Original article

Study of markers of inflammation as predictors and prognosticators of acute coronary syndrome in patients with acute chest pain

NK Pandey, N Shrestha, P Karki
Department of Internal Medicine, B. P. Koirala Institute of Health Sciences. Dharan, Nepal

Abstract

Background: The role of inflammation in the pathogenesis of acute coronary syndrome (ACS) is established, however use of inflammatory markers as predictors for future short-term cardiovascular events in patients of acute coronary syndrome. **Objective:** To assess whether inflammatory markers C-reactive protein (hs-CRP), total leucocyte count (TLC) and serum albumin can correlate with the diagnosis of ACS in patients with acute chest pain and to see whether these markers can be used to predict short-term cardiovascular events in patients of ACS. **Methods:** All Patients presenting within 12 hours of the onset of central non traumatic chest pain were enrolled and investigated, the diagnosis of ACS was made as per JACC 2004 guidelines for ST-elevation myocardial infarction, unstable angina and non-ST elevation myocardial infarction. All patients received routine institutional care and treatment as per diagnosis blinded to CRP, albumin, and total leucocyte count (TLC). The independent predictors of ACS and predictors of adverse events in 30 days was evaluated using multivariate analysis. **Results:** one forty nine patients of ≥ 18 years (88 male, 61 female) which were included in the study, the diagnosis of non-ischemic chest pain (NICP)were in 30 (20%) and ACS in 119 (80%) patients. TLC and hs-CRP levels were higher (11576±3083, 14.04±6.17) in patients with ACS compared to NICP (5596±1370, 2.39±1.55) with significant P-value (<0.001). Significantly high hs-CRP level (19.95±6.46), TLC (15630±3522) and low serum albumin (3.45±0.31) were there in patients in whom adverse cardiovascular events occurred. **Conclusion:** Leucocyte count and hs-CRP level are the independent predictors of ACS in patients presenting to the emergency department with chest pain suggestive of ACS. High hs-CRP, TLC, neutrophil count and low serum albumin, lymphocyte count are independent predictors of adverse short-term cardiovascular events.

Keywords: acute coronary syndrome, albumin, leucocyte count, C-reactive protein

Introduction

Ischemic heart disease causes more deaths and disability and incur greater economic costs than any other illness in the developed world. By the year 2020, it is estimated that coronary artery disease (CAD) will surpass infectious diseases as the world's leading cause of death and disability.[1] South East Asian countries account for about a quarter of world's population and contribute the highest proportion of burden of coronary artery disease.[2,3]

The myocardial ischemia of unstable angina and myocardial infarction results from excess demand or inadequate supply of oxygen. The acute reduction in coronary arterial perfusion resulting in ACS is primarily due to an atherosclerotic plaque disruption with

Address for correspondence
Dr. Naveen Kr. Pandey
Assistant Professor
Department of Internal Medicine, BPKIHS, Dharan
Email: nav_dey31@yahoo.com

superimposed thrombosis. A growing body of evidence supports the concept that local systemic inflammatory response plays a role in the initiation and progression of atherosclerosis and its complications.[4] C-reactive protein (CRP) is an acute phase reactant marker for underlying systemic inflammation. CRP has been reported to be elevated in patients with acute ischemia and Myocardial Infarction (MI). Furthermore, elevated CRP along with other acute phase reactants and cytokines with a focal predominance of inflammatory cells have been found in patients with unstable coronary syndromes.[5] A high white blood cell count and a high erythrocyte sedimentation rate have been thought to reflect the bodies response to tissue injury in patients with Acute Myocardial Infarction (AMI), and TLC correlates with the severity of coronary atherosclerosis. A number of studies in different population settings have noted the association between serum markers of inflammation and the development of cardiac events in individuals with ACS and in those without known cardiovascular disease.[6,7] Though various inflammatory markers have been shown independently as prognostic marker for acute coronary syndrome, their comparison has not been done much. So, the present study was carried out to investigate the role of hs-CRP, albumin and leucocyte count in the diagnosis of ACS and to identify those at higher risk of developing events at 30 days follow up among those presenting to emergency department (ED) with chest pain suggestive of acute coronary syndrome.

Methods

One forty nine patients of 18 years or more arriving to the emergency within 12 hours of the onset of central chest pain of more than 10 minutes were enrolled in the study on a prospective, sequential basis. A full clinical history, physical examination and 12 lead electrocardiograms were done. Standardized clinical data were collected for each patient like approximate duration of symptoms, risk factors for coronary artery disease and previous myocardial revascularization. Blood sample was collected as convenient sampling technique method before therapy was instituted and serum albumin, hs-CRP, Cardiac troponin I, CK-MB/NAC, lipid profile, urea, creatinine, and bilirubin level was measured. Blood was also taken 6 hours later for a second measurement of troponin I and CK-MB/NAC. Pregnant women, patients with evidence of inflammatory or neoplastic conditions or liver or renal disorder were not included in the study.

Final diagnosis of ACS was assigned to one of the following categories:

Unstable angina (UA): Angina pectoris or equivalent ischemic discomfort with at least one of three features: (1) occuing at rest (or with minimal exertion) usually lasting >10 minutes, (2) it was severe and of new onset (i.e. within the prior 4 to 6 weeks) and or (3) occurring with a crescendo pattern (i.e. distinctly more severe, prolonged or frequent than previously).

Non ST-elevation myocardial infarction (NSTEMI): Clinical features of unstable angina with presence of one or more positive cardiac biochemical marker of necrosis without new ST-segment elevation on ECG.

ST-elevation myocardial infarction (STEMI): New or presumed new ST-segment elevation ≥1mm in limb leads or ≥2mm in two or more chest leads or new left bundle branch block (LBBB) and ≥1 positive cardiac biochemical marker of necrosis.

Hs-CRP: The hs-CRP is estimated on the basis of principle of a solid phase enzyme linked immunosorbent assay. The kit was provided by CALBIOTECH INC. high sensitivity CRP ELISA, Catalog No. CR016 CM. The hs-CRP ELISA is intended for the quantitative determination of CRP.

Troponin I: It was measured by rapid chromatographic immunoassay for the qualitative detection of human cardiac troponin I in serum.

Albumin: Albumin concentration was determined by modified Biuret and Dumas method in which serum albumin binds with the dye bromocresol green at pH 3.68 to form a green colored complex the absorbance of which is measured at 600 nm. Levels outside 3.5 to 5 gm/dl were considered abnormal.

Leucocyte count: Total leucocyte count and differential leucocyte count was calculated by coulter counter (automated cell counter). Normal values were 4 to11,000/dl.

Patients were classified as NICP when a documented non- cardiac cause of chest pain will be identified and/or when all of the following criteria were met: negative cardiac enzymes on serial sampling, absence of ECG changes and absence of symptoms suggestive unstable angina. All patients received routine institutional care and treatment as per diagnosis.

Follow up at 30 days

Adverse events in 30 days were recorded by reviewing patients clinical notes during follow up in medicine OPD and by telephone interviews if it was possible. Adverse events were defined as any of the following: 1. Readmission for unstable angina or acute myocardial infarction 2. Death from cardiac cause 3. Need for myocardial revascularization with CABG or PCTA as decided if there was a) recurrent angina at rest/low level activity despite treatment b) recurrent angina/ischemia with CHF symptoms c) new ST-segment depression, persistent deep T-wave inversion(≥0.3 mv) d) prior coronary revascularization(PCI within 6 months or CABG) e) EF<0.40 f) Sustained ventricular tachycardia. 4. Composite of any of above.

Statistical analysis

The data collected was entered in excel software and analyzed in SPSS PC±11.5. Means and standard deviation were calculated for numerical variables. Comparisons of continuous variables were analyzed using Mann-Whitney U test. Discrete variables were compared using a chi-square analysis. P value ≤0.05 was considered significant.

Those variables with P-value <20% were entered to do logistic regression to evaluate independent predictors of ACS on admission in patients with central chest pain and predictors of ACS on admission in patients with central chest pain and predictors of short-term outcome.

Results

Clinical characteristics and risk factors of the 149 patients entered in the study are presented in Tables1 and 2. One hundred and nineteen patients had a final diagnosis of ACS (80%) and 30 (20%) patients were discharged with a final diagnosis of non-ischemic chest pain (NICP). Of the patients with a diagnosis of ACS, 33 had unstable angina, 42 had non-ST elevation myocardial infarction, and 44 had ST-elevation myocardial infarction.

Table 1: Clinical parameters and risk factors

Variables	Chest pain		P-value
	NICP(n=30)	ACS(n=119)	
Sex (male)	15(50%)	73(61%)	0.259
Smoker	18(60%)	74(62%)	0.825
Fam. Hist. of CAD	7(23%)	21(17%)	0.476
Hypertension	17(56%)	72(60%)	0.701
Diabetes	4(13%)	29(24%)	0.145
Documented CAD	4(13%)	14(11%)	0.511
Abnormal ECG	3(10%)	87(73%)	<0.001

Table 2: Biochemical variables with mean values

Variables	Chest pain		P-value
	NICP	ACS	
Age (years)	44.83±11.63	61.58±11.95	<0.001
hs-CRP	2.39±1.55	14.04±6.17	<0.001
TLC	5596.67±1370.5	11576.7±3083.13	<0.001
Neutrophil %	64.53±6.93	69.90±5.79	<0.001
Lymphocyte%	24.63±2.20	25.03±3.61	0.563
Albumin (gm/dl)	3.94±0.3	3.88±0.41	0.448
Total cholesterol	171.7±30.08	171.48±32.29	0.389
HDL C	42.1±1.84	40.38±4.02	0.004
TG	130.53±43.19	137.82±37.56	0.156
LDL C	105.5±28.73	106.14±26.59	0.263

*NICS=Non specific chest pain, ACS= Acute Coronary syndrome

Predictors of ACS

Table 1 and 2 show baseline characteristics and values of serum markers in all patients in the study who were subdivided according to final diagnosis. Patients with ACS were older than patients with non- ischemic chest pain (P<0.001). The admission electrocardiogram was abnormal in a higher percentage of patients with a final diagnosis of ACS than non-ischemic chest pain (10% vs.73%, p<0.001). ACS patients also had higher level of hs-CRP (p<0.001), TLC (p<0.001), neutrophil percentage (p<0.001) and lower level HDL cholesterol (p=0.004). Variables with p value <0.2 in univariate analysis were selected for logistic regression and the independent association of different variables was calculated in multivariate analysis. Age, abnormal ECG, hs-CRP, and TLC were statistically significant and the best combination among them was of hs-CRP and TLC.

Table 3: Logistic regression of variables with p value of clinical and biochemical parameters

Logistic regression	P-value
Age	<0.001
ECG	0.03
hs-CRP	<0.001
TLC	<0.001
Neutrophil %	1.000
HDL	0.997
TG	0.916

Predictors of short term outcome

Out of 119 patients of ACS, 17(14%) patients lost to follow up. In 102 patients during the 30 days follow up from admission 26(25%) had adverse cardiovascular events. Out of 26 patients, 15 patients died, 1 of them were readmitted with chest pain suggestive of ACS and 10 patients were referred to higher center for myocardial revascularization. Diabetes, positive troponin I, abnormal ECG were predictors of adverse events in univariate analysis. Patients with adverse events had also significantly high hs-CRP, TLC, neutrophil count and low albumin level.

Tables 4 and 5 shows characteristics of patients with and those without adverse cardiovascular events.

Table 4

Variables	No Events	Events	p-value
Sex(male)	48(63%)	15(57%)	0.646
Smoker	40(52%	15(57%)	0.655
Fam. Hist. of CAD	11(14%)	8(30%)	0.28
Hypertension	49(64%)	14(53.8%)	0.35
Diabetes	10(13%)	18(69%)	<0.001
Documented CAD	9(11.8%)	5(19%)	0.34
Positive troponin I	24(31%)	20(76.9%)	<0.001
Abnormal ECG	51(67%)	26(100%)	<0.001

Table 5

Variables	No Events	Events	P-value
Age (years)	59.54±11.35	66.85±12.17	0.006
hs-CRP	7.87±2.14	19.95±6.46	<0.001
TLC	10278±1503	15630±3522	<0.001
Neutrophil %	71±9	75±8	0.023
Lymphocyte%	22±9	19±7	0.067
Albumin (gm/dl)	3.9±0.39	3.45±0.31	<0.001
Total cholesterol	169±31	175±28	0.406
HDL C	40.32±3.95	40±3.94	0.726
TG	133±34	144±44	0.229
LDL C	106±25	109±27	0.622

Variables with p value <0.2 in univariate analysis were selected for logistic regression (Table 6) and the independent association of different variables with adverse cardiovascular events was found. All of the variables included were statistically significant.

Table 6: Logistic regression of variables with p value of those with and without adverse cardiac events

Logistic regression	p-value
Age	<0.003
Diabetes	<0.001
Abnormal ECG	<0.001
Hs-CRP	<0.001
TLC	<0.001
Neutrophil percentage	<0.001
Lymphocyte percentage	0.032
Serum albumin	<0.001
Troponin I	<0.001

Discussion

In recent years evidence has accumulated that inflammation plays a major role in the pathogenesis of cardiovascular disease and that inflammatory markers constitute useful indicators of cardiovascular risk.[8] The present study shows that in patients attending emergency department with central chest pain, among the inflammatory markers, hsCRP and leucocyte count are the independent predictors of ACS. Other factors that predict are age and abnormal ECG.

Similarly in patients with ACS hsCRP, total leucocyte count, neutrophil count and lymphocyte count, serum albumin, age and abnormal ECG are independent predictors of clinical outcome. Previous studies have shown that CRP is increased significantly in all ACS patients as compared to patients with non ischemic chest pain.[9,10,11] This study also show significantly higher hsCRP in patients with ACS than in patients with non ischemic chest pain suggesting as one of the useful marker of ACS.

Several studies have demonstrated that high hsCRP measured at either presentation or discharge in patients with ACS has good prognostic value.[12,13] This study has shown that patients of ACS with adverse event at 30 days has significantly increased level of hsCRP.

Previous studies have shown that leucocytosis was an independent predictor of acute myocardial infarction.[14,15] Various other studies have shown that patients presenting with ACS and an elevated total leucocyte count have a higher short term risk of adverse event.[16,17] This study has shown that patients with ACS has significantly increased total leucocyte count than patients with non ischemic chest pain and increased total leucocyte count was also associated with adverse event at 30 days.

In a study done in CAD patients, five year survival was significantly better for patients who had a normal as compared with a low lymphocyte count.[18] In this study increased neutrophil count and decreased lymphocyte count were also associated with adverse events.

It is unclear whether leucocytosis is simply a marker for adverse events in patients with ACS or a direct or indirect causative agent. Our data suggest that leucocyte count is a marker of heightened inflammatory state.

Lower level of serum albumin was found in patients of ACS compared to patients with non ischemic chest pain though it was not significant but patients with adverse events had significantly lower serum albumin. Albumin concentrations have been shown to fall during chronic inflammation and albumin levels are

inversely correlated with CAD risk factors.[6] whether a low level serum albumin is a marker of subclinical disease, reflecting ongoing inflammation or a pathogenic mechanism is speculative. It is possible that albumin may reflect an underlying chronic inflammatory process and may be a marker of long term risk.

Our study has several limitations. We have tried to rule out other inflammatory conditions as the cause of rise of inflammatory markers but because of limited resources and laboratory facilities, we may have not been able to rule out some inflammatory causes. The study was relatively small and the prevalence of ACS in our study population was high possibly indicating the fact that patients were highly selected. We only evaluated markers that can be measured routinely at presentation at presentation, although other markers of inflammation such as fibrinogen, IL-6 and VCAM-1 have been described as predictors of clinical events.

Conclusion

In patients attending the emergency department with chest pain suggestive of ACS, leucocyte count and hs-CRP are the independent marker of risk. High hs-CRP, TLC, neutrophil count as well as low serum albumin and lymphocyte count are independent predictors of adverse clinical outcome

References

1. Antman EM, Selwyn AP, Braunwald E, Loscalzo J. Ischemic Heart Disease. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL et al. editors. Harrison's Principles of Internal Medicine. 16th ed. USA: McGraw-Hill publisher; 2005. P. 1933-44.
2. Reddy KS. Emerging epidemic of cardiovascular disease in developing countries. Circulation 1998; 97:596-601.
3. Reddy KS. Cardiovascular diseases in non-western countries. N Engl J Med 2004; 350:2438-2440.
4. Fuster V. Mechanisms leading to myocardial infarction: insights from studies of vascular biology. Circulation 1994; 90:2126-2146.
5. Ridker PM. Evaluating novel cardiovascular risk factors: can we better predict heart attacks? Ann Intern Med 1999; 130
6. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C reactive protein, albumin, or leukocyte count with coronary heart disease: meta analyses of prospective studies. JAMA 1998; 279:1477–1482.
7. Ridker PM, Cushman M, Stampfer MJ, tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336:973–979.
8. Pepys MB, Berger A. The renaissance of C reactive protein. BMJ 2001; 322:4–5.
9. Sreekanth K Sivaraman1, Geevar Zachariah, Pandapulakkil T Annamalai1. Evaluation of C-Reactive Protein and other Inflammatory Markers in Acute Coronary Syndromes. Kuwait Medical Journal 2004, 36 (1): 35-37.
10. Burta O, Burta OL, Roatis RS, Bradea RC, Minnatullah S. The Diagnostic Application of The Biomarker C-reactive Protien in Patients with Acute Myocardial Infarction. Eur J of Internal Med 19S (2008), S1-S59.
11. GP Parale, SR Wani, SS Rudrakshi, MP Ghatole, PM Kulkarni. Assessing C Reactive Protien as a Marker for Acute Coronary Syndrome in Patients Getting Admitted with Chest Pain. JAPI, Vol. 49, January 2001.
12. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994; 331:417–424.
13. Morrow DA, Rifai N, Antman EM,Weiner DL, McCabe CH, Cannon CP,et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in

myocardial infarction. J Am Coll Cardiol 1998; 31:1460–1465.

14. Friedman GD, Klatsky AL, Siegelaub AB. The leucocyte count as a predictor of myocardial infarction. N Eng J Med 1974; 290:1275-1278.

15. Green SM, Vowels J, Waterman B, Rothrock SG,Kuniyoshi G. Leukocytosis: a new look at an old marker for acute myocardial infarction. Acad Emerg Med 1996; 3:1034-1041.

16. Burr ML, Holliday RM, Fehily AM, Whitehead PJ. Haematological prognostic indices after myocardial infarction: evidence from the diet and reinfarction trial (DART). Eur Heart J 1992; 13:166–170.

17. FurmanMI, Gore JM, Anderson FA, Budaj A, Goodman SG, Avezum A, et al. Elevated leukocyte count and adverse hospital events in patients with acute coronary syndromes: findings from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2004; 147:42–48.

18. Ommen SR, Gibbons RJ, Hodge DO, Thompson SP. Uselfulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. Am J Cardiol 1997; 79:812-814.