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ORIGINAL ARTICLE

Assessment of C-reactive protein to albumin ratio in patients with retinal vein occlusion

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Abstract

Purpose: The relationship between retinal vein occlusion (RVO) and hematologic parameters has been previously demonstrated. However, there is lacking data regarding the role of C-reactive protein (CRP) to Albumin Ratio (CAR) in patients with RVO. In this study, we aimed to investigate the relationship between CAR and RVO.

Methods: A total of 126 people were included in our study, including 63 patients diagnosed with central RVO (CRVO) in our hospital and 63 control patients. All clinical, demographical, and laboratory parameters were entered into a dataset and compared between the CRVO group and the controls.

Results: The mean age of the patients was 54±11 years (Female: 47.6%). CRP and CAR were significantly higher in patients with CRVO compared to controls (p<0.001, p<0.001, respectively). Logistic regression analysis demonstrated that high CAR level was an independent determinant of CRVO (Odds Ratio: 3.300, 95% Confidence interval: 1.681–6.480; p=0.001).

Conclusion: Higher CAR levels may be an associated predictor of CRVO.

Keywords: C-reactive protein to albumin ratio; inflammation; retinal vein occlusion.

Retinal vein occlusion (RVO) is one of the most common causes of acquired retinal vascular abnormality in adults and it is considered to be an important cause of visual loss.[1,2] RVO may exist in large, medium, and small-caliber veins and it is named as branch RVO, hemicentral RVO, and central RVO (CRVO) accordingly. To date, the pathogenesis of RVO has not been elucidated, but the Virchow's triad, consisting of venous stasis, endothelial dysfunction, and hypercoagulability triad, is the generally accepted mechanism to describe the RVO mechanism.[3] On the other hand, there are many influential risk factors among the etiology of RVO. It includes a large number of systemic, local, and hematological conditions. Hypertension (HT), diabetes mellitus (DM), dyslipidemia, atherosclerosis, obesity, smoking, trauma, glaucoma, thrombophilia, hyperviscosity, coagulation anomalies, hyperhomocysteinemia, smoking, oral contraceptive use, and aging are possible risk factors for the development of RVO.[4–6]

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Prisco and Marcucci mentioned for the 1 time that there may be an inflammatory etiology for some types of CRVO, especially in young patients. They defined some local pathological inflammatory changes and mentioned that any immunological diseases might underline the CRVO disease. But still, no definitive inflammatory process was identified.

Focal phlebitis, optic disc edema, and vitreous cells are observed in a significant number of patients, which highlights the possible role of an inflammatory process.[5] As a matter of fact, in some recent studies, it has been shown that the RVO may be associated with some inflammatory parameters and even play a role in the development of the RVO.[7] Furthermore, other biomarkers of systemic inflammatory response such as high C-reactive protein (CRP) levels and low albumin levels and the ratio of CRP to Albumin Ratio (CAR) have also been studied in many diseases.[8,9]

In this study, we aim to investigate whether CRVO, which is already known to be associated with inflammatory parameters, is associated with the CRP/CAR or not.

Materials and Methods

Study Patients

A total of 126 patients, including 63 control groups and 63 CRVO patients, were included in our study between 2009 and 2019 were enrolled in the study. The control group was similar to the patient group in terms of age, gender, and systemic diseases. The patients who had previously malignancy, acute systemic infections, autoimmune diseases, hepatic disorders, renal impairment (serum creatinine >2 mg/dl), cardiovascular diseases, cerebrovascular diseases, vasculitis and blood dyscrasias, ocular diseases, current treatment with anticoagulant medications, anti-hyperlipidemic therapy, and oral contraceptives, and smoking and alcohol consumption were excluded.

Written informed consent was obtained from each participant if needed, and the study protocol was reviewed and approved by the Kartal Koşuyolu Yüksek İhtisas Institutional Ethics Committee (2020.2/05-241). This study was conducted in accordance with the Declaration of Helsinki.

Definitions and Laboratory Measurements

Routine complete blood cell count and blood chemistry tests including the blood glucose, creatinine, albumin, and CRP values were studied on admission. The albumin and CRP levels were measured using a Roche Diagnostics Cobas 8000 c502 analyzer ((Indianapolis, USA). The CAR was calculated as the ratio of CRP to the albumin level multiplied by 100. In the fundus examination of the eye, dilated and curved veins with perivascular exudation, diffuse flame hemorrhages, and macular edema were identified as CRVO.

All clinical, demographical, and laboratory parameters were entered into a dataset and compared between the CRVO group and the controls.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp. Armonk, NY). Continuous variables are expressed as mean±standard deviation, whereas categorical variables are expressed as a percentage. Chi-square or Fisher exact tests were used for comparison of categorical data. The normality distribution of continuous variables was tested with the Kolmogorov-Smirnov test. The correlation of continuous variables was assessed by the Pearson correlation test and non-continuous variables were assessed by the Spearman test. Student t-test or Mann-Whitney U test was used to compare continuous variables between the 2 groups. To identify the independent predictors of CRVO multivariate logistic regression analysis was performed. A 2-sided $p<0.05$ was considered significant. Receiver operating characteristic (ROC) curve analyses were used to determine the best cut-off value of CAR, CRP, and albumin in predicting CRVO. De Long test was used to compare the ROC curves of CAR, CRP, and albumin.

Results

One sixty-three patients diagnosed with CRVO (42 female, 21 male) and 63 age-and sex-matched participants as control (46 female, 17 male) were eligible for the study. Table 1 summarizes the demographic characteristics, CAR, and other hematologic parameters of both CRVO and the control groups.

The median age of the study population was 54 years (IQR 47.5, 58.5). There was no significant difference between patients with and without CRVO in terms of HT, smoking, Systolic blood pressure, White blood cell count, glucose, triglycerides, albumin, and üric acid (Table 1). There was a significant difference between groups in terms of hemoglobin level, high sensitive CRP, CAR, and Low-density lipid (Table 1).

Moreover, there was a significant relationship between CRVO and CAR ($p<0.002$) (Table 1). On the other hand, no significant difference was detected between the groups in terms of gender, age, serum urea and creatinine, diastolic

Table 1. Comprassion of basal characteristics between healthy and retinal vein occlusion patient groups

Variables	Group				p-value
	RVO Patient (n=63)		Control (n=63)		
	Median	IQR 25th, 75th	Median	IQR 25th, 75th	
Age	54	47.5, 58.5	54	43.5, 58	0.95
Gender (female), n (%)	42 (66.7)		46 (73)		0.44
HT (female), n (%)	40 (63.5)		33 (52.4)		0.20
Smoking, n (%)	7 (11.1)		8 (12.7)		0.78
BMI	30.1	27.3, 35.2	29.1	27, 34.8	0.56
SBP	130	125, 142	140	1117, 148	0.64
WBC	7.11	5.95, 8.51	7.03	6.34, 7.58	0.68
Hgb	12.3	11.5, 13,3	14.6	13.6, 14.9	<001
Glucose	90	86, 112	89	88, 99	0.10
Creatine	0.8	0.65, 1.01	0.8	0.75, 1	0.10
Albumine	46	43.5, 48	48	45, 49	0.06
hsCRP	15	11, 22	11	5, 18	0.004
CRP/Albumin	0.30	0.24, 0.48	0.25	0.11, 0.37	0.002
Total cholesterol	173	154, 207	171	154, 189	0.28
HDL	43	36, 48	41	34, 44	0.10
Trigliseride	163	124, 198	141	115, 214	0.41
LDL	112	100, 133	102	84, 112	<001
TSH	1.35	1.00, 1.86	1.43	1.04, 1.70	0.68
Fibrinogen	369	316, 408	383	315, 440	0.31
Uric acid	4.4	4, 5.2	4.3	3.7, 5.4	0.53
Microalbumin	9.3	3.9, 18.8	5.8	3.9, 15.7	0.13

RVO: Retinal vein occlusion; HT: Hypertension; BMI: Body mass index; SBP: Systemic blood pressure; WBC: White blood cell; Hgb: Hemoglobine; hsCRP: High sensitive C-reactive protein; TC: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; TSH: Thyroid stimulant hormone.

Table 2. Univariable logistic regression

Variables	p-value	Odds-ratio	95% CI for EXP(B)	
			Lower	Upper
HT 0.20	1.58	0.77	13.22	
Smoking	0.78	0.86	0.29	2.53
BMI	0.58	1.02	0.95	1.09
SBP	0.61	0.99	0.98	1.01
WBC	0.91	1.01	0.79	1.30
Hgb	<0.001	0.43	0.32	0.60
Glucose	0.01	1.03	1.01	1.05
HDL	0.06	1.04	0.99	1.08
CRP/CAR	0.02	12.3	1.50	91

HT: Hypertension; BMI: Body mass index; SBP: Systemic blood pressure; WBC: White blood cell; Hgb: Hemoglobine; HDL: High density lipoprotein; CRP: C-reactive protein.

blood pressure, body mass index, and total level cholesterol.

Multivariate logistic regression analysis was used to determine the independent predictors of CRVO. Univariate analysis showed that only hemoglobin, glucose, and CAR levels were significantly correlated with CRVO (Table 2). However, in multivariate analysis, CAR (Odds Ratio [OR]: 9.55, 95% Confidence interval [CI]: 1.05–89; p=0.04), glucose (OR: 1.03, 95% CI: 1.01–1.06; p=0.005) and microalbumin (OR: 1.04, 95%CI: 1.01–1.07; p=0.008) were independent predictors of slow coronary flow (Table 3).

Table 3. Multivariable logistic regression

Variables	p-value	Odds-ratio	95% CI lower	95% CI upper
SBP	0.12	1.98	0.95	1.01
LDL	<001	1.03	1.01	1.05
HT 0.25	1.80	0.66	4.88	
Microalbumine	0.008	1.04	1.01	1.07
Glucose	0.005	1.03	1.01	1.06
CRP/CAR	0.04	9.55	1.05	89

SBP: Systemic blood pressure; LDL: Low density lipoprotein; HT: Hypertension; CRP: C-reactive protein.

The ROC curves of CRP, albumin, and CAR were compared in the prediction of CRVO. The area under the curve (AUC) for CAR was significantly greater than that for CRP (AUC: 0.743; 95% CI, 0.697–0.785 vs. 0.673; 95% CI, 0.624–0.719; p<0.05) and for albumin level (AUC: 0.743; 95% CI, 0.697–0.785 vs. 0.649; 95% CI, 0.600–0.696; p=0.001; [Fig. 1]). A CAR >0.17 predicted a CRVO with sensitivity and specificity of 43–94%, respectively.

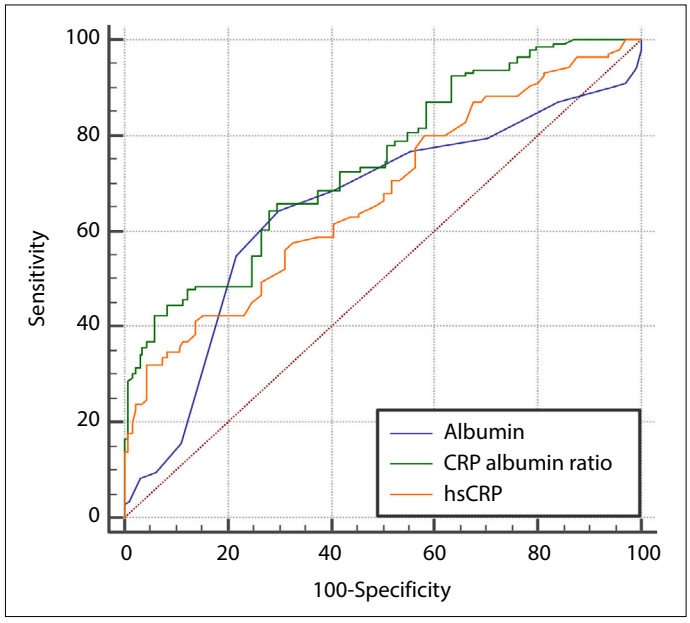

Fig. 1. ROC curve analysis for predicting retinal vein occlusion.

Discussion

Sixty-three patients with a median age of 54 (IQR 47.5, 58.5) years and who had CRVO were included in the present study. According to the statistical evaluation results, a significant correlation was found between CRVO and CAR levels. At the same time, the CAR prediction of CRVO sensitivity and specificity were 43–94%, respectively.

Although CRVO is seen in 0.1–0.5% of the general population, it is more frequently observed in the population over 65 years of age.[1,10] It is a multifactorial disease and its etiology is advanced age, HT, DM, hyperlipidemia, and glaucoma.[11–17] Other etiological factors include causes predisposing to coagulation and inflammatory diseases.[11–18] Although the population under 40 years of age constitutes 10–15% of patients with CRVO, inflammatory diseases come to the fore, unlike the etiological causes of the general elderly population.[19] The physiopathogenesis of CRVO seen in the elderly population includes compression on the central vein secondary to atherosclerotic changes in the central retinal artery due to other factors, especially HT and DM.[20] In the young population, a similar situation in the etiopathogenesis of RVO has not been proven and besides the number of studies on etiological reasons is also limited. In the study performed by Chen et al.,[20] the etiology of CRVO seen in the young population was evaluated and it was emphasized that inflammation was an effective factor in the occlusion process. At the same time, Fong and Schatz demonstrated that collagen vascular diseases are among the etiological risk factors.[19]

Nowadays, CRP/CAR comes to the fore as a currently used laboratory parameter for the indirect prediction of vascular inflammatory diseases. CRP is a positive acute phase reactant and its blood levels increase in inflammatory conditions, while albumin is a negative acute phase reactant and its blood levels decrease in inflammatory events. Recent studies have reported that the CRP/CAR alone is more meaningful as an inflammatory indicator.[21] Although not only in the young population, it has been shown in previous studies that inflammation is involved in the development process of CRVO.[11–17] In the study of Noma et al.,[22] it was emphasized that inflammation is important not only in the pahogenesis of RVO (CRVO) but also in the pathogenesis of macular edema resistant to anti-VEGF treatment and various inflammatory cytokines play a role.[21] Increased serum CRP level is a biomarker used to evaluate macro and microvascular diseases caused by inflammation.[21–24] In the study of Dorajoo et al.,[23] it was shown that increased CRP level is associated with central retinal vein calibration. At the same time, it has been emphasized that CRP and Albumin are effective in the progression of inflammatory diseases and the development of atherosclerosis.[25] Besides, CRP indicates impaired vascular endothelial progenitor cell function and fibrinolysis.[19] The decrease in albumin level is an important follow-up parameter in the process of chronic inflammatory diseases and it has been shown that it is associated with increased blood viscosity, impaired endothelial function, increased platelet activation, and aggregation.[25]

CRP elevation is a parameter associated with acute inflammation, and inflammatory activity is associated with vascular damage.[9] In addition, low albumin may occur secondary to malnutrition or inflammation.[8] The combined change of both parameters expressed as CAR can be used as a stronger parameter.[23–25] Thus, easily accessible CAR can be considered for close follow-up of patients having high residual risk, despite the improvement of classical risk factors such as HT, lipid, and lifestyle. However, it is not possible to talk about the applicability of CAR for evaluation of the disease recurrence, since there is no scoring system for the severity of CRVO. At the same time, it is difficult to declare a conclusion about the therapeutic use of CAR because of no existing large-scale studies. When we look at the literature, no study has investigated CAR and CRVO before. With the present study, it was concluded that CAR is correlated with CRVO and might predict its development.

Conclusion

With the results of this study, it can be also concluded that CAR can predict disease development in both advanced

age CRVO and young age CRVO patient groups. However, future studies with a larger sample size will be needed to confirm the results of the present study.

Ethics Committee Approval: This study was approved by Kartal Koşuyolu Yüksek İhtisas Institutional Ethics Committee (2020.2/05-241).

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