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Original Research Article

Association of Retinal Vein Occlusion with Hematological and Systemic Biomarkers

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Abstract:

Background and Objectives: Retinal Vein occlusion (RVO) is the second most common retinal vascular disorder, after diabetic retinopathy which causes painless visual impairment. Multiple systemic, local, and hematologic disorders can contribute to the multi-factorial etiology of RVO. Recent researches have revealed that some inflammatory biomarkers and hyperlipidemia are associated with RVO more frequently. Our study aims to determine the relationship between hematological and systemic biomarkers with RVO. This association can help patients with RVO identify other systemic illnesses and prevent the development of RVO in additional eyes.

Material and Methods: In this case control study, 50 patients were enrolled in the Department of Ophthalmology, S.S. Medical College and associated Gandhi Memorial Hospital, Rewa (M.P.) after receiving institutional ethical committee permission and informed written consent. Data collection included detailed history; a comprehensive ocular examination was performed for all the subjects under the study followed by laboratory investigations of inflammatory markers (CRP, Homocysteine), lipid profile (Cholesterol, Triglyceride, VLDL, LDL, HDL levels, MHR) parameters and hematological markers (NLR, PLR, MPV). SPSS version 24 was utilized for statistical analysis. Data was presented as mean with standard deviation or proportions as appropriate.

Results: Demographic profile was comparable between the two groups. The mean CRP and Homocysteine levels were significantly higher among the cases as compared to the controls. Among the hematological parameters taken into account, Neutrophil count, Lymphocyte count, Monocytes count, and the Mean Platelet Volume and Platelet-Lymphocyte ratio was significantly higher in cases; whereas Platelet count, and Neutrophil-to-Lymphocyte Ratio was studied to be statistically non-significant. The lipid profile parameters were also significantly increased, except, HDL which was decreased in RVOs and MHR which was not significantly associated with the implication of RVO.

Conclusion: Present study reflects an association of RVO with the inflammatory markers, CRP and Homocysteine, which can be considered as risk factor in the development of RVO. Present study concluded that all individuals with retinal vascular blockage should have their serum cholesterol levels checked. While it's yet unclear whether restoring normal serum lipid levels will enhance vision and stop RVO in the other eye from happening, or whether it may lessen problems and RVO recurrence in the same eye. NLR and PLR parameters can be utilized as independent risk factors in BRVO patients.

Keywords: CRP; Homocysteine; Inflammatory Markers; Lipid Profile; Retinal Vein Occlusion.

Introduction

Retinal Vein occlusion (RVO) is the second most common retinal vascular disorder, after diabetic retinopathy which causes painless visual impairment. Multiple systemic, local, and hematologic disorders can contribute to the multifactorial etiology of RVO. The following conditions could increase the chances of developing RVO: hypertension, diabetes mellitus, dyslipidemia, atherosclerosis, obesity, smoking, trauma, glaucoma, thrombophilia, hyper viscosity,

coagulation abnormalities, hyper-homocysteinemia, oral contraceptive use, and ageing. [1, 2] It is hypothesized that endothelial dysfunction, oxidative stress, and inflammation caused by monocytes may play a significant role in the development of many diseases. HDL cholesterol is well known for its antioxidant and anti-inflammatory properties. As an indication of inflammation, the monocyte/HDL ratio (MHR) has thus been studied in a variety of illnesses. [3] The liver produces C-reactive protein (CRP) in reaction to inflammation, and patients with RVO have higher levels of CRP. [4]

The neutrophil to lymphocyte ratio (NLR) has been suggested as a prognostic marker to identify atherosclerosis and a systemic inflammatory response. [5, 6] It has been proposed that thrombus formation caused by platelet hyperaggregability may play a significant role in the beginning and/or progression of RVO. [7]

An independent risk factor for retinal vascular occlusive disease is elevated homocysteine. [8, 9, 10] Recent research has revealed that people with hyperlipidemia may also experience RVO more frequently.

There are numerous hematological and systemic indicators linked to RVO pathophysiology. Even though, their relationship hasn't been well established yet. Our study aims to determine the relationship between NLR, PLR, MPV, MHR, CRP, lipid profile, MHR, and homocysteine in patients with RVO. This association can help patients with RVO identify other systemic illnesses and prevent the development of RVO in additional eyes.

Aim and Objectives

Present study aims to determine the relationship between hematological and systemic biomarkers with RVO.

Material and Methods

This case control observational study on 50 patients diagnosed with different types of retinal vein occlusion attending the Retina Clinic of Department of Ophthalmology, S.S. Medical College and associated Gandhi Memorial Hospital, Rewa (M.P.) during the period January 2021 to September 2022. The research was accepted by the Ethical Committee and complete informed written consent was acquired from the patients.

Inclusion Criteria: Recently diagnosed retinal vein occlusion (RVO) in at least 1 eye.

Exclusion Criteria:

- Patient on hypolipidemic drug, anticoagulant treatment, using non steroid anti- inflammatory drug and oral contraceptives.
- Patient having other connective tissue disorder.
- Patient having acute and chronic illness in which systemic markers are deranged
- Patient with malignancy

Data Collection and Method

Data collected from all subjects included demographic characteristics like age and gender, detailed history regarding use of medications like hyperlipidemic drug, anticoagulant, nonsteroid anti- inflammatory drug and oral contraceptives, systemic conditions such as diabetes hypertension and cerebrovascular accident, any addiction like tobacco and cigarette smoking.

A comprehensive eye examination was performed in all the study subjects which included visual acuity, intraocular pressure, anterior segment examination, dilated ophthalmoscopy. Simultaneously complete blood count, serum lipid profile, C reactive protein (CRP), serum Homocysteine.

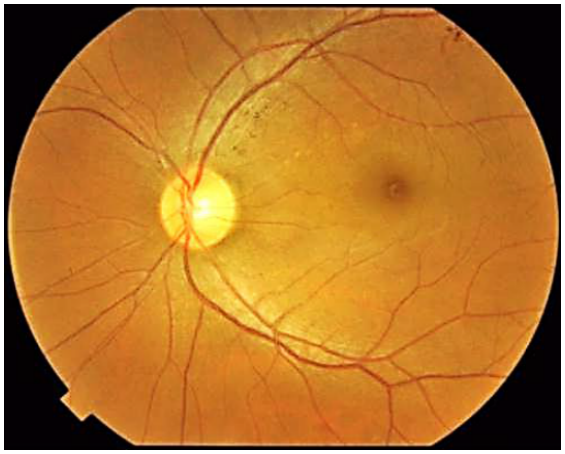

Figure 1: Fundus photograph: Control

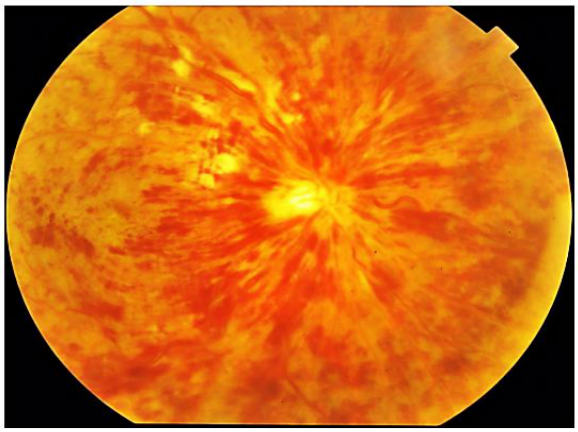

Figure 2: Central Retinal Vein Occlusion (CRVO)

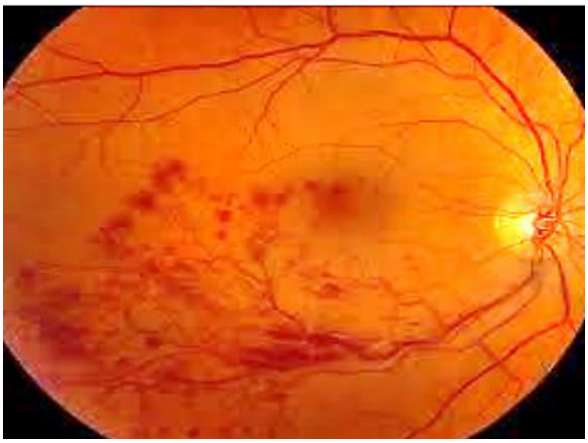

Figure 3: Branch Retinal Vein Occlusion (BRVO)

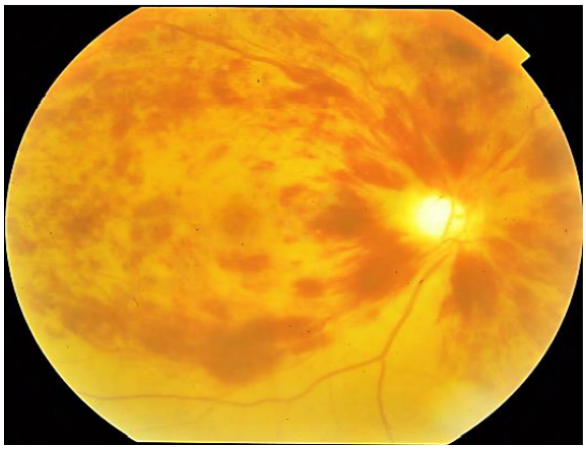

Figure 4: Hemi-Retinal Vein Occlusion (HRVO)

Sample size calculation:

The sample size for the proposed study is approximately 90.

- N (total population in orthopedic determent for our current study) = 316 (near about)
- N (sample size for current study) = 90
- Z= Statistics for level of confidence (i.e. 1.96 for 95% confidence level) or Alpha error
- Confidence level is 95% and 5% confidence interval.
- P= expected prevalence of proximal tibia fractures using CT SCAN based on classification =9% = 0.09
- e = Margin of error = 5%= 0.05 (Allowable error)

n = [{Z2P(1-P)}/e2]/ [1+{Z2P(1-P)}/Ne2]

n= [(1.96)2 (0.09)(1-0.09)]/(0.05)2]/ [1+{(1.96)2 (0.09)(1-0.09)}/316 (0.05)2]

= 90.022 ≈ 90 (This is the required sample size)

Statistical Analysis: All the data would be selected randomly and tabulated, and then analyzed with appropriate statistical tools "SPSS Vs 21". Data will be presented as mean with standard deviation or proportions as appropriate. Mean, median, standard deviation and variance would be calculated and following statistical significance tests would be applied.

1. Statistical analysis was done by using "Chi – square Test" for comparing categorical value.
2. Statistical analysis was done by using "Gaussi-an Test/ Single mean test" for comparing con-tinuous data (age).
3. "POST HOC TEST/Multiple comparison test" [Post Hoc Test is an integral part of Analysis of Variance/ANOVA."
4. Unaired t - test also used for comparing two mean of continuous data.

A "p-value" should be considered to be non-significant if > 0.05 and significant if <0.05.

Results

The demographic profile of study population was as shown in [Table 1].

There were statistically not significant differences between two groups according to their age and gender distribution (p=0.0972) and (p=0.6875), respectively.

There were statistically significant differences among the patients according to mean of CRP & Homocysteine Level (micromole/L) between two groups, with p<0.0001.

Table 1: Demographic variables

Variables			Case (n=50)		Control (n=50)		P-value
Age group (years) (Mean±SD)			57.14±10.55		60.10±6.70		0.0972 (NS)
Gender			Male	32	Male	24	0.6875 (NS)
			Female	18	Female	26	
Distribution of Inflammatory markers	**CRP**	**CRVO**	12.09 ± 7.38		6.07±5.48		<0.0001 **(S)**
		BRVO	13.35 ± 11.13				
		HRVO	25.72 ± 9.15				
	Homocysteine	**CRVO**	23.19 ± 10.94		10.45±4.46		<0.0001 **(S)**
		BRVO	27.01 ± 14.52				
		HRVO	33.26 ± 14.68				

NS- Not Significant, S- Significant

In our study, it was found that the mean MHR among the two groups was statistically non-significant with p value=0.2077. Various hematological parameters were also increased, except platelet count and Neutrophil-lymphocyte ratio which was not seen to have quite a significant association. [Table 2]

Table 2: Distribution of Hematological Markers among groups

Clinical features	CRVO (n=29)	BRVO (n=16)	HRVO (n=5)	Control (n=50)	P-value
Neutrophil Count (thousand/micro liter)	5.23±1.83	5.22±1.62	6.70±4.31	4.50±1.74	0.0261 (S)
Lymphocyte Count (thousand/micro liter)	2.15±0.89	1.99±0.79	2.41±1.72	2.19±0.80	0.5517 (NS)
Monocyte (thousand/micro liter)	0.46±0.14	0.48±0.16	0.58±0.48	0.56 ± 0.19	0.2562 (NS)
Platelet Count (thousand/micro liter)	219.89±68.86	248.19±97.6	239.60±59.05	226.44±54.32	0.2627 (NS)
Mean Platelet Volume (fl)	10.08±1.47	10.84±1.46	10.08±0.76	9.28±0.71	0.0205 (S)
NLR (neutrophil to lymphocyte ratio)	3.18±2.92	3.49±3.61	3.98±4.04	2.79±4.50	0.5729 (NS)
PLR (platelet to lymphocyte ratio)	126.77±81.39	140.58±73.53	164.26±151.29	59.62±37.75	<0.0001 (S)

NS- Not Significant, S- Significant

The Mean Cholesterol, Triglyceride, LDL, VLDL, cholesterol/HDL, LDL/HDL and Triglyceride/HDL was statistically significantly higher among cases than controls with p value being <0.0001. Also, mean HDL among cases and controls was statistically significantly lower among the two groups (p<0.0001). [Table 3]

Table 3: Distribution of Lipid Profile among groups

Clinical features	CRVO(n=29)	BRVO(n=16)	HRVO (n=5)	Control(n=50)	P-value
Total Cholesterol (mg/dl)	207.99±48.62	202.14±36.73	199.69±39.67	173.88±17.15	<0.0001(S)
TG (mg/dl)	176.14±53.94	175.10±55.62	199.15±106.46	114.71±27.51	<0.0001(S)
HDL (mg/dl)	47.95±7.74	44.06±9.89	48.46±10.73	61.59±5.57	<0.0001(S)
LDL (mg/dl)	107.78±38.83	111.72±33.14	108.71±43.60	78.02±15.48	<0.0001(S)
VLDL (mg/dl)	36.18±8.52	35.36±8.84	40.69±8.39	22.25±7.61	<0.0001(S)
Cholesterol/HDL ratio	4.46±1.30	4.79±1.26	4.43±1.80	2.85±0.39	<0.0001(S)
LDL/HDL	2.33±0.98	2.70±1.07	2.46±1.49	1.28±0.31	<0.0001(S)
TG/HDL	3.83±1.48	4.23±1.66	4.62±3.50	1.88±0.47	<0.0001(S)
MHR (monocyte to HDL ratio)	0.009±0.003	0.011±0.004	0.011±0.008	0.009±0.002	0.3077 (NS)

NS- Not Significant, S- Significant

Discussion:

This study was conducted with the aim to assess different roles of inflammatory markers and their association as being risk factors in the implication of RVO. Even though there is no definitive explanation for RVO mechanism, Virchow's triad (venous stasis, endothelial dysfunction and hypercoagulability triad) is by far, the most accepted mechanism for RVO.

The mean CRP value among the cases was statistically significantly higher (p<0.0001) than controls. Furthermore, the mean CRP in HRVO patients was seen to be significantly higher as compared to the mean CRP of BRVO and CRVO patients, which indicates that higher the CRP, more the risk of developing HRVO.

Dodson PM et al [11] concluded that patients with high serum CRP levels who have high blood pressure may be more likely to get retinal vascular occlusion. Lee HH et al [12] and Karagoz IK et al [13] found that high hs-CRP levels might also be a risk factor for the emergence of RVO.

In the present study, the mean Homocysteine levels among the cases were statistically significantly increased (p<0.0001). It was also found that the mean Homocysteine value of HRVO cases is higher than the CRVO, and BRVO cases, which signifies that high homocysteine was more prevalent in HRVO as compared to CRVO and BRVO. Abu El-Asrar AM et al [14], Koylu MT et al [15] and Lahiri KD. et al [16], concluded that patients with retinal vascular occlusive disease had significantly higher plasma total homocysteine levels than healthy controls.

McGimpsey SJ et al [17] and Boyd S et al [18] demonstrated that although the homocysteine levels in the RVO group were higher than those in the control group, the difference was not statistically significant.

The Mean Cholesterol, Triglyceride, LDL, VLDL, cholesterol/HDL, LDL/HDL and Triglyceride/HDL was statistically significantly higher among cases than controls with p value being <0.0001. Also, mean HDL among cases and controls was statistically significantly lower among the two groups (p<0.0001). Agrawal S et al [19] conducted a study between the RVO with serum lipid levels in adults in which they stated that total cholesterol, triglycerides levels were substantially higher in patients with RVO group than in control subjects. The HDL levels were considerably lower in the RVO group as compared to the controls.

Lahiri KD et al [16] and Dodson PM et al [11], also found that patients with RVO had significantly higher levels of total cholesterol, triglyceride, LDL cholesterol, and VLDL cholesterol (P< 0.001) and significantly lower levels of HDL cholesterol (P<0.001) than control subjects, which was in line with our findings.

Lecumberri JJ et al [20] found that RVO patients had higher levels of total cholesterol, LDL-C, and triglycerides, although these differences did not reach statistical significance.

In present study, it was found that the mean MHR among the two groups was statistically nonsignificant with p value=0.2077.

In a study conducted by Satirtur G et al [3] and Duru Z et al [21], concluded that MHR is significantly elevated in patients with BRVO as compared to the control group. They claimed that MHR is a more precise indicator of systemic inflammation than other haematological measurements.

Sahin A et al [22], Pinna A et al [23] and Bawankar P et al [24] studied that the MPV values were found to be significantly higher in patients with RVO, thereby suggesting that high mean platelet volume contributes to the pathogenesis of RVO. Ornek N et al [7] concluded that MPV was significantly lower in patients with RVO as compared with the control group.

Also, Sahin M et al [5], Atum M et al [25] and Zhu DD et al [26] showed in their study that higher NLR and PLR were associated with the development of retinal vein occlusion as compared to the control group. Also he stated that, NLR and

PLR can be used as predictive tools for identifying risk for retinal vein occlusion (RVO).

Limitations of the study: In the present study, the time of assessment from onset varied among the cases which might have affected the results. Due to small sample size, results cannot be implied over general population. The method used to collect blood samples for the current investigation, which depended on when patients visited the ophthalmic unit, was another potential source of bias. As a result, blood was not drawn from patients who were fasting, which may have had a big impact on tHcy. The small number of instances observed in the case group explained why all the parameters those were significantly higher in HRVO cases. Therefore, a bigger sample size is required for further analysis of the inference**.**

Conclusion:

Present study reflects an association of RVO with the inflammatory markers, CRP and Homocysteine, which can be considered as risk factor in the development of RVO. Present study concluded that all individuals with retinal vascular blockage should have their serum cholesterol levels checked. While it's yet unclear whether restoring normal serum lipid levels will enhance vision and stop RVO in the other eye from happening, or whether it may lessen problems and RVO recurrence in the same eye. NLR and PLR parameters can be utilized as independent risk factors in BRVO patients.

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