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C-reactive protein to albumin ratio predicts for severity of coronary artery disease and ischemia

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Abstract. – OBJECTIVE: Myocardial perfusion scintigraphy (MPS) has prognostic importance in demonstrating myocardial ischemia, and the Syntax score (SS) in coronary angiography has prognostic importance in demonstrating the extent of coronary artery disease (CAD). C-reactive protein (CRP) and albumin are prognostic markers for both atherosclerosis and inflammation. In this study, we aimed at investigating the relationship of CRP/albumin ratio (CAR) with the severity of myocardial ischemia and SS in patients with stable CAD.

PATIENTS AND METHODS: We retrospectively evaluated 355 patients between January 2018 and January 2020. Patients were divided into normal, mild-moderate, and severe ischemia groups according to MPS. SS was classified as low risk (< 32) and high risk (≥ 32) groups. The association between CAR, SS, and MPS findings were analyzed.

RESULTS: The median CAR level was higher in the high-risk group compared to the low-risk group (20.7 *vs.* 13.8, $p < 0.05$), and higher in the low-risk group compared to the normal group (13.8 *vs.* 7.4, $p < 0.05$). The increase in CAR level was associated with increased ischemia severity ($p < 0.001$). Increased CAR level was found to be an independent predictor of both high-risk and severe ischemia (OR = 1.04, $p = 0.006$; OR = 1.05, $p = 0.001$, respectively). The cut-off value of CAR > 10.2 was a common point in predicting both low-risk and mild-moderate ischemia (AUC: 0.736, $p < 0.001$; AUC: 0.741, $p < 0.001$, respectively).

CONCLUSIONS: High CAR level was an independent predictor of both the severity of ischemia and the extent of CAD. Therefore, CAR can be a potential screening tool in patients with suspected CAD and in risk stratification.

Key Words:
Myocardial perfusion scintigraphy, Stable coronary artery disease, C-reactive protein to albumin ratio, Syntax score.

Introduction

Coronary artery disease (CAD), which is the leading cause of death worldwide, imposes a serious economic burden on health systems[1]. The presence of CAD is investigated by evaluating the amount of blood reaching the heart muscle or the nutrition of the heart muscle with myocardial perfusion scintigraphy (MPS). It is a widely used diagnostic method in the field of nuclear cardiology to detect patients with suspected or known ischemic heart disease. MPS reduces the number of unnecessary coronary angiography (CAG) and allows appropriate treatment planning[2]. On the other hand, there is a positive correlation between the severity of ischemia evaluated by MPS and the SYNTAX score (SS) evaluated during CAG[3]. Therefore, the MPS method has prognostic significance in patients with CAD[4,5]. However, there are both MPS and angiography costs and radiation risks. For this reason, inflammatory markers, which provide an easy and inexpensive evaluation, show increasing importance among screening methods[6].

CAD is mainly caused by atherosclerosis. It is known that inflammation plays a role in the pathogenesis of the initiation and progression of atherosclerosis. C-reactive protein (CRP) levels remain high as a systemic response in cardiovascular diseases based on atherosclerosis[7]. CRP levels, a marker for systemic inflammation, were found to be elevated in patients with stable and unstable angina who were at risk for myocardial infarction or sudden death[8,9]. Low serum albumin concentrations have been associated with vascular disease, atherosclerosis, and cardiovascular mortality[10,11]. Both CRP and albumin are acute phase reactants and are associated with atherosclerosis. Since the C-Reactive Protein/Albumin Ratio (CAR) reflects the balance between CRP and albumin levels, it has a prognostic significance based on systemic inflammation.

Perfusion defects are not observed in a significant proportion of patients referred to MPS[12]. On the other hand, we hypothesized that CAR levels could be an easy, simple and accessible screening tool for the classification of CAD severity due to systemic inflammation, which is thought to play

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a role in the pathogenesis of CAD. To the best of our knowledge, we could not find any study in which the relationship between CAR and severity of ischemia and the extent of CAD was evaluated together. Therefore, in this study, we investigated the severity of ischemia and the relationship between SS and CAR levels in patients referred to for gated single-photon emission computed tomography (SPECT) MPS and CAG with the suspicion of CAD.

Patients and Methods

Study Population

4,270 patients, who were referred for SPECT MPS from the Cardiology Outpatient Clinic between January 2018 and January 2020, were evaluated retrospectively. Based on the MPS reports, adenosine or dipyridamole was used as a pharmacological stressor and that was confirmed by the Nuclear Medicine Department. Written patient informed consent was obtained from all the participants. Local ethics committee approval was granted by Kirikkale University Non-Invasive Ethics Committee, under decision date and number 10.02.2022/2022.03.16

We excluded 3,915 patients from the study who did not meet the inclusion criteria. The exclusion criteria were heart failure, a history of CAD or revascularization, myocardial infarction, chronic kidney disease (estimated glomerular filtration rate that was < 60 mL/min), hepatic disease (aspartate aminotransferase and alanine aminotransferase levels that were 2-fold above the normal limits), history of systemic inflammatory disease or cancer; use of anti-inflammatory drugs or antibiotic medications within the week before the MPS. After the exclusion, 355 patients were included in the study.

Determination of the cardiovascular risk factors was conducted after reviewing the medical files of the participants. Hypertension was defined as having repeated blood pressure measurements > 140/90 mmHg or currently using antihypertensive drugs. Diabetes mellitus was defined as having multiple measurements of fasting plasma glucose levels ≥ 126 mg/dL or currently using antidiabetic drugs.

Laboratory Measurements

The complete blood count (CBC) values of all the patients were measured one day before the MPS. Routine blood chemistry and lipid panel measurements were conducted in the morning. Hemogram and lipid parameters were determined using a Beckman Coulter LH 780 (Mervue, Galway, Ireland). Using the same blood samples, the CAR value was calculated by dividing the CRP levels by the albumin levels.

Myocardial Perfusion Imaging

A 2-day stress and rest imaging protocol were performed *via* using of technetium 99-m methoxy-isobutylisonitrile (Tc-99 m MIBI) to allow for an evaluation of the myocardial perfusion. During the period of peak exercise or at peak hyperemia of the modified Bruce protocol, radiopharmaceutical agents were injected. An infusion of dipyridamole, at a dose of 0.142 mg/kg/min, or adenosine, at a dose of 0.28 mg/min was used for the stress imaging. The imaging was begun 30 to 45 min following the injection of 15-20 mCi of Tc-99m MIBI. A similar dose was injected for the conduction of the rest imaging if any perfusion defect was suspected on the stress images.

SPECT Imaging Protocol

All images were obtained over an orbit at an angle of 180° from the right anterior oblique, an angle of 45° to the left posterior oblique, and an angle of 45° using MEDISO AntScan SCP dual-head γ-camera (Mediso Ltd., Budapest, Hungary) that was equipped with an ultra-high resolution collimator, 64 × 64 matrix, elliptic orbit set comprising a step and shoot acquisition at intervals of 3° over an angle of 180°, 60 projections, and 9 to 13 s/projection using a 20% energy window that was centered on the 140 keV photopeak of the Tc-99 m. The patients were instructed to lay in the supine position and raise their arms straight above their heads. The image sets that were obtained *via* SPECT analysis were reconstructed on the nucline Anyscan Portal workstation (Mediso Ltd., Budapest, Hungary) using the relative risk and noise reduction parameters. Upon completion of each acquisition, a low-dose CT chest scan (100 keV, 1.0 mA, 0.2-0.3 mS) was conducted to obtain an attenuation map, which was then automatically applied *via* the processing software to effect correction of the emission data. Next, the MPS dataset was very carefully rematched using the CT attenuation map, so as to produce attenuation-corrected images.

The degree of ischemia was classified according to MPS images as follows: 0: No ischemia (n = 154), 1: Ischemia percentage < 5% (mild ischemia) (n = 45), 2: Ischemia percentage 5-9.9% (moderate ischemia) (n = 136), 3: Ischemia per-

centage ≥ 10% (severe ischemia) (n = 37). Patients with normal MPS results were considered the control group for both low SS patients and those with mild/moderate ischemia in MPS.

Coronary Angiography

Regardless of the presence of lesions, vessels with vessel diameter of less than 1.5 mm and/or stenosis of less than 50% were not included in the evaluation, and the SS of these patients was accepted as 0. SS was classified as low risk (< 32) and high risk (≥ 32) groups.

Statistical Analysis

Statistical analyses of collected data were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Determination of the normally distributed data was conducted using the Kolmogorov-Smirnov's test. Numerical variables that had normal distribution were expressed as the mean ± standard deviation, while those with non-normal distribution were expressed as the median (min-max). The categorical variables were expressed as numbers and percentages. One-way ANOVA test (post-hoc: Bonferroni test) was used in the comparison of the groups to determine the parametrical variables, while for the non-parametric variables, the Kruskal-Wallis' H test (post-hoc: Dunn's test) was used. The Chi-square and the Fisher exact Chi-square tests were used in the comparison of the categorical variables. Stepwise multivariable multinomial logistic regression analyses were conducted to establish any possible independent predictors of the severity of ischemia and CAD. Receiver operating characteristic curve analyses were conducted to establish diagnostic discrimination of the independent predictors on the severity of ischemia and CAD. $p < 0.05$ was considered statistically significant.

Results

A total of 355 patients were analyzed in the study, including 55.2% (n = 196) males and 44.8% females (n = 159) with the mean age of 62.1±10.0 years. The demographic and laboratory findings are shown in Table I. The ratio

Table I. Demographic and laboratory findings associated with the presence or severity of coronary artery disease.

Variables	All population n = 355	Normal group n = 154	CAD group		p
			Low SS n = 149	High SS n = 52	
Demographic findings					
Age, years	62.1 ± 10.0	61.8 ± 10.2	62.4 ± 9.6	62.6 ± 10	0.649
Gender, n (%)					
Male	196 (55.2)	68 (44.2)	91 (61.1)	37 (71.2)	0.001*
Female	159 (44.8)	86 (55.8)	58 (38.9)	15 (28.8)	
Diabetes mellitus, n (%)	151(42.5)	57 (37.0)	73 (49.0)	21 (40.4)	0.102
Hypertension, n (%)	260 (73.2)	98 (63.6)	117 (78.5)	45 (86.5)	0.001*
Laboratory findings					
Hemoglobin, g/dL	13.1 ± 1.6	13.1 ± 1.4	13.2 ± 1.7	13 ± 1.6	0.788
Neutrophil, $\times 10^9$/L	4.8 ± 1.4	**4.3 ± 1.3**	5.2 ± 1.4	5.1 ± 1.4	< 0.001*
Platelet count, $\times 10^9$/L	246.9 ± 68	245 ± 71.5	249.5 ± 64.2	244.9 ± 69	0.830
Lymphocyte, $\times 10^9$/L	2.2 ± 0.7	2.2 ± 0.7	2.2 ± 0.8	2.1 ± 0.7	0.417
Monocyte, $\times 10^9$/L	0.7 ± 0.2	**0.6 ± 0.1**	0.7 ± 0.2	0.7 ± 0.2	< 0.001*
RDW, %	13.9 ± 1.4	13.9 ± 1.4	13.8 ± 1.4	14.0 ± 1.3	0.732
PDW, %	12.6 ± 2.3	**13.0 ± 2.7**	12.4 ± 2	12.3 ± 1.4	0.025*
MPV, fL	10.5 ± 1	10.6 ± 1.1	10.4 ± 0.9	10.5 ± 0.7	0.260
HDL-C, mg/dL	45.1 ± 10.9	**47.7 ± 11.3**	42.9 ± 9.8	43.2 ± 11.2	< 0.001*
LDL-C, mg/dL	121 (147-93)	129 (94-150)	115 (90-142)	125.5 (98-158)	0.129
Triglycerides, mg/dL	128 (194-95)	124 (91-186)	132 (102-193)	127.5 (89.5-239.5)	0.606
Creatinine, mg/dL	0.8 (1-0.7)	0.8 (0.6-0.9)	0.8 (0.7-1.0)	**1 (0.8-1.1)**	< 0.001*
Albumin, g/dL	4.1 ± 0.4	**4.3 ± 0.4**	**4.1 ± 0.4**	**3.9 ± 0.5**	< 0.001*
CRP, mg/dL	0.5 (0.8-0.3)	**0.3 (0.2-0.5)**	**0.5 (0.3-0.9)**	**0.8 (0.5-1.2)**	< 0.001*
CAR, %	11.3 (19-6.1)	**7.4 (4.7-11.6)**	**13.8 (8.3-24.3)**	**20.7 (12.4-29.9)**	< 0.001*

Numerical variables were shown as mean ± standard deviation or median (min-max). Categorical variables were shown as numbers (%). *$p < 0.05$ shows statistical significance. Bold characters indicate the difference between groups. *Abbreviations:* CAR, C-reactive protein to albumin ratio; CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; RDW, red cell distribution width.

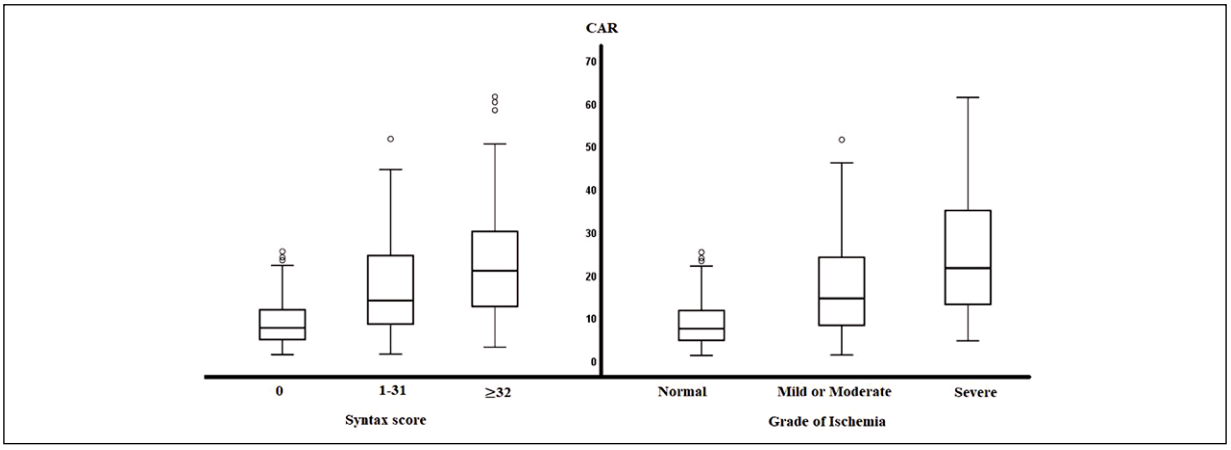

Figure 1. Distribution of CAR by SYNTAX score and degree of ischemia.

of male and hypertension increased from the normal group to the high-risk group (for male; Normal: 44.2% *vs.* Low SS: 61.1% *vs.* High SS: 71.2%, $p = 0.001$; for hypertension; Normal: 63.6% *vs.* Low SS: 78.5% *vs.* High SS: 86.5%, $p = 0.001$). Median CRP levels (Normal: 0.3 *vs.* Low SS: 0.5 *vs.* High SS: 0.8 mg/dL, $p < 0.001$), and CAR levels (Normal: 7.4% *vs.* Low SS: 13.8% *vs.* High SS: 20.7%, $p < 0.001$) (Figure 1) were increased from the normal group to the high-risk group, while mean albumin levels was decreased (Normal: 4.3±0.4 *vs.* Low SS: 4.1±0.4 *vs.* High SS: 3.9±0.5, $p < 0.001$). Median creatinine levels were higher in high-risk group compared to other groups (Normal: 0.8 *vs.* Low SS: 0.8 *vs.* High SS: 1 mg/dL, $p < 0.001$). Other laboratory parameters did not differ significantly in low- and high-risk groups.

Multivariate logistic regression models to predict extent of CAD are presented in Table II. Increased CAR levels were independent predictors of both the low-risk group (*vs.* normal groups) (OR = 1.12, $p < 0.001$) and high-risk group (*vs.* low-risk groups) (OR = 1.04, $p < 0.001$). The threshold value of CAR for predicting the low-risk group (*vs.* normal groups) was 10.2% (AUC ± SE = 0.741 ± 0.03, sensitivity = 68.3%, specificity = 71.4%) (Figure 2A). The threshold value of CAR for predicting the high-risk group (*vs.* low-risk groups) was 15.2% (AUC ± SE = 0.657 ± 0.05, sensitivity = 67.6%, specificity = 54.9%) (Figure 2B).

The ratio of male and hypertension increased from the normal group to the high-risk group (for male; Normal: 44.2% *vs.* Mild/Moderate: 63.4% *vs.* Severe: 64.9%, $p = 0.002$; for hypertension; Normal: 79.9% *vs.* Low SS: 83.8% *vs.* Severe: 86.5%, $p = 0.002$). Median CRP levels (Normal: 0.3 *vs.* Mild/Moderate: 0.6 *vs.* Severe: 0.9 mg/dL, $p < 0.001$), and CAR levels (Normal: 7.4% *vs.* Mild/Moderate: 14.4% *vs.* Severe: 21.5%, $p < 0.001$) (Figure 1) were increased from the normal group to the severe ischemia group, while mean albumin levels was decreased (Normal: 4.3±0.4 *vs.* Mild/Moderate: 4.0±0.4 *vs.* Severe: 3.8±0.4, $p < 0.001$). Median creatinine levels were higher in severe ischemia group compared to other groups (Normal: 0.8 *vs.* Mild/Moderate: 0.8 *vs.* Severe: 0.9 mg/dL, $p < 0.001$). The rest of the laboratory parameters did not differ significantly in terms of the severity between the ischemia groups (Table III).

Multivariate logistic regression models to predict severity of ischemia are presented in Table IV. Increased CAR levels were independent predictors of both the mild-moderate ischemia group (*vs.* normal groups) (OR = 1.14, $p < 0.001$) and severe ischemia group (*vs.* mild-moderate ischemia group) (OR = 1.05, $p = 0.001$). The threshold value of CAR for predicting the mild-moderate ischemia group (*vs.* normal groups) was 10.2% (AUC ± SE = 0.736 ± 0.03, sensitivity = 67.1%, specificity = 71.4%) (Figure 2C). The threshold value of CAR for predicting the severe ischemia group (*vs.* mild-moderate ischemia group) was 16.5% (AUC ± SE = 0.631 ± 0.05, sensitivity = 61.5%, specificity = 63.8%) (Figure 2D).

Angiography results were normal in 109 patients with CAR levels below 10.2%. MPS result was normal in 100 of these patients. In 9 patients, the sign of MPS was mild ischemia. Accordingly,

Table II. Independent predictors of intermediate-high syntax score.

Variables	Univariable regression			Multivariable regression		
	OR	95% CI	p	OR	95% CI	p
SS < 32 (ref: normal)						
Gender						
Male	ref					
Female	0.50	0.32-0.79	0.003*	-	-	-
Hypertension	2.09	1.25-3.48	0.005*	-	-	-
Neutrophil	1.62	1.35-1.95	< 0.001*	-	-	-
Monocyte	13.10	2.9-58.9	< 0.001*	13.30	3.6-62.6	< 0.001*
PDW	0.89	0.80-0.98	0.019*	-	-	-
HDL-C	0.96	0.94-0.98	< 0.001*	0.97	0.94-0.99	0.015*
Creatinine	3.31	1.43-7.65	0.005*	-	-	-
Albumin	0.23	0.12-0.43	< 0.001*	-	-	-
CRP	17.15	7.0-42.07	< 0.001*	-	-	-
CAR	1.14	1.09-1.18	< 0.001*	1.12	1.08-1.17	< 0.001*
				Nagelkerke R2=0.420;		$p < 0.001$*
SS ≥ 32 (ref: SS < 32)						
Gender						
Male	ref					
Female	0.64	0.32-1.26	0.195	-	-	-
Hypertension	1.76	0.72-4.27	0.212	-	-	-
Creatinine	2.57	1.25-5.30	0.010*	2.14	1.02-4.48	0.045*
CRP	2.45	1.30-4.60	0.005*	-	-	-
CAR	1.04	1.02-1.07	0.002*	1.04	1.01-1.06	0.006*
				Nagelkerke R2 = 0.330;		$p < 0.001$*

*$p < 0.05$ shows statistical significance. CAR, C-reactive protein to albumin ratio; CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; RDW, red cell distribution width; CI, confidence intervals; OR, odds ratio; SS, Syntax score.

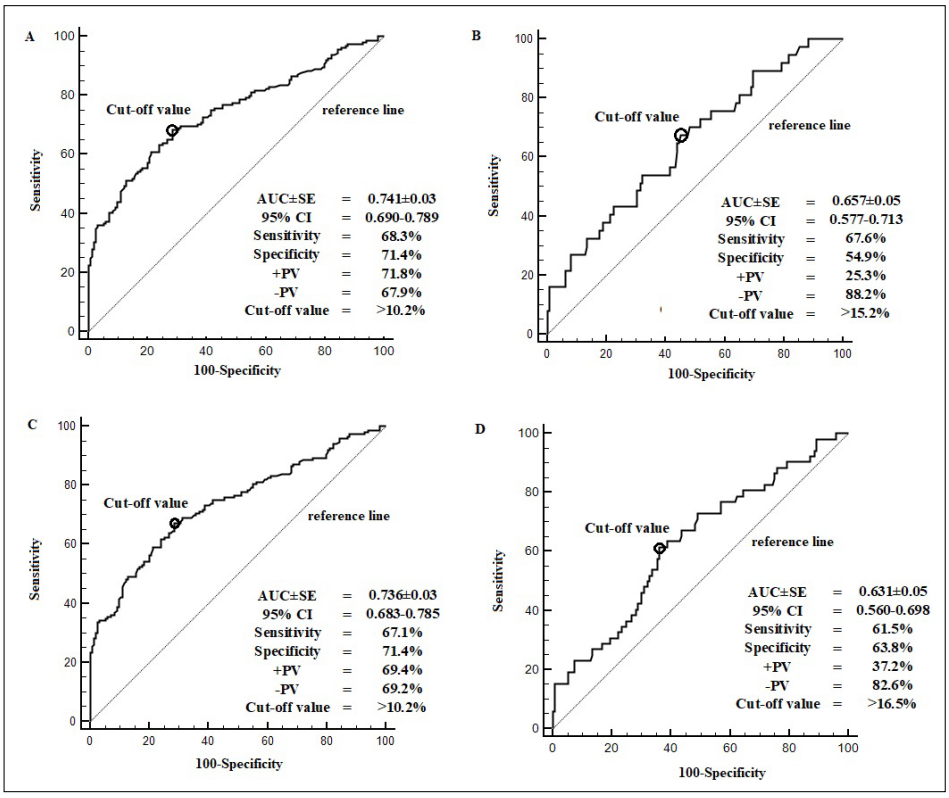

Figure 2. Diagnostic performance assessment of CAR in predicting severity of CAD and ischemia. **A**, Low SYNTAX score *vs.* normal. **B**, High SYNTAX score *vs.* Low SYNTAX score. **C**, Mild or moderate ischemia *vs.* normal. **D**, Severe ischemia *vs.* mild or moderate ischemia.

Table III. Demographic and laboratory findings associated with the grade of ischemia.

Variables	Grade of Ischemia			p
	Normaln = 154	Mild/Moderate n = 164	Severe n = 37	
Demographic findings				
Age, years	64.7 ± 10.2	64.5 ± 9.9	64.2 ± 9.2	0.815
Gender, n (%)				
Male	68 (44.2)	104 (63.4)	24 (64.9)	0.002*
Female	86 (55.8)	60 (36.6)	13 (35.1)	
Diabetes mellitus, n (%)	57 (37.0)	80 (48.8)	14 (37.8)	0.088
Hypertension, n (%)	98 (63.6)	131 (79.9)	31 (83.8)	0.002*
Laboratory findings				
Hemoglobin, g/dL	13.1 ± 1.4	13.2 ± 1.7	13 ± 1.8	0.640
Neutrophil, $\times 10^9$/L	**4.3 ± 1.3**	5.2 ± 1.5	5.2 ± 1.2	< 0.001*
Platelet count, $\times 10^9$/L	245.0 ± 71.5	249.4 ± 62.8	243.4 ± 76.6	0.803
Lymphocyte, $\times 10^9$/L	2.2 ± 0.7	2.2 ± 0.8	2.1 ± 0.7	0.419
Monocyte, $\times 10^9$/L	**0.6 ± 0.1**	0.7 ± 0.2	0.7 ± 0.2	< 0.001*
RDW, %	13.9 ± 1.4	13.9 ± 1.3	13.9 ± 1.6	0.921
PDW, %	**13.0 ± 2.7**	12.4 ± 1.9	12.2 ± 1.7	0.024*
MPV, fL	10.6 ± 1.1	10.5 ± 0.9	10.4 ± 0.8	0.240
HDL-C, mg/dL	**47.7 ± 11.3**	42.8 ± 9.3	43.5 ± 13.7	< 0.001*
LDL-C, mg/dL	129 (94-150)	112.5 (92-141)	134 (114-155)	0.069
Triglycerides, mg/dL	124 (91-186)	136 (97-202)	120 (94-170)	0.372
Creatinine, mg/dL	0.8 (0.6-0.9)	0.8 (0.7-1.0)	**0.9 (0.8-1.1)**	< 0.001*
Albumin, g/dL	**4.3 ± 0.4**	4.0 ± 0.4	**3.8 ± 0.4**	< 0.001*
CRP, mg/dL	**0.3 (0.2-0.5)**	**0.6 (0.3-1.0)**	**0.9 (0.5-1.2)**	< 0.001*
CAR, %	**7.4 (4.7-11.6)**	**14.4 (8.2-24.0)**	**21.5 (13.0-34.9)**	< 0.001*
SYTANX score	**0**	**12.5 (2-30)**	**22 (4-42)**	< 0.001*

Numerical variables were shown as mean ± standard deviation or median (min-max). Categorical variables were shown as numbers (%). *$p < 0.05$ shows statistical significance. Bold characters indicate the difference between groups. CAR, C-reactive protein to albumin ratio; CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; RDW, red cell distribution width.

both MPS and CAG results were found to be normal in 100 patients with a CAR level of < 10.2%, constituting 28.2% of the population.

Discussion

The main findings of our study were as follows: (1) Higher CAR levels were significantly associated with the severity of CAD and ischemia, (2) CAR was a common independent predictor of both the severity of CAD and ischemia, (3) using the CAR threshold level, 28.2% of patients with suspected coronary artery disease (CAD) can recover from MPS and CAG.

The SS evaluates the anatomy and character of the lesions detected on coronary angiography and predicts prognosis and the need for revascularization[13]. However, determining the severity and extent of CAD in the evaluation of myocardial viability is especially important in terms of making the decision for revascularization. High SS is associated with higher adverse cardiovascular outcomes[14]. MPS is a non-invasive imaging modality for the evaluation of myocardial viability[15]. Limited studies[3,16,17] have shown a linear relationship between the extent of CAD and myocardial damage. This relationship was also confirmed in our study. However, a significant proportion of patients with suspected CAD may have normal coronary arteries in MPS and CAG methods. These patients are both at risk of radiation and cause high costs[18,19]. For this reason, biomarkers that can be obtained easily and inexpensively have an increasing interest in the classification of patients with suspected CAD in clinical practice.

Atherosclerosis, the most common cause of CAD, has a long incubation period and the diseases it causes have an acute onset and generally poor prognosis[20]. In atherosclerosis, lipid accumulation in the arterial intima, activation of inflammatory cells such as monocytes and T lymphocytes, recruitment of smooth muscle cells, and production of collagen and matrix proteins play an important role[21,22]. This is consistent with

Table IV. Independent predictors of ischemia severity.

Variables	Univariable regression			Multivariable regression		
	OR	95% CI	p	OR	95% CI	p
Mild/Moderate (ref: Normal)						
Gender						
Male	ref					
Female	0.46	0.29-0.72	0.001*	0.52	0.30-0.91	0.023*
Hypertension	2.27	1.37-3.75	0.001*	-	-	-
Hyperlipidemia	3.47	2.16-5.55	< 0.001*	3.24	1.83-5.73	< 0.001*
Neutrophil	1.58	1.33-1.88	< 0.001*	-	-	-
Monocyte	13.80	3.21-59.65	< 0.001*	16.87	5.43-63.30	< 0.001*
PDW	0.89	0.80-0.98	0.017*	-	-	-
HDL-C	0.95	0.93-0.98	< 0.001*	-	-	-
Creatinine	4.02	1.74-9.33	0.001*	-	-	-
Albumin	0.27	0.15-0.51	< 0.001*	-	-	-
CRP	19.08	7.91-46.08	< 0.001*	-	-	-
CAR	1.14	1.10-1.18	< 0.001*	1.14	1.08-1.19	< 0.001*
				Nagelkerke R2 = 0.452;		$p < 0.001$*
Severe (ref: Moderate)						
Gender						
Male	ref					
Female	0.94	0.45-1.98	0.868	-	-	-
Hypertension	1.30	0.50-3.38	0.588	-	-	-
Hyperlipidemia	1.11	0.48-2.53	0.812	-	-	-
Creatinine	1.97	1.02-4.19	0.037*	-	-	-
CRP	2.47	1.24-4.93	0.010*	-	-	-
CAR	1.05	1.02-1.07	0.001*	1.05	1.02-1.07	0.001*
				Nagelkerke R2 = 0.280;		$p < 0.001$*

*$p < 0.05$ shows statistical significance. CAR, C-reactive protein to albumin ratio; CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; RDW, red cell distribution width; CI, confidence intervals; OR, odds ratio.

the observation of low HDL and high monocyte levels in patients with ischemia and CAD. On the other hand, inflammatory reactions are known to play a key role in atherosclerosis[23]. When tissue damage occurs, macrophages accumulate in the damaged tissue due to the inflammatory response. During this process, IL-6 and TNF-a are secreted and CRP expression is induced and increases with the progression of atherosclerosis[24]. Albumin, a negative acute phase reactant, has low levels in the presence of inflammation and atherosclerosis[25]. Previous studies have shown that high CRP or low albumin levels are associated with high SS levels or ischemia severity in patients with CAD[26-28]. We determined that CRP levels were positively correlated with the severity of myocardial ischemia in patients referred for MPS with suspected CAD, while albumin levels were negative correlated. This relationship was also consistent with the extent of CAD in CAG results to which patients with myocardial ischemia were referred.

It has been suggested[29] that CAR is superior to both its components and other inflammatory markers in determining the presence and severity of CAD. Higher CAR levels have been found in CAD patients with moderate-to-high SS and have been found to be independent predictors[30-32]. In a retrospective study, increased CAR was found to predict the presence of ischemia in 126 patients referred to MPS[33]. However, the relationship between CAR and ischemia severity has not yet been reported in the current literature. In this study, both the severity of ischemia and the extent of CAD were evaluated simultaneously. Current findings show that CAR is an independent predictor in classifying both ischemia severity and coronary atherosclerotic burden. In addition, we found that CAR has a common cut-off value (> 10.2%) in distinguishing patients with normal coronary arteries in both MPS and CAG. With this cut-off value, we determined that 28% of patients with suspected CAD may not be exposed to radiation risk. Thus, a significant portion of pa-

tients with suspected CAD could be followed by CAR, which is an inexpensive and easy screening tool. Moreover, the effectiveness of CAR was not limited to this. Certain cut-off values of CAR were also successful in classifying patients with a high atherosclerotic burden.

Limitations

Although this study is the largest sampled study evaluating the relationship between CAR and MPS, it has some limitations. First, the study is a single-center and retrospective. Second, coronary artery severity based on luminal stenosis was evaluated only by visual coronary angiograms. We did not include additional information on the quantitative assessment of coronary artery atherosclerosis, such as distribution, luminal area, plaque burden, and characteristics. Finally, this study did not include patients with a history of coronary artery bypass grafting and PCI.

Conclusions

High CAR levels in CAD patients are an independent predictor of both the severity of ischemia and the extent of CAD. In both outcomes, CAR has a common cut-off value to distinguish patients with suspected CAD but no perfusion defects or normal coronary arteries. CAR can be a potential screening tool and can be used in risk classification.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and approved by the Non-Interventional Research Ethics Committee, Faculty of Medicine, Kirikkale University, on 10 February 2022, under Decision No. 2022.03.16.

Informed Consent

Written informed consent was obtained from all patients.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author, [C.S.].

Authors' Contribution

Concept – C.S., Design – C.S. and I.H.I., Supervision – C.S.; Materials – C.S. and I.H.I., Data collection and/or processing – C.S. and I.H.I., Analysis and/or interpretation – C.S. and I.H.I., Writing – I.H.I and C.S.; Critical review – I.H.I. All authors read and approved the final version of the manuscript.

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