Original Article

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Association of Low Serum Albumin Levels and its In-hospital Adverse Outcomes among Patients Presenting with Acute Coronary Syndrome in a Tertiary Care Hospital of West Bengal, India

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ABSTRACT

Introduction: Acute Coronary Syndrome (ACS) is characterised by hypercoagulability and inflammation. In acute presentation of Ischaemic Heart Disease (IHD), like ACS, serum albumin may also play an important role. Many patients with ischaemic cerebrovascular accident, a condition similar to ACS, had low serum albumin.

Aim: To estimate serum albumin levels in patient with ACS and its relation to hospital adverse outcome.

Materials and Methods: The present prospective observational study was conducted in the Department of General Medicine at R.G. Kar Medical College and Hospital, West Bengal, India. The duration of the study was 18 months, from July 2019 to October 2020. Patients with ACS were included irrespective of age, sex, race and predisposing factors such as Hypertension (HTN), Diabetes Mellitus (DM), hyperthyroidism and dyslipidaemia. A total of 125 patients included and details such as relevant history, examination findings, laboratory investigation, Electrocardiography (ECG), Echocardiography (ECHO), chest X-ray Posteroanterior (PA) view were included. Chi-square test and logistic regression were applied.

Results: A total of 94 (75.2%) patients were males. 49 (39.2%) study patients had DM. Total 10 (8%) patients presented with cardiac arrest at admission. In-hospital death was happened in 9 (7.2%) cases. 59 (47.2%) patients had normal serum albumin level (3.5-4.5). 61 (48.8%) had mild to moderate hypoalbuminaemia (2.5-3.5) and only 5 (4%) had severe hypoalbuminaemia (<2.5). Association of in-hospital complication vs serum albumin level was statistically significant (p<0.0001). A multivariate logistic regression analysis showed that male gender (p-value=0.026), smoking (p-value=0.008), arrhythmia (p-value=0.002), increased creatinine (p-value=0.032) and hypoalbuminaemia (p<0.001) were statistically significant independent predictors of in-hospital adverse outcomes.

Conclusion: The low serum albumin level, measured immediately on hospital admission in ACS patients was associated with in-hospital complications, and when adjusted for other covariates, hypoalbuminaemia predicts in-hospital adverse outcome independently.

Keywords: Coronary event, Hypoalbuminaemia, In-house complication, Single centre study

INTRODUCTION

The ACS is a hypercoagulable and inflammatory state. It happens due to the mismatch between myocardial oxygen supply and demand as a result of following processes that led to formation of thrombus. These are plaque rupture and erosion causing disruption of unstable coronary plaque or a protruding calcified module leading to formation of intracoronary thrombus and inflammatory response. Patient of Non-ST-elevation Myocardial Infarction (NSTEMI) there are multiple such vulnerable plaques [1]. Normal physiological concentration of serum albumin has it's antioxidant mechanism that provide significant reduction in myocardial injury from ischaemia and reperfusion [2,3]. Albumin helps the formation of prostaglandin D2 and inhibits thromboxane synthase. Hence, albumin enhances inhibition of platelet aggregation. Several conditions are associated with elevated blood viscosity which is an important risk factor for atherosclerosis, cardiovascular and its adverse consequences [4]. In various clinical conditions, serum albumin is being traditionally considered as reliable biomarker for risk prediction. Low serum albumin has been shown to associated with increased risk of cardiovascular mortality and all caused mortality [5,6]. There is still insufficient evidence regarding the factors affecting outcomes after ACS.

In recent times, the clinical manifestation and prognosis of Cardiovascular Disease (CVD) have altered due to emerging medical therapies and innovative revascularisation procedure. So, it is important to identify new biomarkers and revaluate the significance to traditional risk markers.

The association of low serum albumin with Coronary Artery Disease (CAD) and mortality has been shown in different population in several studies [7-9]. In ACS, which is an acute phase of IHD, where serum albumin might have an important role. Low serum albumin has been shown to be an important predictor of mortality in acute ischaemic stroke, a condition resembling ACS [10]. However, the impact of hypoalbuminaemia on outcome of ACS has not been studied well. So, the objectives of the present study were to estimate serum albumin levels in patient presented with ACS and predict in-hospital outcomes according to serum albumin level.

MATERIALS AND METHODS

The present study was a prospective observational study, conducted in the Department of General Medicine at R.G. Kar Medical College, Kolkata, West Bengal, India. The duration of the study was 18 months, from July 2019 to October 2020. Approval of Institutional Ethics Committee was taken prior to the study

(Approval no. RKC/309). A written informed consent was taken from each patient prior to their inclusion in the study.

Inclusion criteria: Patients with ACS who were admitted in General Medicine Ward of the Hospital irrespective of age, sex, race and predisposing factors such as DM, HTN, thyroid disease and dyslipidaemia were included.

Exclusion criteria: Chronic Kidney Disease (CKD) (beyond stage III), chronic liver disease, presence of stroke, recent history of trauma and skeletal muscle injury, malignancy, known patients with chronic inflammatory disease and ongoing infectious disease, venous thromboembolism, patients with heart failure, cardiogenic shock, arrhythmia or valvular heart diseases were excluded.

Sample size calculation: Statistical formula for sample size: N={(Z1-α/2)2xPxQ}/L2. In the present study, putting the below mentioned values (Z1-α/2)=1.96 considering 95% confidence level P=prevalence of adverse outcomes among ACS patients with hypoalbuminaemia i.e., 20% Q=100-P i.e., 80L=precision or margin of error which is less than 10 and less than P, here, the value taken is 7. So, calculating the above equation the sample size (N) of this study was 125. Samples were chosen by systematic random sampling and every 4th patient was selected as their study sample after choosing the first patient randomly. Hence, the authors included 138 patients for the study. 13 patients denied participating in the study, so, the final study sample was 125.

Study Procedure

According to a study conducted by Hartopo AB et al., there was 20% prevalence of adverse outcomes among ACS patients with hypoalbuminaemia [11]. All ACS patient admitted in General Medicine ward at R.G. Kar Medical College and Hospital for management and who had given consent for participation in the present study were evaluated with relevant history taking, examination, laboratory investigations ECG, ECHO, digital chest X-ray PA view. The following outcomes were assessed during hospital admission: Heart failure, arrhythmia, arrhythmia with Left Ventricular Failure (LVF), arrhythmia with pleural effusion, cardiogenic shock and death.

The following is the criteria by which ACS patients were diagnosed and selected for data collection:

Definitions and criteria of Acute Coronary Syndrome (ACS)

a. Clinical criteria [1]:

Typical presentation was with severe chest discomfort with one of these three features:

- Occurrence at rest or with minimal exertion lasting for >10 minutes.
- Relatively recent onset i.e., within prior two weeks.
- A crescendo pattern i.e., distinctly more severe, prolonged or frequent than previous episode. Common site of discomfort: Substernal with radiation to left arm, left shoulder and or upwards to neck or jaw.

b. ECG criteria of ACS [12-14]:

a. ST-elevation Myocardial Infarction (STEMI): Elevation of origin of ST segment at its junction (J point) with QRS complex in two or more contiguous leads of

- 0.1 mv (1 mm) in any lead except V2 and V3.
- In V2 and V3 ST J point elevation of
  - 0.25 mv (2.5 mm) in men <40 years of age.
  - 0.20 mv (2 mm) in men ≥40 years of age.
  - 0.15 mv (1.5 mm) in women.

c. Non ST-elevation Acute Coronary Syndrome (NSTE-ACS):

- New down sloping or horizontal ST segment depression ≥0.05 mv in two contiguous leads.
- T wave inversion ≥0.1 mv in two contiguous leads with prominent R wave or R:S ratio >1

d. Acute Myocardial Infarction (MI) in presence of Left Bundle Brunch Block (LBBB):

- ST elevation ≥1 mm and concordant with a predominantly negative QRS.
- ST depression ≥1 in leads V1, V2 or V3
- ST elevation ≥5 mm and discordant with a predominantly negative QRS.

e. Angina equivalent [1]:

- Dyspnoea
- Epigastric discomfort
- Nausea
- Weakness

Serum Albumin was estimated by dye binding (bromocresol green) method. Patients were classified according to albumin levels into normal albumin group (3.5-4.5 gm/dL), mild to moderate hypoalbuminaemia (2.5-3.5 gm/dL) and severe hypoalbuminaemia (<2.5 gm/dL) group [15,16]. N-Terminal Pro-B type Natriuretic Peptide (NT-ProBNP) was estimated using serum sample by Enzyme-linked Immunosorbent Assay (ELISA) method. A value more than 125 pg/mL was taken as elevated level [17].

STATISTICAL ANALYSIS

Microsoft excel spreadsheet was used for data entry. Statistical analysis was done by Statistical Package for Social Sciences (SPSS) version 27.0; Inc., Chicago, USA) and GraphPad Prism version 5. Data was summarised as count and percentage for categorical variables and mean and standard deviation for numerical variables. For categorical variables a Chi-square test was used and t-test was used for numerical variables. One-way Analysis of Variance (one-way ANOVA) was used to compare the means of three or more samples for numerical data. Logistic regression analysis was done. The p-value ≤0.05 was taken as statistically significant.

RESULTS

Most of the patients 94 (75.2%) were males and 31 (24.8%) patients were females. A 48.0% of study patients were smoker [Table/Fig-1]. Most of the patients (95) had normal pulse rate (60-100 bpm). 20 patients had bradycardia (<60) and 10 patients had tachycardia (>100). Most of the patients had normal Systolic Blood Pressure (SBP) 90/119 56 (44.8%). Patients with SBP <90 were only five and SBP ≥140 were only 22 (17.6%) cases. Total 102 (81.6%) patients had normal Jugular Venus Pressure (JVP). 15 (12%) study patients had raised Jugular Venous Pulse (JVP) and 8 (6.4%) cases had flat JVP.

A total of 55 (44%) patients had raised NT-ProBNP value. Most of the patients had normal chest X-ray findings 82 (65.6%), whereas, 11 (8.8%) cases had apical distribution of vessels. Digital X-ray of chest PA view showed Kerley lines in 9 (7.2%) cases. Normal serum albumin level (3.5-4.5) was found in 59 (47.2%) patients, 61 (48.8%) had mild to moderate hypoalbuminaemia (2.5-3.5) and only 5 (4%) patients had severe hypoalbuminaemia (<2.5) [Table/Fig-2]. Most common in-hospital complication was arrhythmia in 26 (20.8%) cases and least common was arrhythmia with pleural effusion in 2 (1.6%) patients. In-hospital death was reported in 9 (7.2%) cases. No in-hospital complications found in 57 (45.6%) cases. A 47 (37.6%) cases were discharged with complication [Table/Fig-3]. The association between in-hospital complication vs serum albumin level was statistically significant (p<0.0001) [Table/Fig-4]. There was significant association between NT-ProBNP and serum albumin level (<0.001). Among patients in normal albumin group NT-ProBNP was elevated in 10 (16.9%) cases, whereas, it was elevated in 41 (67.2%) cases in mild to moderate hypoalbuminaemia group and 4 (80%) cases in

S. No.	Variables	Number (n)	Percentage (%)
1.	**Age group (years)**		
	31-40	8	6.4
	41-50	31	24.8
	51-60	36	28.8
	>60	50	40.0
2.	**Sex**		
	Female	31	24.8
	Male	94	75.2
3.	**Cardiac arrest at admission**		
	Present	10	8.0
	Absent	115	92.0
4.	**Diabetes mellitus**		
	Yes	49	39.2
	No	76	60.8
5.	**Hypertension**		
	Yes	42	33.6
	No	83	66.4
6.	**IHD**		
	Yes	16	12.8
	No	109	87.2
7.	**Dyslipidemia**		
	Yes	33	26.4
	No	92	73.6
8.	**Smoking**		
	Yes	60	48
	No	65	52
9	**Anaemia (<10 g/dL)**		
	Yes	17	13.6
	No	108	86.4
10	**Leucocytosis (>11,000/cmm)**		
	Yes	68	54.4
	No	57	45.6
11	**Increased creatinine (>1.3 mg/dL)**		
	Yes	28	22.4
	No	97	77.6

[Table/Fig-1]: Baseline characteristics of study participants (N=125).
IHD: Ischaemic heart disease

S. No.	Variables	Number (n)	Percentage (%)
1.	**ST segment**		
	Depression	37	29.6
	Elevation	88	70.4
2.	**S3 Gallop**		
	Absent	85	68.0
	Present	40	32.0
3.	**Abnormal cardiac biomarkers**		
	Yes	120	96.0
	No	5	4.0
4.	**NT-ProBNP**		
	Normal	70	56.0
	Raised (>125 pg/mL)	55	44.0
5.	**Chest X-ray**		
	Normal		
	Apical distribution of vessels	82	65.6
	Kerley lines	11	8.8
	Bat wing with pleural effusion	9	7.2
	Bat wing without pleural effusion	16	12.8
	Without pleural effusion	7	5.6
6.	**Ejection fraction (by echocardiography)**		
	<40	15	12.0
	40-50	42	33.6
	>50	68	54.4
6.	**RWMA (by echocardiography) [1]**		
	Inferior	33	26.4
	Septal	4	3.2
	Anterior	3	2.4
	Apical	6	4.8
	Inferoposterior	8	6.4
	Inferoseptal	16	12.8
	Anteroseptal	34	27.2
	Others	12	9.6
	Nil	9	7.2
7.	**Serum albumin**		
	Normal (3.5-4.5)	59	47.2
	Mild-moderate (2.5-3.5)	61	48.8
	Severe (<2.5)	5	4.0

[Table/Fig-2]: Presenting features of study participants (N=125).
RWMA: Regional wall motion abnormality; NT-ProBNP: N-Terminal B Type Natriuretic Peptide

S. No.	Variables	Number (n)	Percentage (%)
1.	**In-hospital complication**		
	No complication	57	45.6
	Arrhythmia	26	20.8
	Heart failure	16	12.8
	Arrhythmia and LVF	12	9.6
	Arrhythmia and pleural effusion	2	1.6
	Cardiogenic shock	3	2.4
	Death	9	7.2
2.	**Clinical outcome**		
	Discharged with complications	47	37.6
	Discharged without any complications	64	51.2
	DORB	5	4.0
	Expired	9	7.2

[Table/Fig-3]: In-hospital complications and outcome of study participants (N=125).
DORB: Discharged on risk bond; LVF: Left ventricular failure

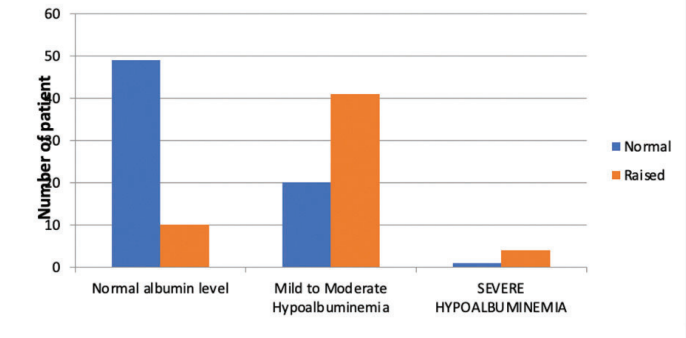
severe hypoalbuminaemia group [Table/Fig-5]. A multivariate logistic regression analysis was done which showed smoking (p-value=0.008), male gender (p-value=0.026), arrythmia (p-value=0.002), increased creatinine (p-value=0.032) and hypoalbuminaemia (p<0.001) were statistically significant independent predictors of in-hospital adverse outcomes [Table/Fig-6].

DISCUSSION

The ACS is a hypercoagulable and inflammatory state. IHD and its most serious acute presentation i.e., ACS are most common causes of mortality and morbidity worldwide [1]. Arques S et al., found the usefulness of serum albumin as an additional prognostic marker to the usual prognostic variables in older patients with severe acute heart failure [18]. In the present study, heart failure was more common in mild to moderate hypoalbuminaemia group (81.3%) than normal albumin group (18.8%) (p<0.001). In ACS patients, Wang W et al., found significantly higher adverse cardiac events in low prealbumin group as compared with normal prealbumin. According to their study with ACS patients, lower serum prealbumin level was shown to be associated with more in-hospital complications [19]. In present study, higher adverse event in hypoalbuminaemia groups were found. A significant association was found between

Variables	Normal albumin	Mild to moderate hypoalbuminaemia	Severe hypoalbuminaemia	p-value
Clinical outcome				
Discharged with complications	5 (10.6)	40 (85.1)	2 (4.3)	<0.0001
Discharged without any complications	52 (81.3)	12 (18.8)	0	
DORB	1 (20.0)	4 (80.0)	0	
Expired	1 (11.1)	5 (55.6)	3 (33.3)	
In-house complication				
Arrhythmia	9 (34.6)	16 (61.5)	1 (3.8)	<0.0001
Heart failure	3 (18.8)	13 (81.3)	0	
Arrhythmia and LVF	0	11 (91.7)	1 (8.3)	
Arrhythmia and pleural effusion	1	1	0	
Cardiogenic shock	1 (33.3)	2 (66.7)	0	

[Table/Fig-4]: Clinical Outcome, in-house complication and serum albumin levels of study participants (N=125).



[Table/Fig-5]: Association between NT-ProBNP and serum albumin level (p<0.001).

Variables	Odds ratio	p-value
Age >50 years	0.685	0.462
Male gender	0.869	0.026
Cardiac arrest at admission	11253.590	0.999
Diabetes mellitus	0.935	0.066
Hypertension (HTN)	0.728	0.170
IHD	1.026	0.216
Smoking	0.721	0.008
Arrhythmia	1.020	0.002
SBP >140	1.839	0.273
DBP >90	1.854	0.155
Anaemia	0.963	0.593
Leukocytosis	0.603	0.484
Increased creatinine	0.809	0.032
Dyslipidemia	0.666	0.054
Hypoalbuminaemia	1.667	<0.001

[Table/Fig-6]: Multivariate Logistic Regression analysis for predictors of in-hospital adverse outcomes (N=125).
SBP: Systolic blood pressure; DBP: Diastolic blood pressure

serum albumin and NT-ProBNP level (p<0.0001), which was more frequently elevated among patients in mild to moderate hypalbuminaemia (67.2%) and severe hypoalbuminaemia (80%) groups than normal albumin group (16.9%). Jäntti T et al., found that, hypoalbuminaemia was commonly seen in early cardiogenic shock. They also noticed plasma albumin decreased frequently during hospital stay. They found the significant association between plasma albumin early at admission and adverse outcome. The baseline low plasma albumin was associated with mortality which was independent of other known risk factors [20]. In present study, mortality was more frequent in mild to moderate hypoalbuminaemia 5 (55.6%) and severe hypoalbuminaemia group 3 (33.3%) than in normal albumin group 1 (11.1%). There was significant association between serum albumin and death (p<0.001). Suzuki S et al., found that Serum albumin was associated with Major Adverse Cardiac Events (MACE) in newly diagnosed stable CAD patients and that association was independent of other risk predictors [21].

In a meta-analysis, Wang Y et al., showed the association between low serum albumin and increased risk of atrial fibrillation [22]. In present study, arrythmia was developed in 26 (20.8%) cases, of them 16 cases were from mild to moderate hypoalbuminaemia group. Arrythmia and LVF were present in 12 (9.6%) cases. Among them 11 cases were from mild to moderate hypoalbuminaemia group. Hartopo AB et al., found that hypoalbuminaemia was associated with 2.8 fold increased risk of developing adverse outcomes in ACS. Though, after adjustment of other known covariates, hypoalbuminaemia did not predict in-hospital complications significantly [11]. In present study, multivariate logistic regression analysis was done where hypoalbuminaemia was a significant independent risk predictor along with other known risk factors like male gender, smoking, increased serum creatinine and arrythmia. Smoking is a known risk factor for atherosclerotic CVD. But, some studies have found lesser in-hospital complications of current smokers after ACS which is known as smoker's paradox. This phenomenon can be largely explained by lesser other risk factors and co-morbidities of smoker patients [23,24]. In the present study, smoking is significantly associated with in-hospital complication with odds ratio 0.721 indicative of less adverse events for smokers. Though, male gender is a risk factor for IHD, higher in-hospital complications have been shown in female in serval studies [25,26]. Cenko E et al., found higher 30 day mortality in young age female with STEMI even after adjustment of medication, Percutaneous Coronary Intervention (PCI) and other co-morbidities [27]. The present study population is male dominant (male 75.2% and female 24.8%). The odds ratio for male gender was 0.869, which indicates less adverse outcome for males than females. Raised creatinine, as seen in renal insufficiency is a known risk factor for CVD. Shlipak MG et al., found higher mortality in patients with renal insufficiency after ACS in elderly patients. One year mortality was 66% for those with moderate renal insufficiency, whereas, it was 46% for mild renal insufficiency and 24% with no renal insufficiency [28]. In the present study, 28 (22.4%) cases had raised creatinine (>1.3 mg/dL) and raised creatinine was significantly associated with in-hospital adverse outcome with the odds ratio of 0.809. In a meta-analysis Zhu L et al., found that low serum albumin was a powerful independent predictor of all-cause mortality in hospitalised ACS patients [29]. In the present study, authors found that hypoalbuminaemia predicted in-hospital outcome significantly even after adjustment with other covariates.

Limitation(s)

In spite of every sincere effort, present study was not devoid of shortcomings. It was a single centric study with relatively small sample size, which may not be sufficient. Pathogenesis of low serum albumin level remains a matter of speculation as, the authors did not measure the biomarkers associated with low serum albumin.

CONCLUSION(S)

The present findings indicate arrhythmia (20.8%) is most common in-hospital complication, followed by heart failure (12.8%) in ACS patient. The low serum albumin measured at the time of hospital admission was associated with in-hospital adverse outcome with odds ratio of 1.667. It was also found that, adverse outcomes were also significantly associated with severity of hypoalbuminaemia. Whether the impact of low serum albumin in early phase of ACS was a result of inflammation or an independent effect, needs to

be cleared, so, further studies are needed. Even after adjustment with other covariates, hypoalbuminaemia independently predicts in-hospital adverse outcomes.

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- iThenticate Software: Jan 27, 2023 (25%)

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AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
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