the prognostic significance of C-reactive protein as an independent predictor for coronary events in Patients presenting with chest pain

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Citation

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Abstract

The aim of this study was to test whether measurement of CRP in patients with chest pain could help in identifying a potentially high risk group for a coronary event. We prospectively studied 1983 consecutive patients presenting with chest pain. A total of 1825 patients were enrolled (mean age 52 ± 6.95; range 25-65; men 68%). The patients were divided in two groups; Group 1 included admitted patients (n=892); Group 2 included patients who were not admitted (n= 812). In Group 1 high CRP was measured in 713 (80%) patients; coronary events were recorded in 704 (79%). In Group 2, coronary events were recorded in 651 (98%) with high CRP and 14 (2%) with normal CRP. The sensitivity, specificity, positive predictive value and negative predictive value for high CRP were 95%, 69%, 92% and 79% respectively. CRP >3 mg/L is an independent predictor of coronary events in patients with chest pain.

INTRODUCTION

Chest pain arising from heart and great vessels may be caused by cardiac ischaemia, pericardial inflammation, aortic dissection, massive pulmonary embolism or other less sinister causes. The clinical history, electrocardiogram (ECG), serum creatinine phosphokinase (CPK) and troponin T/I still provide the most effective means for differentiating an active coronary event from the many causes of chest pain, but their specificity and sensitivity are still far from ideal.[1]

Acute coronary syndromes (ACS) result from coronary thrombosis occurring at sites of plaque rupture or superficial erosion.[2,3,4]

Among the various markers of inflammation proposed to monitor the clinical course of patients with Non-ST elevation acute coronary syndromes, C-Reactive protein (CRP), an acute phase reactant produced by hepatocytes in response to stimulation by inflammatory cytokines, primarily IL-6, is the most widely used. Elevation of inflammatory markers is a common finding in Non-ST elevation ACS.

Inflammation has been recognized to underlie the plaque disruption that contributes to the occurrence of unstable angina.[5] The role of inflammation is suggested by histological studies of unstable coronary plaques, presence of activated circulating leucocytes, evidence of systemic release of thromboxanes, leukotrienes and increased concentration of acute phase reactants of inflammation like CRP, serum amyloid A etc.[6,7]

Increased concentration of CRP have been reported in unstable angina [7] and in acute myocardial infarction[8] . More recently, Liuzzo and associates[9] have shown that concentration of CRP and serum amyloid A in unstable angina increase independently of myocardial cell injury, as shown by normal concentration of creatine kinase and Troponin T. It was also reported that higher concentration of CRP at the time of hospital admission (>3.0 mg/l) were predictive of a poor outcome in unstable angina.[9]

CRP consistently predicts new coronary events, including myocardial infarction and death, in patients with unstable angina and myocardial infarction. The data are very consistent with regard to the long-term outcome, but in many studies are also significant for in-hospital events. The predictive value of CRP is, in the majority of the studies, independent of and additive to that of the troponins.[10]

It has been shown in patients with unstable angina that increased CRP is associated with adverse outcome

independent of an increased cardiac Troponin T or I, which are sensitive and specific markers of myocardial necrosis and strong prognostic indicators.[11,12,13]

Several studies have indicated that small differences in baseline concentrations of CRP[14] in apparently healthy men and in patients with stable angina pectoris constitute an independent risk for first cardiovascular events.[15-18] In addition, both the increase in CRP after acute myocardial infraction (AMI) and CRP concentrations during unstable angina and at discharge correlate with the risk of a recurrent event.[9,19-22]

The evidence of long-term prognostic value of elevated CRP levels was reported in patients with coronary artery disease [23-25] and in healthy individuals with high [14] and low [16] levels of coronary risk factors.

It has been suggested that CRP may not only be a marker of generalized inflammation but directly and actively participates in both atherogenesis[26-28] and atheromatous plaque disruption.[29]

The aim of the present study was to evaluate the prognostic value of C-reactive protein in predicting cardiovascular events in patients who present with chest pain and whether CRP actually helps in distinguishing the high risk group amongst these patients.

METHODS

The study was conducted at Bolan Medical College Complex Hospital, Quetta, Balochistan, Pakistan between March 2002 and February 2004. A total of 1983 consecutive patients presenting to Accident & Emergency Department (A & E) with chest pain were recruited in the study; 158 were excluded from the study as they were found to have other clinical conditions that could result in high serum CRP concentrations; the remaining 1825 patients were enrolled in the study.

Inclusion criteria on admission was typical or atypical chest pain at rest lasting >20 minutes within the preceding 24 hours. (Braunwald class III; A, B).

Exclusion criteria were malignancy, inflammatory disease, surgery or major trauma in previous month, known thrombotic disorders, dilated cardiomyopathy, previous myocardial infarction within 3 weeks, valvular heart disease, active or chronic coronary artery disease, cerebrovascular accident, cardiac resuscitation, or inability or refusal to give informed consent.

All patients gave written informed consent.

The patients were divided into two groups. Group 1 included all patients who were admitted from A & E either for management of a coronary event or further cardiovascular investigations. Group 2 consisted of patients who fulfilled the inclusion criteria but were not considered for admission by the attending physician.

The Groups 1 and 2 were only arbitrary groups depending on whether or not the patients were admitted at the time of their first presentation and hence had reached primary end points, necessitating follow-up only for Group 2 patients till the occurrence of the primary end points.

It was the attending physicians' discretion whether to admit or discharge a patient from A & E, taking into consideration the symptoms, signs, ECG changes, blood tests including CPK, CPK-MB and troponin T but the physicians were unaware of CRP results.

Complete clinical data and blood tests for laboratory measurements were collected at admission. All patients underwent investigations including full blood count, urea & electrolytes, fasting blood glucose, lipid profile (total cholesterol, triglycerides, LDL, HDL), and urine examination (routine & microscopy). Serum CPK, CPK-MB, Troponin T, 12-lead standard ECG and a chest X-ray were also obtained on admission.

CRP was measured with a nephelometric assay (Behring Diagnostics).[30] The detection limit was 0.2 mg/L, the assay was linear from 0.2 to 230 mg/L, and the CV was <3% at a concentration of 2 mg/L. For the present analysis, a cut-off of 3.0 mg/L was used, as reported previously.[22,31,32]

CRP levels were divided into three categories. CRP >50 mg/L were categorized as markedly elevated, between 3-50 mg/L as moderately elevated and <3 mg/L as normal CRP value. This was to identify which of the three categories have a higher risk of having coronary events.

All patients underwent exercise tolerance test or stress echocardiogram, depending upon the health status of the patients.

The primary end points were occurrence of a coronary event or cardiac death.

Coronary event was defined as any severe or acute cardiovascular condition including acute myocardial infarction or unstable angina.

Acute myocardial infarction was diagnosed in the presence of chest pain lasting >20 minutes, characteristic ECG alterations, and plasma CK-MB elevation greater than twice the normal or previous elevated value or positive troponin T (>0.1 ng/ml).

Unstable angina was defined as with typical chest pain at rest (usually more than 20 minutes), new onset of exertional chest pain with marked limitation of ordinary physical activity, or recent (<2 months) increase in the severity of angina.[5]

Cardiac death was defined as a death due to myocardial infarction, cardiac arrhythmias (sustained ventricular tachycardia, ventricular fibrillation and supra-ventricular tachycardia with hemodynamic compromise), cardiogenic shock or congestive cardiac failure.

Sudden cardiac death was defined as death due to cardiac disease within one hour after onset of symptoms.

All patients were followed-up for I year after admission or until occurrence of the primary end points.

p <0.05 was considered statistically significant.

RESULTS

A total of 1825 patients were enrolled in the study (mean age 52.25 ± 6.95 years (range men 25-65; women 40-65 years) (68% men). Baseline characteristics of the patients are given in Table 1.

Figure 1

Table 1 Baseline characteristics of the study population

Demographics	Group 1 (n=892)	Group 2 (n=812)
Age (years)	52.6±7.2	51.8±6.7
Male gender, n (%)	485 (62%)	456 (74%)
Systolic BP (mm Hg)	130±12	132±10
Diastolic BP (mm Hg)	63±15	62±14
BMI (kg/m2)	28±3	27±4
Cardiovascular risk factors		
DM, n (%)	270 (30%)	220 (27%)
Dyslipidaemia, n (%)	450 (50%)	390 (48%)
Hypertension, n (%)	160 (18%)	162 (20%)
Smoking habit, n (%)	351 (39%)	311 (38%)
Family history <60 years, n (%)	187 (20%)	194 (24%)
Treatment at study entry		
Aspirin, n (%)	124 (14%)	146 (18%)
Beta-blockers, n (%)	98 (11%)	73 (9%)
Nitrates, n (%)	0	0
ACEI, n (%)	45 (5%)	37 (4.5%)
HMG CO-A reductase inhibitors, n (%)	18 (2%)	24 (3%)

Group 1

Eight hundred and ninety-two patients were included in Group 1. High CRP levels were measured in 677 (76%); 215 (24%) had CRP within normal limits. Coronary events were recorded in 704 (79%) patients, either on admission or whilst being in the hospital; 188 (21%) did not have any coronary event.

Out of 704 patients who had coronary events, 457 (65%) of patients had markedly elevated CRP; 154 (22%) had moderate elevations of CRP and 93 (13%) had normal CRP concentrations.

In Group 1, no coronary events were recorded in 188 (21%) patients, 15 (8%) had markedly elevated CRP, 51 (27%) had moderate elevations and 122 (65%) had normal CRP values, as shown in Table 1. All these patients were investigated thoroughly from the cardiac point of view as in-patients before being discharged.

The cardiac events recorded in Group 1 were unstable angina in 374 (42%), NSTEMI in 303 (34%), STEMI in 160

(18%) and cardiac deaths in 55 (6%) of patients, as shown in Table 2.

Figure 2

Table 2 Coronary events outcome in the study population

Coronary Events	Group I n= 892(%)	Group 2 n=812(%)
Unstable Angina	374(42)	284(35)
*NSTEMI	303(34)	170(21)
**STEMI	160(18)	251(31)
Cardiac Death	55(6)	107(13)

*NSTEMI: Non-ST Elevation Myocardial Infarction
**STEMI: ST Elevation Myocardial Infarction

Group 2

In Group 2, a total number of 933 patients were recruited; 121 were lost in the follow-up; the remaining 812 patients were enrolled in the study.

High CRP levels were measured in 424 (52%) patients; 388 (48%) had CRP values within normal limits. Coronary events were recorded in 367 (45%) patients, out of which 246 (57%) had high CRP and 121 (28%) had normal CRP concentrations. No coronary events were recorded in 380 (47%) patients, 57 (15%) with high CRP and 323 (85%) with normal CRP.

Among the Group 2 patients, who had coronary events, during the first trimester, 69 (16%) had markedly elevated CRP, 65 (15%) had moderate elevations and 3 (0.7%) patients had normal CRP. During the second trimester, 125 (29%) patients had markedly elevated CRP, 39 (9%) had moderate elevations of CRP while 4 (1%) had normal CRP concentrations. In the third trimester, 48 (11%) had markedly elevated CRP, 38 (9%) had moderate elevations, and 2 (0.5%) had normal CRP. In the fourth trimester, 21 (5%) had markedly elevated CRP, 18 (4%) had moderate elevations of CRP while 1(0.2%) had normal CRP.

In Group 2, unstable angina was seen in 284 (35%), NSTEMI in 170 (21%), STEMI in 251 (31%) and cardiac deaths were seen in 107 (13%) patients, as shown in Table 2.

The incidence of coronary events in relation to CRP <3 mg/L Vs CRP >3 mg/L was statistically significant (p <0.0001).

CRP levels and the presence of absence of coronary events in the two groups are shown in Table 3.

Figure 3

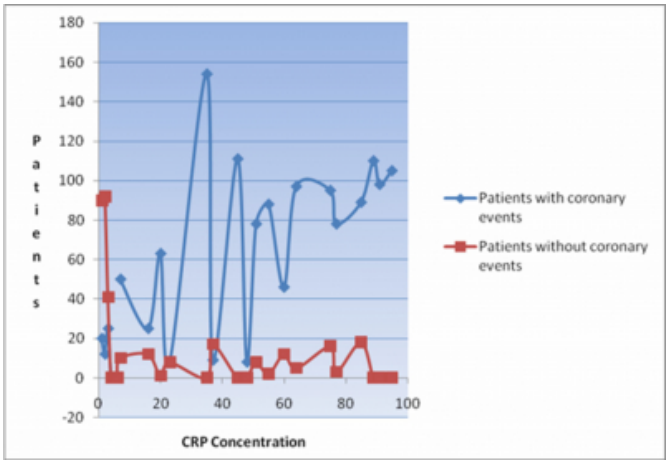
Table 3 CRP levels and coronary events in the study population

CRP Concentrations (mg/L)	Group I (n=892)		Group 2 (n=812)	
	Patients with coronary events (n=704)	Patients without coronary events (n=188)	Patients with coronary events (n=432)	Patients without coronary events (n=380)
<3	93 (13%)	122 (65%)	65 (15%)	323(85%)
3-50	154 (22%)	51 (27%)	121 (28%)	31(8%)
>50	457 (65%)	15 (8%)	246 (57%)	26(7%)

The correlation of CRP concentrations with the occurrence of coronary events in patients are shown in Figure 1.

Figure 4

Figure 1 Correlation of CRP with coronary events in patients with chest pain



DISCUSSION

Our data indicate that elevated CRP (>3 mg/L) predict future coronary events in patients presenting with chest pain to A & E. Those who have markedly elevated CRP have higher risk of having an adverse event compared to those with moderate

elevations. These results are comparable to the several studies done in the past. Liuzzo et al, prospectively studied patients with severe unstable angina, chronic stable angina and those with a myocardial infarction of less than 6 hours duration.[9] Their results showed that the concentration of CRP is elevated in the majority of patients of patients with unstable angina as well as those admitted with myocardial infarction and a history of unstable angina. A CRP value ≥0.3 mg/L on admission had a sensitivity of 90% and a specificity of 82%for predicting subsequent cardiac events such as cardiac death, myocardial infarction, or an urgent need for cardiac revascularization. The sensitivity increased to 100% in patients with CRP ≥1.0 on admission or in those with any rise in CRP level during the study.

It has been shown that CRP levels in general population predict future cardiovascular events, including first ever myocardial infarction, stroke and development of peripheral vascular disease.[34]

According to our data, in Group 1, 87% of patients with high CRP developed a coronary event compared to only 13% with normal CRP. No coronary events were recorded in 65% patients with normal CRP compared to 35% with elevated CRP.

Similarly, in Group 2, 61% of patients with markedly elevated CRP developed a coronary event in one year follow-up while 37% of patients with moderate CRP elevations had an event in the same period of time, signifying that the higher the CRP level, the greater risk of having an adverse event. In the one year follow-up, according to our data, only 2% of patients with normal CRP had a coronary event in the follow-up.

Acute coronary syndromes are characterized by persistent instability for weeks to months after the resolution of the clinical symptoms, resulting in recurrent episodes of unstable angina, myocardial infarction, or death.[33] Recent evidence suggests that the inflammatory process persists despite the resolution of clinical symptoms. Biasucci and associates[22] reported that serum CRP concentrations remained increased at the time of discharge and at three months' follow-up in upto 50% of patients who presented with Braunwald class IIIB unstable angina. This finding of a persistent increase of CRP after an episode of unstable angina was associated with frequent hospital re-admission for recurrent instability.

In 1982, de Beer at al[8] showed that individuals with myocardial infarction developed elevated CRP levels and that there was a significant correlation between the peak CRP and creatine kinase (CK) MB values. In uncomplicated cases, CRP levels tended to return to return to normal; however, in complicated cases, CRP levels remained elevated. In 1992, Berk et al[7] showed that average CRP values were significantly different for patients with unstable angina compared with those with stable angina.

Pasceri et al [27] showed that incubation with recombinant human CRP induces a 10-fold increase in adhesion molecule expression in human endothelial cells, similar to that induced by activation with IL-1-beta, suggesting that such pro-inflammatory effects may contribute to the adverse outcome associated with higher levels of this acute-phase reactant. CRP has been shown to attenuate the production of nitric oxide and prostacycline by endothelial cells, supporting its role in the atherosclerotic process.[35,36]

The TIMI II A sub-study evaluated the role of CRP as a predictor of 14-days mortality in 630 unstable angina/Non-Q-wave myocardial patients alone or in combination with troponin T[12] CRP levels were much higher in patients who died compared to those who survived, strongly suggesting a prognostic role for CRP with respect to short-term mortality. Furthermore, among patients with a negative Troponin T test, a markedly raised CRP level identified patients who remained at increased risk of death at 14 days. The authors supported the use of combination CRP and Troponin T for a 'more comprehensive risk assessment in patients with unstable angina and Non-Q-wave myocardial infarction'.

Haverkate and colleagues[24] also reported similar results.

Bhagat and coworkers[37] studied 44 patients with severe unstable angina and suggested that raised CRP level ≥4 mg/L, by ELISA, is an independent predictor of an adverse cardiac outcome in the short-term and, hence, is useful in the risk stratification of these patients. CRP has a higher specificity, PPV and overall RR for prediction of an outcome than ST segment depression, although it is less sensitive.

Our data shows that CRP has a sensitivity of 86%, a specificity of 78%, a Positive Predictive Value (PPV) of 88% and a Negative Predictive Value (NPV) of 73%, which is comparable to the studies by Liuzzo et al[31], Morrow et al[12] and Bhagat et al[37], as shown in Table 4.

Figure 5

Table 4 Predictive value of CRP for occurrence of adverse effects in various studies

Study	Sensitivity	Specificity	PPV	NPV
Liuzzo et al [31] (CRP ≥3 mg/L)	90%	82%	90%	-
Morrow et al [12] (CRP ≥15.5 mg/L)	86%	76%	-	-
Bhagat et al [37] (CRP ≥4 mg/L)	78.9%	96%	93.75%	85.74%
Our study (CRP ≥3 mg/L)	86%	78%	88%	73%

It can be seen from our data that the patients who had high CRP on admission subsequently had a coronary event even though they were discharged from A & E on the basis of normal cardiology investigations as opposed to those patients with a normal CRP. These are, therefore, a potential group of patients who need more aggressive care and treatment.

CONCLUSIONS

Elevation of CRP in patients presenting with chest pain probably points towards an evolving inflammation in the coronary vessels and this information, therefore, helps in risk stratification of a group of patients who are potential candidates for a an aggressive therapy as they are more prone to develop an acute coronary event compared to those with a normal CRP.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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