of RVO. While inflammation is believed to play a role in RVO development, our findings indicate that these specific ratios may not be directly linked to the condition. However, it's essential to consider that RVO is a multifactorial disease and other factors may contribute to its development. These inflammatory markers might be applicable to predict predisposition for venous thromboembolism in certain hematologic and inflammatory diseases other than RVO.

Based on our findings, we recommend that future research in this area explore a broader range of inflammatory markers and risk factors for RVO. Large-scale studies with diverse populations may provide more conclusive evidence regarding the role of NLR and PLR in RVO prediction.

V. Conclusion:

In conclusion, our study did not find a significant association between NLR and PLR and RVO. The significance of NLR and PLR in RVO is uncertain. NLR and PLR may not be effective standalone markers for predicting RVO, emphasizing the multifactorial nature of RVO pathogenesis. As RVO remains a sight-threatening condition with significant global impact, further research is warranted to reveal its complexities and identify more reliable predictive markers to improve its management and outcomes.

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