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Relevance of high sensitivity C-reactive protein levels in short term outcome in patients with acute coronary syndrome

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Abstract: Background: **Objectives:** To determine the relevance of high sensitivity C-reactive protein levels in short term outcome in patients with acute coronary syndrome.**Study Design:** A Cohort study.**Place and duration of study:** This study was conducted at the department of Cardiology, Shifa International Hospital Islamabad, Pakistan over a period of 4 months from 21st of Feb 2023 to 23rd of June 2023.**Methodology:** A total of 58 adult patients diagnosed with ACS and had their hs-CRP levels >3 mg/l were enrolled in group-A while other 58 adult patients diagnosed with ACS and had their hs-CRP levels ≤ 3 mg/l were enrolled in Group-B through consecutive sampling method.All patients received optimal medical therapy based on the evidence. The clinical follow-ups were done at 2 weeks, 1 month, 2 months, and 4 months (final follow up visit). Events like STEMI, NSTEMI, unstable angina or CV mortality were taken as primary short term outcomes.**Results**: The Mean±SD of age in this study was 61.40±10.15 years. The number of male gender was equal to female gender in overall study population. The Mean±SD of hs-CRP was 4.46±1.01 and1.85±0.56 in Group-A and Group-B respectively. Results of the study showed significantly higher incidence of primary outcomes in Group-A (29.31%) compared to Group-B (8.62%) at the end of 4 months follow up period, p=0.003 (STEMI: 8.62% Vs 3.44%, p=0.242, NSTEMI: 6.89% Vs 1.72%, p=0.170, Unstable angina: 10.34% Vs 1.72%, p=0.05, CV mortality3.44% Vs 1.72%, p=0.55 for Group-A and Group-B respectively). **Conclusions:** The results of this study conclude that base line hs-CRP levels are significantly associated with the short term outcomes in patients with ACS.

Keywords: Acute coronary syndrome, High sensitivity C-reactive protein, Short term outcomes.

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INTRODUCTION

The inflammation in the coronary artery occurs with the formation of atherosclerotic plaque through platelets aggregation, fibrosis and lipid deposition. A strong association is found between this plaque formation and status of inflammation. This plaque can be stable or unstable as high inflammatory conditions in the coronary artery are found to be associated with the unstable plaque leading to the coronary artery syndrome.1,2 It is therefore important to identify the inflammatory condition of coronary artery to diagnose the patient's risk of future cardiac events.

Multiple biomarkers are discovered to identify the coronary inflammatory condition.3 Among these biomarkers, C-reactive protein (CRP) has remained a widely used biomarker to assess the inflammatory status of the coronary artery. CRP belongs to the pentraxins family protein that is synthesized through the hepatocytes. The levels of CRP are increased in the short time in response to the interleukin-6 (Pro-inflammatory cytokines) making it a significant biomarker to assess the risk of coronary artery disease in the short term.4 At first, Tillet and Francis discovered the CRP in 1930s and mentioned that high levels of CRP are present in the serum of the patient having inflammation. They also found that it is the only protein that reacts with the carbohydrate C - polysaccharide antigen of capsule of pneumococcu which is the basic reason behind the formation of its name C-reactive protein.5

C-reactive protein is a widely used biomarker due to its long half-life. High levels of C-reactive protein in patients with acute coronary syndrome (ACS) are indicative of poor prognosis and relates to unidentified inflammatory processes leading to atherosclerosis. Hence these increased levels predict the risk of future cardiac events. It was the significantly associated with the sudden death due to the heart attack in the patients, who were not having the history of ACS. Some later studies however shared that CRP levels were end-protein readout and not a therapeutic target of mechanical pathway that involves interleukin-6.6 These observations suggested the limitations that it could only detect the high inflammation levels and the test assays sensitivity was only >5mg/L. It was also identified that the CRP level can also be increased in the normal person without any CAD symptoms.7

An important advancement to this risk assessment was the use of biomarkers known as high sensitive C-reactive proteins (hs-CRP). These new biomarkers are found to be more reliable in predicting the future CV outcome than the traditional CRP test. The hs-CRP test is conducted on the ultrasensitive automated enzyme immunoassay and can provide the reading of lower level of CRP of up to even the normal value.8 The hs-CRP has the significant relevance with the ACS in short term because its level increases to peak level within 2-3 days just after the ST-elevation myocardial Infarction (STEMI). In the short time, we can identify patient's inflammatory condition and assess the risk of future cardiac events. This prognostic evidence with elevated hs-CRP levels provides a good assessment for the next 6 months after an incidence of acute MI.9 The hs-CRP levels are therefore widely used in the clinical practice of health care professionals. It is the highly studied independent biomarker to identify the risk associated with the level of inflammation. Higher the hs-CRP levels indicate the higher risk for the future cardiac event.10

Early diagnosis of inflammatory condition through hs-CRP levels therefore helps to initiate the therapies for these patients. Anti-Inflammatory therapies reduce the hs-CRP levels to normalize value and help to protect the patients from the recurrence of cardiac events. This leads to the good prognosis in atherosclerotic cardiovascular disease in patients with higher hs-CRP level.11

Our aim to conduct this study was to assess the relevance of hs-CRP in the short term outcome in patients with acute coronary syndrome in our local population. The results of this study will help to advise a more evidence based strategy to improve the prognosis in patients recently diagnosed with acute coronary syndrome.

Methods:

This cohort study was conducted at the department of Cardiology, Shifa International Hospital Islamabad, Pakistan over a period of 4 months from 21st of Feb 2023 to 23rd of June 2023.

All adult patients diagnosed with ACS at cardiology department were measured for their hs-CRP levels and included in the study through consecutive sampling. Patients having hs-CRP levels >3 mg/l were enrolled in group-A while patients ≤ 3 mg/l were enrolled in Group-B through consecutive sampling method.

The Sample size was calculated by OpenEpi software with power=80% and Confidence level=95%. p1 = 18.75%, p2= 2.78%.12 Estimated sample size n1=58, n2=58

Exclusion criteria was set as patients having history of tuberculosis, asthma, pneumonia, chronic pulmonary disease and arthritis.

STEMI: Diagnosed when there was increased chest discomfort > 20 min and not resolved by nitroglycerin or rest, Troponin I ≥ 0.01 ng/ml and confirmed by ECG.

NSTEMI: Diagnosed when there was increased chest discomfort > 20 min and not resolved by nitroglycerin or rest, with elevated Troponin I (≥ 0.01 ng/ml) and with no abnormalities at ECG that shows STEMI. Unstable Angina: Chest discomfort > 20 min and not resolved by nitroglycerin or rest.13.

The levels of hs-CRP were measured in fasting blood samples by using an enzyme-linked immunosorbent assay (ELISA) kit, with a sensitivity range of 0.01 to 10 mg/l.

All patients received optimal medical therapy based on the evidence.

The clinical follow-ups were done at 2 weeks, 1 month, 2 months, and 4 months (final follow up visit). Events like STEMI, NSTEMI, unstable angina or CV mortality were taken as primary outcomes.
Data was analyzed using SPSS version 25. Quantitative variables were expressed in form of mean and standard deviation. Qualitative variables were expressed in form of frequency and percentage. Study outcomes were compared between the 2 groups by applying Chi-square test or Fisher's exact test (whichever valid). P <0.05 was considered statistically significant.

Results:

The Mean±SD of age in this study was 61.40±10.15 years with an age range of 40 to 78 years. The number of male gender was equal to female gender in overall study population. The group wise details of age, gender and other demographics are given in Table-I.

Table-I: Demographics and clinical finding among both the groups.
n=116

Demographics		**Group-A (n=58)**	**Group-B (n=58)**
Age (years) Mean±SD		**60.87±10.37**	**61.93±10**
Gender	Male n (%)	30 (51.72)	28 (48.27)
	Female n (%)	33 (56.89)	25 (43.10)
Index Diagnosis	STEMI	30 (51.72)	28 (48.27)
	NSTEMI	15 (25.86)	20 (34.48)
	Unstable Angina	13 (22.41)	10 (17.24)
BMI (Kg/m²) Mean±SD		31.63±4.89	30.79±4.84
Hypertension n (%)		32 (55.17)	37 (63.79)
Diabetes n (%)		29 (50)	24 (41.37)
Dyslipidemia n (%)		31 (53.44)	35 (60.34)
Smoking n (%)		19 (32.75)	16 (27.58)
Hs-CRP levels (mg/l) Mean±SD		4.46±1.01	1.85±0.56

All patients received optimal medical therapy based on the evidence. Details of the drugs taken by patients in both groups are given in Table-II.

Table-II: Details of the drugs taken in both groups.
n=116

Medication	**Group-A (n=58)**	**Group-B (n=58)**
Aspirin n (%)	50 (86.20)	54 (93.10)
Antiplatelet n (%)	39 (67.24)	38 (65.51)
ACEI/ARB n (%)	42 (72.41)	41 (70.68)
β- βlocker n (%)	45 (77.58)	41 (70.68)
Statins	36 (62.06)	38 (65.51)

The short term outcomes in these patients with ACS in shape of incidence of STEMI, NSTEMI, unstable angina or CV mortality as determined at completion of 4 months follow up shows a significantly high incidence of these outcomes in Group-A compared to Group-B are shown in Table-III.

Table-III: Details of outcomes in both groups.

n=116

Outcomes	Group-A (n=58)		Group-B (n=58)		p-value	RR
	Yes	No	Yes	No		
STEMI n (%)	5 (8.62)	53 (91.37)	2 (3.44)	56 (96.55)	0.242	2.5
NSTEMI n (%)	4 (6.89)	54 (93.10)	1 (1.72)	57 (98.27)	0.170	4
Unstable Angina n (%)	6 (10.34)	52 (89.65)	1 (1.72)	57 (98.27)	0.051	6
CV mortality n (%)	2 (3.44)	56 (96.55)	1 (1.72)	57 (98.27)	0.558	2
Total Outcomes n (%)	17 (29.31)	41 (70.68)	5 (8.62)	53 (91.37)	0.003	3.6

DISCUSSION

Different studies have been conducted in last few years to find the relevance of hs-CRP as a predictor of risk of CV events and CV mortality over a short term and long term.

Ribeiro DR et al studied the association between hs-CRP and recurrent major adverse CV events including new revascularization, reinfarction, heart failure and death in patients with STEMI. The results of this study did not show any statistically significant relevance between hs-CRP and major CV events however a statistically significant association was found between hs-CRP and 30 days mortality (p=0.005).14

Karadeniz M et al studied the relevance of hs-CRP with short term and long term mortality rate in patients with ACS. The results showed that increased hs-CRP levels are predictors of high SYNTAX score in these patients. The researchers therefore concluded that the levels of serum hs-CRP at the time of admission of patients with ACS are a good predictor of the complexity and severity of coronary atherosclerosis.15

Liu Y and co-workers evaluated the relevance of hs-CRP on CAD severity. The study showed a positive association between the raised hs-CRP and major CV outcomes (p=.006). They also mentioned significant relevance between hs-CRP and mortality (p < 0.001). The research concluded that the levels of serum hs-CRP are useful biomarkers of severity of CAD.1
Nath R K et al evaluated the role of hs-CRP levels in predicting the risk of short term event rate in chronic stable angina patients. The results did not show an association of hs-CRP with the risk of MI or death in groups of patients having hs-CRP >3 mg/l Vs group of patients having hs-CRP ≤ 3 mg/l. However a significant relevance was proven between hs-CRP levels and risk of angina and need for revascularization.12

A detailed study over the topic was published in JAMA in 2019 which provides the relevance of hs-CRP with the short term relevance of hs-CRP with CV events and CV mortality after ACS in a 16 weeks follow up period. The study proved that higher baseline hs-CRP levels and higher longitudinal hs-CRP levels are independently associated with major adverse CV events (p=0.001). A similar association was also found between hs-CRP levels and CV death (p=0.02). The study therefore importantly revealed the association between initial and subsequent rise in hs-CRP levels and the short term (16 weeks) risk of combined major CV events and CV mortality after ACS despite taking the recommended evidence based therapies.16

The Mean±SD of age in this study was 61.40±10.15 years. The male gender was 54.31% while female gender was 45.68% in overall study population. Index diagnosis reported STEMI in 50%, NSTEMI in 30.17% while unstable angina in 19.82 % of overall study population. A good proportion of the patients were hypertensive, diabetic and dyslipidemic. The Mean±SD of hs-CRP was 4.46±1.01 and1.85±0.56 in Group-A and Group-B respectively. Patients were taking aspirin, antiplatelet agents, ACEIs/ARBs, β-blockers and statins as per the evidence.

The results of the study show a high although statistically non-significant incidence of STEMI in Group-A as compared to Group-B (8.62% Vs 3.44%, p=0.242), a high but statistically non-significant incidence of NSTEMI in Group-A as compared to Group-B (6.89% Vs 1.72%, p=0.170), a high and statistically significant incidence of unstable angina in Group-A as compared to Group-B (10.34% Vs 1.72%, p=0.05) and a high but statistically non-significant incidence of CV mortality in Group-A as compared to Group-B (3.44% Vs 1.72%, p=0.55).

Results also showed significantly higher incidence of total primary outcomes in Group-A compared to Group-B at the end of 4 months follow up period (29.31% Vs 8.62%, p=0.00). The results of our study

are in line with studies conducted previously over this topic and discussed above.1,12,14,15,16 Hence the results of this study provide good evidence for relevance of hs-CRP to the short term outcomes in patients with ACS.

The limitations of this study include a small sample size and a single center based study. Future studies involving multiple centers and larger number of patients will be helpful in formulating strategies to improve the prognosis in patients recently diagnosed with acute coronary syndrome.

CONCLUSION

The results of this study show a significant relevance between the hs-CRP levels with short term outcomes of ACS especially unstable angina and composite of total CV outcomes at 4 months follow up period. Hence the base line hs-CRP levels can be used for predicting associated risk and suggesting the appropriate treatment strategies.

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