

# Association of Hypoalbuminaemia with the Angiographic Severity of Coronary Artery Disease in Patients with Acute Coronary Syndrome

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## Abstract

**Introduction:** Serum albumin as a biomarker of coronary artery disease (CAD) severity and mortality in patients with acute coronary syndrome (ACS) is presently a subject of growing interest. Evidences accumulated from the studies suggest a possible association between serum albumin and severity of CAD.

**Aim of the study:** The aim of this study was to find the association between serum albumin level and severity of CAD in patients of ACS.

**Methods:** The present cross-sectional analytical study was carried out in the Department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh, over a period of 1 year from July 2017 to June 2018. A total of 104 ACS patients undergoing coronary angiogram in the above-mentioned hospital during the index hospitalization within the specified time-frame were included in the study.

**Result:** None of the demographic characteristics and traditional risk factors for CAD except age was found to be associated with severity of CAD. Friesinger Score was significantly higher in patients with low serum albumin than that in patients with normal serum albumin ( $8.84 \pm 3.71$  vs.  $6.38 \pm 3.02$ ,  $p < 0.001$ ). Leaman Score was also significantly higher in the former group than that in latter group ( $12.48 \pm 8.44$  vs.  $8.50 \pm 4.94$  mm,  $p = 0.004$ ). The risk of having severe CAD in patients with low serum albumin was 5.46(95% CI = 2.141 – 13.925) ( $p < 0.001$ ) times higher in terms of Friesinger score and 2.58(95% CI = 1.097 – 6.083) ( $p = 0.03$ ) times higher in terms of Leaman score than that in patients with normal serum albumin. Spearman's correlation revealed that the two variables serum albumin and Friesinger score, exhibit a significantly inverse correlation ( $r = -0.323$ ,  $p = 0.001$ ). Serum albumin demonstrated a significantly inverse correlation with Leaman score ( $r = -0.254$ ,  $p = 0.009$ ).

**Conclusion:** The study concluded that serum albumin concentration was significantly associated with the severity of coronary artery disease with low serum albumin carrying at least two-fold higher risk of having severe CAD, as measured by the Friesinger and Leaman score, in patients with ACS.

**Key words:** Hypoalbuminaemia, Serum Albumin, Angiographic severity, Friesinger score, Leaman score, Acute Coronary Syndrome.

University Heart Journal 2022; 18(1): 44-49

## Introduction

Cardiovascular disease (CVD) is a global non-communicable epidemic, and is the leading cause of mortality and morbidity in both developed and developing countries.<sup>1-2</sup> CVD is account for more than 17 million deaths globally each year. South Asians are more prone to develop CAD.<sup>3</sup> Like other South Asians, Bangladeshis are unduly prone to develop CAD, which is often premature in onset, follows a rapidly progressive course and angiographically more severe.<sup>1</sup> Acute coronary syndrome (ACS) spectrum ranges from acute ST-segment

elevation myocardialinfarction (STEMI), or new-onset LBBB, to non-ST-elevation ACS (NSTEMI-ACS). NSTEMI-ACS can be further subdivided into non-ST elevation myocardial infarction (NSTEMI), which is diagnosed in cases of elevated cardiac biomarkers such as troponin-I, and unstable angina, in the absence of elevated biomarkers.<sup>4</sup> ACS is the important cause of mortality and morbidity. It is usually due to an abrupt reduction in coronary blood flow.<sup>5</sup> During the past 2 decades, extensive research has established that atherosclerosis is an inflammatory disease. All ACS events result from coronary

atherosclerosis, generally with superimposed coronary thrombosis caused by rupture or erosion of an atherosclerotic lesion.<sup>6</sup> Serum albumin, the most important protein of human serum, has several important physiological functions in the body. Increased inflammatory response has been associated with decreasing synthesis and increasing catabolism of the albumin.<sup>7</sup> Lower serum albumin levels may increase blood viscosity and disrupt endothelial functions. Additionally, serum albumin is an important inhibitor of platelet activation and aggregation and an important mediator of platelet-induced coronary artery narrowing.<sup>8</sup> Besides, one of the most important functions of serum albumin is its antioxidant activities.<sup>9</sup> Another possible underlying mechanism linking serum albumin concentration and high SYNTAX score may be increased oxidative stress. Oxidative stress has been suggested to play an important role in atherosclerosis. Oxidative stress is an important contributor to severity of CAD in young smokers with acute myocardial infarction.<sup>10</sup> There is evidence that the inflammatory activity reflected by hs-CRP levels was a strong etiological factor in association with lower levels of serum albumin in ACS. So being a principal negative acute phase reactant, levels of serum albumin decrease in well-described response to inflammation during chronic systemic diseases and acute critical illnesses.<sup>11</sup> Multivariate analysis shows that after adjusting for clinical variables that are known, strong predictors of mortality, lower serum albumin level was an independent predictor of in-hospital mortality, across the whole spectrum of ACS. Hypoalbuminaemia may also contribute to the progression of heart failure by favouring myocardial oedema, it may also facilitate pulmonary oedema by decreasing serum oncotic pressure. Possible mechanisms by which lower serum albumin levels correlate with in-hospital mortality in ACS may be related to a serious inflammatory state.<sup>11</sup> Longitudinal studies have provided robust evidence that a decrease in serum albumin concentration might be associated with an increased risk in the incidence of both CVDs and heart failure.<sup>12</sup> Hypoalbuminaemia is associated with poor epicardial and tissue-level reperfusion after primary PCI. This may be because of its relation to the severity of atherosclerosis. The incidences of multi-vessel disease, lesion length, and angiographic thrombus burden were higher in patients with hypoalbuminemia. Serum albumin also plays a direct role in the pathophysiology of no-reflow phenomenon. Hypoalbuminaemia may cause aggravated ischemia and reperfusion injuries, which are the two main pathogenetic components of the no-reflow phenomenon.<sup>13</sup> Admission serum albumin concentration

is inversely associated with high SYNTAX score and in-hospital mortality in patients with ACS. A decreased serum albumin is associated with cardiovascular events and may be useful as a biomarker of the extent and complexities of CAD.<sup>8</sup> So, the aim of this study was to assess the level of serum albumin to predict the angiographic severity of CAD in patients with ACS.

### Objectives

- a) **General objective:** To evaluate the relationship between serum albumin level and angiographic severity of coronary artery disease in patients with ACS.
- b) **Specific Objectives:**
  - To estimate the serum albumin level of acute coronary syndrome patients on admission.
  - To see the angiographic severity of coronary artery disease in patients with acute coronary syndrome.
  - To correlate the serum albumin level with the severity of coronary artery disease in patients with acute coronary syndrome in order to determine the association between these two variables.

### Methodology & Materials

This was a Cross sectional, analytical study and was carried out in the Department of Cardiology, National Institute of Cardiovascular Disease (NICVD), Dhaka, Bangladesh, over a period of one year from July 2017 to June 2018. The sample size was 104 and the study subjects were divided into 2 groups on the basis of serum albumin level: Group I-ACS patients with low serum albumin <3.5gm/dl; Group II-ACS patients with normal serum albumin ≥3.5gm/dl. Statistical analyses were performed using Statistical Package for the Social Sciences software by SPSS Inc., Chicago, IL, USA, version 25.0.

### Inclusion criteria:

- Patients with acute coronary syndrome undergoing coronary angiography during index hospitalization at NICVD.

### Exclusion criteria:

- Chronic kidney disease
- Hepatic cirrhosis
- Malnutrition
- Malignancy
- Other significant comorbidities e.g., COPD
- Valvular heart diseases, congenital heart diseases

## Result

The present cross-sectional study aimed at finding the relationship between serum albumin and severity of coronary artery disease (CAD) in patient with ACS included a total of 104 patients of documented CAD (by angiogram). The study subjects were divided into 2 groups on the basis of serum albumin level : Group I-ACS patients with low serum albumin <3.5gm/dl ; Group II-ACS patients with normal serum albumin  $\geq$ 3.5gm/dl then severity of CAD was determined by Friesinger score and Leaman score ; the higher the score the more severe was the disease. The median values of the respective scores were considered as the cut-off values in the present study. Accordingly, patients with Friesinger score >8 and Leaman score  $\geq$ 9 were considered as severe disease. Age distribution shows that, patients with low serum albumin were generally older than the patients with normal serum albumin ( $54.1 \pm 7.9$  vs.  $50.2 \pm 7.2$ ,  $p=0.009$ ) and the difference in mean age was statistically significant. The table also indicates that the most of the patients were in the age range of 50-59 years in both study groups. In both groups, there was male predominance, however, the difference in gender was not statistically significant ( $p=0.37$ ). The table also provides that among the study patients, male patients were 91 (87.5%) and female

patients were 13 (12.5%). None of the traditional risk factors for CAD (smoking, diabetes mellitus, hypertension, dyslipidaemia, family history of IHD and overweight or obesity) presented in the above table differed between the groups with low and normal serum albumin ( $p>0.05$ ). The above table shows the status of the study subjects by biochemical parameters and LVEF. The above table describes that mentioned characteristics were found almost identical in both groups of patients with no significant difference ( $p>0.05$ ). Friesinger Score was significantly higher in group I than that of group II ( $8.84 \pm 3.71$  vs.  $6.38 \pm 3.02$ ,  $p<0.001$ ). Leaman Score was also significantly higher in group I than that of group II ( $12.48 \pm 8.44$  vs.  $8.50 \pm 4.94$  mm,  $p=0.004$ ). In Friesinger Score, the variable low albumin <3.5 mg/dl was found to be significantly associated with CAD severity with the ORs being 4.42. In Leaman Score, the variable low albumin < 3.5 mg/dl was found to be significantly associated with CAD severity with the ORs being 2.21. Spearman's correlation shows that the two variables, serum albumin and Friesinger score, exhibit a significantly inverse correlation ( $r = -0.323$ ,  $p = 0.001$ ). The significant level reached from Correlation t-test (Figure-I). Serum albumin bears a significantly inverse correlation with Leaman score ( $r = -0.254$ ,  $p = 0.009$ ) by Spearman's correlation. The significance level reached from Correlation t-test (Figure-II).

**Table-I**

*Comparison of the study patients according to their demographic characteristics (N=104)*

Characteristics	Group I (n=52)		Group II (n=52)		P-value	
	n	%	n	%		
Age (in years)	30– 39	1	1.9	3	5.8	0.009 <sup>s</sup>
	40 – 49	11	21.2	18	34.6	
	50 – 59	25	48.1	27	51.9	
	$\geq$ 60	15	28.8	4	7.7	
	Mean $\pm$ SD (Range)	$54.1 \pm 7.9$ (37-75)	$50.2 \pm 7.2$ (35-70)			
Gender	Male	44	84.6	47	90.4	0.37 <sup>ns</sup>
	Female	8	15.4	5	9.6	

**Table-II**

*Distribution of study subjects by risk factors (N=104)*

Risk Factors	Group I (n=52)		Group II (n=52)		P-value
	n	%	n	%	
Smoking	46	88.5	45	86.5	0.76 <sup>ns</sup>
Hypertension	28	53.8	24	47.1	0.49 <sup>ns</sup>
Diabetes mellitus	36	69.2	30	58.8	0.27 <sup>ns</sup>
Dyslipidaemia	16	30.8	13	25	0.51 <sup>ns</sup>
Family H/o of CAD	18	34.6	10	19.2	0.07 <sup>ns</sup>
Overweight	13	25	11	21.2	0.64 <sup>ns</sup>

**Table-III**  
*Association between biochemical parameters and LVEF (N=104)*

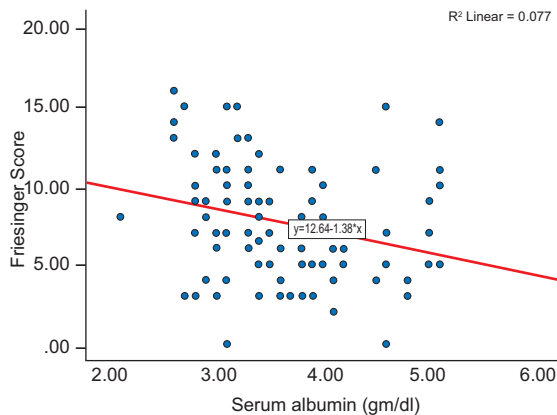
Characteristics	Group I (n=52) Mean ± SD	Group II (n=52) Mean ± SD	P-value
Serum creatinine (mg/dl)	1.12 ± 0.22	1.09 ± 0.22	0.59 <sup>ns</sup>
Troponin I ng/dl	14.94 ± 17.87	16.68 ± 19.84	0.64 <sup>ns</sup>
LVEF (%)	50.6 ± 7.9	52.0 ± 7.7	0.36 <sup>ns</sup>

**Table-IV**  
*Coronary artery disease severity of the study subjects (N =104)*

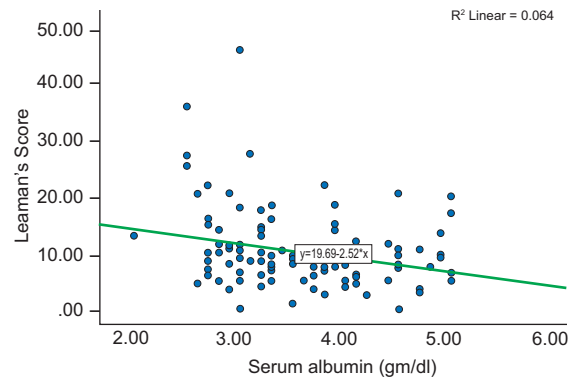
CAD severity	Group I (n=52) Mean ± SD	Group II (n=52) Mean ± SD	P-value
Friesinger Score	8.84±3.71	6.38±3.02	<0.001 <sup>s</sup>
Leaman Score	12.48±8.44	8.50±4.94	0.004 <sup>s</sup>

**Table-V**  
*Multivariate logistic regression analysis for CAD severity (Friesinger Score and Leaman Score) with age and low albumin (N=104)*

Variables of interest	Regression coefficient (β)	Odds Ratio (OR)	95% CI of OR	p value	
<b>Friesinger Score)</b>	Age (≥50 years)	0.172	1.19	0.469 – 3.007	0.72 <sup>ns</sup>
	Low albumin (<3.5 mg/dl)	1.487	4.42	1.873 – 10.442	0.001 <sup>s</sup>
<b>Leaman Score</b>	Age (≥50 years)	-0.07	0.93	0.396 – 2.198	0.87 <sup>ns</sup>
	Low albumin (<3.5 mg/dl)	0.791	2.21	1.027 – 5.902	0.04 <sup>s</sup>



**Fig.-1:** Correlation between serum albumin and Friesinger score



**Fig.-2:** Correlation between serum albumin and Leamanscore

## Discussion

The present study investigated whether admission serum albumin level is associated with severity of CAD as determined by Friesinger and Leaman score in patients with ACS. In present study, patients with low serum albumin were significantly older than those with high serum albumin. However, the groups were not different with respect to sex. Among the biochemical parameters, no significant differences were found between more severe and less severe CAD patient groups as measured by both Friesinger score and Leaman score. Contrary to these findings of the present study, serum creatinine level differed between high and low SYNTAX score in the study by Murat et al.<sup>8</sup> Serum creatinine was found more raised/elevated in patients with low serum albumin and more severe CAD in comparison to the counterparts in Oduncu et al.'s study.<sup>13</sup> One probable explanation in serum creatinine between present study and the above mentioned two studies may be the differences in average age and BMI of the study subjects. As only one confounding variable age was found to be associated with low serum albumin, regression analysis was done to rule out its influence on the severity of coronary artery disease. The multivariate logistic regression analysis revealed that the variable low albumin < 3.5 mg/dl was found to be significantly associated with CAD severity with odds of having severe CAD in patients with low serum albumin was observed to be more than 2.5-fold. Had the findings of the present study been compared and contrasted with similar studies at home and abroad, a conclusive remark could be made regarding the association between serum albumin and severity of CAD. But after using all the available means of literature search, no head-to-head study was found to be compared. However, the findings of the following studies are considered of value to compare the findings of the present study with them. Contrast to the findings of the present study, serum troponin I level differed between high and low SYNTAX score group in the study by Murat et al.<sup>8</sup> In the study by Oduncu et al.<sup>13</sup> there was significant difference ( $P=0.002$ ) of serum troponin I between low serum albumin group and normal or high serum albumin group. Contrast to the findings of the present study, LVEF significantly differed ( $P<0.001$ ) between high and low SYNTAX score ( $38\pm 11\%$  vs  $48\pm 10\%$ ) in the study by Murat et al.<sup>8</sup> Oduncu et al.<sup>13</sup> also found significant difference ( $P<0.001$ ) of LVEF (%) between patients of low serum albumin group and normal or high serum albumin group ( $45.4\pm 9\%$  vs  $47.4\pm 8\%$ ). In this study, Friesinger score and Leaman score differed between patients with low serum albumin and normal

albumin level. Patients with more severe CAD generally had low serum albumin than the patients with normal serum albumin. Considering Leaman score, patients of low serum albumin had more severe CAD than patients normal serum albumin do. As per investigation of Murat et al.<sup>8</sup> mean serum albumin level was lower in patients with high SYNTAX score ( $\geq 33$ ) than that in patients with low SYNTAX score ( $\leq 32$ ) ( $3.46\pm 0.42$  vs.  $3.97\pm 0.37$ ) ( $P<0.001$ ). Whereas Oduncu et al.<sup>13</sup> demonstrated that patients of multivessel CAD were more in low serum albumin group (44.9%) than high serum albumin group (38.4%) ( $p=0.012$ ). So, the findings of current study correlate well with those of the studies by Murat et al.<sup>8</sup> and Oduncu et al.<sup>13</sup> Zhang and associates in an attempt to investigate the relationship between prealbumin (PA) and angiographic severity of CAD found an independent negative correlation between PA and Gensini score ( $p=0.015$ ). Logistic regression analysis revealed that adjusted odds ratio of triple-vessel disease and high Gensini score were 2.47 (95% CI: 1.66–3.67) and 1.83 (95% CI: 1.50–3.49) respectively.<sup>14</sup> These findings are to some extent consistent with the findings of the present study though the tools of severity of CAD measurement were different in our study. In the current study, binary regression analysis was done to find the independent predictor of severity of CAD and only serum albumin level emerged as independent predictor of CAD severity.

## Limitations of the study

The present study was conducted in a selected hospital on ACS patients. Therefore, the findings of the study do not necessarily have external validity. The sample size was relatively small. Measurement of serum albumin levels were not evaluated over a prolonged period following the ACS event. We did not have access to information about patients' prior serum albumin levels, so we cannot be sure that hypoalbuminaemia in our sample does not represent a chronic inflammatory state. We did not measure oxidative stress markers in our study population and their correlations with serum albumin. Our questionnaire did not include information about the presence of proteinuria or fluid overload (hemodilution), which are potential causes of hypoalbuminaemia.

## Conclusion and recommendations

The study concluded that low serum albumin in patients of ACS carries at least 2-fold higher risk of having severe CAD, as measured by the Friesinger and Leaman score in patients with ACS. However, it cannot be conclusively remarked that the association is a causal one. That means whether lower serum albumin plays a causative

role in the severity of CAD, or it's just a manifestation of the severity of the disease still remains unanswered. Based on the findings of the study we recommend that further, large-scale, multi-center study is essential to validate the findings of the present study. Study may be carried out comparing single versus serial measurement of serum albumin which correlates best with the severity of CAD in patients with ACS. If the utility of estimation of serum albumin is proven in future studies, this may be added to the preprocedural work-up of ACS patients undergoing PCI. A serial measurement of serum albumin from admission to endpoint study is recommended to see the changes in the levels with change in clinical and angiographic severity of the disease.

**Funding:** No funding sources

**Conflict of interest:** None declared

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