IN-HOSPITAL OUTCOME OF ACUTE CORONARY SYNDROMES WITH INCREASED NEUTROPHIL TO LYMPHOCYTE RATIO

Ali Raza, Shahid Hameed, Abdul Rehman Abid, Muhammad Imran Farooq, Naeem Asghar, Waqar Hassan

ABSTRACT
Objectives: To compare the outcome between patients with acute coronary syndromes (ACS) with normal vs. increased neutrophil to lymphocyte ratio (NLR).

Materials and methods: This Cohort study was conducted at the Department of Cardiology, Punjab Institute of Cardiology, Lahore from December 2009 to May 2010. Cases were selected in the Emergency Department. All patients were explained the purpose and procedure of study and any risk involved was addressed in Emergency Department. Informed consent was taken. Patients of either sex, of age 30 to 70 years, presenting within 24 hours of first event of ACS were included. Patients with evidence of pneumonia, urinary tract infection, prior history of stroke and acute pericarditis were excluded from the study. Investigations including electrocardiography (ECG) and serum Troponin T for ACS, complete blood count for NLR were recorded. Patients were followed for in hospital mortality or discharge from the hospital.

Results: In the study group, patients of ACS were young with mean age of 52.8±7.45 years. There were 68% male and 32% female patients in both groups. 40% patients were diabetic in Group I and 29.3% in Group II. 9.3% patients died in Group I and 2.7% in Group II with statistically significant result and p<0.015. However mortality difference in diabetics and non-diabetics (6.7% vs 5.6%, p=0.698), male and female (5.9% vs 6.3%, p=0.9) was not significant. Similarly patients of 30-55 years vs 56-70 years had a mortality of 5.9% vs 6.3%, p=0.9. So result was not statistically significant.

Conclusion: Patients with acute coronary syndrome with increased neutrophil to lymphocyte ratio (NLR) have significantly increased in-hospital mortality than those with normal NLR.

Key words: Acute coronary syndrome, Neutrophil to lymphocyte ratio, In-hospital mortality


INTRODUCTION
The term acute coronary syndromes refer to a range of acute myocardial ischemic states. It encompasses unstable angina, non-ST segment elevation myocardial infarction and ST segment elevation myocardial infarction (persistent ST segment elevation usually present).

Coronary Heart disease (CHD) is a global epidemic which is associated with significant morbidity and mortality. CHD comprises more than half of all cardiovascular events in men and women under age 75. An estimated 700,000 Americans will have a new coronary attack and about 500,000 will have a recurrent attack in next year. CHD caused one of every five deaths in the United States in 2004. CHD is a single largest killer of American males and females. About every 26 seconds, an American will suffer a coronary event, and about every minute someone will die from it. The World Health Organization (WHO) estimates that by 2020 the global number of coronary artery disease (CAD) will rise from 7.1 in 2002 to 11.1 million. Pakistanis are part of an ethnic group which suffers from the highest prevalence rates of coronary artery disease.

Acute coronary syndromes (ACS) are caused...
by rupture of atherosclerotic plaques followed by thrombosis. Recent research has shown that inflammation plays a key role in coronary artery disease and other manifestations of atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes. ACS is associated with significant morbidity and mortality.

Treatment of ACS ranges from antiplatelets, anticoagulants, GP IIb/IIIa inhibitors, thrombolitics and primary percutaneous coronary intervention. So it is important to stratify the patients according to the severity of illness in order to guide further treatment.

In order to decrease morbidity and mortality associated with ACS, it is important to treat the patients according to risk stratification. As inflammation plays a key role in pathophysiology of ACS, inflammatory markers are studied for risk stratification of patients with ACS. WBCs are one of the major mediators of inflammation so WBCs and their differential have been studied to predict cardiovascular outcome. It has been observed that increased white blood cell (WBC) count on admission in patients with anterior wall myocardial infarction predicts increased left ventricular remodeling. Increased neutrophils are associated with poor functional recovery after coronary angioplasty and extension of infarct size upon reperfusion in ACS patients.

In ACS, the relative lymphopenia is a stress response and increased neutrophil to lymphocyte ratio (NLR) at admission is related with increased in hospital (8.5 Vs 1.8) and six months (11.5 Vs 2.5) mortality.

In our country, levels of C-reactive protein (CRP) in relation to increased mortality in patients with ACS have been studied. But no study has been done regarding prognostic significance of NLR. CRP is expensive and not widely available. In contrast WBCs with differential is a routinely performed and inexpensive test and NLR can be easily calculated from it. It is important to conduct this study in our population to determine usefulness of NLR for detection of high risk population. So that aggressive management should be directed towards high risk population.

This study was designed to compare the outcome of patients with acute coronary syndrome with normal and increased neutrophil to lymphocyte ratio (NLR).

**MATERIAL AND METHODS**

This Cohort study was conducted at the Department of Cardiology, Punjab Institute of Cardiology, Lahore from December 2009 to May 2010.

Sample size of 300 cases; 150 in each group was calculated with 95% confidence level, 4% margin of error and taking expected percentage of in-hospital mortality i.e 8.5% and 1.8% in patients with increased NLR and normal NLR respectively.

Non-probability, purposive sampling technique was used.

Inclusion criteria were patients of both genders with an age range of 30-70 years. Patients presenting within 24 hours with 1st event of acute coronary syndrome.

Exclusion criteria were, patients with pneumonia as evidenced by effusion or opacity on chest X-ray (CXR). Patients with urinary tract infection as evidenced by more than 5 WBCs/ HPF on urine sample. Patients with prior history of stroke. Acute pericarditis as evidenced by concave ST segment elevation.

Group I consisted of patients with NLR more than 2 and Group II included Patients with NLR 2 or less.

After informed consent, all patients meeting inclusion criteria were enrolled from Cardiology Department. All patients were managed indoor on standard protocol for acute coronary syndromes. Patients were followed till discharge from the hospital. All the information obtained was recorded on a standardized Proforma.

Acute coronary syndrome was defined as presence of any two of the following:

1. Patients presenting to the emergency department with typical chest pain or shortness of breath.
2. ST segment deviation of $\geq 2$ mm and or T wave inversion in at least two contiguous ECG leads.
3. CK-MB $>25$ IU/L or troponin T $>100$ pg/ml.

Neutrophil to Lymphocyte ratio (NLR) was obtained by dividing Neutrophil count by the Lymphocyte count on WBC differential. Normal Ratio was $\leq 2$ and increased Ratio was $>2$.

In-hospital mortality was defined as death during hospital admission.

**DATA ANALYSIS**

All data was entered into a computer using
SPSS version 10 for Windows. Categorical variables like gender and in hospital mortality were expressed as frequencies and percentages. Numerical variable like age was presented as mean and standard deviation. Outcome variable i.e. in hospital mortality was compared in both the groups by using chi square test. Data was stratified for age (< 55, > 55), gender, diabetes mellitus to address effect modifiers. A p value of ≤ 0.05 was considered statistically significant.

RESULTS

Total 300 patients with acute coronary syndromes were studied from emergency department of Punjab Institute of Cardiology and divided in two equal groups of 150 patients. Group I with increased NLR and Group II with normal NLR.

Mean age of the total patients was 52.8 ± 7.45 years. Patients in Group I and II had a mean age of 53.1 ± 7.06 years and 52.5 ± 7.83 years respectively which was not statistically significant (p ≤ 0.587). 204 (68%) patients were between 30-55 years of age, while 96 patients (32%) were between 56-70 years of age. 104 (69.3%) patients in Group I and 100 (66.7%) patients in Group II had age 30-55 while 46 (30.7%) in Group I and 50 (33.3%) in Group II had age above 55 years (Table 1).

204 (68%) of patients were male and 96 (32%) were females. 104 (34.7%) patients were diabetic. Incidence of diabetes was 60 (40%) in Group I and 44 (34.7%) patients in Group II.

Total 18 (6%) in-hospital deaths were observed. In Group I, 14 (9.3%) patients died while 136 (90.7%) were discharged from the hospital. While in Group II 4 (2.7%) died and 146 (97.3%) were discharged. Results were statistically significant between the two groups (p < 0.015) (Table 2).

Regarding gender, 12 (5.9%) male died and 192 (93.8%) discharged while 6 (6.3%) female died and 90 (93.8%) discharged from the hospital. (p = 0.9) (Table 2).

Out of 104 diabetic patients 7 (6.7%) died while 97 (93.3%) discharged. On the other hand in the non diabetic patients 11 (5.6%) died and 185 (94.4%) discharged. (p = 0.698) (Table 2).

Age was also taken as effect modifier. Patients with age between 30-55 years had 12 (5.9%) deaths and 192 (94.18%) were discharged. While patients with age 56-70 year had 6 (6.3%) deaths and 90 (93.8%) were discharged from the hospital. (p = 0.9) (Table 2).

DISCUSSION

Acute coronary syndromes refer to a range of acute myocardial ischemic states. It encompasses unstable angina, non-ST segment elevation myocardial infarction, and ST segment elevation infarction (persistent ST segment elevation usually present).1

Coronary Heart disease is a global epidemic which is associated with significant morbidity and mortality. CHD comprises more than half of all cardiovascular events in men and women under age 75.2 Acute coronary syndromes are caused by rupture of atherosclerotic plaques followed by thrombosis. Recent research has shown that inflammation plays a key role in coronary artery disease and other manifestations of atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes.3-8% of patients with ACS die in hospital instead of standard treatment.11 Within one month after discharge, 10-20% of the patients of ACS die or are readmitted with recurrent myocardial infarction (MI),12 and 5% go on to develop congestive heart failure

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(CHF). Risk prediction based simply on clinical, electrocardiogram (ECG) and biochemical markers is relatively inaccurate. Inflammation plays a key role in the pathogenesis of atherosclerosis. Inflammatory mediators such as CRP, leukocytosis, neutrophilia and lymphopenia have been found to be associated with increased morbidity and mortality in ACS.

Increased neutrophil to lymphocyte ratio (NLR) is associated with increased short term and long term morbidity and mortality in patients with acute coronary syndrome. Tamhane et al studied in-hospital and 6 month mortality in patients with ACS in relation to NLR and found it to be an independent predictor of mortality. In one study in Pakistan 133 patients of ACS were assessed for one year mortality. NLR at the time of admission was a strong predictor of one year mortality. We evaluated 300 patients with ACS for their in-hospital mortality and discharge in relation to their admission NLR.

Patients were divided in two groups each of 150 patients. Group I with increased NLR and Group II with normal NLR. Mean age of the patients was 52.8±7.45 years. This was similar to the mean age of patients in a study conducted by Jafary et al i.e.52.5±10.8 years. Mean age in Group I and group II was 53.1±7.06 and 52.5±7.83 while Tamhane et al observed mean age 61±13 and 67±13.8 in patients in low NLR and high NLR groups respectively. This shows that patients in our population present at much younger age with ACS than in western population.

Out of 300 patients, 18 (6%) deaths were observed of these 14 (9.3%) patients were in Group I and 4 (2.7%) were in Group II. Tamhane et al reported 8.5% vs. 1.8% mortality in ACS in two groups. Our results are similar to this study. While Jafary et al reported only 2.5% in-hospital mortality but 16.4% patients were referred to other specialized centers for further investigations whose outcome is not known.

In the study 204 (68%) patients were male and 96 (32%) patients were female. Iqbal et al reported 77.1% male and 22.9% female patients presenting with STEMI. While Jafary et al reported 68.1% male and 31.9% female patients. So our results were almost similar to these studies. 12 (5.9%) deaths in males and 6 (6.3%) deaths in females were observed in our study. Minor difference in mortality was not statistically significant p < 0.9. Aguado-Romeo et al observed an overall mortality of 8.3% and 11.8% in male and female patients respectively with p < 0.0001. But mortality difference in the age range of 45-64 years was 4% for men and 3.8% for women with p=0.63. As majority of our patients were in this age range so our results were in agreement with this study.

In our study 104 (34.7%) patients were diabetic. In The GRECECS study, in the patients with ACS 32% patients were diabetic. While Jafary et al reported 37.8% diabetics in patients with Acute myocardial infarction. Diabetes is more prevalent in ACS patients in our population than in European population. In our study 60(40%) patients in Group I and 44 (29.3%) patients in Group II were diabetic. However Tamhane et al reported 27.2% and 33.9% diabetic in low and high NLR tertiles respectively. Seven (6.7%) diabetic and 11 (5.6%) non-diabetic patients died in-hospital.

Patients were also evaluated for their outcome in relation to age and for this purpose they were divided into two groups i.e. 30-55 years and 56-70 years of age. 104(69.3%) in Group I and 100 (66.7%) in Group II were in the age range of 30-55. Mortality in two age groups was 5.9% and 6.3% and was not statistically significant.

STUDY LIMITATIONS

The sample size of the study was small as compared to the international studies, however it provides significant result that increased neutrophil to lymphocyte ratio (NLR) in patients with ACS at the time of admission is associated with higher in-hospital mortality and provides an important and inexpensive tool for risk stratification of patients with ACS. However larger studies involving large number of patients and more information about the patients including type of ACS (UA, NSTEMI, STEMI), time from symptom to admission may aid its prognostic value.

CONCLUSION

Patients with acute coronary syndrome with increased neutrophil to lymphocyte ratio (NLR) have significantly increased in-hospital mortality than those with normal NLR. Diabetics and females also had increased in-hospital mortality but results were not statistically significant.
REFERENCES