

# RELATIONSHIP BETWEEN C- REACTIVE PROTEIN/ALBUMIN RATIO AND CORONARY ARTERY DISEASE SEVERITY IN PATIENTS WITH STABLE ANGINA

By

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## ABSTRACT

**Background:** CAD is the largest contributor of cardiovascular diseases (CVDs) and mortality rate is due in prevalence to atherosclerosis. Syntax score (SS), which is an angiographic tool used in grading the complexity of coronary artery disease (CAD), has a prognostic importance in coronary artery disease (CAD) and provides important information regarding selection of revascularization strategy.

**Objective:** To assess the relationship between C reactive protein/albumin ratio (CAR), severity of coronary atherosclerosis assessed by the syntax score (SS) in patients with stable coronary artery disease.

**Patients and Methods:** This study was a prospective cohort study conducted on 100 patients divided into two equal groups according Syntax score. All patients underwent elective percutaneous coronary angiography, and have the following: hemoglobin levels, serum creatinine, serum cholesterol, serum albumin, C- reactive protein, resting 12-lead electrocardiography and Doppler – echocardiography.

**Results:** C-reactive protein/albumin ratio was significantly higher in patients with intermediate-high SS group. In multivariate regression analysis, CAR remained an independent predictor of intermediate-high SS group together with serum Cholesterol, HDL and LDL.

**Conclusion:** C-reactive protein/albumin ratio was more tightly associated with the complexity and severity of CAD, and was found to be an independent predictor for intermediate-high SS group.

**Key words:** C-reactive protein/albumin ratio, Syntax score, coronary angiography.

## INTRODUCTION

Coronary artery disease (CAD), the leading cause of mortality worldwide, places a serious economic burden on healthcare systems (Karabağ *et al.*, 2018). It is mainly due to atherosclerosis (Michelsen *et al.*, 2016). Inflammation plays a role in pathogenesis of onset and

progression of atherosclerosis (Poddar *et al.*, 2016). Serum albumin has many physiological properties, including anti-inflammatory, antioxidant and antiplatelet aggregation activity. It also plays an essential role in the fluid exchange across the capillary membrane (Adach and Olas, 2020).

In the more specific context of cardiovascular diseases, serum albumin is independently associated with the development of a variety of deleterious conditions such as coronary artery disease, heart failure, atrial fibrillation and stroke (*Wu et al., 2018*).

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 (*Wu et al., 2018*).

The syntax 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 (*Neumann et al., 2019*).

Clinical studies have shown that SS has prognostic importance in CAD and provides important information regarding the selection of revascularization strategy (*Franzone et al., 2016*).

The relationship between CAR and severity and complexity of CAD is not yet known. Because CAD is an essential inflammatory disease, CAR could be associated with complexity of CAD as assessed by SS (*Karabağ et al., 2018* and *Kundu et al., 2018*).

The aim of the present study was to assess the relationship between C reactive protein/albumin ratio (CAR), and the severity of coronary atherosclerosis assessed by the syntax score (SS) in patients with stable coronary artery disease.

## PATIENTS AND METHODS

Our study was a prospective cohort study carried one MAHALLA CARDIAC CENTER during the period from May 2017 to February 2020 included 100 randomly selected patients who were admitted to coronary care unit for elective coronary angiography divided into two equal groups:

- **Group I:** High-intermediate syntax scores.
- **Group II:** Low syntax score.

### Inclusion criteria:

Patients with stable angina pectoris (SAP) who underwent coronary angiography for suspected CAD who aged above 18 years old were enrolled in our study.

### Exclusion criteria:

History of coronary artery bypass graft surgery, percutaneous coronary intervention, history of malignancy, history of active infection, history of connective tissue disorder, history of liver disease (cirrhotic liver), or patients refusal.

All patients underwent complete history taking, Full clinical examination and cardiac assessment, Electrocardiogram (ECG), Doppler – echocardiography, Laboratory investigations (hemoglobin level, serum creatinine, serum cholesterol, serum albumin, C- reactive protein and C-reactive protein/albumin ratio), calculating syntax score and percutaneous coronary angiography.

**Statistical Analysis:**

Data were analyzed using Statistical program for the Social Sciences (SPSS) version 23. Quantitative data were expressed as mean  $\pm$  standard deviation (SD). Qualitative data were expressed as frequency and percentage.

We used the following tests of significance: Independent-samples t-test, Mann Whitney U test, Chi-square ( $X^2$ )

test. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values and to calculate sensitivity, specificity, PPV (positive predictive value), NPV (negative predictive value). Statistical significance was assessed at P values less than 0.05.

**RESULTS**

In group I, there were 54% diabetic patients while in group II there were 32% diabetic patients. There was a statistically significant difference between the groups, P value  $< 0.03$ .

In group I, there were 66% hypertensive patients, while in group II there were 40% hypertensive patients. There was a statistically significant difference between the groups (P value  $> 0.01$ ).

In group I, there was a 32% smoker patient, while in group II there was 44% smoker patients. There was a statistically non-significant difference between the groups (P value  $< 0.05$ ).

Regarding Family history of CVD, in group I, there were 26% patients with positive history, while in group II there was a 28% patient with positive history. There was a statistically non-significant difference between the groups (P value  $< 0.05$  (Table 1).

**Table (1): Comparison between cases with high-intermediate syntax scores versus those with low score as regard demographic characteristics**

Score Parameters	High-intermediate syntax scores N=50	low syntax score N=50	p-value
Age	58.5 $\pm$ 6.4	56.02 $\pm$ 6.33	$> 0.05$
Gender	Male (54%)	Male (40%)	$> 0.05$
	Female (46%)	Female (60%)	
Smoking	32%	44%	$> 0.05$
DM	54%	32%	$< 0.03$
HTN	66%	40%	$< 0.01$
Family history of CVD	26%	28%	$> 0.05$

Serum Cholesterol, in group I, mean was 205.24  $\pm$  40.04, while in group II the mean was 184  $\pm$  35.28. The main difference between the groups was statistically significant with P value =

0.006. Serum LDL, in group I, mean was 110.7  $\pm$  36.6, while in group II the mean was 92.12  $\pm$  16.82. The main difference between the groups was statistically significant with P value = 0.002.

Serum HDL, in group I, mean was  $54.36 \pm 9.42$ , while in group II the mean was  $48.22 \pm 8.92$ . The main difference between the groups was statistically significant with P value =0.001. Regarding serum creatinine in group I, mean was  $0.98 \pm 0.34$ , while in group II the mean was  $0.99 \pm 0.35$ . The main difference between the groups was statistically non-significant with P value =0.001.

Regarding Syntax Score in group I, the mean was  $33.98 \pm 6.56$ , while in group II the mean was  $12.36 \pm 5.6$ . The main difference between the groups was statistically highly significant with P value <0.001.

CRP in group I, median was 0.47(0.21-0.93), while in group II the median was 0.21(0.06-0.34). The main difference between the groups was statistically highly significant with P value <0.001. Crp/Alb ratio, in group I, median was 12.7 (5.6-29.1), while in group II the median was 5.6 (1.8-8.4). The main difference between the groups was statistically highly significant with P value <0.001.

Regarding EF, in group I, the mean was  $50.52 \pm 6.18$  while in group II the mean was  $57.8 \pm 6.47$ . The main difference between the groups was statistically highly significant with P value <0.001 (**Table 2**).

**Table (2): Comparison between cases with high intermediate syntax scores versus those with low score as regard Results of investigations**

Parameters \ Score	High intermediate syntax scores	Low syntax score	p-value
	N=50	N=50	
S Cholesterol(mg/dl)	$205.24 \pm 40.04$	$184 \pm 35.28$	< 0.006
LDL (mg/dl)	$110.7 \pm 36.6$	$92.12 \pm 16.82$	< 0.002
HDL(mg/dl)	$54.36 \pm 9.42$	$48.22 \pm 8.92$	= 0.001
Cr (mg/dl)	$0.98 \pm 0.34$	$0.99 \pm 0.35$	> 0.05
HGB(g/dl)	13.4(9.6-13.7)	13.7(7.5-15.9)	> 0.05
Dominant Syst	Rt (64%)	Rt (68%)	> 0.05
	Lt (36%)	Lt (32%)	
Syntax Score	$33.98 \pm 6.56$	$12.36 \pm 5.6$	< 0.001
CRP(mg/l)	0.47(0.21-0.93)	0.21(0.06-0.34)	< 0.001
Alb (g/dl)	3.5(2.9-4.9)	3.7(3.2-4.4)	> 0.05
CRP/Alb Ratio	12.7(5.6-29.1)	5.6(1.8-8.4)	< 0.001
EF (%)	$50.52 \pm 6.18$	$57.8 \pm 6.47$	< 0.001

A multivariate logistic regression model was performed to ascertain the effects of DM, HTN, cholesterol, LDL, HDL and CRP/Alb Ratio on the likelihood

that participants in intermediate-high syntax score and showed statistically significant difference (**Table 3**).

**Table (3): Logistic regression analysis of intermediate-high syntax score**

Parameters	Score	Odd ratio	95% C.I	P value
DM(mg/dl)		2.42	1.27 – 7.34	< 0.05
HTN(mmHg)		3.06	1.02 – 5.74	= 0.012
S Cholestrol(mg/dl)		1.016	1.004 - 1.02	< 0.01
LDL(mg/dl)		1.025	1.008 – 1.042	= 0.004
HDL (mg/dl)		0.931	0.89 – 0.974	= 0.002
Crp/Alb Ratio		3.7	1.92 – 7.13	< 0.001

Correlation between CRP/ Albumin ratio, CRP, Albumin showed statistically significant differences (P value <0.001)

with CRP/ Albumin ratio and CRP, while non-significant difference (P value >0.05) with Albumin (**Table 4**).

**Table (4): Correlation between CRP/Alb ratio, CRP, Alb and high syntax score**

Items	Pearson correlation coefficient(r)	P value
CRP/Alb ratio	0.662	<0.001
CRP	0.667	<0.001
Alb	0.005	>0.05

ROC curve analysis was done for prediction of high syntax score and found that C-reactive protein/albumin ratio and

C-reactive protein was the best predictor of high syntax score (**Table 5**).

**Table (5): Receiver-operating characteristic (ROC) curves for C-reactive protein/albumin ratio, C-reactive protein for high syntax score**

Item assessed	95% Confidence Interval		Cutoff point	Sensitivity	Specificity	AUC	P value
	Lower Bound	Upper Bound					
CRP	0.935	0.999	0.26	91%	82%	0.967	<0.001
Crp/Alb Ratio	0.947	1.000	7.2	93%	85%	0.974	<0.001

## DISCUSSION

In our study as regarding the age, in group I the Mean age was 58.5±6.4 years, and group II mean age was 56.02±6.33 years. The main difference between the groups was statistically non-significant. Regarding gender, group I there were 54% males and group II there were 40% males with non-statistically significant difference between the two groups.

*Yahagi et al. (2015)* stated that most of the underlying systemic risk factors for coronary artery disease are similar between men and women. However, the impact of various risk factors is different between men and women, with smoking being a stronger risk in women than men, especially in younger women. Furthermore, the influence of the menopause is also unique and important in

women: incidence of plaque rupture is higher in older women as compared to younger.

Our results showed a statistically significant difference in between the two groups as regarding DM and HTN with non-significant difference with the other risk factors.

A study by *Oh et al. (2017)* stated that hypertension was the most common comorbidity. Men were more common in the non-survivor group. A history of cancer was more common among non-survivors, whereas hypertension was more common among survivors, but with non-significant difference as regarding DM and other risk factors.

On the other hand, *Suzuki et al. (2019)* enrolled 204 patients (mean age, 72 years; male, 69%) and found no significant difference in between all patients as regarding the risk factors.

In our study as regarding serum cholesterol, in group I, the mean was  $205.24 \pm 40.04$ , while in group II the mean was  $184 \pm 35.28$  with statistically significant with P value =0.006.

For serum LDL, in group I, the mean was  $110.7 \pm 36.6$ , while in group II the mean was  $92.12 \pm 16.82$  with a statistically significant difference. for serum HDL, in group I, the mean was  $54.36 \pm 9.42$  while in group II the mean was  $48.22 \pm 8.92$  with a statistically significant difference.

Our results were concordant with *Suzuki et al. (2019)* which stated that there was a statistical significant difference as regarding total cholesterol and LDL, with non-significant difference as regard HDL. On contrary, *Duman et al. (2019)* stated

that there is no statistically significant difference as regarding LDL and HDL.

Our results showed that Syntax Score, in group I, was  $33.98 \pm 6.56$ , while in group II the mean was  $12.36 \pm 5.6$  with statistically significant difference, and for CRP, in group I, the median was 0.47 (0.21-0.93), while in group II the median was 0.21 (0.06-0.34) with statistically significant difference.

On a study by *Karabağ et al. (2018)*, they stated patients with stabile angina pectoris, who underwent coronary angiography for suspected CAD, have a high significant difference as regarding CRP between the high and low SS groups. Also, *Kayapinar et al. (2019)* had the same results as regarding hs-CRP.

In our study, CAR, in group I, median was 12.7 (5.6-29.1), while in group II was 5.6 (1.8-8.4). The main difference between the groups was statistically significant. Our results showed a multivariate logistic regression model which was performed to ascertain the effects of DM, HTN, cholesterol, LDL, HDL and Crp/Alb ratio on the likelihood that participants in intermediate-high syntax score, and showed a statistically significant difference. The correlation between CRP/ Albumin ratio, CRP, Albumin and high syntax score showed statistically significant difference with CRP/ Albumin ratio and CRP, while non-significant with Albumin.

*Oh et al. (2017)* stated that the relationship between albumin, CRP level, and SS were 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.

Blood urea nitrogen, hemoglobin, albumin, sodium and hs-CRP values showed statistically significant associations with all-cause in-hospital mortality. After adjusting for these variables, the hs-CRP/albumin ratio still showed an association with all-cause in-hospital mortality. Patients in the fourth quartile were 5.94 times more likely to die compared with those in the lowest quartile of the hs-CRP/albumin ratio. When the hs-CRP/albumin ratio was examined as a continuous variable, it still showed an association with all-cause in-hospital mortality.

*Kurtul et al. (2016)* 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. They also stated 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.

A study by *Kinoshita et al. (2015)* indicated that CAR levels were significantly associated with SS and were independent predictors for intermediate-high SS group in patients who had undergone coronary angiography due to SAP. Furthermore, the CAR predicted intermediate-high SS group more accurately than either CRP or SA alone.

## CONCLUSION

C-reactive protein/albumin ratio was more tightly associated with the complexity and severity of CAD, and was found to be an independent predictor for intermediate-high SS group.

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## العلاقة ما بين البروتين المتفاعل سي الي نسبة الالبومين ودرجة اعتلال الشريان التاجي في مرضى الذبحة الصدرية المستقرة

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**خلفية البحث:** يعتبر قصور الشريان التاجي من اكبر المساهمين في امراض القلب و الاوعيه الدمويه ومعدل الوفيات يرجع في معدل الانتشار إلى تصلب الشرايين. و يعتبر حساب سينتاكس أداة أنجيوغرافية تستخدم في تصنيف تعقيد مرض الشريان التاجي لها ايضاً أهمية تنبئية في مرض الشريان التاجي وتوفر معلومات مهمة فيما يتعلق باختيار ستراتيجية إعادة الأوعية الدموية. وبروتين سي التفاعلي هو مؤشر على التهابات، وترتبط مستويات عالية منه مع إرتفاع درجه حساب سينتاكس.

**الهدف من البحث:** تقييم العلاقة بين نسبة البروتين سي التفاعلي إلي نسبه الألبومين وشدة تصلب الشرايين التاجية التي تم تقييمها من خلال درجة حساب سينتاكس في المرضى الذين يعانون من مرض الشريان التاجي المستقر.

**المرضى وطرق البحث:** أجريت هذه الدراسة على 100 مريض مقسمة إلى مجموعتين متساويتين وفقاً لدرجة حساب سينتاكس وخضع جميع المرضى لتصوير الأوعية التاجية الاختياري وتم تقييم جميع المرضى وإجراء التحاليل المعملية على مستويات الهيموجلوبين و الكرياتينين و الكوليسترول في الدم والألبومين وبروتين سي التفاعلي و تخطيط القلب الكهربائي دوبلر وتخطيط صدى القلب.

**نتائج البحث:** كان بروتين سي التفاعلي إلي نسبة الألبومين أعلي بكثير في المرضي أصحاب حساب سينتاكس المتوسط و العالي. وفي تحليل الانحدار متعدد المتغيرات، ظلت بروتين سي التفاعلي الي نسبه الألبومين مؤشراً مستقلاً لمجموعة حساب سينتاكس متوسطة الإرتفاع مع الكوليسترول في الدم والكوليسترول الخفيف و المتكدث.

**الاستنتاج:** كان بروتين سي التفاعلي الي نسبه الألبومين أكثر إرتباطا بإحكام مع تعقيد وشدة قصور الشريان التاجي ويمكنه أن يكون مؤشرا مستقلا لمجموعة حساب سينتاكس المتوسطة و العالية.