C-reactive protein in unstable angina: clinical and angiographic correlation

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ABSTRACT

Objective To assess prevalence, in-hospital prognostic significance and angiographic correlation of C-reactive protein (CRP) elevation in patients with unstable angina.

Design Prospective observational study.

Setting Royal Hospital, Muscat, Oman.

Patients 100 patients admitted between July 2008 and January 2009.

Interventions Patients with unstable angina and ECG changes without biochemical evidence of necrosis (negative first troponin T), had CRP measured at admission by rate nephelometry (≥10 mg/l abnormal).

Main outcome measures In-hospital cardiac events and severity of coronary artery disease (CAD) in patients with and without CRP elevation.

Results 42% had CRP elevation ≥10 mg/l (Group I), and 58% had levels <10 mg/l (Group II). When compared with Group II, Group I patients had more anginal episodes (mean=4.6±2.5 episodes/patient vs 1.6±2.4; p<0.0001), myocardial infarction (58% vs 17%; p<0.01), in-hospital mortality (9% vs 0%; p=0.03) and severe triple vessel disease (71% vs 24%; p<0.01), and a higher total number of events (86% vs 24%; p<0.0001). Elevated admission CRP as a marker of in-hospital cardiac events showed a sensitivity of 72%, specificity of 88% and positive predictive value of 85%, and, as a marker of significant CAD, showed a specificity of 83% and a positive predictive value of 85%.

Conclusions Raised admission CRP level is predictive of increased in-hospital cardiac events and severe CAD in patients with unstable angina. CRP can be used to risk-stratify unstable angina patients independent of troponin levels. Patients with abnormal CRP should undergo coronary angiography either on-site or transferred to a centre with catheterisation facility during the index hospital admission.

INTRODUCTION

There is growing controversy regarding the prognostic importance of C-reactive protein (CRP) in acute coronary syndromes (ACS). Inflammation is an important factor involved in endothelial injury and atherothrombosis resulting in accelerated atherosclerosis as well as precipitating acute plaque rupture or erosion.[1] The serum or plasma concentration of high-sensitivity CRP, a marker of inflammation, is increased in patients with ACS and predictive of in-hospital outcome and future risk.[2 3] Although CRP is mainly produced by hepatocytes in response to stimulation by inflammatory cytokines, a recent clinical study suggested that CRP is endogenously produced in coronary atherosclerotic plaques.[4] Many studies have demonstrated an independent association between the concentrations of CRP and late cardiac events including long-term mortality in patients with non-ST-elevation ACS[5–11] and ST-elevation ACS.[8 10] On the contrary, a recent study involving 1210 patients with all types of ACS found that CRP measured acutely and 1 month after hospital discharge had a modest but not independent ability to predict death, but does not predict myocardial infarction or unstable angina at 1 year's follow-up. The CRP measured at hospital discharge appeared to have no predictive ability.[12] In addition, there is an opinion that CRP is not helpful for identifying patient groups who might benefit from particular treatment strategies.[13]

Cardiac troponins are established markers of myocardial necrosis for risk stratification among patients presenting with ACS but have a relatively low diagnostic sensitivity for unstable angina, with only 22% to 50% of patients with unstable angina having positive troponin tests.[14] A correlation exists between troponin elevation and CRP levels, although a significant percentage of patients without troponin elevation have elevated levels of CRP. The cause of CRP elevations in the absence of overt myocardial necrosis is uncertain but may be related to plaque instability or myocyte necrosis below the limit of detection of standard assays.[15]

At present, other than ECG (with low sensitivity), there are no markers to risk-stratify unstable angina patients without troponin elevation. Many hospitals in developing countries do not have cardiac catheterisation facilities, and it is necessary to risk-stratify unstable angina patients with respect to transferring high-risk patients to a catheterisation facility or to take elective coronary angiography date, in patients with a low risk. Based on previous reports, it can be hypothesised that elevated CRP in patients with unstable angina is more useful in predicting acute cardiac events rather than follow-up events, and its measurement on admission may be useful to risk-stratify unstable angina patients and help in deciding on the need for early coronary angiography and revascularisation. The aims of this study were to assess the prevalence, in-hospital prognostic significance and angiographic correlation of CRP elevation in patients with unstable angina.

METHODS

In this prospective study, we included 100 consecutive patients admitted to the coronary care unit for ischaemic chest pain at rest (lasting ≥20 min) during the 24 h before admission associated with ECG changes of ST depression or T inversion and negative first troponin T level. Patients with ST-elevation myocardial infarction (STEMI) and those with abnormal elevation of troponin T (non-STEMI) on

admission were excluded. Patients with left bundle-branch block, secondary angina (angina pectoris subsequent to a precipitating extra cardiac cause), myocardial infarction in the preceding 1 month, concomitant infectious or inflammatory diseases, cancer or other significant heart diseases were excluded. The study was conducted during July 2008 to January 2009 at the Royal Hospital, Muscat, Oman. The study protocol was approved by the local ethics committee, and informed consent was taken from all patients.

Complete clinical data and blood samples for laboratory measurements were collected at admission. Baseline ECG was obtained at entry and repeated at 24 and 48 h or during recurrence of angina. Troponin T level was obtained at entry and repeated at 6, 12 and 24 h to determine patients developing non-STEMI. Troponin T was measured by enzyme immunoassay (Boehringer-Mannheim, Germany), and a level of ≥0.1 μg/l was considered abnormal. Coronary angiography was done in all patients before discharge to determine the severity of coronary artery disease (CAD) and culprit lesion characteristics. Single-vessel disease was present if there was more than 70% diameter stenosis on visual assessment in the left anterior descending, left circumflex or right coronary arteries, or a major branch. Coronary lesions were classified according to American College of Cardiology/American Heart Association (ACC/AHA) nomenclature.[16] A lesion was classified as type A if it was discrete (<10 mm in length), concentric with a smooth contour, non-calcified, non-ostial, no thrombus, not bifurcated or angulated. A diffuse lesion (>20 mm in length) with proximal tortuosity, angulated segment >90° or total occlusion was considered as type C. All other lesions were classified as type B. Not all features that qualify a lesion as type B or C in the ACC/AHA classification system are associated with an acute inflammatory process. Therefore, for the main analysis, high-risk/acute culprit lesions indicating ruptured plaque were those with thrombus, and those that were eccentric and/or irregular and not totally occluded.[17–19] All patients were followed up in-hospital.

Determination of CRP

CRP was measured on admission before any treatment was given. Blood samples were stored in evacuated tubes at −20°C to be processed within 24 h. Plasma CRP was measured by rate nephelometry (Behring Diagnostics, Germany; normal value <10 mg/l). The lower detection limit for CRP was 0.1 mg/l. The interassay and intraassay coefficients of variations were 0.3% and 0.3%, respectively.

The major in-hospital cardiac events evaluated were recurrent angina during hospital stay, myocardial infarction (prior to any intervention) (non-STEMI or STEMI), cardiac death and urgent revascularisation. The definition of recurrent angina during hospitalisation was based on the appearance of ischaemic chest pain at rest associated with or without ST-segment/T wave alterations in patients treated with nitroglycerine, aspirin, clopidogrel, β-blockers and intravenous heparin or low-molecular-weight heparin. Death was considered as cardiac unless otherwise demonstrated. Myocardial infarction was documented by the troponin T rise (≥0.1 μg/l) with either ischaemic symptoms or ST elevation/depression, or new pathological Q waves on the electrocardiogram. Urgent revascularisation by either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) was carried out for recurrent angina. Stable patients underwent coronary angiography before discharge and underwent PCI when the anatomy was suitable for PCI, and the rest of the patients were scheduled for CABG.

Statistical analysis

Data are presented as number (%) and/or mean±SD. Unstable angina patients were grouped into those with CRP elevation ≥10 mg/l as Group I and those with normal CRP levels <10 mg/l as Group II. The Fisher exact test and unpaired t tests were used to compare variables between the two groups. p Values lower than 0.05 (two-tailed) were considered to indicate statistical significance. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of admission CRP level ≥10 mg/l as a marker of in-hospital cardiac events and significant CAD were calculated.

RESULTS

Forty-two patients (42%) had a CRP elevation of ≥10 mg/l (Group I), and 58 patients (58%) had levels <10 mg/l (Group II). The mean time from the last anginal episode was 5±5 h. Table 1 shows the baseline characteristics of patients with unstable angina. There were no differences between Groups I and II with respect to baseline clinical characteristics. The median CRP level on admission in Group I was 18.5 mg/l (range=10.0–162.0) compared with 4.0 mg/l (range=0.1–7.5) in Group II.

Table 2 shows the in-hospital cardiac events. Group I patients had more symptomatic anginal episodes in hospital than Group II patients (mean=4.6±2.5 episodes/patient vs 1.6±2.4; p<0.0001). Twenty-four patients subsequently had non-STEMI,

Table 1 Baseline characteristics of patients with unstable angina

Characteristic	Group1 (C-reactive protein ≥10 mg/l) (n=42)	Group2 (C-reactive protein <10 mg/l) (n=58)	p Value
Age	60±11	63±9	0.13
Males	30 (71)	38 (65)	0.66
Hypertension	22 (52)	30 (52)	1.00
Hyperlipidaemia	18 (43)	26 (45)	1.00
Diabetes	14 (33)	22 (38)	0.60
Current smoker	10 (24)	16 (27)	0.80
Family history of coronary artery disease	06 (14)	10 (17)	0.70
Old myocardial infarction	08 (19)	12 (20)	1.00
Previous percutaneous coronary intervention	04 (9)	06 (10)	1.00
Previous coronary artery bypass surgery	02 (5)	02 (3)	1.00
Aspirin	10 (24)	12 (20)	0.80
Statins	14 (33)	22 (38)	0.66
Median C-reactive protein mg/l (range)	18.5 (10.0 to 162.0)	04 (0.1 to 7.5)	

Values are n (%) or mean±SD unless specified.
CRP, C-reactive protein.

Table 2 In-hospital cardiac events in patient with unstable angina

Characteristic	Group1 (C-reactive protein ≥10 mg/l) (n=42)	Group2 (C-reactive protein <10 mg/l) (n=58)	p Value
Recurrent angina/patient	4.6±2.5	1.6±2.4	<0.0001
Non-ST elevation myocardial infarction	24 (58)	10 (17)	<0.01
Death	04 (9)	00	0.03
Urgent percutaneous coronary intervention	08 (19)	04 (7)	Non-significant
Total events	36 (86)	14 (24)	<0.0001

Values are n (%) or mean±SD.

four died, and eight required immediate coronary revascularisation in Group I, compared with no deaths, 10 non-STEMI and four cases of urgent revascularisation in Group II. More patients in Group I subsequently showed an increase in troponin T levels suggesting non-STEMI (p<0.01). None of the patients developed STEMI. There was a 9% in-hospital mortality in Group I, which was statistically significant when compared with Group II (p=0.03). The total number of events in Group I was 36 (86% of patients) versus 14 (24% of patients) in Group II (p<0.0001).

There was a significant difference between Group I and Group II with regard to the mean time from admission to coronary angiography (25.5±10.7 vs 39.2±15.6; p=0.0001). The median time from admission to coronary angiography was 23 h (range=8–54) in Group I and 35 h (range=12–72) in Group II. At angiography, 30 patients (71%) in Group I had severe triple-vessel disease as compared with 14 patients (24%) in Group II (p<0.01). There was a significant difference in occurrence of normal coronaries or mild CAD between the groups. There was no difference in ACC/AHA type of lesions between two groups, but high-risk lesions were more frequent in Group I patients (table 3). Eccentric/irregular lesions with macroscopic thrombus were seen more in patients with CRP elevation (p=0.03).

More patients with elevated CRP were referred for revascularisation but were not statistically significant when compared with the patients without CRP elevation who were referred for revascularisation. The sensitivity of admission CRP level ≥10 mg/l as a marker of subsequent in-hospital cardiac events was 72%, the specificity was 88%, the PPV was 85%, and the NPV was 75%. Elevated admission CRP as a marker of significant CAD showed a low sensitivity of 56%, but specificity was high at 83%, a PPV of 85% and NPV of 51% (table 4).

DISCUSSION

The results from this study show that an increased concentration of CRP (≥10 mg/l) in patients with unstable angina was associated with an increase in hospital cardiac events and correlated with severe CAD on angiography. In their pioneering work, Liuzzo *et al*[2] reported that elevated CRP with normal cardiac troponin T levels in patients presenting with unstable angina was associated with poor in-hospital outcome: a significantly greater risk of angina and trends for the need for revascularisation and for death/myocardial infarction. Likewise, in the Thrombolysis in Myocardial Infarction 11A substudy, Morrow *et al*[6] confirmed the short-term prognostic value of CRP in ACS; CRP was related to the 14-day mortality, even in patients with a negative result on rapid troponin T assay. In the present study, CRP elevated patients had significantly more anginal episodes as well as in-hospital cardiac events such as non-STEMI and death, thus confirming results from previous studies.

Previously, CRP has been found to correlate with specific high-risk angiographic features of coronary lesions in patients with unstable angina.[17–20] In a recent study[18] involving non-ST-elevation ACS patients, both admission elevation of CRP and increase at 24 h showed a trend towards a higher incidence of

Table 3 Coronary angiography results including type and lesion characteristics in patients with unstable angina

Characteristic	Group1 (C-reactive protein ≥10 mg/l)	Group2 (C-reactive protein <10 mg/l)	p Value
Median time between admission and coronary angiogram*	23 (8 to 54)	35 (12 to 72)	
Mean time between admission and coronary angiogram†	25.5±10.7	39.2±15.6	0.0001
Normal or mild coronary artery disease	06/42	30/58	<0.01
Single-vessel disease	02/42	04/58	NS
Double-vessel disease	04/42	10/58	NS
Triple-vessel disease	30/42	14/58	<0.01
Revascularisation	36/42	28/58	NS
Type A	10/36	08/28	NS
Type B	22/36	18/28	NS
Type C	04/36	02/28	NS
Total occlusion	02/36	00/28	NS
Eccentric/irregular	22/36	06/28	NS
Macroscopic thrombus	04/36	00/28	NS
High-risk lesion	26/36	06/28	0.03

Values are n of total.
*In hours (range).
†Mean±SD.
NS, non-significant.

Table 4 Sensitivity, specificity, positive predictive value and negative predictive values of admission C-reactive protein level ≥10 mg/l in patients with unstable angina

Characteristic	Sensitivity	Specificity	Positive predictive value	Negative predictive value
In-hospital cardiac events	72 (36/50)	88 (44/50)	85 (36/42)	75 (44/58)
Significant coronary artery disease	56 (36/64)	83 (30/36)	85 (36/42)	51 (30/58)

Values are percentages.

multivessel disease as well as higher incidences of severe stenosis, complex culprit lesions and revascularisation. Recent studies using angioscopy/atherectomy and intravascular ultrasound have reported that ruptured plaques demonstrated higher intimal CRP and necrotic core volume in patients with ACS.[21–23] In the present study, patients with elevated CRP had a higher prevalence of triple-vessel disease, more high-risk angiographic features of culprit coronary lesions and an increased trend towards revascularisation procedures. Moreover, an elevated admission CRP itself risk-stratified unstable angina patients as high risk for overall in-hospital cardiac events and severe CAD on angiography.

Aspirin or statin therapy has been shown to decrease cardiac events indicating an anti-inflammatory effect of these medications mediated in part by a decrease in CRP level.[24 25] In our study, there was no significant difference in the use of aspirin or statins between two groups to evaluate this hypothesis.

The ACC/AHA guidelines for the management of non-ST-elevation ACS recommend early invasive management for high-risk patients.[26] Our findings suggest that the CRP level at admission is a useful variable for the risk assessment of patients with unstable angina. Thus, an early measurement of CRP, which may best reflect the inflammatory status influencing the index event, is most useful for identifying those patients at highest risk who may benefit from early coronary angiography and revascularisation performed either on-site or transferred to a facility with cardiac catheterisation. Measurement of CRP within the first 24 h of unstable angina presentation may offer important in-hospital prognostic information and could be added to critical pathways to improve the management of patients with unstable angina.

STUDY LIMITATIONS

The limitations of this study are those inherent to all prospective, but non-randomised studies. The major limitation of our study is the small sample size. Although our sample size was small, differences between patients with and without CRP elevation are striking in spite of compromised statistical power, and further studies in larger patient cohorts are needed. Covariates mentioned in table 1 can have an additional potential confounding influence on CRP levels. Since our study involved a small sample size, this does not allow us to run a multivariate analysis. The decision to perform PCI was not randomised but rather was at the discretion of the treating physician. Quantification of coronary angiographic findings was limited to the visual interpretation of the attending cardiologist, which is representative of real-world practice. Intravascular ultrasound could be expected to give details of culprit plaque characteristics, although this would be impractical to apply routinely.

CONCLUSIONS

Raised CRP level is predictive of increased risk for major in-hospital cardiac events in patients with unstable angina, and it has a good correlation with increased severity of coronary artery disease on angiography. CRP can be used to risk-stratify unstable angina patients independent of troponin levels and can be used along with other risk-scoring systems. Patients with abnormal CRP should undergo coronary angiography either on-site or transferred to a centre with a catheterisation facility during the index hospital admission. Patients with normal CRP can be managed with optimisation of antianginal therapy, followed by elective coronary angiography at a later date.

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the institutional ethics committee.

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