International Journal of Research in Medical Sciences
Datta GC et al. Int J Res Med Sci. 2025 May;13(5):1797-1802
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20251272

Original Research Article

Association of C-reactive protein to albumin ratio with angiographic severity of coronary artery disease in non-ST elevation myocardial infarction patients

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Received: 07 January 2025
Revised: 07 February 2025
Accepted: 11 February 2025

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ABSTRACT

Background: The C-reactive protein to albumin ratio (CAR) is a potential biomarker for inflammation and nutrition in cardiovascular diseases. Elevated CRP indicates inflammation, while albumin reflects nutritional status, offering insights into the pathophysiology and severity of coronary artery disease (CAD). This study aimed to investigate the relationship between the CRP to Albumin ratio (CAR) and the angiographic severity of CAD in non-ST elevation myocardial infarction (NSTEMI) patients.
Methods: This study was conducted at the National Institute of Cardiovascular Diseases (NICVD) Dhaka, Bangladesh from May 2018 to April 2019, involving 200 patients with NSTEMI undergoing coronary angiography (CAG). The patients were divided equally into two groups based on the CAR: Group I had a CAR of >11, and Group II had a CAR of ≤11. Data were analyzed by the SPSS version 26.0 program.
Results: The mean SYNTAX score (SS) was higher in Group I than in Group II ($p<0.001$). CAR>11 independently predicted intermediate-high SS ($p<0.001$). CAR and SS correlated significantly ($p<0.001$). The ROC curve showed an AUC of 0.878 for CAR (Sensitivity: 77.3%, Specificity: 70.0%).
Conclusions: CAR is significantly associated with the severity of CAD, as measured by the SYNTAX score, in patients with NSTEMI. CAR can be used as a reliable marker in the prediction of CAD severity in patients with NSTEMI.

Keywords: CAD, Coronary artery disease, CAR, C-reactive protein to albumin ratio, C-reactive protein, CRP, NSTEMI, SYNTAX score

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of early mortality worldwide, constituting 50% of non-communicable disease fatalities each year, with ischemic heart disease (IHD) accounting for over eight million deaths.[1] In Europe, IHD causes nearly 1.8 million deaths annually, making up 19% of all deaths.[2] Bangladeshis, like other South Asians, are particularly predisposed to developing coronary artery disease (CAD) early, which progresses rapidly and shows more severe angiographic characteristics.[3] The prevalence of coronary artery disease (CAD) in rural Bangladesh is 4.5%, which is comparable to rates in developed countries. Key risk factors in this region include male gender, higher socioeconomic status, hypertension, and diabetes. Since younger individuals face

risks similar to those of older people, primordial and primary prevention efforts are crucial.[4] Ischemic heart disease (IHD) presents as either chronic stable angina or acute coronary syndrome (ACS). ACS divides into ST-segment elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA), with NSTEMI and UA collectively known as non-ST elevation acute coronary syndrome (NSTE-ACS). Since 1999, the age and sex-adjusted incidence rates of NSTEMI have gradually risen.[5] Worldwide, the burden of NSTEMI is increasing compared to ST elevation MI, and NSTE-ACS remains the leading cause of mortality among individuals with coronary artery disease (CAD).[6] Current evidence supports a significant role for inflammation throughout the atherosclerotic process. Molecular data highlight the involvement of inflammatory pathways in early atherogenesis, lesion progression, and thrombotic complications.[7] Studies show that elevated inflammatory marker levels correlate with CAD severity and poorer cardiovascular outcomes.[8] During inflammation, biomarkers such as fibrinogen, C-reactive protein (CRP), sialic acid, and ceruloplasmin are released.[9] Elevated CRP levels at hospital admission indicate a poor prognosis.[10] CRP is associated with multiple complex coronary stenoses in acute coronary syndrome patients, as well as with the severity and progression of coronary atherosclerosis, leading to worse outcomes.[11,12] Conversely, albumin is a negative acute-phase protein, with levels decreasing in line with inflammation severity. Serum albumin inhibits TNF-alpha-induced expression of vascular cell adhesion molecule-1, monocyte adhesion, and nuclear factor activation in endothelial cells. Lower albumin levels may increase blood viscosity and impair endothelial function.[13] Reduced albumin levels can lead to increased oxidative stress, which contributes to the atherosclerotic burden. Oxidative stress is a significant factor in CAD severity, particularly in young smokers with acute myocardial infarction.[14] Both CRP and albumin serve as indicators of inflammation, with CRP being a positive acute-phase reactant (APR) and albumin a negative APR. These markers are linked to the presence, severity, and adverse cardiovascular events in CAD patients.[15] Recently, the C-reactive protein to albumin ratio (CAR) has been suggested as a superior indicator of inflammatory status and prognosis compared to CRP or albumin alone in various clinical contexts.[16,17] CAR has been identified as an independent prognostic marker in malignancies and critical illnesses.[18] In our country, the relationship between several inflammatory markers and CAD severity has been explored. Datta et al (2018) examined the association of CAD with the neutrophil-to-lymphocyte ratio (NLR), while Chowdhury et al (2019) investigated the platelet-to-lymphocyte ratio (PLR).[19,20] Some studies have linked CRP levels with CAD severity.[21,22] Additionally, Parvez et al (2019) researched the relationship between hypoalbuminemia and angiographic severity.[23] This study aimed to investigate the relationship between CAR and CAD severity, as identified by the SYNTAX score in patients with non-ST elevation myocardial infarction (NSTEMI).

METHODS

This was a cross-sectional observational study that was conducted at the National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh from May 2018 to April 2019 on 200 patients with NSTEMI undergoing coronary angiography (CAG). The sample was collected by a consecutive sampling method. According to the inclusion criteria, the study included patients experiencing their first non-ST elevation myocardial infarction (NSTEMI) who underwent coronary angiography during index hospitalization at NICVD. The exclusion criteria ruled out patients with active infectious or inflammatory diseases, connective tissue diseases, chronic kidney disease, hepatic cirrhosis, malnutrition, congestive heart failure, malignancy, valvular or congenital heart diseases, cardiomyopathy, myocarditis, or pericarditis. The study further excluded patients with a history of previous myocardial infarction, percutaneous coronary interventions (PCI), coronary artery bypass grafting (CABG), or other severe comorbidities. Informed written consent was obtained from each patient before their enrollment in the study. CRP levels were measured within 48 hours of admission using a Beckman Coulter Analyzer (Model- OLYMPUS AU 480) by a quantitative method. The patients were divided equally into two groups based on the CAR: Group I (CAR >11) and Group II (CAR ≤11). Coronary angiography was performed, and the SYNTAX score was calculated for each patient. CAG was conducted via either the transfemoral or transradial approach. The angiograms were recorded digitally for quantitative analysis using a DICOM viewer and evaluated by two experienced cardiologists. Coronary arteries with a diameter greater than 1.5 mm and obstructions over 50% were included in the SYNTAX score (SS) calculation, using the online SS calculator. The correlations of CRP, albumin, and CAR with SS were assessed using the Pearson correlation coefficient test. The predictive value of CAR for intermediate-high SS was evaluated through ROC curve analysis. Statistical analysis was performed using SPSS 25.0, with statistical significance set at $p<0.05$ throughout the study.

RESULTS

In this study, almost half (43.0%) of patients belonged to age 51-60 years in group I and 39.0% in group II. The mean age was 54.01±8.67 years in Group I and 51.69±9.95 years in Group II. The difference was statistically not significant between the two groups ($p>0.05$). The majority of the patients were male in group I and group II which was 88% and 85% respectively. The difference was statistically not significant between the two groups ($p>0.05$). None of the traditional risk factors for CAD presented in the above table differed between the groups except Diabetes mellitus. Diabetes mellitus was found significantly higher in group I than in group II (59.0% vs. 48.0%, $p=0.038$). The mean albumin was 36.15±7.85 (g/l) in group I and 40.53±7.89 (g/l) in group II. The mean CAR × 100 was 41.08±17.39 in group I and 7.95±2.81 in group

II. The comparison of all three biochemical markers between the two groups revealed a statistically significant difference between the two groups (p=0.001). In this study, 69.0% of patients had intermediate to high SS≥22 in group I and 28.0% in group II. On the other hand, patients having low SS was 31.0% in Group I and 72% in Group II. This difference between the two groups was statistically highly significant (p<0.001). The mean syntax score was 23.45±8.13 in group I and 16.25±9.51 in group II. The mean SS differed between the two groups which was statistically highly significant (p<0.001). It was observed that 60.0% of the patients had TVD in group I and 25.0% in group II. 27% of the patients had SVD in Group II, whereas only 7% in Group I. The number of the involved vessels was significantly different between the two groups (p<0.001). None of the biochemical parameters differed significantly in their mean values between the two groups (p>0.05). Pearson's correlation coefficient test was done to see the correlation. The scatter plot shows that there was a moderately positive correlation (r=0.530) between CRP and SYNTAX score which was statistically highly significant (p<0.001). Another scatter plot shows that there was a weak inverse correlation (r=-0.246) between Serum Albumin and SYNTAX score which was statistically significant (p=0.041). Another scatter plot shows that there was a moderately positive correlation (r=0.645) between CAR and SYNTAX scores which was statistically highly significant (p<0.001). This indicates that patients who have higher CAR tend to have higher SYNTAX scores. Univariate logistic regression analysis of the determinants likely to be associated with severe CAD (intermediate-high syntax score). Albumin, but not CRP, was included in the regression analyses because of the excellent correlation between CAR and CRP (r=0.981; p<0.001). DM, Albumin <35 g/l, and CAR >11 were significant independent predictors of severe CAD. Among the variables with p=0.013, 0.026, and <0.001 respectively). Age >50 years, hypertension, dyslipidemia, smoking, and family history of CAD were not included in multivariate regression analysis as univariate analysis yielded them as statistically insignificant in the current study. DM and albumin <35 g/l, were significant in univariate analysis and found to be insignificant (p=0.080 and 0.114 respectively) in multivariate regression analysis. CAR>11 was the significant independent predictor of severe CAD after adjustment by multivariate logistic regression analysis with p<0.001. Besides, in ROC curve analysis a CAR>11 predicted severe CAD with sensitivity and specificity of 77.3% and 70.0%, respectively.

Table 1: Comparison of the study patients by CRP, albumin, and CAR.

Variables	Group-I (n=100) Mean±SD	Group-II (n=100) Mean±SD	p value
CRP (mg/l)	15.41±8.79	5.32±2.51	0.001[s]
Albumin (g/l)	36.15±7.85	40.53±7.89	0.001[s]
CAR ×100	41.08±17.39	7.95±2.81	0.001[s]

s-significant

Table 2: Comparison of the study groups by SYNTAX score.

Score	Group-I (n=100) N	%	Group-II (n=100) N	%	p value
IHSS (>22)	69	69.0	28	28.0	[a] <0.001[s]
LSS (≤ 22)	31	31.0	72	72.0	
Mean±SD	23.45±8.13		16.25±9.51		[b] <0.001[s]

s-significant

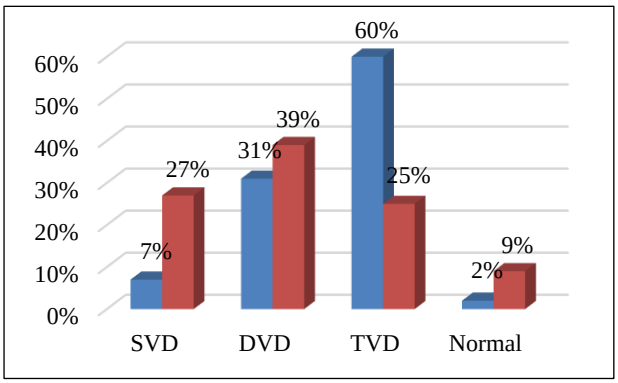

Figure 1: Column chart showed the comparison of the study groups by the number of involved vessels.

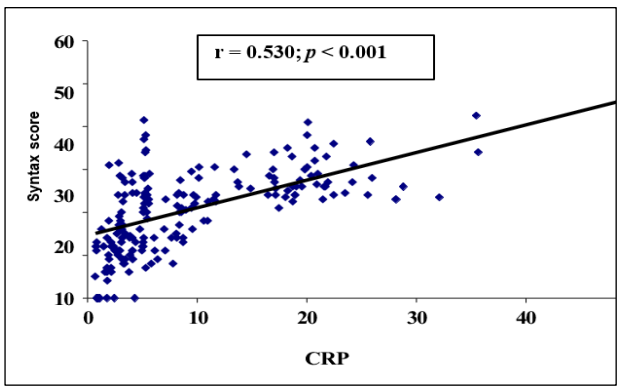

Figure 2: Scatter plot showing the correlation between C-Reactive protein and SYNTAX score.

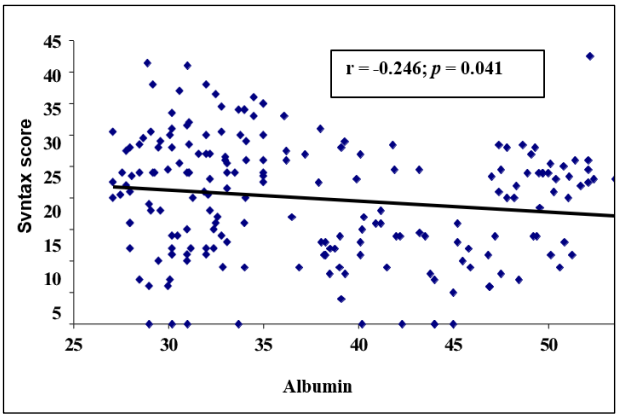

Figure 3: Scatter plot showing the correlation between serum albumin and SYNTAX score.

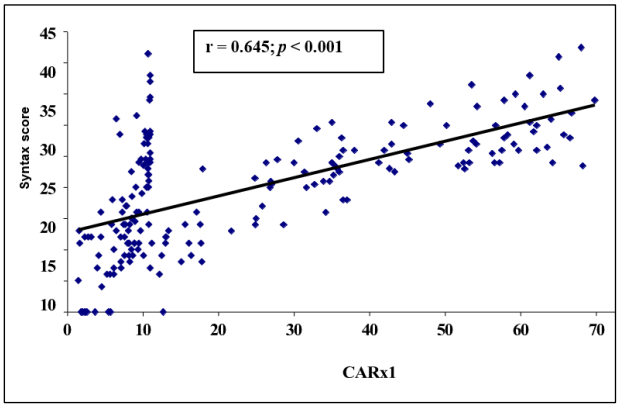

Figure 4: Scatter plot showing the correlation between CAR and SYNTAX score.

Table 3: Univariate logistic regression analysis of the determinants of severe CAD (intermediate-high SYNTAX score, SS>22).

Variables	SRC (β)	OR	p value
Age>50 yrs.	0.394	1.482	0.207^{ns}
HTN	0.235	1.265	0.408 ^{ns}
DM	0.721	2.056	0.013s
Dyslipidemia	0.361	1.435	0.204 ^{ns}
Smoking	0.316	1.371	0.267 ^{ns}
Family H/o CAD	-0.219	0.803	0.463 ^{ns}
Albumin <35 g/l	0.531	1.36	0.026 s
CAR >11	1.745	5.724	<0.001s

s-significant; ns-non-significant

Table 4: Multivariate logistic regression analysis of the determinants of severe CAD (intermediate-high SYNTAX score, SS>22).

Variables	SRC (β)	OR	p value
DM	0.578	1.783	0.080
Albumin <35g/l	0.438	1.11	0.114
CAR>11	1.663	5.276	<0.001s

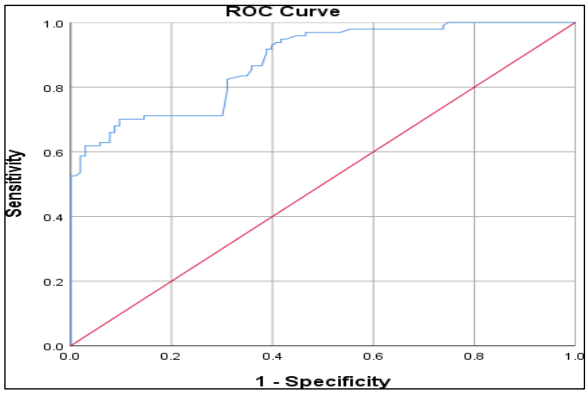

Figure 5: Area under the curve, test result variable (S): CAR.

Table 5: The receiver operating characteristic (ROC) curve analysis of CAR in predicting severe CAD (intermediate-high SYNTAX score (SS>22).

			Asymptotic 95% Confidence interval	
Area	Std. error	Asymptotic sig.	Lower bound	Upper bound
0.878	0.023	0	0.832	0.923

DISCUSSION

In this study, there was no significant difference between Group I and Group II patients regarding CAD risk factors such as hypertension, dyslipidemia, smoking, and family history of CAD, except for DM. In Group I, 59% of patients were diabetic, compared to 48% in Group II, with this difference being statistically significant (p=0.038). This finding aligns with results from Chowdhury et al, who studied NSTEMI patients at NICVD and found a similar distribution of risk factors.[20] Additionally, all major biochemical variables in the present study, albumin, and CAR-showed statistically significant differences between Group I and Group II (p=0.001). In this study, Group I had mean CRP, albumin, and CAR values of 15.41±8.79 mg/l, 36.15±7.85 g/l, and 41.08±17.39, respectively. Group II had values of 5.32±2.51 mg/l for CRP, 40.53±7.89 g/l for albumin, and 7.95±2.81 for CAR. Kalyoncuoglu and Durmus also reported significant differences in these parameters between the two groups: CRP (14.1±7.8 mg/l vs. 5.9±4.5 mg/l), albumin (37.7±3.8 g/l vs. 39.2±3.6 g/l), and CAR (37.8±20.5 vs. 15.8±13.3).[24] Additionally, the study found no significant differences between groups for other biochemical parameters like random blood sugar, creatinine, troponin I, and fasting lipid profile. Similar findings were reported by Karabag et al.[25] In your study, the severity of CAD, assessed by the SYNTAX score, differed significantly between Group I and Group II. A significantly higher percentage of patients with severe CAD was observed in Group I (69.0%) compared to Group II (28.0%), with a p value of <0.001. The mean SYNTAX score was also significantly higher in Group I (23.45±8.13)

than in Group II (p<0.001). This aligns with the findings by Cagdas et al., where a higher mean SYNTAX score was seen in the high CAR group compared to the low CAR group (p<0.001).[6] Similarly, Kalyoncuoglu and Durmus reported consistent results.[24] In this study, 60.0% of patients in Group I had TVD, compared to 25.0% in Group II. Conversely, 27% of patients in Group II had SVD, compared to only 7% in Group I. The two groups differed significantly in the number of involved vessels (p<0.001). Similarly, Kalyoncuoglu and Durmus found a significantly higher number of TVD patients in the high CAR group compared to the low CAR group (p<0.001).[24] However, Cınar et al did not observe significant differences in the number of TVD patients between groups in their study with STEMI patients (p=0.134).[26] The study found a significantly positive correlation between the C-reactive protein to albumin ratio (CAR) and the SYNTAX score, with higher CAR associated with higher SYNTAX scores. Specifically, there was a moderately positive correlation (p<0.001). Additionally, there was a moderate positive correlation between CRP and SYNTAX score (p<0.001) and a weak inverse correlation between albumin levels and SYNTAX score (p=0.041). These results align with Cagdas et al, who also found significant correlations of the SYNTAX score with CAR (p<0.001), CRP (p<0.001), and albumin (p<0.001).[6] Similarly, Kalyoncuoglu and Durmus (2019) reported a significant positive correlation between CAR and the SYNTAX score (p<0.001).[24] Parvez et al found a significant weak inverse correlation between serum albumin and the Leaman score (p=0.009) in their study at NICVD.[23] In the current study, both univariate and multivariate logistic regression analyses were conducted on variables potentially contributing to severe CAD. The univariate analysis identified DM, albumin levels <35g/l, and CAR>11 as significant predictors of severe CAD, with CAR>11 being the strongest independent predictor (p<0.001). After conducting the multivariate analysis, DM and albumin <35 g/l were no longer significant predictors. CAR>11 remained an independent predictor of severe CAD with adjusted odds (p<0.001). The findings of this study align with those of Kalyoncuoglu and Durmus.[24] In this study, the ROC curve analysis for CAR in predicting severe CAD (SYNTAX score >22) showed an area under the curve (AUC) of 0.878 (p<0.001). A CAR>11 predicted an intermediate-high SYNTAX score with a sensitivity of 77.3% and specificity of 70%. Kalyoncuoglu and Durmus reported an AUC of 0.829 (p<0.001) for CAR, while Cagdas et al found it to be 0.765 (p<0.001).[6] In the study conducted by Cagdas et al., the sensitivity and specificity of CAR>11 for predicting an intermediate-high SYNTAX score were 71.7% and 71.4%, respectively,[6] which aligns with the current study's findings. This comparison and observations from other researchers both locally and internationally highlight the significant association between the CAR and the angiographic severity of CAD, as assessed by the SYNTAX score, in NSTEMI patients.

The limitations of the study include its single-center design, limiting generalizability, and its focus solely on NSTEMI patients, which may not apply to other CAD types. The sample size may not fully reflect diverse comorbidities, and the observational nature prevents causal inference. Measurement biases in CRP and albumin levels could also exist.

CONCLUSION

The cross-sectional observational study indicates that a higher C-reactive protein (CRP) to albumin ratio (CAR) is significantly linked with more severe coronary artery disease (CAD) in patients with non-ST elevation myocardial infarction (NSTEMI). There is a significant positive correlation between CAR and CAD severity, assessed using the SYNTAX score, with patients exhibiting higher CAR also having higher SYNTAX scores. Therefore, CAR may serve as an independent predictor of severe CAD in NSTEMI patients.

Recommendations

The C-reactive protein to albumin ratio (CAR) may serve as a valuable biomarker for assessing coronary artery disease (CAD) severity in non-ST elevation myocardial infarction (NSTEMI) patients. Incorporating CAR into risk stratification could aid in early intervention. Further multicenter and longitudinal studies are needed to validate its prognostic value, explore causal relationships, and assess the impact of therapeutic interventions on CAD outcomes.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Datta GC, Sen T, Debnath DD, Enayetur Rashul AHM, Saha M, Alam I, et al. Association of C-reactive protein to albumin ratio with angiographic severity of coronary artery disease in non-ST elevation myocardial infarction patients. Int J Res Med Sci 2025;13:1797-802.