International Journal of Cardiology Research

ISSN Print: 2663-4104
ISSN Online: 2663-4112
Impact Factor: RJIF 5.2
IJCR 2024; 6(1): 07-11
www.cardiologyjournal.in
Received: 08-11-2023
Accepted: 15-12-2023

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Relationship between C reactive protein to serum albumin ratio and the coronary artery disease severity in non-ST segment elevation myocardial infarction patients

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DOI: https://doi.org/10.33545/26634104.2024.v6.i1a.42

Abstract
Background: The C-reactive protein (CRP) to albumin ratio (CAR) is considered to provide a more precise measure of inflammatory state compared to CRP or albumin separately. Additionally, CAR has been linked to a less favorable outcome for individuals with critical conditions and malignancies. The purpose of the research was to correlate the CRP to CAR with the extent of coronary artery disease (CAD) in non-ST segment elevation myocardial infarction (NSTSEMI) patients.
Methods: The current work was carried out on 100 individuals aged from 40 to 68 years old, both sexes, with clinical criteria of NSTSEMI. Resting 12 electrocardiogram (ECG) leads, transthoracic echocardiography (echo), diagnostic coronary angiography and SYNTAX score (SS) calculation were assessed in all patients.
Results: The cut off value of >24.39 × 100 CAR yielded a sensitivity of 40.82%, a specificity of 96.08%, a positive predictive value (PPV) of 67.5% and a negative predictive value (NPV) of 63.3% in prediction of intermediate-high SS (>22) with AUC of 0.708 and P = <0.001. Normal ECG and ejection fraction (EF) were substantially greater in low SS group contrasted to intermediate-high SS group, but ST depression, inverted T, regional wall motion abnormalities, left main, left circumflex and right coronary arteries had been significantly decreased in low SS group contrasted to intermediate-high SS group (p<0.05).
Conclusion: Increased CAR was shown to be directly linked to the degree, intensity, and intricacy of coronary atherosclerosis as measured by the SS. CAR may serve as a biomarker to assess the magnitude and complexities of CAD in individuals with NSTEMI.

Keywords: C reactive protein, serum albumin, ratio, non-ST segment elevation, syntax score, myocardial infarction

Introduction
Coronary artery disease (CAD) is the primary reason of death globally. The primary cause of CAD is atherosclerosis. Inflammation is recognized as a contributing factor in the development and advancement of atherosclerosis [1].
The severity of CAD has a strong connection with mortality. The Synergy among Percutaneous Coronary Intervention (PCI) with *Taxus* and cardiac surgeries syntax score (SS) is the prevailing scoring method utilized to assess CAD severity. Elevated SS has been linked to higher death rates, both in stable CAD and in acute coronary syndrome, involving NSTSEMI [2, 3].
The SS is a measurement utilized via angiography to assess the level of complexity in CAD. The SS was created by researchers at the Thorax center, Erasmus Medical Center in The Netherlands, led by senior expert Prof Patrick Serruys. The SYNTAX angiographic grading tool was initially released in 2005 [4].
Recognizing the characteristics linked to intermediate-high severity of CAD might enhance the prognosis of individuals. This can be achieved by facilitating quick referrals for angiography of the coronary artery and revascularization, and by providing constant monitoring throughout hospitalization as well as following discharge [5]. The assessment of inflammation may be conducted by quantifying acute phase reactants (APRs). The widely used markers, C-reactive protein (CRP) and albumin, referred to as positive and negative APRs correspondingly, are linked to the existence of CAD, the severity of CAD, and unfavorable cardiovascular events [6, 7].

The recently developed indicator, CRP to albumin ratio (CAR), is considered to be a more precise predictor of the inflammatory condition compared to CRP or albumin separately. Additionally, CAR has been linked to a less favorable outcome among individuals with critical conditions and malignancies [8, 9].
The objective of the research was to establish a correlation between the ratio of CRP to serum albumin and the severity of CAD among individuals with NSTSEMI.

Patients and Methods

This current work was performed on 100 patients aged from 40 to 68 years old, both sexes, with clinical criteria of NSTSEMI. The study was done from January 2020 until June 2020 following permission from the Ethics Committee Tanta University Hospitals, Tanta, Egypt. The participants provided a well-informed written consent.
The criteria for exclusion encompassed individuals who had a prior history of CAD and had been managed with coronary artery bypass grafting or PCI. Additionally, those suffering from STEMI, malignancies, active infections, connective tissue disease, chronic kidney disease, and liver disease were also excluded.

All individuals had been exposed to: History taking, clinical examination, resting 12 electrocardiogram (ECG) leads, transthoracic echocardiography (echo), laboratory investigation [CRP, serum plasma Albumin, complete blood count (CBC), troponin, serum urea, serum creatinine and virology], diagnostic coronary angiography and SS calculation.

CAR

Before usage, the serum ought to be diluted by a factor of 100. Subsequently, we dispense 10 µl of undiluted CRP standards, diluted samples, and diluted controls into the relevant wells. Subsequently, we incubate the samples at room temperature (18-25 °C) for 45 minutes. Lastly, we interpret the finding. Reference value in adult serum: <6 mg/l.
The biuret reaction is the most frequently utilized technique for quantifying blood protein levels. The underlying mechanism of this reaction involves the interaction between serum proteins and copper sulfate in the presence of sodium hydroxide, resulting in the formation of a distinct violet "biuret" complex. The degree of violet coloration is directly correlated with the protein content. Reference value in adult serum: 3.5-5.5 g/dl.
Resting standard 12-lead ECG was obtained. Non-ST-segment elevation ACS (NSTEACS) may have various ECG alterations, including as chronic or temporary ST-segment depression, flat T waves, T wave inversion, or false normalization of T waves. In certain cases, there may also be transitory ST-segment elevation, while in others, the ECG may seem normal [11].
Two dimensions transthoracic echo was performed before coronary angiography. The ECHO study was performed by 2 operators for each case using (Vivid 6, Vingmed-General Electric, Horten, Norway) machine. Estimation of left ventricle (LV) systolic function, Estimation of left ventricular dimensions left ventricular end systolic diameter (LVESD). Estimation of left atrial and aortic dimensions, Estimation of regional wall motion abnormalities as left ventricular anterior, apical, septal (mid, basal), inferior, posterior and lateral walls were assessed. Assessment of mitral regurge using color flow doppler, pulsed and continuous doppler.

Coronary angiographic evaluation: By using seldinger technique by introducing 6 French femoral or radial sheaths in right femoral artery or right radial artery, engagement of left and right system, angiogram in multiple projection was done to complete visualize both systems.
The SS is computed using a computer software that comprises of sequential and interactive self-directed inquiries. The algorithm has 12 primary inquiries. They may be categorized into two distinct groups: The first 3 factors ascertain the dominance, total lesion count, and the number of vessel segments affected per lesion, and they arise only once. The maximum allowable number of lesions is 12 with each lesion being identified by a number ranging from 1 to 12. The lesions will be evaluated based on the number sequence provided in question 3. Each lesion has the potential to affect a single segment or several. Each vessel segment that is implicated incorporates to the grading of the lesion in this specific instance. No restriction on the number of segments per lesion was existed [4]. The last 9 inquiries pertain to unfavorable lesion features and are repeated for each individual lesion. The first question pertains to a complete blockage. If a complete blockage is recorded, responses must be provided for specific sub-queries in a comprehensive manner. The last sub-question pertains to the existence or nonexistence of lateral branches and their dimensions [12].

Statistical analysis

The statistical analysis was conducted utilizing SPSS v26 (IBM Inc., Chicago, IL, USA). The quantitative parameters were expressed as the mean and standard deviation (SD) and contrasted among both groups using an unpaired Student's t-test. The qualitative parameters were shown as frequencies and percentages (%) and assessed by the Chi-square or Fisher's exact test, as applicable. The area under the curve (AUC) is a measure used to assess the overall performance of a test. An AUC value more than 50% indicates acceptable performance, while a value approaching 100% represents the greatest possible performance for the test. The qualitative parameters were shown as frequencies and percentages (%) and were examined using the Chi-square test. A two-tailed P value < 0.05 was considered statistically significant.

Results

Regarding demographic data (age, gender, height, weight and BMI), no substantial variation was existed among the two groups. Table 1.

Table 1: Demographic data of studied patients

		Low SS (n = 51)	Intermediate-high SS (n = 49)	P value
Age (years)		55.41±7.17	53.59±8.55	0.251
Sex	Male	32 (62.75%)	31 (63.27%)	0.957
	Female	19 (37.25%)	18 (36.73%)	
Height (cm)		175.43±4.50	176.16±5.14	0.450
Weight (kg)		86.67±7.07	85.59±9.26	0.515
BMI (kg/m²)		28.23±2.87	27.61±3.07	0.159

Data are presented as mean ± SD or frequency (%). BMI: Body mass index, *significant p value<0.05

Regarding transient ST elevation, EDD, ESD, LA, AO, MR and LAD, there was insignificantly different both groups. Regarding normal ECG and EF, there was substantially greater in low SS group contrasted to intermediate-high SS group, but ST depression, inverted T, RWMA, LM, LCX and RCA had been substantially reduced in low SS group than intermediate-high SS group (p<0.05). Table 2.

Table 2: ECG, echocardiography and angiography of studied patients

	Low SS (n = 51)	Intermediate-high SS (n = 49)	P value
ECG			
Normal	25 (49.01%)	5 (10.2%)	<0.001*
ST depression	5 (9.80%)	10 (20.4%)	0.009*
Inverted T	13 (25.4%)	25 (51.02%)	0.010*
Transient ST elevation	4 (7.84%)	5 (10.20%)	0.450
Echo			
EDD(mm)	62.63±5.18	64.10±6.51	0.212
ESD(mm)	45.90±8.42	49.49±9.97	0.054
EF(%)	57±14	49±16	0.017*
RWMA(%)	11 (21.56%)	24 (48.97%)	0.008*
LA (mm)	39.75±7.47	41.47±9.28	0.309
AO (mm)	28.41±3.40	29.43±3.45	0.141
MR	13 (25.49%)	19 (38.78%)	0.155
Angiography			
LM	3 (5.88%)	10 (20.41%)	0.039*
LAD	41 (80.39%)	45 (91.84%)	0.149
LCX	14 (27.45%)	29 (59.18%)	0.001*
RCA	20 (39.22%)	36 (73.47%)	0.001*
SS	23.20±13.27		

Data are presented as mean ± SD or frequency (%), * significant as p value <0.05, ECG: electrocardiogram, Echo: echocardiography, EDD: End diastolic diameter, ESD: End systolic diameter, EF: Ejection fraction, RWMA: Regional wall motion abnormalities, LA: Left atrium, AO: Aorta, MR: Mitral regurgitation, LM: Left main, LAD: Left anterior descending artery, LCX: left circumflex artery, RCA: Right coronary artery, SS: Syntax score

CRP and CAR were significantly decreased in low SS group than intermediate-high SS group (p<0.05). Albumin was substantially greater in low SS group than intermediate-high SS group (p<0.05). Table 3.

Table 3: Laboratory investigations between both groups

	Low SS (n = 51)	Intermediate-high SS (n = 49)	P value
CRP (mg/L)	5.9±5	12.7±10.2	<0.001*
Albumin (gm/dL)	3.94±0.41	3.72±0.33	0.003*
CAR	1.5±1.27	3.47±2.84	<0.001*

Data are presented as mean ± SD or frequency (%), * significant as p value <0.05, SS: Syntax score, CRP: C-reactive protein, CAR: C-Reactive protein/albumin ratio × 100

Normal ECG was independent predictor of less association with intermediate–high SS (OR: 0.195; 95% CI: 0.046-0.821). CAR was independent predictor of higher association with intermediate - high SS (OR: 1.38; 95%CI: 1.17-1.62). Others (Inverted T wave, ST depression, EF, RWMA, CRP and albumin) weren't independent predictors of intermediate–high SS. Table 4.

Table 4: Multivariate logistic regression to show independent predictors of intermediate - high SS (>22)

Variable	P value	Odds ratio	95% CI
Normal ECG	**0.026***	0.195	0.046-0.821
Inverted T wave	0.737	1.23	0.373-4.04
ST depression	0.534	1.53	0.403-5.79
EF	0.323	0.175	0.005-5.55
RWMA	0.0524	3.39	0.988-11.69
CRP	0.675	1.17	0.560-2.45
Albumin	0.131	0.198	0.024-1.62
CAR	0.008*	1.38	1.17-1.62

SE: Standard error, Data are presented as number* significant as p value <0.05, ECG: electrocardiogram, Echo: echocardiography, EF: Ejection fraction, RWMA: Regional wall motion abnormalities, CRP: C-reactive protein, CAR: C-Reactive protein/albumin ratio × 100

The cutoff value of >10 for CRP yielded a sensitivity of 34.69%, a specificity of 100.0%, a positive predictive value (PPV) of 67.5% and a negative predictive value (NPV) of 63.3% in prediction of intermediate-high SS (>22) with AUC of 0.703 and P = <0.001. The cutoff value of ≤38 for albumin yielded a sensitivity of 100.0%, a specificity of 45.10%, a PPV of 52.9% and a NPV of 55.1% in prediction of intermediate-high SS (>22) with AUC of 0.677 and P = 0.001. The cutoff value of >24.39 for CAR yielded a sensitivity of 40.82%, a specificity of 96.08%, a PPV of 67.5% and a NPV of 63.3% in prediction of intermediate-high SS (>22) with AUC of 0.708 and P = <0.001. Figure 1.

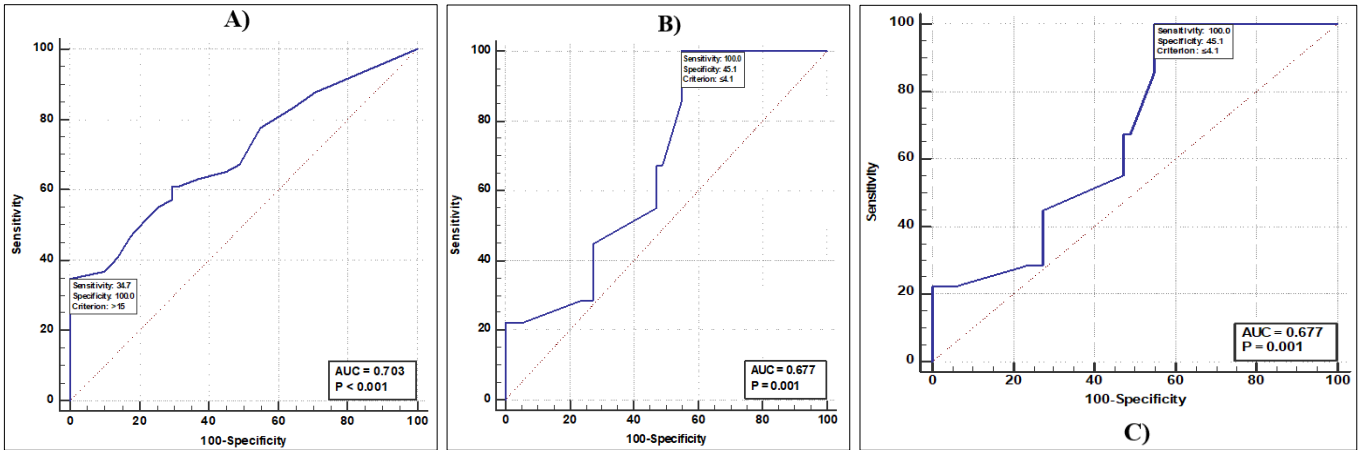

Fig 1: ROC curve of A) CRP, B)aalbumin and C) CAR in prediction of intermediate-high SS (>22)

Discussion

The utilization of inflammatory biomarkers has been on the rise in assessing the severity of cardiac disorders. CRP and albumin show a robust correlation with individual CAD. CAR has shown superior ability to assess the inflammatory state and predict prognosis compared to individual markers such as CRP or albumin separately. This has been seen in patients in critical conditions, those with acute medical illnesses, and individuals with malignancies [13].

Our results illustrated that CRP and albumin ratio (CAR) were substantially reduced in low SS group than intermediate-high SS group. Albumin was substantially greater in low SS group contrasted to intermediate-high SS group.

The obtained results are in line with Acet *et al.* [14] who assessed his study to examine the association of CAR with short-term MACE in STEMI individuals underwent primary percutaneous coronary intervention (pPCI). The study involved 539 STEMI patients managed with pPCI in this work. Individuals had been split into 2 groups: MACE with high SS group and no MACE with low SS group. Individuals with high SS had higher CRP level and CAR than the low SS group. Moreover, the albumin level was significantly decreased in high SS patients contrasted to individuals with low SS.

These results are in coordination with Mirbolouk *et al.* [15] the work included 158 individuals with diagnosis of NSTEMI at the time of discharge to evaluate the ECG alterations and coronary findings among individuals with NSTEMI. Demographic characteristics, electrocardiographic changes and angiography data had been utilised to measure a SS for each individual. The individuals had been split into 3 groups depending on this score: high risk >32, intermediate risk 22-32, and low risk < 22. Involved vessels, including the LAD, RCA, LCX, and LM were also determined. The low SS group showed significantly lower frequency of LM, LCX and RCX vessels compared to the high and intermediate SS group. While LAD lesion frequency was substantially elevated in the high SS group contrasted to the low and intermediate SS group.

Moreover, another important finding of this study is the ROC curve that was done for detection the prediction performance CRP level to predict the intermediate-high SS (>22). CRP level with a cutoff value of >10 provided a sensitivity of 34.69% and a specificity of 100.0% in prediction of intermediate–high SS (>22) with AUC of 0.703.

Nasr *et al.*, (2020) [16] reported that, based on the ROC curve, the CRP level with a cutoff value of 0.26 had a sensitivity of 91% and specificity of 82% in prediction of high SS.

Additionally, the ROC curve showed that the cutoff value of ≤3.8 for albumin provided a sensitivity of 100.0%, a specificity of 45.10% in prediction of intermediate–high SS (>22) with AUC of 0.677.

Kurtul *et al.* [17] did research to examine the potential correlation between serum albumin (SA) concentrations at admission and the likelihood elevated SS and in-hospital mortality among individuals with ACS. The research included a total of 1303 individuals diagnosed with ACS who undergone the medical procedure known as coronary angiography (CA). The participants were categorized into two groups: an elevated SS group consisting of 33 individuals and a low SS group consisting of 32 individuals. The ROC curve analysis demonstrated that the SA level was a robust predictor of elevated SS in ACS cases. The optimal cutoff value for SA was found to be below 3.65 mg/dL, which produced a sensitivity of 80% and a specificity of 70%. The AUC was calculated to be 0.820, indicating a significant discriminatory power of SA in identifying high SS in ACS.

Furthermore, our study reported that the ROC curve revealed that the cutoff value of >24.39 for CAR yielded a sensitivity of 40.82% and a specificity of 96.08% in prediction of intermediate–high SS (>22) with AUC of 0.708.

Nasr *et al.* [16] results demonstrated that the ROC curve with the cutoff value of 7.2 for CAR yielded a sensitivity of 93%, a specificity of 85% in prediction of elevated SS with AUC of 0.974.

Finally, multivariate logistic regression showed independent predictors of intermediate-high SS. Moreover, the normal ECG was independent predictor of less association with intermediate–high SS. CAR was independent predictor of higher association with intermediate-high SS.

Karabağ *et al.* [10] conducted research with 403 consecutive individuals with stable angina pectoris. The subject's undergone coronary angiography to investigate probable CAD. The participants were categorized into 2 groups based on their SS to assess the correlation among severity of coronary atherosclerosis, as measured by SS, and the CAR among individuals with stable CAD. The low SS group included individuals with a severity score of 22 or below, whereas the intermediate-high SS group included

individuals with a severity score higher than 22. The researchers utilized multivariate logistic regression analysis to identify the independent predictors of the intermediate-high SS group. The findings indicated that the CAR was an independent predictor strongly associated with high SS.
Limitations: The limited number of patients as large samples are required to attain more definite results, the study did not follow up the patient, the survival rate was not included in the statistical analysis and MACE were not included or followed in this study whether in patients treated by PCI or referred to urgent CABG.

Conclusion
The study found a significant correlation between higher CAR and the degree, extent, and complexity of coronary atherosclerosis as evaluated by the SS. CAR may serve as a biomarker to assess the magnitude and intricacy of CAD in these individuals.

Financial support and sponsorship: Nil.
Conflict of Interest: Nil.

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How to Cite This Article
Seyam MA, Ibrahim IK, Sokkary HME, Elsheikh RG. Relationship between c reactive protein to serum albumin ratio and the coronary artery disease severity in non-ST segment elevation myocardial infarction patients. International Journal of Cardiology Research. 2024;6(1):07-11.