

To Determine the Frequency of in-Hospital Mortality in Patients of Acute Coronary Syndrome with Increased Neutrophil to Lymphocyte Ratio (NLR)

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ABSTRACT

Background: Coronary heart disease (CHD) is the leading cause of mortality worldwide. ¹ACS is caused by the rupture of the atherosclerotic plaque & inflammation plays a key role. ²White blood cells (WBCs) are the major mediators of inflammation so WBCs & their differential have been studied to predict cardiovascular outcome & early risk assessment.

Aim: To determine the frequency of in-hospital mortality in patients of acute coronary syndrome with increased neutrophil to lymphocyte ratio (NLR).

Study Design: Cross sectional survey.

Setting: Emergency department & West Medical Unit, Mayo Hospital Lahore.

Duration of Study: Six months i.e. from 01.04.2010 to 30.09.2010.

Method: 550 patients meeting inclusion criteria were enrolled in the study from emergency department & West Medical unit of Mayo Hospital, Lahore. History for ischemic heart disease, smoking as well as diabetes was taken. On admission white blood count was done & used to calculate Neutrophil to Lymphocyte ratio. Patients with increased NLR were followed for 7 day in hospital mortality after admission. The information obtained was recorded on a standardized performa.

Results: Results showed that patients with increased NLR at admission were having increased in hospital mortality at 7 days. Diabetes was not found to have a major impact on NLR. Moreover the patients who were suffering from myocardial infarction & patients who were smoker were having higher NLR as compared to other patients.

Conclusion: NLR may be used to identify the high risk patients for early mortality after acute coronary syndrome but its utility may be limited by its non-specificity. More studies are needed to exactly identify the cut off level of NLR to be used as significant.

Keywords: Acute coronary syndrome, Neutrophil, Lymphocyte, Mortality.

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of mortality worldwide and caused 1 of every 5 deaths in the United States in 2004¹. In 2008, an estimated 770000 Americans had a new coronary attack & about 430000 had a recurrent attack.¹ Most common presentation of CHD in emergency room is with acute coronary syndrome (ACS) which is a clinical entity including unstable angina, ST segment & non ST segment elevation myocardial infarction.

ACS is caused by the rupture of the atherosclerotic plaque & inflammation plays a key role.² White blood cells (WBCs) are one of the major mediators of inflammation so WBCs & their differential have been studied to predict cardiovascular outcome. Neutrophils may make atherosclerotic plaque rupture easier through the release of proteolytic enzymes, arachidonic acid derivatives, and superoxide radicals. Increased

neutrophils are associated with poor functional recovery after coronary angioplasty & extension of infarct size upon reperfusion in ACS patients.^{3, 4} On the other hand studies have demonstrated that absolute and relative lymphocyte concentrations are significantly lower in patients with cardiac events and such patients are exposed to higher risk of future cardiac events^{8,9}. In ACS, the relative lymphopenia is a stress response. The increased (more than 2) neutrophil to lymphocyte ratio (NLR) at admission is shown to be independently associated with increased early i.e., 7 days mortality (5.6 %).⁵ So elevated NLR as an independent predictor integrates the predictive risk of these two WBC subtypes into a singular risk factor.

Early risk assessment is useful both in predicting the risk of recurrent cardiac events & in identifying patients who would derive the greatest benefit from aggressive interventions. Risk assessment can be done by clinical scoring systems, as derived from GRACE scoring system or Thrombolysis in Myocardial Infarction (TIMI) Trials⁶.

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In our country, levels of C-reactive protein (CRP) in relation to increased mortality with ACS have been studied⁷ but no study is done regarding prognostic significance of NLR. CRP is expensive & not widely available. In contrast, WBCs with differential is a routinely performed, inexpensive test & NLR can easily be calculated from it. It is important to conduct a study in our country to determine the usefulness of NLR in predicting short term mortality in ACS so that we can manage such patients aggressively with early angiographic intervention.

MATERIAL AND METHODS

This cross sectional survey was conducted in the Emergency Department & West Medical Unit, Mayo Hospital Lahore for a period of six months from 01-04-2010 to 30-09-2010. Sample size of 550 cases was calculated with 95 % confidence level, 2 % margin of error and taking expected percentage of early mortality i.e., 5.96 % in patients of ACS having increased NLR (>2). Sampling technique was non probability purposive sampling. Both male and female patients between 35-65 years of age, presenting within 12 hours with 1st event of acute coronary syndrome (as per operational definition) and with NLR > 2 were included in the study.

Exclusion Criteria

- 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 complete.
- Patients with prior history of stroke.
- Acute pericarditis as evidenced by concave ST elevation.

Data collection: After informed consent, 550 patients meeting inclusion criteria were enrolled in the study from emergency department of Mayo Hospital, Lahore. Demographic profile (name, age, gender) was noted. Patient's history for smoking and diabetes was taken and blood drawn to calculate random blood sugar level in patients who were not known diabetics (random blood sugar level (BSR) >200 mg/dl was taken as diabetes mellitus). All patients were managed in indoor department on standard protocol for acute coronary syndrome. Patients with increased NLR (as per operational definition) were followed for mortality upto 7 days in the hospital. All the information obtained was recorded on a standardized Performa (annexure 1) attached.

Data analysis procedure: All data was processed and analyzed using SPSS version 11.0 for windows. Numerical variables like age are presented by calculating mean and standard deviation. Categorical

variables like gender & in-hospital mortality is calculated by frequency and percentage. Data was stratified for diabetes mellitus (known diabetics taking anti-diabetic drugs or BSR >200 mg/dl) and smoking (5 pack years or more, which was calculated by multiplying average number of packs of cigarettes smoked per day with the total number of years of smoking) to address effect modifiers.

RESULTS

Results were compiled after studying the specific variables. 550 cases of acute coronary syndrome were taken from emergency department, Mayo Hospital, Lahore. Acute coronary syndrome was diagnosed by the presence of the typical chest pain or shortness of breath in combination with either > 2 mm ST segment deviation &/or T wave inversion in at least two consecutive ECG leads or elevated CK-MB > 25 IU/L. Simultaneously, differential white blood count was done & Neutrophil to Lymphocyte ratio was calculated simply by dividing the neutrophil count to lymphocyte count.

Mean age of the patients included in the study was 54.7±8.3 years. 83 patients (15.09%) were in the age range of 35 to 45 years & 189 patients (34.36%) out of total 550 were in age range of 46 to 55 years. The largest group was made by the age range of 56 to 65 years, which comprised of 278 patients (50.55%). The youngest patient in our study was 35.7 years old while the oldest was of 65 years. Mean age of male patients was 58.2±6.1 years while of female patients was 53.3±5.3 years. Age detail is given in Table 1 & Fig. 1.

Out of 550 patients 337 (61.27 %) patients were male & 213(38.72%) patients were female. Male to female ratio was 1.58: 1. Sex distribution is given in Table 2.

Data was also analyzed according to smoking & diabetes. Smoking as a risk factor was found to be present in 167 patients, out of these 167, 9 were female smokers. Diabetes as a risk factor was present in 207 patients, out of whom 141 were males and rest were females. 49 patients among all were having both diabetes & smoking as risk factors. No risk factor was found in 225 patients with acute coronary syndrome.

The results also showed that majority of patients with acute coronary syndrome were having Non ST segment elevation Myocardial Infarction. 216(39.27%) were noted to have NSTEMI, while 176(32%) patients were having unstable angina. Out of total 550, 158(28.72%) patients presented with ST segment elevation Myocardial Infarction (Fig. 2). NLR according to their mode of presentation is also tabulated in Table 3.

Table 1: Age distribution of patients (n=550)

Age (Years)	No. of patients
35-45	83 (15.09%)
46-55	189 (34.36%)
56-65	278 (50.55%)
Mean±SD	54.7± 8.3 years

Key: (SD) Standard deviation

Table 2: Sex distribution of patients (n=550)

Sex	No. of patients
Male	337 (61.27%)
Female	213 (38.72%)
Total	550 (100%)
M: F ratio	1.58: 1

Key: M: F ratio male to female ratio

Table 3: Mean NLR of Study Variables

Study variable	NLR (Mean)
Males	3.9
Females	3.2
Smokers	4.1
Unstable Angina	2.9
NSTEMI	3.8
STEMI	5.6
Alive at 1 week	4.4
Expired Patients	5.8

Fig. 1: Analysis of patients according to age (n=550)

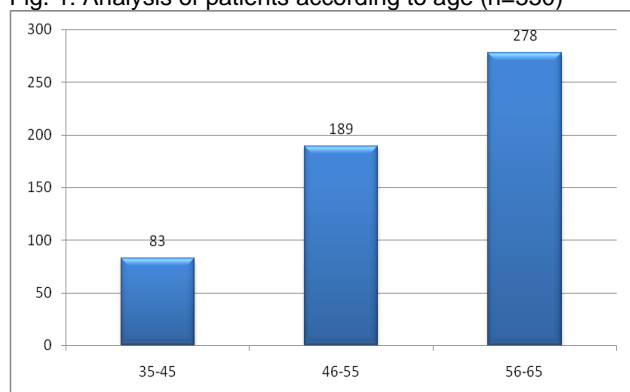
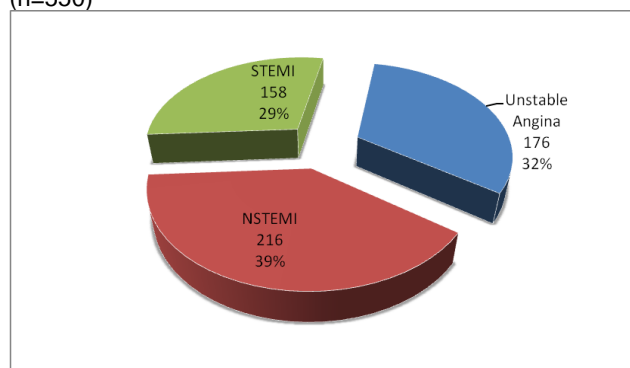


Fig. 2: Analysis of patients according to their presentation (n=550)



Forty six (8.36%) patients expired during their hospital stay within 7 days. Neutrophil to lymphocyte ratio was calculated in all the patients at the time of admission. Interestingly, it was noticed that neutrophil to lymphocyte ratio was more than 4.9 in all the expired patients except three and mean was 5.8 as compared to patients who survived at seven days. Mean neutrophil to lymphocyte ratio among patients who survived was 3.9.

The highest NLR was seen mostly among patients who were smokers. Mean Neutrophil to lymphocyte ratio among smokers was 4.1. Diabetics were not found to have any major difference in NLR as compared to non diabetics. Overall male patients were found to have higher mean NLR i.e., 3.9 as compared to females in which mean NLR was 3.2. The NLR according to patient presentation and study variables is shown in Table 3.

DISCUSSION

Coronary heart disease (CHD) is the leading cause of mortality worldwide & caused 1 of every 5 deaths in the United States in 2004.¹ Acute coronary syndrome (ACS) is an umbrella term usually denoting one of the spectrum of myocardial ischemia involving the coronary arteries: ST elevation myocardial infarction (30%), non ST elevation myocardial infarction (25%) or unstable angina (38%)¹.

Early risk assessment is useful both in predicting the risk of recurrent cardiac events & in identifying patients who would derive the greatest benefit from aggressive interventions. Physicians have long been trying to identify the mortality prone population in whom timely intervention might avert death or accompanying disability of ACS.

The patients admitted in our hospital with acute coronary syndrome were not representative of any specific area or socio-economic class, however belonging mainly to middle & lower socioeconomic strata. The study included a total of 550 consecutive acute coronary syndrome patients; all presented either with unstable angina or ST segment / non ST segment elevation myocardial infarction proven by history, ECG or elevated CK MB.

Our study has demonstrated that white blood count and specifically NLR, which is low cost & simple test, is not only an independent marker but probably can predict the risk of complications including mortality post ACS. The results are consistent with a number of studies which showed the predictive value of total leukocyte count and its subtypes in patients with coronary artery disease.

Hitinder et al¹³, at University of Michigan, retrospectively studied 2833 patients with ACS and stratified patients into low, medium and high risk

groups at the time of their admission. They concluded that patients with high NLRs were significantly more likely to die both in hospital and at 6 months after discharge. The in-hospital mortality was 8.5% in high NLR group as compared to lowest NLR group in which it was 1.8%. The 6 months mortality was also higher 11.5% vs. 2.5%, respectively. This study findings and results are quite similar to our study, as mortality in our study was 8.36% in patients who were having NLR more than 4.9 and mean 5.8. Moreover the mean NLR was 3.9, in patients who survived after 1 week of ACS.

Basem et al¹⁴, concluded that NLR is an independent predictor of short term and long term mortality in patients with NSTEMI with an average NLR of more than 4.7. Our study included patients not only with NSTEMI but also unstable angina and STEMI. However we also concluded that NLR was more than 4.9 in all the expired patients. In this regard the results are quite similar to study done by Basem et al.

In the CAPRIE study, although not the primary outcome measure, neutrophilia was an independent risk marker for cardiovascular disease. Indirectly, our study results also showed an increased neutrophil count over lymphocyte count in patients with ACS, who were at greater risk of complications and death.

A study done by Munir et al¹² at Shifa International Hospital, Islamabad found that the Neutrophil to Lymphocyte ratio was highest among patients with STEMI as compared to patients with NSTEMI & unstable angina and reported that NLR is a better predictor of mortality for ACS than other leukocyte subtypes. The sample size was smaller than our study (550 patients) and included only 130 patients with ACS.

Huang G et al¹⁰, conducted a study to look at the usefulness of WBC count and differential in patients with CAD. They included 623 patients, slightly larger sample size than our study and the study end point was the major adverse cardiac events (including death, CCF as well as stroke) as compared to our data as we probed only into the early mortality after ACS and its relation to NLR. They concluded that raised level of neutrophils after ACS are predictive of major adverse coronary events, in this regard results were similar to our study.

Papa A¹¹ et al conducted a study for an association between WBC count and mortality after ACS. This study did not look into acute mortality rather the end points were death and non fatal MI at 3 years. Although they did not probe into mortality after 1 week, but the results were similar as NLR emerged as an independent predictor of cardiac death.

Nunez J et al¹⁵ analyzed 515 patients with STEMI and concluded that Neutrophil to lymphocyte ratio is a useful marker to predict subsequent mortality in patients with STEMI, however they only analyzed the long term mortality. We only analyzed in hospital mortality at 1 week. The outcome variables (long term vs. in hospital) were different in both of these studies but NLR was found to be a useful adjunct in patients with ACS, to predict mortality.

CONCLUSIONS & RECOMMENDATIONS

The results of the present study and the review of literature show that NLR may be an inexpensive and easy to use method to predict high risk patients of ACS. However its usefulness may be limited due to its non specificity and low sensitivity. We recommend more studies to delineate the usefulness of NLR as a predictor of mortality in patients with ACS.

Limitations: The present study has some limitations. As this study was a single hospital-based study conducted on patients belonging to lower socioeconomic status having a different clinical and risk factor profile, these results cannot be applied to the general population. Moreover the follow up / outcome measure was of only 1 week so the results of this study cannot be generalized.

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