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Original Article

The Relationship of Markers With Carotid Artery Stenosis and Lesion Hardness: Superiority of C-Reactive Protein and Uric Acid

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Abstract

Background: Atherosclerosis is a disease that cholesterol plaque builds up inside arteries. The process of atherosclerosis starts when certain substances such as cholesterol, fats, and cellular waste products accumulate in the walls of arteries, and the immune system responds to these substances, triggering inflammation. Over time, this inflammation can cause the plaque to grow and harden, narrowing the artery and reducing blood flow. Carotid artery disease (CAD) is a conclusion of plaques in carotid artery. CAD can increase the risk of stroke, a potentially life-threatening condition that occurs when blood flow to the brain is interrupted.

Objectives: The objectives of this study were to detect the association between carotid artery stenosis and inflammatory markers.

Methods: This study was designed prospectively and included 109 and 100 patients having mild carotid stenosis and severe carotid stenosis, respectively. Further, 101 patients were included in the control group. The carotid ultrasonography was evaluated in all patients. After classifying the plaques into < 60% (mild stenosis) and 60% > (severe stenosis) categories, they were also grouped into echogenicity plaques, namely, echolucent (soft) and echogenic (hard) plaques.

Results: The uric acid (UA) values of the mild and severe stenosis groups were higher than that of the control group ($P<0.01$). The mean C-reactive protein (CRP) value was the highest in the severe stenosis group, and the lowest CRP value was found in the control group ($P<0.01$). A one-unit increase in UA could increase the risk by 2.203 times. The CRP value was higher in the soft lesion group without calcification than in the hard lesion group with calcification.

Conclusion: Our findings demonstrated that age, UA, and CRP values were identified as predictors independent of each other in the development of carotid stenosis. Regarding plaque classification, our results identified CRP, mean platelet volume (MPV), white blood cell, and lymphocyte values as negative predictors. The findings of our study indicate that CRP and UA are valuable in predicting the severity of stenosis and the formation of soft plaque.

Keywords: Atherosclerosis, Carotid, Inflammation

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Background

Atherosclerosis is a systemic inflammatory disease characterized by the progressive accumulation of inflammatory cells and oxidized lipoproteins within the arterial walls, and inflammation plays a pivotal role in the onset and every aspect of the atherosclerotic process (1,2).

Carotid artery disease (CAD) is a robust predictive indicator of worldwide cardiovascular morbidity and mortality. CAD is related to an increased risk of stroke and acute coronary syndrome (3). Therefore, aggressive treatment regimens are warranted to prevent affected patients by ischemic/embolic endpoints, especially in severe CAD. Moreover, the degree of carotid stenosis and the composition of plaques were suggested to have possible utilization in determining stroke risk (4,5). In addition, some studies have shown a close relationship between CAD in patients with unstable carotid plaques (6,7). Previous studies have demonstrated that inflammation is associated with parameters such as monocyte/high-density lipoprotein cholesterol (HDL-C) ratio (MHR), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and white blood cell/monocyte (WMR). Other studies have suggested that

these parameters are related to the presence and severity of CAD and may be useful in predicting future coronary events and mortality (8-11). It has been found that these parameters are closely related to ischemic stroke and CAD (12). Inflammation is a significant factor in the development of atherosclerosis at every stage, including the destabilization of plaques in the arteries. Soft plaques more are available for destabilization than hard plaques. Hence, inflammatory parameters are higher in patients who have a soft plaque.

Xanthine oxidase is responsible for the production of uric acid (UA) by oxidizing hypoxanthine and xanthine, which are the byproducts of purine metabolism (13). UA is the end product of this process. Elevated levels of UA can potentially contribute to the advancement of arteriolosclerosis and atherosclerosis (14). In this study, we planned to investigate the relationship of routinely checked inflammation parameters and UA with carotid plaque severity and plaque morphology. Plaques that appeared echolucent and echogenic on ultrasonography were defined as soft hard plaques, respectively. An echogenic plaque is a type of atherosclerotic plaque that appears brighter than the surrounding tissue on an ultrasound image due to its high calcium content. Echolucent plaques typically have a higher content of lipids and inflammatory cells. Echolucent carotid artery plaques (soft plaques rich in lipids and/or intraplaque hemorrhage) are linked to a higher risk of stroke regardless of the severity of artery narrowing (13).

Materials and Methods

Study Design and Patient Choice

The study was conducted in the cardiology clinic between May 2021 to November 2021. Our study was designed prospectively and included 209 patients diagnosed with carotid stenosis, including 35% (n = 109) and 32% (n = 100) with mild and severe carotid stenosis, respectively, and 101 patients (33%, n = 101) were included in the control group. The study included patients who were presented to the emergency department with cerebrovascular events and diagnosed with carotid stenosis based on clinical, imaging, and laboratory evaluations. Patients with a history of cancer, acute or chronic coronary syndrome, systemic inflammatory disease, heart failure, significant heart valve disease, chronic obstructive pulmonary disease, hepatic or renal insufficiency, hematological disorders, or acute infection were excluded from the study.

The patients' demographic information, including age and gender, was documented, and a thorough physical examination was conducted to check for acute or chronic illnesses. The patients were also interviewed to gather information about any significant medical history. Either a composed or an oral-saw informed assent was gotten from every one of the partaking patients given at the emergency service. Our review was performed following the administrators by the Announcement of Helsinki and was endorsed by the local ethics committee.

Blood Sample Collection

Blood samples for all analyses were drawn by aseptic venipuncture from an antecubital vein into routine biochemistry tubes containing K2EDTA. Complete blood and routine biochemistry parameters were measured immediately. The biochemical parameters and hematological were analyzed using the Abbott ARCHITECT c8000 and Cell-Dyn 3700 devices manufactured by Abbott Laboratories in the USA.

Ultrasonographic Evaluation

All patients evaluated the carotid intima-media thickness in the longitudinal plane using a 13 MHz linear probe with the Toshiba Aplio 500 (Toshiba Medical Systems Corporation, Tokyo, Japan). Initially, the patient was supine, and the neck was angled approximately 20° to the opposite side. Then, the posterior wall of the middle part of the right and left common carotid arteries were measured, and the carotid intima medial distance was measured from a distance between the echogenicity of the vessel lumen and the echogenicity of the media layer. A space above 1 mm for each carotid artery was considered abnormal (15). Plaques were classified into echolucent (soft plaques in the article) and echogenic (hard plaques in the article) categories. In the transverse orientation, the most stenotic area of the carotid vessels is carefully examined, and measurements are taken to determine the extent of the narrowing. This is performed by assessing the percentage of area/diameter stenosis and/or residual lumen diameter. The percent diameter stenosis method is used to express the degree of narrowing in the carotid vessels. This measurement is calculated as a percentage of the original vessel diameter using the following formula (16):

Percent diameter stenosis = [(1 - minimal lumen diameter/normal vessel diameter) × 100%]

Plaques were divided into two groups based on the estimated surface area of stenosis, including mild stenosis for surface areas less than 60% and severe stenosis for surface areas greater than or equal to 60% (17).

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows (Version 21.0), and the Kolmogorov-Smirnov and Shapiro-Wilk tests tested the normality assumption. The type of variable and the state of assumptions determined the use of the chi-square test, Fisher's exact test, Mann-Whitney U test, and independent *t* test for the univariate analysis of variables in the study. Descriptive statistics for variables are reported as the mean + standard deviation and median (interquartile ranges at the 25th and 75th percentiles). Duncan multiple comparison tests were used to collate the groups with statistical differences between them as a result of variance analysis. After finding significant differences among three or more groups using the Kruskal-Wallis H test, the Mann-Whitney U test was employed to compare each pair of groups. To control for the risk of obtaining false positives from

multiple comparisons, the *P* values were adjusted using the Bonferroni correction. The relationship between the CRP variable and other variables was examined with the Spearman correlation test. Multinomial logistic regression analysis was used to determine whether variables included in the study were an important risk factor for stenosis formation. First, univariate multinomial logistic regression analysis was applied to determine the effects of individual variables. Then, stepwise multivariate multinomial logistics regression analysis was utilized to find the most successful logistic model in predicting stenosis groups. The control group was used as the reference category when applying the multinomial logistic regression analysis. Multivariate logistic regression analysis was applied to examine the importance of variables on calcification formation. For all statistical analyses, results with a *P* value lower than 0.05 were considered statistically significant and interpreted accordingly.

Results

The study group comprised 209 patients diagnosed with carotid stenosis. A control group was constructed that included 101 healthy control subjects. The baseline clinical, laboratory, and univariate analysis results of the study population are summarized in Table 1. Based on the analysis findings (Table 1), there was a statistically significant difference between the groups in terms of the urea variable ($P<0.01$). There was no significant difference in mean Urea values of severe and mild stenosis groups. However, the mean urea value of both groups was statistically different from that of the control group ($P<0.01$). The urea value of the severe and mild stenosis groups was higher than the control group. In addition, both mild and severe stenosis groups showed higher creatinine levels compared to the control group ($P<0.01$). The difference between mild and severe stenosis groups in the creatinine value was statistically nonsignificant. The UA values of mild and severe stenosis groups were higher than that of the control group ($P<0.01$).

Of the compared groups, the severe stenosis group had the highest mean CRP value, while the control group had the lowest CRP value ($P<0.01$). The lowest level of alanine transaminase (ALT) was found in the severe stenosis group, whereas the highest level was observed in the control group. The difference between the severe and mild stenosis groups in mean ALT values was statistically nonsignificant. The mean ALT values of both groups were statistically different from the mean ALT value of the control group ($P<0.01$). The control group had a higher mean gamma-glutamyl transferase (GGT) value than the other groups ($P<0.05$).

The hemoglobin values of mild and severe stenosis groups were lower than that of the control group ($P<0.01$). The difference between severe and mild stenosis groups in the red blood cell distribution width (RDW) value was statistically nonsignificant. The difference between the RDW value of both groups and the control group was statistically significant ($P<0.05$). The procalcitonin (PRCT) value of the control group was higher than the PCT value of the mild and severe stenosis groups ($P<0.01$). The highest NLR value was observed in the severe stenosis group, while the lowest value was found in the control group ($P<0.01$).

The reference category for the analysis was the control group. The results of the multinomial logistic regression analysis applied to determine which variables are effective predictors of stenosis are provided in Table 2. According to the results of univariate logistic regression analysis (Table 2), the effective predictors of the mild stenosis (<60) group were identified as age ($\beta=0.159$, $P<0.001$), UA ($\beta=0.391$, $P=0.004$), CRP ($\beta=1.189$, $P<0.001$), ALT ($\beta=-0.048$, $P=0.001$), NLR ($\beta=0.461$, $P=0.002$), HG ($\beta=-0.276$, $P=0.001$), UREA ($\beta=0.091$, $P<0.001$), creatinine ($\beta=3.914$, $P<0.001$), LYMP ($\beta=-0.481$, $P=0.005$), and CT ($\beta=-5.815$, $P=0.003$). Effective predictors of the severe stenosis (>60) group were determined as age ($\beta=0.166$, $P<0.001$), UA ($\beta=0.513$, $P<0.001$), CRP ($\beta=1.403$, $P<0.001$), ALT ($\beta=-0.046$, $P=0.002$), NLR ($\beta=0.533$, $P<0.001$), HG ($\beta=-0.273$, $P=0.002$), RDW ($\beta=0.274$, $P=0.021$), UREA ($\beta=0.094$, $P<0.001$), creatinine ($\beta=3.373$, $P\leq0.001$), GGT ($\beta=-0.022$, $P=0.048$), NEUT ($\beta=0.230$, $P=0.018$), LYMP ($\beta=-0.618$, $P=0.001$), and PLR ($\beta=0.008$, $P=0.007$).

According to the results of multivariate logistic regression coefficients, effective predictors of the mild stenosis (<60) group were identified as age ($\beta=0.171$, $P\leq0.001$) and UA ($\beta=0.790$, $P\leq0.001$). An increase of one unit in the age variable could increase the risk of entering the mild stenosis group by 1.187 times. Moreover, a one-unit increase in UA increased the risk by 2.203 times. The severe stenosis (>60) group was identified as age ($\beta=0.152$, $P\leq0.001$), UA ($\beta=0.871$, $P\leq0.001$), and CRP ($\beta=0.757$, $P=0.034$). A one-unit increase in the age variable increased the risk of the patient entering the severe stenosis (>60) group by 1.165 times. Furthermore, an increase of one unit in UA could increase this risk by 2.389 times. An increase of one unit in the CRP value increased the risk of entering the severe stenosis (>60) group by 2.132 times.

The descriptive statistics and univariate analysis results of the means of the groups with and without calcification are presented in Table 3. According to these results, 59.61% (n = 62) of patients in the soft lesion group without calcification had HT, while 81.90% (n = 86) in the hard lesion group with calcification had HT ($P<0.01$). The urea value of the hard lesion group was higher than that of the soft lesion group ($P<0.05$). The difference in mean creatinine values was statistically significant ($P<0.05$). The CRP value was higher in the soft lesion group without calcification than in the hard lesion group with calcification. This difference was statistically significant ($P<0.01$). The difference between the groups in terms of the WBC value was statistically significant ($P<0.05$). In terms of monocyte, the mean platelet volume (MPV), platelet distribution width (PDW), and MHR values, the

Table 1. The Baseline Clinical, Laboratory, and Univariate Analysis Results of the Study Population

Variables	Control Group (No Stenosis) n=101	Mildly Stenosis (<60%) n=109	Severe Stenosis >60% n=100	Difference Between Groups by ANOVA and Kruskal Wallis	K-<60%	K->60%	<60%->60%
Age (y)	52.62±14.18	72.47±9.76	73.14±9.08	**<0.001**	**<0.001**	**<0.001**	**0.613**
Gender (Male/female)	47/54	59/50	61/39	0.943	N/A	N/A	N/A
BMI (kg/m^2)	26.88±1.70	26.90±1.63	27.11±1.67	0.602	N/A	N/A	N/A
DM (present/absent)	31/70	34/75	29/71	0.938	N/A	N/A	N/A
HT (present/absent)	79/22	83/26	65/35	0.074	N/A	N/A	N/A
HL (present/absent)	39/62	40/69	29/71	0.316	N/A	N/A	N/A
Smoking (present/absent)	46/55	52/57	47/53	0.951	N/A	N/A	N/A
CAD (present/absent)	62/39	63/46	47/53	0.102	N/A	N/A	N/A
PAD (present/absent)	5/96	7/102	9/91	0.512	N/A	N/A	N/A
LVEF (%)	62 (62~65)	62 (62~65)	62 (62-65)	0.865	N/A	N/A	N/A
Glucose (mg/dL)	90 (67~129.5)	107.5 (90~142.0)	109.0 (93~139)	0.204	N/A	N/A	N/A
Urea (mg/dL)	29 (25.65~35.0)	40.50 (32.25~48.75)	40 (30~52.0)	**<0.001**	<0.001	<0.001	0.935
Creatinine (mg/dL)	0.80 (0.67~0.93	0.99 (0.83~1.18)	0.93 (0.78~1.12)	**<0.001**	<0.001	0.001	0.504
Uric acid (mg/dL)	4.90 (4~6)	6 (5~6.15)	6 (5~6.10)	**<0.001**	**<0.001**	**<0.001**	**0.284**
T. Chol (mg/dL)	181.81±35.99	179.18±39.43	184.82±40.86	0.605	N/A	N/A	N/A
LDL-C (mg/dL)	105.91±27.97	103.55±35.78	110.32±35.98	0.374	N/A	N/A	N/A
HDL-C (mg/dL)	43 (38.25~51)	44 (38~55.5)	40 (34.25~49)	0.338	N/A	N/A	N/A
TG (mg/dL)	134 (102~186)	128.5 (92.75~169.50)	165.50 (101.5~253)	0.868	N/A	N/A	N/A
CRP (mg/dL)	0.27 (0.10~0.40)	0.48 (0.19~0.91)	0.66 (0.34~1.34)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
AST IU/L)	17 (15~21)	17 (14~20.75)	17 (15~22)	0.281	N/A	N/A	N/A
ALT (IU/L)	17 (14~24)	14 (10.25~18)	12 (9.5~19.5)	<0.001	<0.001	<0.001	0.775
GGT (U/L)	24 (16~30)	19 (14~26.75)	19 (15.5~24)	0.044	0.047	0.024	0.995
WBC (10^9/L)	7.87±1.75	8.28±5.40	8.01±2.07	0.692	N/A	N/A	N/A
Hb (gr/dL)	14.35±1.56	13.59±1.90	13.60±1.63	**0.001**	**0.002**	**0.001**	**0.979**
RDW (%)	13 (12.6~13.7)	13.4 (12.8~13.9)	13.45 (12.9~14.1)	**0.014**	**0.019**	**0.007**	**0.698**
Platelet (10^9/L)	264.75±64.19	241.95±69.32	256.160±87.35	0.080	N/A	N/A	N/A
Neutrophil (10^9/L)	4.17 (3.53~5.10)	4.47 (3.69~5.44)	4.30 (3.69~5.96)	0.163	N/A	N/A	N/A
Lymphocyte (10^9/L)	2.57±0.75	2.24±0.85	3.97±1.81	0.443	N/A	N/A	N/A
Monocyte (10^9/L)	0.60 (0.53~0.74)	0.61 (0.45~0.74)	0.69 (0.52~0.81)	0.365	N/A	N/A	N/A
MPV (fL)	10.30 (9.75~10.80)	10.40 (9.8~11)	10.25 (9.7~11.25)	0.642	N/A	N/A	N/A
PCT (%)	0.27 (0.23~0.32)	0.24 (0.20~0.28)	0.25 (0.20~0.31)	**0.003**	**0.001**	**0.060**	**0.215**
PDW (%)	12 (10.9~13.2)	12 (10.7~13.1)	12.25 (10.8~14.25)	0.436	N/A	N/A	N/A
NLR	1.71 (1.28~2.12)	2.02 (1.62~2.81)	2.10 (1.53~2.91)	**<0.001**	**0.001**	**<0.001**	**0.561**
MHR	0.014 (0.01~0.017)	0.013 (0.009~0.01)	0.015 (0.01~0.02)	0.078	N/A	N/A	N/A
PLR	99.25 (81.54~140.67)	110.98 (82.98~148.81)	111.40 (91.14~155.85)	0.135	N/A	N/A	N/A
WMR	0.72 (0.64~0.85)	0.71 (0.60~0.89)	0.71 (0.62~0.93)	0.882	N/A	N/A	N/A
Calcification (Hard/soft)	N/A	58/51	47/53	0.370	N/A	N/A	N/A

Note. BMI: Body mass index; DM: Diabetes mellitus; HT: Hypertension; HL: Hyperlipidemia; CAD: Coronary artery disease; PAD: Peripheral artery disease; LVEF: Left ventricular ejection fraction; T. CHOL: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; C-RP: C-reactive protein; AST: Aspartate transaminase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; WBC: White blood cell count; Hb: Hemoglobin; RDW: Red blood cell distribution width; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; N/A: Not available; NLR: Neutrophil/lymphocyte ratio; MHR: Monocyte/high-density lipoprotein cholesterol (HDL-C) ratio; PLR: Platelet/lymphocyte ratio; WMR: White blood cell/ monocyte.

mean values of the hard lesion group with calcification were lower than those of the soft lesion group without calcification. These differences between the groups were statistically significant ($P<0.01$).

A regression model, whose coefficients are presented in Table 4, was derived from the multivariate logistic regression analysis to identify the risk factors that affect calcification. The logistic regression model developed using the backward elimination method achieved a percentage of correct predictions of 82.4%. The accurate estimation value of the model obtained according to the Hosmer-Lemeshow test score was quite good ($\chi^2=15.216$,

Table 2. Multinomial Logistic Regression Analysis Results

		Univariate Logistic Regression						Multivariate Logistic Regression					
	Variables	**β**	**SE**	**Wald**	***P* Value**	**Exp(B)**	**95% CI for Exp(B) Lower-Upper**	**B**	**SE**	**Wald**	***P* Value**	**Exp(B)**	**95% CI for Exp(B) Lower-Upper**
<60	Age	0.159	0.020	61.971	**<0.001**	1.172	1.127-1.220	0.171	0.030	31.811	<0.001	1.187	1.118-1.260
	Uric acid	0.391	0.137	8.165	**0.004**	1.479	1.131-1.934	0.790	0.225	12.348	<0.001	2.203	1.418-3.424
	CRP	1.189	0.347	11.720	**<0.001**	3.284	1.662-6.486	0.611	0.363	2.842	0.092	1.843	0.905-3.750
	ALT	0.048	0.015	10.509	**0.001**	0.953	0.926-0.981	0.031	0.026	1.421	0.233	0.970	0.922-1.020
	NLR	0.461	0.146	9.922	**0.002**	1.586	1.190-2.114	0.415	0.252	2.713	0.100	1.515	0.924-2.483
	Hb	0.276	0.086	10.194	**0.001**	0.759	0.641-0.899	0.169	0.149	1.285	0.257	0.844	0.630-1.131
	RDW	0.220	0.119	3.417	0.065	1.247	0.987-1.575	N/A	N/A	N/A	N/A	N/A	N/A
	Urea	0.091	0.015	34.915	**<0.001**	1.096	1.063-1.129	N/A	N/A	N/A	N/A	N/A	N/A
	Creatinine	3.914	0.716	29.884	**<0.001**	50.075	12.310-203.696	N/A	N/A	N/A	N/A	N/A	N/A
	GGT	0.009	0.009	0.977	0.323	0.991	0.975-1.008	N/A	N/A	N/A	N/A	N/A	N/A
	WBC	0.023	0.074	0.097	0.755	0.977	0.846-1.129	N/A	N/A	N/A	N/A	N/A	N/A
	Platelet	0.004	0.002	4.866	**0.027**	0.996	0.992-1.000	N/A	N/A	N/A	N/A	N/A	N/A
	Neutrophil	0.111	0.098	1.298	0.255	1.118	0.923-1.353	N/A	N/A	N/A	N/A	N/A	N/A
	Lymphocyte	0.481	0.172	7.826	**0.005**	0.616	0.441-0.866	N/A	N/A	N/A	N/A	N/A	N/A
	Monocyte	0.079	0.664	0.014	0.906	1.082	0.295-3.973	N/A	N/A	N/A	N/A	N/A	N/A
	MPV	0.062	0.149	0.172	0.679	1.064	0.794-1.426	N/A	N/A	N/A	N/A	N/A	N/A
	PCT	5.815	2.125	7.486	**0.006**	0.003	<0.0014-0.192	N/A	N/A	N/A	N/A	N/A	N/A
	PDW	0.027	0.066	0.162	0.688	1.027	0.902-1.169	N/A	N/A	N/A	N/A	N/A	N/A
	PLR	0.004	0.003	2.011	0.156	1.004	0.998-1.010	N/A	N/A	N/A	N/A	N/A	N/A
	WMR	0.341	0.466	0.536	0.464	1.406	0.565-3.503	N/A	N/A	N/A	N/A	N/A	N/A
>60	Age	0.166	0.021	63.916	**<0.001**	1.181	1.134-1.230	0.152	0.029	27.331	<0.001	1.165	1.100-1.233
	Uric acid	0.513	0.139	13.656	**<0.001**	1.671	1.273-2.193	0.871	0.223	15.319	<0.001	2.389	1.545-3.695
	CRP	1.403	0.346	16.412	**<0.001**	4.068	2.063-8.021	0.757	0.357	4.487	0.034	2.132	1.058-4.297
	ALT	0.046	0.015	9.314	**0.002**	0.955	0.927-0.984	0.032	0.025	1.634	0.201	0.968	0.922-1.017
	NLR	0.533	0.147	13.172	**<0.001**	1.704	1.278-2.272	0.487	0.248	3.849	0.050	1.628	1.001-2.650
	Hb	0.273	0.088	9.694	**0.002**	0.761	0.640-0.904	0.115	0.148	0.606	0.436	0.891	0.666-1.192
	RDW	0.274	0.119	5.308	**0.021**	1.315	1.042-1.660	N/A	N/A	N/A	N/A	N/A	N/A
	Urea	0.094	0.016	36.841	**<0.001**	1.099	1.066-1.133	N/A	N/A	N/A	N/A	N/A	N/A
	Creatinine	3.373	0.717	22.115	**<0.001**	29.513	7.149-118.886	N/A	N/A	N/A	N/A	N/A	N/A
	GGT	0.022	0.011	3.922	**0.048**	0.979	0.958-1.000	N/A	N/A	N/A	N/A	N/A	N/A
	WBC	0.039	0.074	0.286	0.593	1.040	0.900-1.202	N/A	N/A	N/A	N/A	N/A	N/A
	Platelet	0.001	0.002	0.638	0.424	0.999	0.995-1.002	N/A	N/A	N/A	N/A	N/A	N/A
	Neutrophil	0.230	0.097	5.622	**0.018**	1.259	1.041-1.522	N/A	N/A	N/A	N/A	N/A	N/A
	Lymphocyte	0.618	0.181	11.619	**0.001**	0.539	0.378-0.769	N/A	N/A	N/A	N/A	N/A	N/A
	Monocyte	1.018	0.654	2.422	0.120	2.767	0.768-9.970	N/A	N/A	N/A	N/A	N/A	N/A
	MPV	0.210	0.150	1.968	0.161	1.234	0.920-1.655	N/A	N/A	N/A	N/A	N/A	N/A
	PCT	1.679	2.008	0.699	0.403	0.187	0.004-9.544	N/A	N/A	N/A	N/A	N/A	N/A
	PDW	0.137	0.065	4.503	**0.034**	1.147	1.011-1.302	N/A	N/A	N/A	N/A	N/A	N/A
	PLR	0.008	0.003	7.211	**0.007**	1.008	1.002-1.013	N/A	N/A	N/A	N/A	N/A	N/A

Note. CI: Confidence interval; S.E.: Standard error; C-RP: C-reactive protein; ALT: Alanine aminotransferase; NLR: Neutrophil/lymphocyte ratio; Hb: Hemoglobin; RDW: Red blood cell distribution width; GGT: Gamma-glutamyl transferase; WBC: White blood cell count; MPV: Mean platelet volume; N/A: Not available; PCT: Plateletcrit; PDW: Platelet distribution width; PLR: Platelet/lymphocyte ratio; WMR: White blood cell/monocyte.

$P>0.05$). Multivariate logistic regression results are also listed in Table 4. Based on the results (Table 4), CRP, MPV, WBC, and LYMP were found to be important risk factors in determining whether the patients belonged to the soft or hard lesion group. A 1-unit increase in the CRP value increased the risk of belonging to the soft lesion group by 2.624 times ($\beta=0.965$, $P=0.004$). A one-unit increase in MPV could increase the patient's risk of the soft lesion by 2.168 times ($\beta=0.774$, $P=0.003$). A one-unit increase in the WBC variable increased the patient's risk of soft lesion by 2.785 times ($\beta=1.024$, $P=0.011$). Finally, a one-unit increase in the LYMPH variable could increase the risk of

Table 3. The Descriptive Statistics and Univariate Analysis Results of the Means of the Groups About Echogenicity and With/Without Calcification

Variables	Soft Lesion (n = 104)	Hard Lesion (n = 105)	*P* Value
Age (y)	73.80 ± 10.44	71.79 ± 8.22	0.122
BMI (kg/m^2)	26.92 ± 1.83	27.07 ± 1.45	0.504
DM (present/absent)	33/71	30/75	0.619
HT (present/absent)	62/42	86/19	**< 0.001**
HL (present/absent)	32/72	37/68	0.492
Smoking (present/absent)	52/52	47/58	0.448
CAD (present/absent)	50/54	60/45	0.189
PAD (present/absent)	7/97	9/96	0.617
LVEF (%)	62 (61.25~65)	62 (62~65	0.913
Glucose (mg/dL)	105.5 (85~127)	109 (92~144)	0.508
Urea (mg/dL)	35.5 (31.5~53.75)	41 (31~49.5)	**0.034**
Creatinine (mg/dL)	1 (0.88~1.12)	0.98 (0.81~1.22)	**0.036**
Uric acid (mg/dL)	5.95 (5~6.25)	6 (5~6.45)	0.653
T. Chol (mg/dL)	179.42 ± 41.11	184.20 ± 39.27	0.414
LDL-C (mg/dL)	106.97 ± 35.67	106.80 ± 36.39	0.974
HDL-C (mg/dL)	40 (36~49)	41 (34~47.50)	0.559
TG (mg/dL)	140.5 (97.75~196)	171 (103~228)	0.138
CRP (mg/dL)	0.55 (0.29~2.33)	0.52 (0.33~0.77)	**0.003**
AST, IU/L	16 (13.25~19)	17 (15~23)	0.249
ALT, IU/L	13.5 (10~18.75)	12 (10~20)	0.907
GGT, U/L	19 (14.25~29)	20 (16~26.5)	0.216
WBC, 10^9/L	8.19 ± 2.00	7.60 ± 1.91	**0.030**
Hb, gr/dL	13.57 ± 1.72	13.61 ± 1.83	0.879
RDW, %	13.40 (12.7~13.9)	13.30 (12.85~14)	0.547
Platelet, 10^9/L	242.18 ± 81.66	255.25 ± 75.27	0.230
Neutrophil, 10^9/L	4.96 (3.45~6.14)	4.43 (3.50~5.20)	0.257
Lymphocyte, 10^9/L	2.31 ± 0.93	2.09 ± 0.70	0.057
Monocyte, 10^9/L	0.68 (0.57~0.99)	0.57 (0.44~0.72)	**0.001**
MPV, fL	11.05 (10.55~12.05)	10.10 (9.7~10.8)	**< 0.001**
PCT, %	0.22 (0.20~0.36)	0.24 (0.21~0.30)	0.835
PDW, %	14.15 (12.20~17)	11.5 (10.7~12.8)	**< 0.001**
NLR	2.08 (1.64~2.96)	2.18 (1.41~2.72)	0.425
MHR	0.017 (0.01~0.025)	0.013 (0.009~0.021)	**0.009**
PLR	93.8 (72.2~136.14)	114.08 (90.68~182.39)	0.159
WMR	0.70 (0.62~0.89)	0.70 (0.57~0.87)	0.232

Note. BMI: Body mass index; DM: Diabetes mellitus; HT: Hypertension; HL: Hyperlipidemia; CAD: Coronary artery disease; PAD: Peripheral artery disease; LVEF: Left ventricular ejection fraction; T. CHOL: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; C-RP: C-reactive protein; AST: Aspartate transaminase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; WBC: White blood cell count; Hb: Hemoglobin; RDW: Red blood cell distribution width; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; NLR: Neutrophil/lymphocyte ratio; MHR: Monocyte/high-density lipoprotein cholesterol (HDL-C) ratio; PLR: Platelet/lymphocyte ratio; WMR: White blood cell/ monocyte.

the soft lesion by 2.451 times (β = 0.896, *P* = 0.022).

In the study, the effect of CRP on both stenosis formation and calcification was found to be statistically significant. Therefore, a Spearman-Rho correlation analysis was conducted to investigate the linear relationship between CRP and other variables. The Spearman Rho coefficients showing the direction and size of the relationship between CRP and other variables are provided in Table 5. According to these coefficients, a significant negative correlation was found between CRP and HDL (Rho = -0.179, *P* < 0.05). There was a significant positive correlation between GGT and CRP (Rho = 0.214, *P* < 0.05). Statistically, a significant positive relationship was observed between the neutrophile variable and CRP (Rho = 0.162, *P* < 0.05). Additionally, a significant positive correlation was identified between the PCT variable and CRP (Rho = 0.183, *P* < 0.05). Similarly, there was a significant positive correlation between NLR and CRP (Rho = 0.162, *P* < 0.05). Moreover, a strong positive correlation was detected between CRP and MHR (Rho = 0.224, *P* < 0.01). Eventually, the positive relationship between CRP and PLR variable was statistically significant (Rho = 0.167, *P* < 0.05).

Discussion

Carotid artery stenosis has mortal complications such as stroke, transient ischemic attack, aneurysm, and carotid artery dissection. The determinants of carotid artery stenosis risk include life-saving conditions. Inflammatory parameters facilitate detecting and monitoring risks and conditions associated with carotid stenosis. In our study, age, UA, and CRP values were determined as independent predictors for the development of carotid stenosis. Regarding plaque classification, CRP, MPV, WBC, and lymphocyte values were determined as negative predictors. CRP alone was found to be useful in predicting stenosis severity and soft plaque formation. Furthermore, serum UA levels were highly associated with the risk of stenosis than the other variables because a one-unit increase in UA could extremely increase the risk of stenosis. Both CRP and UA are effective in predicting the severity of stenosis and the formation of soft plaques. Soft plaques, which are non-calcified, are considered more unstable than hard plaques and pose a greater risk of thromboembolism, stroke, and rupture. Soft plaques are associated with inflammation in the arterial wall, and this is associated with the higher CRP value in the soft lesion group. Van Lammeren et al demonstrated that individuals with asymptomatic carotid plaques exhibit more stable plaque characteristics such as greater smooth muscle cell content and calcification rate, and a lower incidence of intraplaque bleeding than those with a history of cerebrovascular accident (17). Inflammation has an effect on plaque morphology and instability, thus it has been known that inflammatory markers may be predictive of thromboembolic events. Inflammation plays a critical role in both the initiation and progression of atherosclerosis, including its complications. PLR and NLR are new markers that have been shown to increase in various inflammatory diseases, and studies indicate that they are associated with atherosclerotic diseases. İdil Soylu et al concluded that PLR is useful in

Table 4. The Result of the Multivariate Logistic Regression Analysis Applied to Determine Risk Factors Affecting Calcification

Variables	B	SE	Wald	*P* Value	Exp(B)	95%CI for Exp(B) Lower-Upper
Urea	0.028	0.016	3.001	0.083	1.028	0.996-1.062
CRP	0.965	0.338	8.156	0.004	2.624	1.353-5.086
MPV	0.774	0.259	8.898	0.003	2.168	1.304-3.604
WBC	1.024	0.402	6.499	0.011	2.785	1.267-6.119
Platelet	-0.006	0.004	2.714	0.099	0.994	0.986-1.001
Lymphocyte	0.896	0.391	5.255	0.022	2.451	1.139-5.274
NLR	0.190	0.186	1.051	0.305	1.210	0.841-1.741

Note. CI: Confidence interval; S.E.: Standard error; C-RP: C-reactive protein; MPV: Mean platelet volume; WBC: White blood cell count; NLR: Neutrophil/ lymphocyte ratio.

Table 5. The Direction and Size of the Relationship Between CRP and Other Variables

Variables	CRP
Age	-0.034
BMI	-0.050
LVEF	0.109
Glucose	0.136
Urea	-0.060
Creatinine	-0.017
Uric acid	0.020
T-CHOL	0.026
LDL-C	0.075
HDL-C	-0.179*
TG	-0.044
AST	-0.001
ALT	0.159
GGT	0.214*
WBC	0.119
Hb	-0.017
RDW	0.144
Platelet	0.151
Neutrophile	0.162*
Lymphocyte	-0.047
Monocyte	0.104
MPV	-0.015
PCT	0.183*
PDW	0.034
NLR	0.162*
MHR	0.224**
PLR	0.167*
WMR	0.141

Note. BMI: Body mass index; LVEF: Left ventricular ejection fraction; T. CHOL: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; C-RP: C-reactive protein; AST: Aspartate transaminase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; WBC: White blood cell count; Hb: Hemoglobin; RDW: Red blood cell distribution width; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; NLR: Neutrophil/lymphocyte ratio; MHR: Monocyte/high-density lipoprotein cholesterol (HDL-C) ratio; PLR: Platelet/lymphocyte ratio; WMR: White blood cell/ monocyte.

predicting the degree of stenosis and the risk of stroke in patients with carotid stenosis (18). In our study, the PLR value increased significantly in the group with advanced stenosis compared to the control group. On the other hand, it was observed that there is a significant increase in the NLR value in both mild stenosis and advanced stenosis groups compared to the control group.

In our study, markers such as MPV and PDW, which were found to be useful in predicting the development of atherosclerotic disease in previous studies, were evaluated as well (19,20). This study reported no association between the development of carotid stenosis and MPV and RDW values. However, both markers were markedly elevated in individuals with soft plaques compared to those with hard plaques. It was concluded that MPV might be useful in predicting soft plaque formation. This finding is consistent with those of previous studies, representing high MPV levels in instances of arterial thrombotic events, including acute myocardial infarction and ischemic stroke (21,22). Chen et al determined that MHR could be a predictive marker for developing and progressing subclinical carotid atherosclerosis in diabetic patients (23). In our study, no significant difference was observed between the development of stenosis and MHR levels; it can be concluded that it can be a valuable marker in predicting soft plaque formation. The relationship between CRP and carotid artery stenosis has been detected in some studies (24,25). In our study, it was found to be the only marker with a predictive value in evaluating the degree of stenosis and plaque structure. In the study of Xiong et al on 115 patients undergoing carotid endarterectomy, the correlation between plaque fragility and CRP levels was remarkable (24). In a study conducted by Huang et al on 5349 asymptomatic people, it was observed that both basal and chronic CRP elevations were associated with carotid artery stenosis (25).

Carotid plaques from symptomatic patients (cerebrovascular events) had a higher quantity of UA than those from asymptomatic patients. The levels of UA (measured in micrograms per gram) present in atherosclerotic plaques demonstrated a positive correlation with the levels of SUA (serum UA). In addition, UA is useful for the degree of stenosis, and UA was detected to be associated with cerebrovascular events (26).

In a study performed by Ma et al on 11382 people, including 7597 participants in the high UA group and 3785 in the control group, the high UA group was significantly higher than that in the control group, and the difference was significant (27).

Limitations of the Study

There were several limitations to our study. First, the sample size needed to be more significant to draw definitive conclusions. Additionally, the study was conducted at a single centre, which might have limited its generalizability to the broader population.

Conclusion

Overall, our findings revealed that the CRP level is associated with both the stenosis level and plaque morphology. According to the results, this relationship was more valuable than the other inflammatory parameters. Therefore, CRP is most superior in terms of its association with the degree of carotid stenosis. In addition to these results, one unit increase of the UA level was more related to the risk of carotid stenosis than the other inflammatory markers, demonstrating that CRP and serum UA levels are precious for the detection of carotid artery stenosis and risk of carotid artery stenosis.

Authors' Contribution

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Competing Interests

All authors declare that they have no conflict of interests.

Ethical Approval

The Ethics Committee Resolution number 2019-10/118, dated 28.05.2019, was obtained from the Clinical Research Ethics Committee of the Faculty of Medicine, Ahi Evran University.

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