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C-REACTIVE PROTEIN, LEUKOCYTE COUNT AND MYELOPEROXIDASE AS PREDICTORS OF ADVERSE CARDIAC EVENTS IN ACUTE CORONARY SYNDROME PATIENTS

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All the authors contributed significantly to the research that resulted in the submitted manuscript.

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ABSTRACT

Objective: The aim of the present study was to evaluate the role of C-reactive protein (CRP), leukocyte count and myeloperoxidase (MPO) in predicting adverse outcomes in acute coronary syndrome patients.

Methodology: Ninety consecutive patients with acute coronary syndrome (ACS) were enrolled from Coronary Care Unit of Shaikh Zayed Hospital, Lahore from January 2012 to April 2013. Baseline leukocyte count was determined by Abacus cell counter while CRP and MPO levels were determined by using commercially available enzyme immunoassays. Mortality and adverse cardiac events were recorded for a follow up period of 6 months.

Results: Out of ninety patients 65 (72.2%) were males. Mean age of patients was 56.25±13.01 years (male patients 55.43±14.02 while female patients 58.4±9.88). Number of adverse events was highest (18.6%) in CRP > median category, followed by leukocyte count > median (17.9%) and MPO > median category (17.1%), respectively. Adverse event rate was found to be significantly higher ($p = 0.043$) in CRP > median category as compared to CRP < median category. Adverse event rate was also higher ($p = 0.08$) (clinically significant) in > median category of leukocyte count but in case of MPO level it did not reach level of statistical or clinical significance ($p = 0.12$).

Conclusion: CRP is a predictor of adverse outcome in acute coronary syndrome patients and may serve as a marker in prognosis of ACS. Further studies with large sample size are required for confirmation of predictive role of leukocyte count.

Key Words: C-Reactive Protein, Leukocyte Count, Myeloperoxidase, Acute Coronary Syndrome, Adverse Cardiac Events

INTRODUCTION

The onset of coronary artery disease (CAD) is on rise in prevalence and is anticipated to be the major cause of death by the year 2020.[1] One of the clinical manifestations of CAD is Acute coronary syndrome (ACS), it is an unstable condition and is among the cardiovascular diseases that present a health hazard. Inflammation contributes to development and progression of atherosclerosis and hence ACS.[2] Atherosclerosis is a condition that develops when plaque (a substance mainly composed of fats) deposits inside the arterial walls of coronary arteries. Different epidemiological studies have revealed that there is a strong and constant association between clinical manifestations of atherosclerosis and systemic markers of inflammation like white blood cell count, C-reactive protein, B-type natriuretic peptide, interlukin-6 and myeloperoxidase (MPO).[3] These biomarkers have been supposed to have prognostic role in predicting adverse events in ACS patients.

CRP plays a direct inflammatory role in development of atherosclerosis by a number of mechanisms. CRP upsurge interlukin 8 production in vitro in monocytes, inhibit nitric oxide synthase present in endothelial cells, alter the defences mediated by antioxidants and promote apoptosis in endothelial progenitor cells.[4] MPO has also been revealed to be a probable marker for determining atherosclerosis.[5] MPO is dumped in azurophilic granules of neutrophils and macrophages. It is implicated in oxidation of lipids confined within LDL cholesterol.[6] In addition MPO utilizes endothelially derived nitrous oxide, thereby decreasing its bioavailability and weakening its vasodilating and anti-inflammatory functions in arteries.[7]

Elevated leukocyte count generally characterizes infection and inflammation and contributes in atherosclerosis development.[8] There exists a strong, constant and biologically logical association between elevated leukocyte count and CAD.[9] Acute MI triggers a systemic response to a necrotic insult characterized by leukocytosis and acute phase protein synthesis.[10] Elevated leukocyte count, take part in the repairing process that occur, to substitute the necrotic tissue for collagen.[8] Recent research has demonstrated that leukocytes un-stabilize coronary artery plaque at the onset of ACS therefore elevated leukocytes may serve as a predictor of cardiac related deaths and adverse cardiac outcomes, in ACS patients and in normal healthy population. The objective of the present study was to determine the role of CRP, Leukocyte count and MPO in predicting adverse events in ACS patients.

METHODOLOGY

This prospective cohort study was carried out at Coronary Care Unit of Department of Cardiology and National Health Research Complex, Shaikh Zayed Hospital, Lahore from January 2012 to April 2013. A total of 90 consecutive patients of ACS were enrolled in the study. Study protocol was approved by Ethical Review Board of Shaikh Zayed Post Graduate Medical Institute, Lahore and written informed consent was obtained from ACS patients for participation in the study. The diagnostic criteria for ACS was that of American College of Cardiology and European Society of Cardiology and required the presence of at least 2 of the following:[11]

1. Typical chest pain 2. ECG alterations (For STEMI, new or presumed new ST segment elevation at the J point in two or more adjacent leads with the cut-off points 0. 2 mV in leads V1 through V3 and 0.1 mV in other leads. For NSTEMI, ST segment depression or T wave abnormalities in two or more adjacent leads). 3. Biochemical changes (Concentration of troponin I greater than 99th percentile of the values for a reference normal control group, on at least one instance during the first 24 hours of the indexed clinical event). Criteria for Unstable Angina (UA) was, typical chest pain and ECG alterations such as ST segment depression or T wave inversion in $\geqslant$ 2 leads and absence of biochemical alterations.

Inclusion criteria for the study was, ACS patients of both genders in the age group of 30-75 years. Patients with recent surgery, thyroid disorders, diabetes, renal disorders, chronic liver diseases, rheumatic diseases and cancer were excluded from the study. For enrolled patients variables like age, gender, BMI, ECG changes, Troponin I level (where required), smoking history, WBC count, CRP and MPO level were recorded on prescribed study proforma. White blood cell count was determined by Abacus automated hematology analyzer, at the initial blood test at study entry while for measurement of MPO and CRP levels, blood samples were collected within 18 ± 6 hours of hospitalization. Venous blood samples (5 cc) were drawn under aseptic conditions and collected in serum vacutainers, samples were centrifuged at 2500 rpm for 20 minutes within 1 hour of collection. After centrifugation, separated serum was stored in 2 aliquots at -40ºC until analysis. Levels of MPO in serum samples of ACS patients were determined by using Quantikine Human MPO Immunoassay from R&D Systems USA and levels of CRP were determined by using high sensitivity hs-CRP kit from Kalon Biological limited UK, according to instructions of the manufacturer.

Coronary angiography was performed through radial or femoral approach using nonionic contrast. Coronary arteries were reported according to the 29 segment model of coronary arteries. Coronary stenosis was assessed by two expert angiographers. Their consensus was reported as final. In case of difference of opinion, coronary stenosis was measured using software (Toshiba infinix/vc). Single vessel CAD was defined as > 50% stenosis by subjective coronary

examination in one of the major coronary arteries i.e. right coronary artery (RCA), left anterior descending artery (LAD) or left circumflex (LCx). Similar stenosis in a large (>2mm) diagonal, marginal branch or ramus intermedius was also considered as single vessel CAD. Double vessel CAD was defined as > 50% stenosis in two major coronary arteries. Severe triple vessel CAD was defined as > 50% stenosis in the left main stem or ⩾3 vessels CAD.

Follow up of study participants was done telephonically and through out-patient department at the end of six months period. The definite adverse events were death from cardiac cause, non-fatal myocardial infarction (MI) and recurrent unstable angina. Patients were contacted telephonically and those who reported re-hospitalization during follow up period were requested to visit cardiology OPD for clinical evaluation. During follow up visit, data about cause of re-hospitalization and adverse events (MI and Unstable angina) was attained from patient's clinical history file. Attendants of patients (who died during follow up period) were requested to provide hospital documentation for establishing cause of death.

Data was entered and analyzed using SPSS version 16.0. Continuous variables are expressed as mean and minimum and maximum values. Mann Whitney U test was applied to check the differences in level of biomarkers, age and BMI according to gender, smoking status and diagnosis (STEMI/NSTE-ACS) of patients. Fischer exact test was applied to evaluate the association between adverse events and level of biomarkers (CRP, leukocyte count and MPO). Statistically significant difference was considered at $p < 0.05$ in all cases.

RESULTS

During follow up period, there were 6 deaths (all of which were cardiac related), 7 patients were re-hospitalized (2 MI, 1 NSTEMI, 1 UA, 1 high BP and 2 non-cardiac reasons) and 5 patients were lost for follow up. Clinical data and lab tests were available for all 90 patients while information about adverse events was available for 85 patients. Baseline characteristics are shown in Table 1. Out of ninety, 65

Table 1: Demographic and Clinical Characteristics of Acute Coronary Syndrome Patients

S. No.	Variables	No. of patients	Percentage
1	**Gender**		
	Male	65	72.2
	female	25	27.8
2	**Age**		
	⩽ 35	5	5.6
	36-50	31	34.4
	51-65	35	38.9
	⩾66	19	21.1
3	**Diagnosis**		
	STEMI	54	60
	NSTE-ACS	36	40
4	**BMI**		
	Normal (18.5-24.9)	39	43.3
	Overweight (25-29.9)	32	35.6
	Obese (⩾30)	19	21.1
5	**Current smoker**		
	Yes	37	41.1
	No	53	58.9
6	**Angiographic severity** (n = 54)		
	Normal coronary arteries	6	11.1
	SVD	17	31.5
	DVD	12	22.2
	TVD	19	35.2
7	**Medication at time of enrollment**		
	Aspirin	80	88.88
	ß-blockers	18	20.0
	Nitrates	68	75.55
	ACEI	29	32.22
	HMG CO-A reductase inhibitors	76	84.44
	Streptokinase	40	44.44

(72.2%) patients were male and 25 (27.8%) were females. Thirty seven (41.1%) patients were current smokers and 5 (5.55%) were past smokers. Fifty four (60%) patients were diagnosed to have STEMI and 36 (40%) patients had NSTE-ACS. Angiography details were available for 54 patients, out of which 6 had normal coronary arteries (Table 1). Among patients with STEMI, twenty nine (53.7%) were current smokers and in NSTE-ACS group 8 (22.2%) were current smokers.

Table 2, 3 and 4 represents age, BMI and level of biomarkers according to gender, smoking status and diagnosis, respectively. In case of gender, BMI of female patients was

Table 2: Age, BMI, and Level of Biomarkers According to Gender

Parameter	Male (n = 65)	Female (n = 25)	P-value
Age (years)	55.43 (30-75)	58.4 (40-73)	0.269
BMI (Kg/m²)	25.24 (18.76-38.9)	27.82 (20.4-39.2)	0.018
Leukocyte count (X10⁹/L)	10.99 (3.86-19.1)	9.48 (4.49-15.43)	0.056
CRP level (mg/L)	35.22 (0.25-91)	19.96 (1.99-95)	0.124
MPO level (ng/ml)	2636 (456.3->5000)	1749 (267->5000)	0.047

significantly higher ($p = 0.018$) as compared to male patients while MPO level was found to be significantly elevated ($p = 0.047$) in male patients. Smokers were younger ($p = 0.030$) as compared to non-smokers. MPO level (0.022) and WBC count ($p = 0.049$) of smokers was found to be significantly elevated as compared to non-smokers. Leukocyte count was also found to be significantly elevated ($p = 0.001$) in STEMI patients as compared to NSTE-ACS patients (Table 4).

Table 5, represents association of WBC count, CRP level and

Table 3: Age, BMI, and Level of Biomarkers According to Smoking Status

Parameter	Smokers (n = 37)	Non-smokers (n = 53)	P-value
Age (years)	52.5 (30-63)	58.8 (37-75)	0.030
BMI (Kg/m²)	24.77 (18.76-31.2)	26.78 (19.8-39.2)	0.09
Leukocyte count (X10⁹/L)	11.31 (3.86-18.76)	10.06 (4.51-19.1)	0.049
CRP level (mg/L)	36.74 (0.3-95)	26.96 (0.25-91)	0.758
MPO level (ng/ml)	3083 (266.8->5000)	1905 (456->5000)	0.022

Table 4: Age, BMI, and Level of Biomarkers According to Diagnosis

Parameter	STEMI (n = 54)	NSTE-ACS (n = 36)	P-value
Age (years)	54.7 (30-71)	58.5 (30-75)	0.173
BMI (Kg/m²)	25.84 (18.76-39.2)	26.12 (20.1-38.9)	0.879
Leukocyte count (X10⁹/L)	11.55 (4.99-19.1)	9.107 (3.86-16.4)	0.001
CRP level (mg/L)	33.7 (0.28-95)	26.8 (0.25-93)	0.211
MPO level (ng/ml)	2494 (456.3->5000)	2233 (266.8->5000)	0.169

MPO level with adverse events. Number of adverse events was highest in CRP > median (sample size was small therefore, median values of CRP, WBC and MPO of enrolled patients were calculated instead of tertiles or quartiles) (median values were calculated by entering CRP, WBC and MPO levels of all 90 study participants in SPSS software) category, followed by WBC > median and MPO > median category, respectively. Adverse event rate was significantly higher ($p = 0.043$) in CRP > median category as compared to CRP < median category. Adverse event rate was also higher ($p = 0.08$) (clinically significant) in > median category of WBC count but in case of MPO level, adverse event rate did not reach level of either statistical or clinical significance ($p = 0.12$).

Table 6, shows levels of biomarkers in ACS patients with single vessel disease, double vessel disease and triple vessel disease. Significant difference was not found between levels of CRP, leukocyte count and MPO as per angiographic findings, may be due to small number of patients in each group.

DISCUSSION

Understanding the role of biomarkers for diagnosis, management and prognosis of ACS patients is rapidly growing. Inflammation is known to have a key role in progression of disease and development of complications in the setting of acute coronary syndrome. A number of inflammatory pathways are involved in coronary plaque erosion and rupture.[12] Biomarkers of inflammation highlight a different aspect of ACS pathophysiology and therefore, may contribute in providing distinctive information to the clinician, in addition to that provided by markers of myocyte damage.[12] Current study evaluated the prognostic value of CRP (which is a proven marker of general and systemic inflammation), WBC count (which indicates infection and inflammation) and MPO (which specifies neutrophill activation) in predicting adverse outcome in acute coronary syndrome patients.

Table 5: Association of CRP Level, Leukocyte Count and MPO Level with Adverse Events in Acute Coronary Syndrome Patients

Biomarker by Median	No. of Patients (n)	Adverse Events (n)	Event rate %	P-value
CRP (median=11.23mg/L)				
> median	43	8	18.6	0.043
< median	42	2	4.8	
WBC count (median=10.56X10^9/L)				
> median	39	7	17.9	0.08
< median	46	3	6.5	
MPO (median=1541ng/ml)				
> median	41	7	17.1	0.12
< median	44	3	6.8	

Among study participants, 37 were current smokers; 35 (94.6%) males and 2 (5.4%) females. Smoking habit was more prevalent in STEMI patients as compared to NSTE-ACS patients and smokers were younger as compared to non-smokers, which suggest early onset of ACS in smokers. Smoking is the most common risk factor for heart diseases and is associated with MI at younger age.[13,14] A study showed high prevalence of smoking in younger (< 45 years) patients with percutaneous coronary intervention proven (PCI) coronary heart disease, compared to patients over 60 years (58.7 vs. 43%).[15] These findings emphasize the need of launching community based smoking prevention programs for young citizens. WBC count ($p = 0.049$) and MPO level ($p=0.022$) of smokers was found to be significantly elevated as compared to non-smokers, which is consistent with the study done by Ferrante et al.[16] MPO level was found to be significantly higher in male patients, this may be due to increased prevalence of smoking habit in male patients. A study done by Apple et al, also reported that ACS patients with MPO values > 250 μg/L were more often male compared to those having MPO level < 250 μg/L.[17]

In the current study, 11.1% ACS patients had normal coronary arteries, on cardiac catheterisation. ACS is usually associated with obstructive coronary arteries but is not always related with angiographic lesions in coronary arteries. Association of myocardial infarction with normal coronary arteries is well-known, differential diagnosis is therefore important for proper treatment of ACS patients. The overall prevalence rate of ACS with normal coronary arteries is considered to be low, varying from 1% to 12% .[18-20] A study showed that, in ACS patients with no culprit lesion, STEMI (2/108 patients) and NSTEMI (28/196) are less common as compared to Unstable angina (108/184).[21] Some probable causes of myocardial infarction with normal coronary arteries are, small vessel disease e.g. various collagen vascular diseases, hypercoagulable states, coronary artery embolism, myocarditis, tako-tsubo cardiomyopathy and coronary artery spasm.[22-26] Coronary spasm is a major differential finding in Asian patients with ACS and normal coronary arteries.[21] Wang et al, found a high frequency (74%) of coronary spasm, in a Taiwanese population, especially in patients with troponin I positive ACS and normal coronary arteries.[26]

Results of the present study are comparable to other studies demonstrating that CRP is an independent predictor of adverse events in ACS patients.[17,27-29] Event rate for CRP > median category in current study was 18.2% whereas Apple et al. reported event rate of 15.8%.[17] CRP stimulates production of tissue factor by mononuclear cells, the main initiator of blood coagulation.[30] In addition, CRP together with phospholipase A2 may cause activation of complement system and assists phagocytosis of damaged cells by activated neutrophils.[31] Therefore, elevated CRP levels signify ongoing activation of inflammation that characterizes unstable coronary artery disease and indeed may be one of the causes of instability.

Adverse event rate in WBC count > median category approached statistical significance as compared to WBC < median category which is consistent with the results of other studies.[8,10,32,33] Leukocytes contribute to progression of coronary artery disease by mechanisms like; endothelial cell injury caused by proteolytic and oxidative damage, vessel plugging, affecting the blood flow through the cardiac microvasculature, decreased perfusion, hyper-coagulable state with decreased epicardial patency and increased ischemic burden, blocking of micro vessels (by abnormal

Table 6: Level of Biomarkers in ACS Patients with SVD, DVD and TVD

Angio-graphy Details	Level of Biomarkers (mean)					
	CRP (mg/L)	P-value	WBCs(X 10^9/L)	P-value	MPO (ng/ml)	P-value
SVD (n=17)	30.61	0.91	10.07	0.71	1903	0.277
DVD (n=12)	30.88		11.7		1274	
DVD (n=12)	30.88	0.41	11.7	0.74	1274	0.48
TVD (n=19)	26.01		10.18		2361	
SVD (n=17)	30.61	0.54	10.07	0.53	1903	0.75
TVD (n=19)	26.01		10.18		2361	

SVD = Single Vessel Disease, DVD = Double Vessel Disease, TVD = Triple Vessel Disease

leukocyte aggregation) and increased expression of monocytes tissue factors.[34,35]

In case of MPO, results of present study are in contrast with most of the studies which showed that high level of MPO is an independent predictor of adverse events in ACS patients.[36-39] However, our results are in consistence with the study done by Borges et al.[40] The reason for this lack of association between MPO levels and adverse events may be that MPO levels were determined in serum samples. Shih et al, reported that MPO levels are consistently elevated in serum samples as compared to samples collected in EDTA or Citrate tubes, because of leakage of MPO from neutrophils.[41]

Limitations: Some of the limitations of the study are, first, small sample size which decreases statistical power and generalizability. Second, only a single measurement of biomarkers (WBC, CRP, and MPO) was done at the time of admission. Serial and temporal measurement of biomarkers may be more beneficial in understanding their potential prognostic role and in devising therapeutic strategies for management of ACS patients. Third, MPO levels were determined in serum samples whereas, EDTA and Sodium citrate samples are reported to be more appropriate for MPO quantification.

CONCLUSION

CRP level is a predictor of adverse cardiac outcome in ACS patients. WBC count showed a trend towards predicting adverse events in ACS patients. Further studies with large sample size are required for confirmation of these results.

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