Original article

Correlation of hs-CRP with in-hospital Outcome of Patients with Acute Coronary Syndrome (ACS)

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Abstract:

Background and Objectives: Coronary artery disease (CAD) is a worldwide health epidemic. Acute coronary syndrome (ACS) is a potentially life-threatening condition of CAD. Serum high-sensitivity C Reactive Protein (hs-CRP) is being increasingly used as a marker for cardiac risk assessment and as a prognostic tool in acute coronary syndrome. The objective of this study was to evaluate the prognostic value of hs-CRP in predicting cardiovascular outcome in patients presenting with acute coronary syndromes.

Methods: This prospective observational study was carried out in the department of cardiology of Chittagong Medical College Hospital (CMCH), Chittagong, from April 2013 to March 2014. Total 100 patients presenting with acute coronary syndromes who fulfilled the selection criteria were included in the study. Serum hs-CRP of all patients was assayed on admission and study population divided into 4 groups according to hs-CRP quartiles. All four groups were followed-up till discharge and occurrence of any cardiovascular events were sought.

Results: Mean hs-CRP was 18±2.9mg/L (mean±SD), ranged from 1.6 mg/L to 71.2 mg/L /L. The mortality was significantly higher in quartile-4 (7%, p-0.001) and quartile-3 (4%, 0.005) as compared to quartile-1 and 2 (0% and 2% respectively). 12% patients developed heart failure in quartile-4 vs 2% in quartile-1 (p-0.045). Similarly other cardiac complications like cardiogenic shock, arrhythmias and heart blocks occurred in increasing frequency among patients of higher quartiles.

Conclusions: Elevated hs-CRP is a predictor of adverse outcome in patients with acute coronary syndromes and helps in identifying patients who may be at risk of cardiovascular complications.

Key words: *Acute coronary syndromes, C-reactive protein, In-hospital outcome*

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Introduction:

Acute coronary syndrome (ACS) is a spectrum of life-threatening disorders that includes Unstable Angina (UA), non-ST-segment elevation Myocardial Infarction (NSTEMI), and ST-segment elevation Myocardial Infarction (STEMI). ACS is a common presentation of coronary artery disease (CAD) and significant cause of mortality and morbidity worldwide. Cardiovascular diseases (CVD) have no geographic, gender, or socio-economic boundaries. The global burden of CVD is increasing, principally because of a sharp increase in low and middle income countries (LMIC). Altered diets, diminished physical activity and tobacco use are critical factors contributing to the acceleration of CVD epidemics.[1] Being a member of LMIC it is assumed that CVD burden is being worse in Bangladesh also. A recent study conducted among rural population of Bangladesh

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showed a dramatic increase in CVD from 1986 to 2006.[2] Presentation of ACS is diverse. Some are haemodynamically stable and can be managed conservatively but some require aggressive management including catheter based interventional procedures. In our settings as not all cardiac centers are equipped with facilities for urgent interventional procedures, the importance of early risk stratification is paramount.

Inflammation is an established cause in pathogenesis of ACS. Of the numerous inûammatory markers investigated over the past decade, C-reactive protein (CRP) measured by high-sensitivity assay (hs-CRP) is the most widely studied and is linked to adverse events. Hs-CRP has prognostic usefulness in cases of acute ischemia, even without troponin level elevation, suggesting that an enhanced inflammatory response at the time of hospital admission can determine subsequent plaque rupture[3]. These findings help explain why individuals with elevated hs-CRP levels are also more likely to be benefitted from early interventions.

The admission CRP value reflects the baseline inflammatory status of the patient; thus, patients with ACS and high CRP levels at admission usually experience more cardiovascular complications during follow-up. Since the maximum CRP level occurs at around 48 hours after the onset of symptoms, there is no need to continue monitoring the CRP levels after this time[4]. Reliable, hs-CRP assay is available at a relatively low cost. By this simple tool we may able to discriminate high risk patient of ACS early after admission and can triage them accordingly. High risk patients can be managed appropriately or be referred to centers' having urgent intervention facilities. Moreover this study will help us in better understanding about in-hospital complications of ACS in our perspective which we can be utilized for proper management of ACS patients.

Methods:

This prospective observational study was conducted at the department of Cardiology, Chittagong Medical College Hospital (CMCH) from April 2013 to March 2014. Patients with acute coronary syndrome (ACS) admitted to the Department of Cardiology, CMCH, within the study period and who met selection criteria were included.

Inclusion Criteria:

Diagnosed cases of ACS admitted to the Department of Cardiology, CMCH.

Exclusion criteria:

ACS patients with concomitant-

1. Malignancies,
2. Rheumatological/ Autoimmune diseases,
3. Chronic inflammatory disorders,
4. Acute infections and with renal/hepatic compromise
5. Patient admitted beyond 48 hours of onset of symptoms.
6. Unwilling to give consent.

Ethical Consideration:

Prior to the commencement of this study, the research protocol was approved by the Research Review Committee of Department of Cardiology and the Ethical Review Committee of CMCH, Chattogram. The aims and objectives of the study along with its procedure, alternative diagnostic methods, risks and benefits was explained to the patients in easily understandable local language and then informed consent was taken from each patient. It was assured that all records were kept confidential and the procedure will be helpful for both the physician and patients in making rational approach regarding management of the case.

Methods of data collection:

Information from the patients and relatives were collected through preformed case record form. Patients were evaluated by history, clinical examination and investigations. Blood samples for estimation of cardiac markers (Troponin-I) were collected after 4 hours of onset of symptoms. In few cases where initial Troponin-I assay was negative repeat assay was done after 6 hours. ACS was diagnosed by history, physical examination, electrocardiographic analysis and cardiac biomarkers (Troponin-I).

Venous blood for estimation of serum hs-CRP was collected within 48 hours of onset of Estimation of hs-CRP was carried out by particle enhanced Immuno-nephelometric method using BN system (BN Pro-spec, DADE-BEHRING). Estimation blood glucose, Lipid profile and renal function tests were also done. Patients were followed-up till their discharge and occurrence of pre-specified outcomes such as heart failure, arrhythmias, conduction block or death were sought.

Statistical analysis:

The statistical analyses were performed with Statistical Package for the Social Sciences (SPSS), version 19.0.

The continuous variables with a normal distribution are described as the mean±standard deviation (SD). The Student's t test (within two groups) and ANOVA (analysis of variance) test (more than two groups) were used for the comparisons between groups. The continuous variables without normal distribution are described as the median. The categorical variables were expressed as absolute values and percentages and comparison with the groups done by using chi square test and fisher-exact test. A multivariable logistic regression model was used to evaluate the independent contribution of hs-CRP levels to in-hospital events. For any analytical test the level of significance was 0.05 and p value<0.05 was considered significant.

Results:

Total 100 patients were selected for the study. The detection limit of hs-CRP was 0.2mg/L and assay was linear from 0.2mg/L to 230mg/L. Hs-CRP level ranged from 1.6 mg/L to 71.2 mg/L. Mean hs-CRP was 18+2.9 (mean+SD). 100 patients under study were arranged in ascending order of admission hs-CRP level and were classified into four groups according to quartiles of hs-CRP level. The 4 groups were Q1 or 1st quartile (hs-CRP<6.8mg/L), Q2 or 2nd quartile (hs- CRP 6.8-14.6mg/L), Q3 or 3rd quartile (hs-CRP 14.6-30.5mg/L) and Q4 or 4th(hs-CRP >30.5mg/L). Appropriate statistical techniques were used for data analysis. Results were presented with tables and graphs where required.

Table-I

Distribution of ACS patients among different quartiles according to age (100).

Age Groups	1st quartile (<6.8mg/L) Q1	2ndQuartile (6.8-14.6mg/L) Q2	3rd Quartile (14.6-30.5mg/L) Q3	4th Quartile (>30.5mg/L) Q4	P Value[a]
35-44 Years	03	03	04	03	0.135NS
45-54 Years	07	07	08	07	0.145NS
55-64 Years	06	06	09	07	0.125NS
65-74 Years	05	05	04	06	0.125NS
≥75 Years	03	02	02	03	0.145NS

Data were presented as frequencies.
[a]P value reached from Analysis of variance (Anova) test, NS- Not significant.

Above table shows the age distribution of study subjects. Almost similar number of subjects of different age groups belongs to all 4 quartiles (24, 23, 27 and 26 in Q1, Q2, Q3 and Q4 respectively) which are not statistically significant.

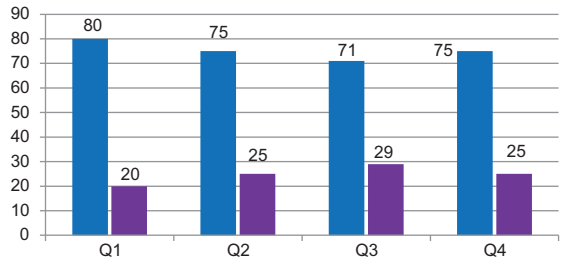

Fig.-1: *Sex distribution (%) among quartiles.*

Table-II

Distribution of presenting symptoms (n=100)

Symptoms	N	%
Chest pain	87	87
Sweating	59	59
Breathlessness	36	36
Vomiting	18	18
Syncope	09	09
Others	07	07

n- Number of patients presented, %- Percentage

Bar diagram showing distribution of the sex between groups. It shows male subjects in all quartiles is ranges from 71-80% and that of females is 20-29%. Distribution of male and female among quartiles are not statistically significant.

Table-II showed the distribution of presenting symptoms. Chest pain was the most common symptom and accounting for 87% of patients, followed by sweating 59%, breathlessness 36%, Vomiting 18%, Syncope 09% and others 07%. Feeling uneasy, Palpitations, vertigo, abdominal discomfort etc. were included in others.

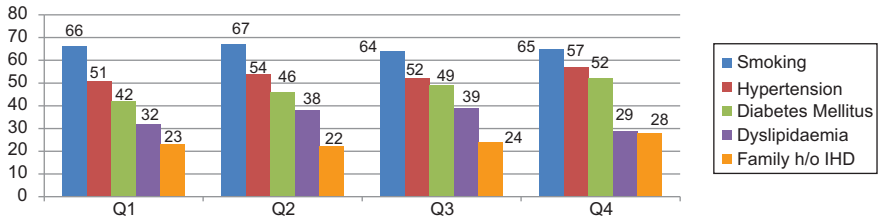

Fig.-2: *Distribution of risk factors (%) among quartiles*

Table-III

Mean hs-CRP of 4 quartiles.

	1st Quartile (<6.8mg/L) Q1	2ndQuartile (6.8-14.6mg/L) Q2	3rd Quartile (14.6-30.5mg/L) Q3	4th Quartile (>30.5mg/L) Q4	P-Value[a]
Mean hs-CRP (mg/L)	4.5±1.3	13.7±1.9	21.6±2.6	42.9±3.2	0.010[S]

Data were presented as mean±SD.
[a]P value reached from Analysis of variance (ANOVA) test, S-Significant

Table-IV

In-hospital complications of study population (n=100)

Complications (%)	1st Quartile Q1 (<6.8mg/L)	2nd Quartile Q2 (6.8-14.6mg/L)	3rd Quartile Q3 (14.6-30.5mg/L)	4th Quartile Q4 (>30.5mg/L)	P-Value[a]
Heart Failure (HF)	2	4	7	12	0.045[S]
Cardiogenic Shock (C.Shock)	0	1	2	4	0.055[NS]
Arrhythmias:					
Supraventricular	0				
Ventricular	0	1	2	3	0.650[NS]
Total	0	0	2	4	0.045[S]
		1	4	7	0.550[NS]
Conduction block:					
AVBlock	0				
BB Block	0	1	2	4	0.075[NS]
Total	0	1	1	2	0.625[NS]
		2	3	6	0.055[NS]

Data were presented as frequencies.
P value reached from Fisher exact test with Bonferroni correction
S-Significant, NS-Not significant,
AV- Atrioventricular block, BB- Bundle branch block

Figure-2 shows that, smoking was the leading risk factor for patients of all quartiles. Hypertension, diabetes mellitus, dyslipidaemia and positive family history for ischaemic heart disease (IHD) were other risk factors in descending order of frequency.

Table-IV shows the In-hospital complications. Heart failure was more frequent (25%) and occurred more in higher quartiles which is statistically significant (pÂ0.050). Other complications were arrhythmias (10%), conduction blocks (10%) and cardiogenic shock (7%). Arrhythmias were both ventricular and supraventricular.

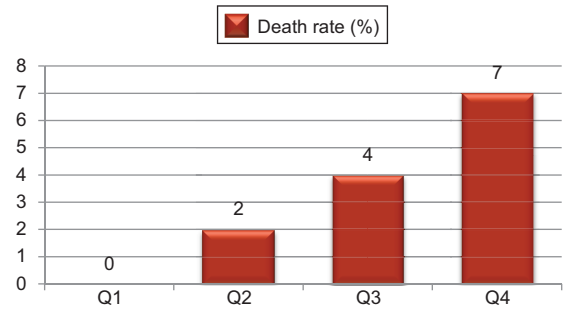

Fig.-3: *Death rate among different quartiles*

Table-V

Multivariate regression analysis for in-hospital mortality of the study population.

Variables	HR	95% CI	P- value
Age (years)	1.07	1.05-1.09	0.001^{S}
Hypertension	1.01	1.00-1.02	0.03^{S}
Diabetes mellitus	1.03	1.02-1.04	0.02^{S}
HF during hospitalization	1.02	1.01-1.03	0.002^{S}
Type of MI	1.06	1.03-1.09	0.055^{NS}
Received thrombolysis	1.05	1.02-1.08	0.001^{S}
Hs-CRP level (mg/L)	1.04	1.03-1.05	0.045^{S}

HR- hazard ratio, CI- confidence intervals, HF- heart failure, MI- myocardial infarction. S- significant, NS- not significant.

Premature ventricular complexes (PVCs) were more frequent ventricular arrhythmias (3% out of total 6%) likewise AF (Atrial fibrillation) in supraventricular. Out of 100, 7 patients of STEMI (7%) presented with cardiogenic shock.

To evaluate the independent predictive power of hs-CRP on in-hospital mortality, the 7clinical and biochemical variables were entered into a multivariable logistic regression model. The multivariable analysis showed hs-CRP as a strong predictor of in-hospital all-cause mortality as shown in table V.

Discussion:

Serum hs-CRP is being increasingly used as a marker for cardiac risk assessment and as a prognostic tool in acute coronary syndrome[5]. In the present study; we examined the prognostic value of admission hs-CRP in a hospitalized population with ACS. For this purpose study population were divided into 4 quartiles according to their hs-CRP levels.

Mean age of patients in the study was 54.6±5.4 (mean ± SD). It is comparable to a study from United Arab Emirates[6] where mean age of ACS patients were 52 ± 11 years (mean ± SD) but lower than the findings of a Spanish study (2012)[7] where mean age of ACS patients were 60.0±13.5 years (mean±SD) and a Thai study (2007)[8] study (65.2±12.3 years). This may be due to larger sample size and geographical variation of the two studies and support an study among Asian Indians in the UK (Enas EA et al 2001)[9] where it was revealed that onset of first myocardial infarction in south Asians is 5 to 10 years earlier than other region.

Our study revealed that most o f the ACS patients are male (75%) which is similar with the findings of in Sergio Raposeiras-Roubý´n[7] et al. study (2012) where 73.5% patients were male. In Paolo Ortolani et al (2007)[10] and AFMS Haque et al (2010)[11] study 64-76% and 82.81 % were male respectively.

In this study, smoking was the most common risk factor among the patients of all 4 hs-CRP quartiles (64-67%). It is in harmony with the study of Shahzada Selim et al (2013)[12] in Dhaka, Bangladesh where around 70% of ACS patients were smoker. According to Non Communicable Disease risk factor survey, Bangladesh 2010[13] prevalence of overall smoking is 26.2% but it is 54.8% among males. As most of our study population are male (75%), it is nearer to our study. In a British study of Kaski et al (2004).[14] 67% of ACS patients were smokers.

Chest pain was the most common symptom (87% of patients) of the study. It is comparable to Suphot Srimahachota et al[8] study, where 96.7% of UA, 86.0% patients of NSTEMI and 91.6% patients of STEMI were presented with chest pain.

Mean hs-CRP of study population is 18±2.9 mg/L (mean±SD). It was comparable to study of Sheikh AS et al (2011)[5] of Quetta, Pakistan where it was 17.6±7.96 mg/L (mean±SE). Mean hs-CRP of 1st to 4th quartiles are 4.5±1.3, 13.7±1.9, 21.6±2.6 and 42.9±3.2. Data from the Women's Angiographic Vitamin and Estrogen (WAVE)[15] study showed the similar result.

Death rate was 13% as a whole. It was comparable with Suphot Srimahachota[8] et al (2007) study where the rate of all cause mortality is 12.6%. The risk of death increased in a stepwise fashion

across increasing quartiles of hs-CRP. Patients in the 4th quartile (Q4) had nearly 4 fold increased risk of death in comparison to 2nd quartile (Q2). It was similar to the study of Paolo Ortolani et al (2007).[10]

Regarding in-hospital complications, rate of development of heart failure was 2%, 4%, 7%, and 12% in 1st, 2nd, 3rd, and 4th quartiles respectively. In Paolo Ortolani et al[10] (2007) study, Killip class e"2 heart failure was 9, 16, 18, and 36 percent in 4 mentioned quartiles (p-0.001). Though frequency of heart failure is more in

comparison to our study, but the study was conducted among STEMI fraction of ACS patients. This difference is likely due to the greater extent of necrosis in STEMI. No cardiogenic shock occurred among study population of 1st quartile, but occurred with increasing frequencies in subsequent quartiles (1, 2 and 4% in 2nd, 3rd and 4th quartile respectively). Paolo Ortolani et al study (2007) showed that cardiogenic shock occurred by 7, 11, 9 and 19% among 1st, 2nd, 3rd and 4th hs-CRP quartile of the study population. Though frequency of cardiogenic shock is more in Q2 than Q3, but in Q4 it is clearly higher than Q1, Q2 and Q3. It reflects that cardiogenic shock occurs more in higher hs-CRP group among population of ACS.

Conclusion:

A higher incidence of in- hospital mortality and morbidity showed in patients with higher hs-CRP level. Raised hs-CRP level revealed as an important marker of adverse outcomes. So, Plasma hs-CRP levels on admission can be utilized to identify high risk patients in the setting of acute coronary syndromes, who may be at high risk of complications. These patients may need aggressive management and close monitoring after discharge.

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