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HS- C- Reactive Protien (HS-CRP): A Dependable Prognostic Marker in Acute Coronary Syndromes.

KEYWORDS: C- reactive Protien, Coronary Artery Disease, Acute Coronary Syndromes

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ABSTRACT *Aims and Objectives: To determine the prognostic value of serum C-Reactive Protein (CRP) in patients of Acute Coronary Syndromes. To compare the prognostic value of C-Reactive Protein (CRP) with the other known prognostic variables for Acute Coronary Syndromes.*

Methods: All the patients were evaluated with a detailed history and clinical examination. The relevant past history profile, Coronary artery disease (CAD) risk factors, drug and treatment history were noted. In addition, all the patients were subjected to a detailed general and systemic physical examination, with particular reference to the presence of any complications of CAD (e.g. CHF, hypotension, pulmonary edema) and any signs of a systemic illness. The cases were divided into 2 groups. Group 1 consisted of patients with Acute MI and group 2 consisted patients with unstable angina. All the base line investigations including ECG and 2D ECHO evaluation were done. C-reactive protein (CRP) estimation - CRP estimation was done once at the time of admission in all the patients using a high sensitivity Microwell (solid phase) enzyme-linked immunosorbent assay: HS-CRP ELISA. All patients were assessed for the adverse outcome measures like reperfusion failure , Recurrent angina ,non fatal myocardial infarction, serious arrhythmias, cardiogenic shock, cardiac death, left ventricular dysfunction on 2-D echocardiography, and congestive heart failure. Statistical analysis was done using the following tests where applicable: analysis of variance (ANOVA), Student's t-test, Fisher's exact test and chi-square (x2) test. The statistical significance was evaluated by calculating the P value. The difference was considered significant when the P value was < 0.05 (one in twenty). The prognostic value of CRP for prediction of an adverse outcome was defined in terms of statistical parameters (i.e. sensitivity, specificity, positive predictive value, negative predictive value and relative risk) and was compared with those of other known prognostic variables.

Results: 40.0% of the study population had a CRP value > 8 mg/L. The mean CRP level (ELISA method) in our study was 9.8 ± 5.22 mg/L. The mean CRP values in group I (AMI) and group II (Unstable Angina) patients were 9.8 ± 6.08 mg/L, and 9.7 ± 4.36 mg/L, respectively. , those group I patients who had reperfusion failure or recurrent angina, had a significantly higher level of CRP than those who did not have them (P < 0.01 and = 0.04, respectively). Group II patients who had recurrent angina or LV dysfunction on 2-D echo; LVEF < 40%, had a significantly higher level of CRP than those who did not have them (P = 0.01 and 0.05, respectively). , there is a statistically significant correlation between reperfusion failure or recurrent angina as adverse outcomes, and CRP (ELISA) level > 8 mg/L in group I (AMI) patients (P < 0.01 and = 0.03, respectively), there is a statistically significant correlation between recurrent angina or LV dysfunction on 2-D echo; LVEF < 40% as adverse outcomes, and CRP (ELISA) level > 8 mg/L in group II (UA) patients (P = 0.03 and 0.02,respectively).

Conclusion: The present study demonstrates that C-reactive protein (CRP) has an independent prognostic significance in the patients of acute coronary syndromes, as the value of CRP > 8 mg/L, on admission [quantitative estimation by high sensitivity Microwell (solid phase) ELISA method] correlates well with an increased overall risk of adverse cardiac outcome during the short term follow up. an elevated serum CRP level (CRP > 8 mg/L) on hospital admission is predictive of an increased risk of recurrent angina and left ventricular dysfunction in the patients of unstable angina.

INTRODUCTION

Acute Coronary Syndrome refers to a spectrum of clinical conditions comprising of Unstable Angina, Non-Q-wave Myocardial Infarction and Acute Myocardial Infarction. Unstable Angina (UA) is defined as angina pectoris (or equivalent type of ischemic chest discomfort) with presence of at least one of the following three features[1]:

1) It occurs at rest (or with minimal exertion) usually lasting more than 20 minutes (if not interrupted by nitroglycerin);
2) It is severe and described as frank pain and of new onset (i.e. within 1 month); and
3) It occurs with a crescendo pattern (i.e. more severe, prolonged, or frequent than previously).

Unstable Angina is classified according to Braunwald's classification[2], which is based on the severity of the ischemia. Patients with unstable angina may be further divided according to the intensity of the prior treatment for angina and on the basis of the presence or absence of electrocardiographic changes during the episode of pain. In unstable angina, ST segment depression (or transient ST segment elevation) and T wave changes occur in upto 50 per cent of patients.[3]

Non-Q-wave Myocardial Infarction (Non-ST segment elevation MI, NSTEMI)

Among the patients with the pattern of ischemic chest discomfort consistent with unstable angina, especially those with prolonged rest pain, the diagnosis of NSTEMI is made if there is biochemical evidence of myocardial necrosis, that is, a positive CK-MB, troponin T or I or potentially other markers of injury.

Acute Myocardial Infarction: The classic WHO criteria for the diagnosis of acute myocardial infarction require that at least two of the following three elements be present7:

1) A history of ischemic type chest discomfort for atleast 30 minutes,
2) Evolutionary changes on serially obtained ECG tracings, and

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3) A characteristic pattern of rise and fall in serum cardiac markers (CK, CK-MB, cardiac specific Troponins- TnT & TnI, Myoglobin and LDH).

The underlying morphological lesion in acute coronary syndromes is an atheromatous plaque causing variable degree of luminal narrowing. Unlike stable angina, in which such coronary plaques may remain stable for years or only progress slowly without acute clinical deterioration, the coronary lesions of acute coronary syndrome may progress rapidly and are then usually associated with abrupt development of new symptoms or acute changes in the pre-existing symptoms. Morphologically, such an unstable coronary lesion is represented by a raised atheromatous plaque with ruptured surface causing variable degree of hemorrhage into the plaque.

The precise cause of sudden disruption of a previously intact plaque and conversion of stable angina to UA/ AMI have been proposed to explain increased predisposition to the plaque rupture.[5,6,7] These include high wall shear stress on account of local flow disturbances[5], hypercholesterolemia induced endothelial cell dysfunction causing decreased synthesis of EDRF (NO)6, and plaque inflammation resulting in destabilization of the fibrous cap, making it prone to rupture.[7]

In recent years, underlying inflammation has been recognised as an important cause of the plaque disruption. The role of plaque inflammation in acute coronary syndromes is suggested by histological studies of unstable coronary plaques[7], evidence of systemic release of thromboxanes/ leukotrienes, the presence of activated circulating leukocytes and increased concentration of plasma acute phase reactants like C-reactive protein, serum amyloid A, etc.[8,9]

Because the most intense inflammation is present in the area of an occlusive thrombus, it has been proposed that the inflammatory response preceded the terminal event i.e. plaque rupture.

The precise trigger for this inflammatory reaction is however, still elusive. But whatever be the underlying cause, the presence of inflammation has led to a search for certain markers of inflammation which will help in identification, management, prognostication and probably, the prevention of acute coronary syndromes. Majority of research has focused on various acute phase reactants, including C-reactive protein (CRP), serum amyloid A, interleukin-6, etc.[9,10] Of these, CRP has been found to be of particular value.

CRP is an acute phase reactant and is mainly produced by hepatocytes in response to cytokines produced by activated macrophages and other cells. The acute phase response is a non-specific phenomenon triggered by most forms of inflammation, infection and tissue damage/ necrosis. Elevated CRP has also been associated with smoking, high body mass index and hyperlipidemia (which by themselves are risk factors for atherosclerosis)[11] as well as in response to infections such as Chlamydia pneumoniae, Helicobacter pylori, CMV or HSV which have often, but not conclusively, been associated with coronary atherosclerosis.[12]

However, recent studies have shown that the elevation of CRP in patients of atherothrombotic disease who have no evidence of any other illness (which can trigger an acute phase response) may be a result of plaque inflammation. Various studies have demonstrated increased CRP levels in acute coronary syndromes.

Various studies have shown that in patients of AMI with a history of UA, CRP is elevated at the time of hospital admission when creatine kinase and troponin T were within normal limits, indicating that CRP is not induced by myocardial necrosis.[13]

High sensitivity assays for CRP (hs-CRP) have now been developed and enable detection of even the mild elevation of CRP within the normal range. These assays, which include high sensitivity enzyme immunoassays and particle enhanced immunonephelometric assays, are reliable, fully automated and highly sensitive.[14,15]

Although there are several reports available from abroad regarding the prevalence of CRP in patients of CAD and its short term and long term prognostic significance in patients of acute coronary syndromes, there is a paucity of data on this aspect from India.

The present study was conducted to estimate CRP levels in patients of acute coronary syndromes (AMI and Unstable Angina) using the high sensitivity enzyme immunoassay, in order to evaluate its prognostic significance in these patients. Simultaneously, the prognostic value of CRP has been compared with some of the other known variables predicting the outcome in acute coronary syndromes.

AIMS AND OBJECTIVES

1. To determine the prognostic value of serum C-Reactive Protein (CRP) in patients of Acute Coronary Syndromes.
2. To compare the prognostic value of C-Reactive Protein (CRP) with the other known prognostic variables for Acute Coronary Syndromes.

All patients presenting to the medicine ICU fulfilling the diagnostic criteria for Acute myocardial infarction and Unstable angina.

Exclusion criteria

1. Patients having one or more of the following, were excluded from the study, 1. 1.left bundle branch block
2. Active infection or chronic inflammatory disease
3. Significant hepatic or renal dysfunction malignancy
4. History of CABG
5. Past history of MI or percutaneous coronary intervention.

Study Protocol

All the subjects were evaluated with a detailed history, including past history, risk factors for CAD, treatment history and clinical examination.

Other specific investigations carried out were as follows.

- ECG - Standard 12-lead electrocardiography was performed in all patients on admission, and repeated frequently thereafter as indicated, during the first 48 hours of admission. Patients admitted in the CCU were put on continuous ECG monitoring. After 48 hours, ECG was done at least once daily and also" during any intercurrent episodes of chest pain.
- ***Cardiac enzyme estimation:***
  Creatine Kinase (CK) - MB fraction - was estimated at admission, after 6 hrs., and also repeated as indicated. (Reference normal value: < 20 IU/L)
- ***C-reactive protein (CRP) estimation*** - CRP estimation was done once at the time of admission in all the patients using a high sensitivity Microwell (solid phase) enzyme-linked immunosorbent assay: HS-CRP ELISA.

Measurement of CRP by High Sensitivity Enzyme Immunoassay

Enzyme immunoassay based on 'Sandwich' technique using polystyrene microtiter wells as the solid phase was standardized for estimation of CRP levels in serum. It was reproducible and the assay range was wide enough to detect from physiological to raised pathological values (O.lmg/L to 30mg/L).

Necessary reagents, reference standard CRP solutions, enzyme substrates, unlabeled and peroxidase labeled mouse immunoglobulin to human CRP, and microtiter plate were obtained in form of a HS-CRP ELISA kit.

As per the standards of HS-CRP test kit used in our study, the cut off normal value for CRP (ELISA) level in adult serum

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was 8 mg/L.

- 2-D Echocardiography and Doppler Echocardiography - 2-D echo and Doppler echo were dTone in all except two patients, prior to discharge to evaluate for any regional wall motion abnormality (RWMA) at rest, left ventricular ejection fraction (LVEF) and mechanical complications of AMI. 2-D echo could not be done in two patients of AMI who died during the hospital stay.

METHODS

On admission, 20ml of peripheral venous blood was collected from the ante-cubital vein of the patient using a disposable syringe and needle, under aseptic precautions and immediately sent to the laboratory in different vials depending upon the investigations ordered.

For CRP estimation, 5 ml of blood was kept in a clean glass tube for 20 minutes at room temperature and allowed to clot. Then the glass tube containing the clotted blood was centrifuged at 2000 rpm for 20 minutes and the supernatant serum was separated and placed in another clean glass tube. The serum samples were stored in a deep freezer at -20°C. The coded samples were analyzed in batches of 10 each within 2-4 weeks. All decisions regarding management of the patients were made independent of these measurements.

Treatment Protocol

Standard protocol for the treatment of patients with ST elevation MI and Unstable angina was followed.

Follow up

After discharge, the patients were followed up by weekly visits in the outpatient department for 4 weeks and assessed for the adverse outcome measures i.e. recurrence of angina (including the number of episodes), CHF or serious arrhythmias, cardiogenic shock, myocardial infarction and cardiac death.

Adverse outcome measures

All patients were assessed for the adverse outcome measures like Reperfusion failure , Recurrent angina , Non fatal myocardial infarction, Serious arrhythmias, Cardiogenic shock, Cardiac death Left ventricular dysfunction on 2-D echocardiography, and Congestive heart failure.

Primary outcome measures

- Reperfusion failure: Complete ST-segment resolution was considered to be a >70% reduction of the sum of the ST-segment elevation between the ECG on admission in the CCU and the ECG 2 hours after IV thrombolysis initiation. Incomplete/ no ST-segment resolution in response to IV thrombolysis was defined as reperfusion failure.16
- Recurrent angina: Defined as 2 or more episodes of ischemic chest pain lasting more than 10 minutes after 24 hours of initiation of treatment (as quoted by Kane et al in their study).17 Any readmission for UA was also considered under this heading.
- Non fatal myocardial infarction during the follow-up period in patients of UA.
- Serious arrhythmias: Documented Sustained ventricular tachycardia, ventricular fibrillation and supraventricular tachycardia, requiring immediate medical treatment.
- Cardiogenic shock: This is characterized by marked and persistent (>30 min) hypotension with systolic arterial pressure less than 80 mm Hg, and
- Cardiac death: Any incidence of sudden unexplained death, death occurring due to fatal MI, cardiac arrhythmias or heart failure.3

Secondary outcome measures

- Left ventricular dysfunction on 2-D echocardiography: Presence of left ventricular ejection fraction (LVEF) < 40%.18,19
- Congestive heart failure (CHF).

STATISTICAL ANALYSIS

In the present study, statistical analysis was done using the following tests where applicable: analysis of variance (ANOVA), Student's t-test, Fisher's exact test and chi-square (x2) test. The statistical significance was evaluated by calculating the P value. The difference was considered significant when the P value was < 0.05 (one in twenty). The prognostic value of CRP for prediction of an adverse outcome was defined in terms of statistical parameters (i.e. sensitivity, specificity, positive predictive value, negative predictive value and relative risk) and was compared with those of other known prognostic variables.

To find out the independent prognostic value of CRP, a stepwise multiple logistic regression analysis was done regarding the predefined outcome measures. The variables that were evaluated for prognostic significance were age, diabetes mellitus, hypertension, family history of premature CAD, prior history of angina, and smoking.

OBSERVATIONS

Table 1: Correlation of baseline characteristics with CRP level, more than and less than 8 mg/L, in the present study

		CRP mg/L		***P* value**
Baseline characteristics		>8	<8	
Age years (Mean ± SD)		56.6 ±5.69	55.1 ±5.65	0.44 (NS)
BMI kg/ m^2 (Mean ± SD)		25.3 ±4.00	25.2 ±4.35	0.93 (NS)
CK-MB at admission, IU/L (Mean ± SD)	in AMI patients	57.0 ±24.67	66.8 ±36.79	0.52 (NS)
	in UA patients	17.0 ±3.96	17.0 ±3.49	0.99 (NS)
CK-MB 6 hrs. after admission, IU/L (Mean ± SD)	in AMI patients	107.0 ±17.50	99.4 ±20.17	0.40 (NS)
	in UA patients	22.8 ±5.31	19.8 ±4.24	0.19 (NS)
Length of qualifying episode of chest pain, hours (Mean ± SD)		3.2 ±2.39	4.0 ±2.25	0.31 (NS)
Smoking		+ 13	8	**0.01** (S)
		- 5	16	
Diabetes mellitus		+ 8	11	0.80 (NS)
		- 8	13	
Hypertension		+ 8	11	0.80 (NS)
		- 8	13	

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Dyslipidemia	+ 6	10	0.79 (NS)
	- 10	14	
Family h/o premature CAD	+ 6	4	0.14 (NS)
	- 10	20	
Past h/o angina	+ 12	14	0.25 (NS)
	- 4	10	
ECG changes (ST segment deviation > 1 mm)	+ 15	16	0.73 (NS)
	- 1	8	

In this table, on multiple logistic regression analysis, smoking is the only baseline characteristic having a statistically significant correlation with CRP level > 8 mg/L on admission in the study group (P = 0.01).

Table 2. Correlation of primary and secondary outcome measures with respect to CRP level on admission in group I (AMI)

Outcome measure	**n = 20**	CRP level Mean ± SD (mg/L)	***P* value**
Reperfusion failure	+ 8	14.2 ±7.98	**< 0.01 (S)**
	- 12	6.9 ±0.61	
Recurrent angina	+ 8	12.8 ±8.90	0.04 (S)
	- 12	7.8 ± 1.68	
Cardiogenic shock	+ 4	7.5 ± 1.40	0.47 **(NS)**
	- 16	10.4 ±6.68	
Serious arrhythmias	+ 2	6.8 ± 1.89	0.41 **(NS)**
	- 18	10.2 ±6.32	
Cardiac death	+ 2	6.8 ± 1.89	0.41 **(NS)**
	- 18	10.2 ±6.32	
CHF	+ 2	8.2 ±0.13	0.70 **(NS)**
	- 18	10.0 ±6.40	
LV dysfunction on 2-D echo **n** =18" (LVEF < 40%)	+ 5	11.3 ± 5.41	0.84 **(NS)**
	- 13	9.8 ±6.79	
RWMA **n =18***	+ 18	10.2 ±6.32	00
	- 0	0	

* 2-D echo could not be done in 2 patients due to their death during the hospital stay co P value cannot be computed because one of the variable is constant

As per this table, those group I patients who had reperfusion failure or recurrent angina, had a significantly higher level of CRP than those who did not have them (P < 0.01 and = 0.04, respectively). However, for the occurrence of other outcome measures there was no statistically significant difference in the level of CRP.

Table 3: Correlation of primary and secondary outcome measures with respect to CRP levels on admission in group II (UA)

Outcome measure	**n = 20**	CRP level Mean ± SD (mg/L)	***P* value**
Recurrent angina	+ 8	12.7 ±4.71	0.01 (S)
	- 12	7.7 ±2.80	
Non fatal AMI	+ 0	0	00
	- 20	9.7 + 4.36	
Cardiogenic shock	+ 0	0	**00**
	- 20	9.7 ±4.36	
Serious arrhythmias	+ 0	0	**00**
	- 20	9.7 ±4,36	
Cardiac death	+ 0	0	00
	- 20	9.7 ±4.36	
CHF	+ 0	0	00
	- 20	9.7 ±4.36	
LV dysfunction on 2-D echo (LVEF < 40%)	+ 3	12.0 ±4.40	**0.05 (S)**
	- 17	9.3 ±4.35	
RWMA	+ 7	11.0 ± 4.51	0.27 **(NS)**
	- 13	9.0 ±4.28	

GO P value cannot be computed because one of the variable is constant According to this table, group II patients who had recurrent angina or LV dysfunction on 2-D echo; LVEF < 40%, had a significantly higher level of CRP than those who did not have them (P = 0.01 and 0.05, respectively). However, no statistically significant difference in the level of CRP was found for the occurrence of other outcome measures in this group.

Table 4:Correlation of significant outcome measures in group I (AMI) with CRP levels, more than and less than 8 mg/L on admission

Group I (n = 20)				
Outcome	n	CRP level > 8 mg/L (n = 8)	CRP level < 8 mg/L (n = 12)	*P* value
Reperfusion failure	8	8	0	< 0.01 (S)
Recurrent angina	8	6	2	0.03 (S)

As per this table, there is a statistically significant correlation between reperfusion failure or recurrent angina as adverse outcomes, and CRP (ELISA) level > 8 mg/L in group I (AMI) patients (P < 0.01 and = 0.03, respectively),

Table 5 : Correlation of significant outcome measures in group II (UA) with CRP levels, more than and less than 8 mg/L on admission

Group II (n = 20)				
Outcome	n	CRP level > 8 mg/L (n = 8)	CRP level < 8 mg/L (n = 12)	***P* value**
Recurrent angina	8	6	2	0.03 (S)
LVEF < 40%	3	3	0	0.02 (S)

According to this table, there is a statistically significant correlation between recurrent angina or LV dysfunction on 2-D echo; LVEF < 40% as adverse outcomes, and CRP (ELISA) level > 8 mg/L in group II (UA) patients (P = 0.03 and 0.02, respectively),

DISCUSSION

The present study was conducted in a prospective manner in the Department of Medicine, Jawaharlal Nehru Medical College and associated Acharya Vinoba Bhave Rural Hospital, Sawangi (M), Wardha over a period of 2 years with the aim of

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evaluating the prognostic significance of C-reactive protein (CRP) in the patients of acute coronary syndromes (Acute ST elevation MI and Unstable Angina) and also comparing its relative prognostic value with respect to the known prognostic variables of acute coronary syndromes.

The study comprised of 40 patients of acute coronary syndromes (AMI and Unstable Angina: 20 each) who were selected randomly based on certain inclusion and exclusion criteria. The patients were given treatment for AMI or Unstable Angina, according to the usual protocol. Their clinical course was monitored throughout the hospital stay as well as during the follow up period of 4 weeks for the occurrence of any adverse outcome, primary (reperfusion failure, recurrent angina, non fatal myocardial infarction in UA patients, serious arrhythmias, cardiogenic shock and cardiac death) and secondary (LV dysfunction on 2-D echo; LVEF < 40% and CHF).

Clinical profile
The mean age of the subjects in study group was 55.7 ± 5.57 years (range 45-65 years). The maximum number of patients in our study were in the age group of 51-60 years (57.5%). As regards to the sex distribution in the present study, males and females accounted for 67.5% and 32.5% of the study population, respectively.

Regarding the distribution of risk factors of CAD in the present study, smoking was the most common risk factor present in 20 cases (50.0%) followed by diabetes mellitus in 19 cases (47.5%), hypertension in 19 cases (47.5%), dyslipidemia in 16 cases (40.0%) and family history of premature CAD in 10 cases (25.0%).

The mean length of the qualifying episode of chest pain in the present study was 3.7 ± 2.28 hours while the average number of chest pain episodes at rest in the last 48 hours was 1.3 ± 0.47. The longer duration of the pre-hospital delay in our study can be attributed to the lack of adequate transport facilities in the region.

Profile of C-reactive protein levels
The mean CRP level by ELISA method in our study was 9.8 ± 5.22 mg/L. As per the standards of HS-CRP ELISA kit used in our study, the cut off normal level for CRP was 8 mg/L. It was observed that 40.0% subjects in our study had CRP level of > 8 mg/L. Likewise, in the study by Winter et al20, 41.0% patients had CRP level of > 5.0 mg/L. Mishra et al21 found that 62.0% patients had CRP value > 6 mg/L. The variability in the cut off levels of CRP in different studies is due to the different methods of CRP assay having been used in these studies. The CRP levels in our study also correlate well with those in the studies by Mach et al22, Morrow et al23, and Rebuzzi et al24.

In our study, the mean serum levels of CK-MB, at admission, in AMI (group I) and Unstable Angina (group II) patients were 62.9 ± 31.32 IU/L, and 17.0 ± 2.47 IU/L, respectively. A similarly high value of mean CK-MB level (40.6 ± 19.30 IU/L) was reported in the study of AMI patients by Zairis et al.25

In the present study, the mean CRP values in AMI (group I) and Unstable Angina (group II) patients were 9.8 ± 6.08 mg/L, and 9.7 ± 4.36 mg/L, respectively.

Thus, CRP levels were found to be elevated in both the groups (AMI & Unstable Angina) independent of the serum cardiac marker levels. Anzai et al26 and Mishra et al21 have also reported elevated CRP levels in AMI patients. Similarly, Berk et al9 and Winter et al have found raised CRP levels in patients of UA. These observations lend support to the contention that raised levels of CRP in patients of acute coronary syndromes are because of the underlying plaque inflammation and not as a result of myocardial necrosis. It has been demonstrated that an elevated CRP is not necessarily induced by ischemic injury, as normal CRP levels were measured after an episode of a ischemia in patients with variant angina without atherosclerotic coronary artery disease. Moreover, although myocardial necrosis can cause an acute phase reaction by itself, Liuzzo et al13 reported an elevation of CRP in UA patients without an evidence of myocardial necrosis in form of an abnormal troponin T level. Haverkate et al27 have attributed this rise in the CRP levels in patients of acute coronary syndromes to intrinsic inflammation and tissue damage within the arterial lesions themselves.

On analyzing the association of various baseline characteristics and risk factors of CAD with CRP in the present study, only smoking as a risk factor of CAD was found to have a significant correlation with elevated CRP levels (CRP > 8 mg/L). This is in agreement with the study by Haverkate et al.27

Profile of adverse outcome measures
The break up of various primary and secondary end points in the present study revealed that in group I (AMI), 11 patients (55.0%) had an adverse outcome, of which reperfusion failure and recurrent angina were the most frequent, each reported in 8 patients (40.0%). Zairis et al25 have reported reperfusion failure in 51.4% patients of AMI. LV dysfunction on 2-D echo; LVEF < 40% was found in 5 out of 18 patients (27.8%) in this group. RWMA was present in all the patients due to associated myocardial necrosis. (2-D echo could not be done in 2 patients due to their death during the hospital stay). Cardiogenic shock developed in 4 patients (20.0%) of this group. Serious arrhythmias were seen in 2 patients (10.0%). 2 patients (10.0%) had cardiac death and CHF developed in 2 patients (10.0%). These observations are consistent with the findings of Kiran Babu et al 28 and Mishra et al 21 .

Amongst the group II (UA) patients, 9 (45.0%) had an adverse outcome. Recurrent angina was the most common, seen in 8 patients (40.0%). LV dysfunction on 2-D echo; LVEF < 40% was reported in 3 patients (15.0%). RWMA was seen in 7 (35.0%) patients of this group. Our observations are similar to those reported by Jos et al29 and Agarwal et al30.

Correlation of CRP levels with adverse outcome measures
The mean CRP level was significantly higher in the group I (AMI) patients who had reperfusion failure or recurrent angina than those who did not have these adverse outcomes (P < 0.01 and = 0.04, respectively, Table 2). Amongst the group II (UA) patients, the mean CRP level was significantly higher in those who had recurrent angina or LV dysfunction on 2-D echo; LVEF < 40% (P = 0.01 and 0.05, respectively, Table 3). However, no statistically significant difference was observed in the mean CRP levels for other adverse outcome measures.

In our study, out of the total 20 patients who had an adverse outcome, 15 had CRP level > 8 mg/L.

In group I (AMI), (table 4) all cases of reperfusion failure and 6 out of 8 patients with recurrent angina had CRP > 8 mg/L, which were found to be statistically significant, (P < 0.01 and - 0.03, respectively). No significant difference in CRP levels was reported for the other adverse cardiac outcomes. Similarly, Zairis et al25 found in their study that 66% of patients with CRP > 3 mg/L had reperfusion failure as compared to only 30% of patients with CRP < 3 mg/L, (P < 0.001). Mishra et al21 found that the complications like arrhythmias & recurrent angina were present in 71.0% patients of AMI with increased CRP response (> 6 mg/L) on admission as compared to 25.0%) patients with normal CRP response (< 6 mg/L), (P < 0.05).

In group II (UA), (Table 5), 6 out of 8 patients with recurrent angina and all the 3 patients with LV dysfunction on 2-D echo; LVEF < 40% had CRP > 8 mg/L, which were statistically significant (P = 0.03 and 0.02, respectively), while no significant difference in CRP levels was reported for other adverse cardiac outcomes. Similarly, Biasucci et al31 found that 69%> of UA patients with CRP level > 3 mg/L at dis-

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charge were readmitted because of recurrence of instability compared with only 15% of patients with CRP level < 3 mg/L, (P < 0.01). Kiran Babu et al also have reported a higher incidence of severe LV dysfunction in patients with high CRP level (> 3.1 mg/L), (P = 0.001). Agarwal et al30 have observed higher CRP levels in patients of unstable angina with RWMA at rest. Winter et al20 in a study of UA patients found that the incidence of a major cardiac event was significantly higher among the patients with CRP level > 5 mg/L than in other patients, (P = 0.00001). Liuzzo et al13 found a similarly high incidence of coronary events beyond a cut off level of CRP (ELISA) > 3 mg/L. Haverkate et al27 identified a cut off level of CRP (ELISA) > 3.6 mg/L that would indicate a higher risk of adverse events.

The statistical parameters of the prognostic significance of CRP level > 8 mg/L for the prediction of an adverse outcome in the patients of acute coronary syndromes in the present study are compared with those observed in other studies in the table given below.

Study	Sensitivity	Specificity	**Positive predictive value**	**Negative predictive value**
Liuzzo et al[13] (CRP > 3 mg/L)	87.0%	54.0%	24.0%	96.0%
Morrow et al[23] (CRP > 15.5 mg/L)	86.0%	76.0%	-	-
Present study (CRP > 8 mg/L)	75.0%	95.0%	93.8%	79.2%

This table highlights the fact that higher levels of CRP (with various cut off levels in different studies) are predictive of a worse outcome in patients of acute coronary syndromes.

Study limitations

- The group size in our study was small and studies with larger cohort size are recommended to validate the results.
- The lack of facility of rescue percutaneous coronary intervention at our institute should be taken into account in the interpretation or possible generalization of our results.

CONCLUSIONS

1. The present study demonstrates that C-reactive protein (CRP) has an independent prognostic significance in the patients of acute coronary syndromes, as the value of CRP > 8 mg/L, on admission [quantitative estimation by high sensitivity Microwell (solid phase) ELISA method] correlates well with an increased overall risk of adverse cardiac outcome during the short term follow up.
2. Reperfusion failure and recurrent angina are the adverse cardiac outcomes found to be significantly associated with an elevation of serum CRP level (CRP > 8 mg/L) early after an acute myocardial infarction.
3. Likewise, an elevated serum CRP level (CRP > 8 mg/L) on hospital admission is predictive of an increased risk of recurrent angina and left ventricular dysfunction in the patients of unstable angina.

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