Multiple Inflammatory Prognostic Factors in Acute Coronary Syndromes: A Prospective Inception Cohort Study

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Abstract- Inflammatory basis in pathopoiesis of coronary artery disease (CAD) have been demonstrated in recent decades. Elevated C-Reactive Protein (CRP) and leukocytosis were associated with an elevated risk for acute coronary syndrome (ACS). To evaluate the relationship between quantitative CRP and cardiac troponin I in conjunction with white blood cell (WBC) count and 30 days outcomes and treatment planning in patients with ACS. A concurrent inception cohort study was designed involving 200 patients as exposed and 200 patients as non exposed groups. We evaluated the relationship between baseline CRP and WBC count and cardiac troponin I , other risk factors and biomarkers, angiographic and other para-clinical tests and clinical outcomes with ACS. Higher CRP and WBC count were associated with additional coronary care unite (CCU) admission days (P = 0.002), hospitalization days (P = 0.007), arrhythmia type (P = 0.007), receiving streptokinase (P = 0.001), angiographic findings (P = 0.003), final myocardial infarction versus unstable angina (P = 0.001), date of complication (P = 0.001) and the date of cardiopulmonary resuscitation (if incident) (P = 0.015). In a multivariate Cox proportional hazard model high CRP and WBC count remained strong predictor of mortality (P = 0.028), angiography findings (three Vessel disease (3VD) and left main (LM) disease) (P = 0.001), and readmission in CCU (P = 0.002). A cardiac troponin I above 0.1 µg/lit was considered elevated. Elevated troponin level, demonstrated a significant relationship with MI incidence between two groups (P= 0.001) (89% in troponin positive group versus 11% in troponin less than 0.1 µg/lit). Inflammatory markers including, CRP and WBC count can be used to predict mortality, readmission, 3VD and LM disease in patients with ACS. In a Cox Proportional Hazard Model cardiac troponin above 0.1 µg/lit was significant predictors of MI (P = 0.003) and CPR (P = 0.044) at 30 days follow up period.

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Key words: Coronary artery disease; acute coronary syndrome; cohort studies

Introduction

The role of inflammation in the development and progression of atherosclerosis (AS) has been clarified. Circulatory indicators of inflammation are correlated with an increased risk of cardiovascular events in healthy individuals (2), patients with stable and unstable coronary artery disease (CAD) (1). Elevated CRP in unstable angina pectoris at the time of admission was been a strong predictor of mortality. Elevation of inflammatory factors have an essential role in AS and acute coronary syndrome (AS) .These markers include elevated WBC counts and CRP level (3). Pathopoiesis of the local and systemic inflammation in ACS is promoting plaque fissuring or erosion (4). Elevated WBC count is a predictive factor for long term survival in patients with myocardial infarction (5), aspirin and angiotensin-converting enzyme inhibitors modulated the inflammation in acute myocardial infarction (AMI) (6). Elevated WBC count on admission in MI patients have accompanied with higher 30 days case fatality rate and adverse angiographic findings (7). To investigate the impact of elevated CRP level, cardiac troponin I and WBC count on prediction of the end points in ACS we

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designed and performed a concurrent prospective inception cohort study in patients with ACS.

Patients and Methods

Study population

200 patients with evidence of ACS and quantitative CRP > 10 mg/DL and WBC count > 10000 cell/DL defined as exposed and 200 of them with evidence of ACS and quantitative CRP less than 10 mg and WBC count lower than 10000 cell were defined as non exposed group.

CRP and WBC count and other laboratory data

Blood samples were obtained at base line for CRP, WBC count, cardiac troponin, platelet count, lipid profiles, and blood sugar.

Clinical end points

After completion the follow up period (30 days) these pre-specified clinical end points were detected: Death, non fatal MI, re-hospitalization for ACS, hospitalization days, arrhythmia, and cardiac block.

Angiographic, Echo cardio graphic and electro cardio graphic (ECG) analysis

Cardiologists interpreted the findings of angiography ,echocardiography and ECG. To eliminate possible information bias, evaluation of the relationship between CRP and WBC count and troponin and pre-specified clinical outcomes were all blinded.

Other risk factors

We collected the data of all other risk factors such:

Age, gender, diabetes mellitus, hypertension, dyslipidemia, familial history of CAD, cigarette smoking (active, passive and ex-smokers) and history of other cardiac diseases.

The protocol was approved by the institutional review board. Written informed consent was obtained from all subjects.

Statistical analysis

Continuous variables were reported as mean, standard deviations. The end points processed in tables.

Chi-square test, independent sample T-test and relative risks were used for univariate analysis. Mantel-Hanszel was used for bivariate analysis. Multivariate-adjusted associations between CRP, WBC counts and clinical 30 days end points were evaluated using Cox proportional hazard models.

Results

Baseline characteristics

Baseline CRP, WBC counts, other known cardiac risk factors, cardiac troponin (4 times) and platelet counts are demonstrated in table 1.

Baseline characteristics were gathered in 203 ACS patients with elevated CRP level and WBC count and 200 ACS patients without the above exposures. CRP level, WBC count, platelet count, cardiac troponin measured in four consecutive times, blood sugar and triglyceride demonstrated a significant difference in two groups.

Relationship of CRP and WBC count to clinical outcomes

For the 30 days follow up period, mortality, incidence of recurrent MI, arrhythmia, cardiac block, readmission, CPR, CCU admission days and days of hospital stay for two groups were compared (in univariate model).

- Medication after enrollment of patients demonstrated in table 3.

Relationship of CRP level and WBC count to angiographic findings

Among patients in the exposed group (elevated CRP and high WBC count) the angiographic finding were: single vessel disease (SVD) in 14.3%, two vessel disease (2 VD) in 14.8%, 3 vessel disease (3VD) in 31.5%, left main disease (LMD) in 1% and normal angiography in 2%, however, in non exposed group (ACS patients with low CRP level and WBC counts) the results were 10%, 20.5%, 32%, 1% and 6% respectively. In this group 4.5% as minimal CAD was detected. Association of angiographic finding to CRP level and WBC count were statistically significant (P = 0.003), even in multivariate analysis that adjusted for potential confounders (P = 0.001). Beyond associations reported earlier there was also a statistically significant relation between CRP level and WBC count based on risk ratios (Table 4).

- Relationship of CRP level and WBC count in bivariate model (Mantel-Haenszel Test): all pre specified end points in this investigation among the confounders subgroups were calculated, results showed that:

- After modification by gender the RR for arrhythmia in ACS patients with elevated CRP level and WBC count and positive family history of CAD versus non exposed group were 2.64 (95% CI 1.22-5.69), for type of arrhythmia, PVC in male gender versus female in

Table 1. Baseline characteristics of exposed and non exposed groups

Variables	Exposed group	Non exposed	Significance Level
Age (year)	64.07 (± 13.29)	60.60 (± 12.02)	0.006
Female	31%	38.5%	0.11
Male	69%	61.5%	0.16
Positive family history	32.5%	44%	0.018
Active smokers	32%	28.5%	0.44
Passive smokers	2.5%	5%	0.17
Ex-smokers (in recent 10 years)	6.4%	4%	0.27
Positive past medical history of cardiac diseases	79%	76%	0.001
Cardiac troponin I (µg/lit) T1	3.12 (±1.10)	0.4863 (± 0.13)	0.005
T2	9.33 (±1.9)	1.20 (± 0.29)	0.005
T3	9.91 (± 1.75)	1.13 (± 0.24)	0.005
T4	19.92 (± 7.84)	2.53 (± 1.31)	0.012
CRP (quantitative (Mg/L)	22.56 (±13.16)	5.64 (± 1.89)	0.001
WBC count	13269.95 (±3207.43)	7363 (± 1471.11)	0.001
Platelet count	239655.17 (±66866.27)	209560 (± 65003.25)	0.001
Blood sugar (Mg/dl)	157.5 (± 78.96)	116.11 (± 48.43)	0.001
Total cholesterol (Mg/dl)	182.94 (± 33.29)	183.77 (± 43.47)	0.82
Triglyceride (Mg/dl)	169.44 (± 98.99)	194.35 (± 113.58)	0.019
LDL-C (Mg/dl)	109.69 (± 30.53)	103.13 (± 36.97)	0.65
HDL-C (Mg/dl)	43.24 (± 9.44)	43.37 (± 9.78)	0.88
Systolic blood pressure (mmHg)	133.37 (± 22.69)	129.86 (± 22.73)	0.12
Pack-year cigarette smoking	29.91 (± 17.45)	24.24 (± 14.02)	0.09

µg : microgram lit : liter Mg: milligram
LDL-C:LDL cholesterol HDL-C:HDL cholesterol mmHg : millimeter Hg

these two group were higher (P = 0.003), cardiac block was higher (P = 0.03), SVD, and 2VD in angiography also was higher in male patients (P = 0.001), MI and unstable angina were higher in male (P = 0.001), the RR for readmission for male patients was 2.30 (95% CI 1.14-4.65).

- Modification by dyslipidemia revealed that, in patients with dyslipidemia mortality rate in exposed versus non exposed ACS patients was higher (P= 0.004), RR for the medication by streptokinase in patients with dyslipidemia in exposed versus non exposed group was 12.98 (95% CI 1.64-16.28), Angiography findings in patients with dyslipidemia showed more SVD, 2VD, 3VD and left main diseases (P = 0.009).

Table 2. Pre specified end points in two groups patients

Outcomes	Exposed	Non exposed	Significance level
Arrhythmia	23.6%	16.5%	0.074
AMI (during CCU admission)	0.5%	1.5%	0.30
Death	4.4%	1%	0.06
Cardiac block	7.9%	8%	0.96
Final diagnosis of MI	72.4%	24.5%	0.001
Final diagnosis of unstable angina	27.6%	75.5%	0.001
Readmission	16.7%	12.5%	0.22
Cardio pulmonary resuscitation (CPR)	6.9%	1.5%	0.007
CCU admission days	5.51 (± 2.63)	4.73 (± 2.35)	0.002
Hospital stay days	11.23 (± 8.64)	9.26 (±5.60)	0.007

AMI: acute myocardial infarction MI: myocardial infarction CCU: coronary care unit

Table 3. Relative frequency of medication after allocation of patients

Drug types	Exposed group	Non exposed group
Aspirin	97%	96.5%
IV heparin	91.6%	90%
Statin	58.2%	48%
Beta-blockers	32%	23%
Calcium antagonists	39%	56.5%
Angiotensin converting enzyme inhibitors (ACEI)	41.5%	71%
streptokinase	10.8%	2%

IV: intra venous

Multivariate Analysis

In a Cox proportional hazard model that controlled for all potential confounders (including age, gender, all cardiac risk factors, prior MI and other cardiac disease and CAD presentations and troponin I level) patients with a high CRP and elevated WBC counts remained at significantly higher risk of death at 30 days ($P = 0.028$), 3VD and left main disease ($P = 0.001$) and readmission ($P = 0.002$).

Cardiac troponin I also analyzed as categorical variable. A cardiac troponin above 0.1 µg/lit was considered elevated. We found out a significant difference in MI incidence between two groups ($P = 0.001$) (89% in troponin positive group versus 11% in troponin less than 0.1 µg/lit).

Table 4. Relative risk of relationship between CRP level and WBC counts and clinical endpoints and baseline characteristics

variables		Non exposed group	Exposed group	PV	Relative risk	95% confidence interval
- gender	Female	38.5%	31%	0.116	0.84	0.68-1.04
	Male	69%	61.5%			
- Positive family history		44%	32.5%	0.018	1.28	1.03-1.59
- Active smokers		28.5%	32%	0.442	0.92	0.75-1.31
- Passive smokers		5%	2.5%	0.179	1.53	0.74-3.15
- Former smokers		4%	6.4%	0.278	0.80	0.56-1.14
- Arrhythmia		16.5%	23.6%	0.074	0.81	0.65-1.05
- PVC		16%	18.8%	0.007		
- Recurrent MI		1.5%	0.5%	0.308	2.02	0.37-11.08
- Streptokinase need		2%	10.8%	0.001	0.56	0.46-0.68
- Echo cardio	MR	49%	43.8%			
graphical	TR	20.5%	15.7%			
findings	PS	1%	1.5%			
- Cardiac block		8%	7.9%	0.965	1.08	0.70-1.44
- Final diagnosis of MI		75.5%	27.6%	0.001	2.77	2.18-3.51
- Readmission		12.5%	16.7%	0.228	0.85	0.66-1.08
- CPR		1.5%	6.9%	0.007	0.59	0.46-0.75
- CCU admission day				0.002		
2-7 days		91.5%	92.1%			
More than 7 days		8.5%	7.9%			
- Length of hospital stay (days)				0.015		
3-10		73.5%	68.5%			
11-18		17%	17.2%			
19-24		7.5%	8.4%			
More than 24 days		2%	5.9%			

PVC = premature-ventricular-tachycardia
TR = tricuspid-regurgitation
PV estimated with pearson chi2 test
MI: myocardial infarction
CCU: coronary care unit
MR = Mitral valve -regurgitation
PE = pulmonary-valve-steno sis
RR computed for exposed VS /non exposed group
CPR: Cardio pulmonary resuscitation

In a Cox proportional hazard model the effect of the elevated cardiac troponin (above 0.1 µg/lit) on clinical end points was predictive of increased risk of MI (*P*= 0.003) and CPR (*P*= 0.044) after completing 30 days follow up period.

Patients with elevated CRP and WBC counts were more likely to need statins, beta-blockers and thrombolytic therapy.

Discussion

Friedman *et al.* (8) reported that an elevated WBC count was associated with an increased risk of developing an MI, and Schlant *et al.* (9) observed that an increased WBC count was a predictor of post MI mortality. Barron *et al.* (10) have shown poor cardiac perfusion with adverse clinical end points. Cannon *et al.* (5) demonstrated that raised WBC count was associated with higher short-term and long-term mortality in ACS.

The role of inflammation in plaque instability have been recognized (11). Local inflammatory activity at the site of plaque rupture is demonstrated (12) and even elevated CRP level is predicted the MI in healthy individuals (13). Sabatine *et al.* (3) found that the extended CAD as presented at angiography is related to the elevated WBC count.

To our search strategy this is the first study in this region to look at CRP and WBC counts and cardiac troponin and considering all other cardiac risk factors, medications, and para-clinical findings in two groups of patients with ACS.

There have been several recent studies regarding elevated level of CRP in patients with unstable angina.(14-17) They found that CRP was predictive of adverse clinical outcomes in these patients. The strength of the present study are a well defined cohort of ACS patients, and consideration of multiple inflammatory prognostic factors in a single study so we expected CRP and WBC and also troponin to be a valid predictor of the risk of ACS.

In our investigation the elevated CRP level and WBC counts was associated with a higher incidence of cardiac events during the follow up period. Any elevation of cardiac troponin was also associated with an increased risk of subsequent MI and CPR, which is concordant with K. James and *et al.* (1) study.

We found that an elevated baseline CRP level and WBC count were associated with a higher mortality rate at 30 days that is in agreement with the Sabatine *et al.* (3) study. That found this relation with WBC count .also in our study we observed that an elevated CRP and WBC count were strong predictor of 3VD and left main disease in angiography and readmission because of ACS. In the previous studies, because of their study design we may not found any report regarding this findings. We have shown that elevation of inflammatory markers (CRP, WBC count) are also a strong predictor of recurrent events in patients with ACS and others have shown that elevation of CRP is a powerful predictor of recurrent events in patients with ACS (3,18,19),

The current studies show that CRP, WBC count and troponin are significant predictors of adverse outcomes after an attack of ACS .In the present study increased CRP level and WBC counts during the acute stage of ACS were associated to increased mortality. James *et al.* (1) also found that increased CRP levels in unstable CAD can lead in increased mortality.

A randomized controlled trial of patients with ACS and WBC count of > 10000 cell/ DL was demonstrated an increased 30-days mortality rate after AMI (5) that is consistent with our results and the multiple risk factor intervention trial (MRFIT) (20).

WBC count was predicted coronary heart disease prevalence, risk of non fatal MI and risk of sudden cardiac death, too (21). Patients with higher level of WBC count need least therapies (anti coagulants, anti-platelet agents, β-blockers, calcium antagonists, or thrombolysis) (22). Beyond local inflammatory response a systemic inflammatory activity explain in patients with AMI , where the expression of interleukin (IL)-1β and IL-8 in leukocytes are stimulated.(21) Also revealed that low CD4/CD8 ratio and low CD4 cell count on the first day of AMI were significantly associated with decreased left ventricular ejection fraction (EF) and larger myocardial destruction . Also high levels of SIL-2R and IL-1β have been detected. A meta analysis (23) of 11 prospective studies investigating populations without vascular disease reported the adjusted relative risk of CHD related to elevated CRP 2.0 (95% CI 1.6-2.5) that is in agreement with our findings.

In contrast to the James *et al.* (1) report the prognostic capacity of TNT regarding mortality, we have found that troponin as categorical variable (higher than 0.1 µg/lit) was an independent predictor of MI.

Strength and Limitations

There are limitations to the present study. As an observational investigation, it can only identify associations and not causality. Strength: We collected information on all possible confounders at the design of the study and also have managed the remaining confounders in the analysis. Blinding in detection of the

out comes have managed the role of possible information biases. In conclusion, in patients with ACS elevation in CRP level and WBC count even after adjusting for traditional risk factors can be used to predict mortality, readmission for ACS, 3VD and LM disease and troponin above 0.1 µg/lit in a cox proportional hazard model remained a strong predictor of myocardial infarction and CPR at 30 days follow up period. Patients with elevated CRP and WBC counts were more likely to receive statin ,beta-blockers and thrombolytics.

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