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RESEARCH ARTICLE

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Relationship between C-reactive protein/albumin ratio and coronary artery disease severity in patients with stable angina pectoris

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Background: Syntax score (SS), which is an angiographic tool used in grading the complexity of coronary artery disease (CAD), has prognostic importance in coronary artery disease (CAD) and provides important information regarding selection of revascularization strategy. C-reactive protein (CRP) and albumin are indicators of inflammation, and high levels of them are associated with high SS. We aimed to investigate whether baseline CRP to albumin ratio C-Reactive Protein/Albumin Ratio (CAR), an easily available and novel inflammatory marker, is associated with SS.

Method: A total 403 consecutive patients with stabile angina pectoris, who underwent coronary angiography for suspected CAD from January 2015 to June 2016, were classified into two groups, low SS (≤22) and intermediate-high SS (>22).

Results: C-Reactive Protein/Albumin Ratio was significantly higher in patients with intermediate-high SS group ($P < .001$). In multivariate regression analysis, CAR remained an independent predictor of intermediate-high SS group together with hypertension and LDL. The predictive performance of CAR, CRP, and albumin was compared by ROC curve analysis. CAR surpassed CRP and albumin in predicting intermediate-high SS group. CAR >6.3 predicted an intermediate-high SS with sensitivity and specificity of 86.8% and 43.4%, respectively.

Conclusion: C-Reactive Protein/Albumin Ratio was more tightly associated with the complexity and severity of CAD than CRP and albumin alone and was found to be an independent predictor for intermediate-high SS group.

KEYWORDS

albumin, coronary artery disease severity, C-reactive protein, C-reactive protein/albumin ratio, stable angina pectoris, syntax score

1 | INTRODUCTION

Coronary artery disease (CAD), the leading cause of mortality worldwide, places a serious economic burden on healthcare systems. CAD is mainly due to atherosclerosis. It is known that inflammation plays a role in pathogenesis of onset and progression of atherosclerosis.[1] C-reactive protein (CRP) and albumin are indicators of inflammation and are both associated with atherosclerosis and CAD.[2-6] Current data regarding the prognosis in critical illnesses and malignancies suggest that C-Reactive Protein/Albumin Ratio (CAR) reflects the balance between CRP and albumin levels and has prognostic significance based on systemic inflammation.[7]

The syntax (Synergy between PCI with TAXUS and Cardiac Surgery) score (SS), which is an angiographic tool used in grading the complexity of CAD, is assessed according to the coronary anatomy and characteristics of the coronary lesion.[8] Clinical studies have shown that SS has prognostic importance in CAD and provides important information regarding the selection of revascularization strategy.[9,10]

However, the relationship between CAR and severity and complexity of CAD is not yet known. Because CAD is an essential inflammatory disease, we hypothesized that CAR could be associated with complexity of CAD as assessed by SS. This study aimed to assess the relationship between CAR and the severity of coronary atherosclerosis assessed by SS in patients with stable CAD.

2 | METHODS

2.1 | Study population

We enrolled 403 consecutive patients with stabile angina pectoris (SAP) who underwent coronary angiography for suspected CAD from January 2015 to June 2016. The patients with a history of coronary artery bypass graft surgery or percutaneous coronary intervention, SS = 0, malignancy, active infection, and connective tissue disorder were excluded from the study. Our local Ethics Committee approved the study protocol in accordance with the Declaration of Helsinki.

2.2 | Laboratory measurements

Blood samples were collected before the index coronary angiography after an overnight fast and analyzed in the laboratory of our institution. The laboratory variables including hemoglobin levels, blood glucose, creatinine, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), albumin, and CRP were studied. Cobas 8000 c502 (Roche Diagnostics, Tokyo, Japan)) analyzer was used to measure albumin and CRP levels. Normal ranges were 0.0-0.80 mg/dL for CRP and 3.5-5.3 g/dL for albumin. CAR was calculated as the ratio of CRP to the albumin level multiplied by 100. Estimated glomerular filtration rate (eGFR) was determined using Cockroft-Gault formula. Left ventricle ejection fraction (LVEF) was assessed using a modified Simpson's method.

2.3 | Angiographic analysis

All patients underwent coronary angiography via standard Judkins technique. Selective coronary angiograms were recorded using a digital angiographic system (Dicom-viewer; MedCom GmbH, Darmstadt, Germany) for quantitative analysis. According to the baseline coronary angiograms, SS was calculated in all patients by two experienced cardiologists who were blinded to all other data. The SS was determined for each coronary lesion producing >50% diameter stenosis in vessels >1.5 mm, based on the SS calculator.[11]

2.4 | Statistical analyses

Data were represented as mean ± standard deviation or median for quantitative variables and counts or percentage for categorical variables. Differences between 2 groups were tested with a *t* test or Mann-Whitney *U* test for continuous variables and chi-square or Fisher's exact tests as appropriate for categorical variables. Multivariate logistic regression (stepwise backward conditional) analysis was used to determine independent predictors of intermediate-high SS group using variables that were found to be significant in univariate analysis ($P < .05$). Multicollinearity between CAR and its components (CRP and albumin) was assessed by Eigen value and condition index. Linearity was tested by interacting with the logarithmic transformation of each parameter itself. Receiver-operating characteristic (ROC) analyses were used to compare the performance power of the CAR, CRP, and albumin for intermediate-high SS group. The predictive validities were quantified as the area under the ROC curves (c statistics), and the comparisons of c statistics were performed by De long's test. The data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois) and MedCalc statistical software (version 11.3.8.0, Mariakerke, Belgium).

3 | RESULTS

The study included 403 patients (62.52 ± 11.69 years, 75.9% males). The SS ranged from 5.0 to 56, with a mean of 26.5 ± 13.3. There were 214 (53.1%) patients with intermediate-high SS group (SS > 22), and 189 (46.9%) patients low SS group (SS ≤ 22). The baseline characteristics of the patients are shown in Table 1. The patients with intermediate-high SS group were older and had a higher prevalence of hypertension and diabetes compared to low SS group. The CAR (5.4 [2.9-9.4] vs 2.7 [1.8-5.3]; $P < .001$), the levels of CRP, hemoglobin, creatinine, LDL-C, triglyceride, and platelet were higher in the patients with intermediate-high SS group than low SS group. However, the albumin, fasting blood glucose, and eGFR and LVEF values were lower in the patients with intermediate-high SS group ($P < .001$).

Multivariate logistic regression analyses were used to reveal the independent predictors of intermediate-high SS group using variables that showed an association in the univariate analyses (age, hypertension, diabetes, hemoglobin, platelet count, blood glucose, eGFR, CAR, albumin, LDL-C, triglyceride, LVEF), except the angiographic parameters. History of hypertension, elevated LDL-C, and CAR (odds ratio: 1.290; 95% confidence interval: 1.128-1.475; $P < .001$) were found to be associated with high SS after potential confounding factors were adjusted (Table 2).

Receiver-operating characteristic curves were compared to determine whether there was an additional benefit of using CAR on CRP and albumin for predicting intermediate-high SS. The area under the curve (AUC) for CAR was significantly

TABLE 1 Demographic, clinical, laboratory, and coronary angiographic characteristics of all patients, patients with low and high syntax score with *P* value

	Syntax score (SS)			
	All patients (n:403)	SS ≤22 (n = 189)	SS >22 (n = 214)	*P* Value
Age (y)	62.52 ± 1.69	60.95 ± 12.18	63.92 ± 11.08	.021
Male—Gender n (%)	306 (75.9)	145 (76.7)	161 (75.2)	.728
Diabetes mellitus n (%)	85 (21.1)	31 (16.4)	54 (25.2)	.030
Hypertension n (%)	193 (47.9)	77 (40.7)	116 (54.2)	.007
Smoking n (%)	151 (37.5)	78 (41.3)	73 (34.1)	.139
Body mass index(kg/m^2)	28.29 ± 5.51	28.22 ± 6.35	28.35 ± 4.65	.139
Hemoglobin, (g/dL)	14.2 (12.6-15.3)	13.2 (12.6-14.9)	14.6 (13.7-15.7)	.003
White blood cell, 10/μL	9.35 ± 3.26	9.26 ± 2.97	9.39 ± 3.41	.910
Platelet count, 10/μL	229.13 ± 80.93	195.04 ± 88.35	245.72 ± 71.70	<.001
Fasting blood glucose, mg/dL	114.91 ± 45.48	125.10 ± 48.76	109.95 ± 43.10	.013
Creatinine, mg/dL	1.02 ± 0.51	.92 ± 0.33	1.10 ± 0.62	<.001
eGFR (mL/min)	92.29 ± 40.52	99.43 ± 42.21	85.98 ± 37.95	<.001
C-Reactive protein (mg/dL)	0.14 (0.82-0.24)	0.10 (0.71-0.19)	0.19 (0.10-0.32)	<.001
Serum albumin (g/dL)	3.68 ± 0.46	3.75 ± 0.42	3.61 ± 0.48	<.001
Crp/albumin ratio × 100	3.9 (2.3-7.0)	2.7 (1.8-5.3)	5.4 (2.9-9.4)	<.001
Total cholesterol, mg/dL	163.68 ± 47.86	164.31 ± 46.84	162.43 ± 50.02	.494
LDL-C, mg/dL	89.87 ± 37.10	98.53 ± 38.67	81.90 ± 33.76	<.001
HDL-C, mg/dL	41.53 ± 15.44	40.09 ± 11.56	44.00 ± 20.28	.153
Triglyceride, (mg/dL)	112 (74-154)	116 (79-163)	99 (71-142)	.048
LVEF (%)	49.81 ± 10.48	53.94 ± 9.66	46.16 ± 9.81	<.001
LMCA disease n (%)	119 (29.5)	36 (19.0)	83 (38.8)	<.001
Multivessel disease n (%)	232 (57.6)	94 (49.7)	138 (64.5)	.003
RCA dominance, n (%)	343 (85.1)	150 (79.4)	193 (90.2)	.002
Lesion length >20 mm, n (%)	170 (42.2)	55 (29.1)	115 (53.7)	<.001
Chronic total occlusion, n (%)	71 (17.6)	2 (1.1)	69 (32.2)	<.001
Bifurcation, n (%)	135 (33.5)	6 (3.2)	129 (60.3)	<.001
Severe tortuosity, n (%)	119 (29.5)	59 (31.2)	60 (28.0)	.486
Heavy calcification, n (%)	58 (14.4)	12 (6.3)	46 (21.5)	<.001
Syntax score	26.58 ± 13.32	15.04 ± 4.97	36.77 ± 9.53	<.001

Acronyms and their meanings are as follows: eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; IRA, infarct-related artery; LAD, left anterior descending; LMCA, left main coronary artery.

TABLE 2 Univariate and multivariate logistic regression analysis of intermediate-high syntax score

	Univariate analysis of intermediate-high SS group			Multivariate analysis of intermediate-high SS group		
	Odd ratio	95% C.I.	*P* value	Odd ratio	95% C.I.	*P* value
Hypertension	1.722	1.159-2.557	.003	2.571	1.126-5.873	.025
LDL-C	1.087	1.082-1.093	<.001	1.013	1.002-1.025	.018
Crp/albumin ratio (per 1 point increase)	1.281	1.189-1.381	<.001	1.290	1.128-1.475	<.001

SS, syntax score.

higher than AUC for CRP (AUC: 0.716; 95% CI: 0.667-0.765 vs AUC: 0.701; 95% CI: 0.651-0.751; *P*:.002) and albumin levels (AUC: 0.716; 95% CI: 0.667-0.765 vs AUC: 0.611; 95% CI: 0.556-0.666; *P*:.003) (Figure 1). CAR >6.3 predicted an intermediate-high SS with sensitivity and specificity of 86.8% and 43.4%, respectively.

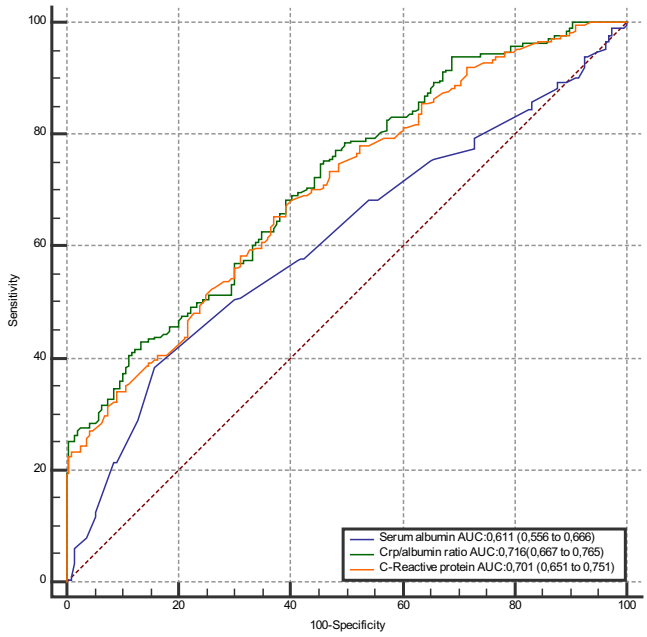

FIGURE 1 Receiver-operating characteristic (ROC) curves for C-reactive protein/albumin ratio, C-reactive protein, and albumin for high syntax score

4 | DISCUSSION

The present study indicated that CAR levels were significantly associated with SS and were an independent predictor for intermediate-high SS group in patients who had underwent coronary angiography due to SAP. Furthermore, the CAR predicted intermediate-high SS group more accurately than either CRP or SA alone.

The SS accounts for the number and the location of the coronary lesion and thus tries to determine the myocardium under the risk of ischemia. High SS is probably a sign of high coronary atherosclerotic burden that correlates with adverse cardiac events and poor prognosis.[12] Numerous validation studies since the syntax trial confirm that SS is an independent predictor of short- and long-term morbidity and mortality and adverse cardiovascular outcomes in a wide range of patients, including stable CAD.[13-16] Determination of high SS may have a positive influence in the management of these patients. In our study, presence of hypertension, elevated values of LDL-C, and CAR were found to be independent predictors of intermediate-high SS. The relationship between hypertension, elevated LDL-C, and CAD severity was determined in previous studies.[17-19]

Inflammation plays an important role in all stages of atherosclerosis.[20] CRP and SA are markers of inflammation that are frequently used in clinical practice. Serum CRP, an acute phase protein from the liver, is elevated in response to inflammation and improved risk prediction for patients with CAD.[21] In addition, high CRP levels have been shown to be associated with the severity of coronary involvement in patients with stable CAD.[22] Although the physiopathogenesis of the relationship between CRP and CAD severity is not fully understood, multiple mechanisms may be involved. CRP has been shown to impair the endothelial progenitor cells, impair fibrinolysis, increase collagen degradation in monocytes, activate the complement system, and may be involved in the uptake of LDL-C by macrophages and turning them into foam cells.[23-25] Decreased albumin level may be associated with increased risk of morbidity and mortality in a range of cardiovascular diseases.[3,26,27] Kurtul and colleagues demonstrated that decreased albumin level is an independent predictor of high SS and in-hospital mortality in patients with acute coronary syndrome.[28] Decreased albumin level, which is associated with the chronic nature of the disease, represents the inflammatory status.[2] In addition, decreased albumin level is associated with increased blood viscosity, impaired endothelial function, increased platelet activation and aggregation, and increased synthesis of an important mediator of platelet-derived coronary artery narrowing.[29-32] These may be the underlying mechanisms that link SA and the severity of CAD. In our study, the relationship between albumin, CRP level, and SS was similar to that reported in previous trials.

Merging albumin and CRP into a single index is demonstrated to be associated with poor prognosis in a variety of disorders including cancer and sepsis.[33-36] We assumed that increased CRP/albumin ratio indicates a higher inflammatory state and may be superior to CRP and albumin alone in determining the prevalence and severity of CAD. To our knowledge, this is the first study that evaluates the relationship between CAR level and coronary atherosclerotic burden in patients with stable CAD. In this study, we found that elevated CAR levels in stable CAD patients were independent predictors of intermediate-high SS group, and the predictive accuracy of CAR was better than CRP and albumin level, as per the comparison of the ROC curves.

5 | CONCLUSION

Higher CAR on admission was independently associated with the extent, severity, and complexity of coronary atherosclerosis, determined by SS, in patients with SAP. CAR was found to be a more accurate marker than CRP or albumin in detection of the patients with high SS. For this reason, CAR assessment can be considered for early risk stratification of the patients with SAP in clinical practice.

6 | LIMITATIONS

Our study had some limitations; first of all, it was a retrospective study. Secondly, the patients, in whom history of coronary artery bypass graft surgery or percutaneous coronary intervention, were not included, which means that there was a potential bias in the selection of the study subjects.

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DISCLOSURES

None.

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