ORIGINAL ARTICLE

IN-HOSPITAL MORTALITY AMONG PATIENTS WITH ACUTE CORONARY SYNDROME WITH HIGH NEUTROPHIL TO LYMPHOCYTE RATIO

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Background: High neutrophil to lymphocyte has a great impact on mortality in people with coronary artery disease. Objective of the study was to find out the frequency of in hospital mortality in acute coronary syndrome and high neutrophil to lymphocyte ratio **Methods**: This study was conducted in cardiology unit, Khyber Teaching Hospital Peshawar from 28th May to 27th November 2019. All patient with ACS and high neutrophil to lymphocytes ratio (NLR >4.7), of age 40–70 years old and both genders were included in the study. All those with infection/sepsis, hematological disorders, previous history of coronary artery diseases, using of immunosuppressed were excluded from the study. **Result:** Mean age was 55.61±6.65 years, Mean BMI was 25.25±4.32 kg/m^2, Male were 130 (70.3%) and female were 55 (40.0%), Diabetes was present in 111 (60.0%) and non-diabetics were 74 (40.0%), Hypertension was present in 122 (65.9%), Smoking history was positive in 81 (43.8%). ≤45 years old were 15 (8.1%) and >45 years old were 170 (91.9%). Of BMI ≤27.00 were 126 (68.1%) while >27.00 were 59 (31.9%). The mortality rate was 14.6% (27) in hospital. Only diabetes was significant associated with mortality (*p* value <0.05). The gender, BMI, Hypertension, age and smoking did not show significant difference in mortality (*p*-value >0.05). **Conclusion:** There is high rate of in hospital mortality in patient with high neutrophil to lymphocytes ratio. The mortality rate further increases when the patients is diabetics. Further studies are recommended to reject or further strengthen this result.

Keywords: Acute coronary syndrome; High neutrophil to lymphocytic ratio; In hospital mortality

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INTRODUCTION

Coronary artery disease is a universal medical issue in both male and female and is the main cause of mortality in the advance nations. The relationship between financial status and result of myocardial infarction (MI) is commonly all around reported in western nations demonstrating that those with lower financial status suffers the most burden.[1] Due to increased risk of death and morbidity, acute myocardial infarction stays a main target of cardiovascular therapeutics. Besides, 30-days deaths and hospitalized rates of acute myocardial infarction (MI) are openly detailed with an end goal to advance ideal acute myocardial infarction care, and whole spectrum of myocardial infarction care conveyance are the focal point of regional, local, and national quality initiatives.[2,3]

The ratio of coronary artery disease is similarly high in south Asia with inclusion of Pakistan[4]. Based on the studies, it is estimated that 100,000 people in our country are reported with acute myocardial infarction in the year 2002.[5]

The neutrophil-to-lymphocyte ratio (NLR) is easily assessed in the peripheral blood. High neutrophil count indicates inflammation, and decrease lymphocyte count shows physiologic stress.[6] Besides, in past studies, Neutrophil to lymphocyte ratio has shown relation to in-hospital deaths caused by cardiovascular diseases and patients died after long term with ST elevation MI[7]. But, the outcomes of other studies are different.[8] White blood cell counts are simple and universally available markers of inflammation. Several studies observed that patients with acute MI and more recently with unstable angina and NSTEMI who has elevated white blood cell counts have higher mortality and recurrent myocardial infarction.[9] Of all leukocyte parameters NLR was the strongest predictors of adverse outcome.[10]

The reported prevalence of in-hospital death among patients with ACS and having high NLR is 8.7%[11], 8.36%[12]. In another study, ACS patients with high neutrophil to lymphocyte ratio group has high in-hospital deaths as compared to low and the moderate neutrophil to lymphocyte ratio (35.8%, 7.5% and 1.9%, *p*<0.001).[13]

The present study is designed to the frequency of in-hospital mortality among ACS patients presenting with high neutrophil to lymphocyte ratio. As mentioned above, ACS is not uncommon in our population and NLR can be used as a marker of predicting the worse outcome in those patients. Moreover, as mentioned, there are studies

on high NLR and its outcome in ACS patients but the results are variable and change from one population to another. This provides us local extent of the mortality among ACS patients with high NLR.

Objective of the study was to determine the frequency of in-hospital mortality among patients with acute coronary syndrome with high neutrophil to lymphocyte ratio.

As it comprises of unstable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), initially evaluated by 12-lead electrocardiogram (ECG), it was defined as[7, 10,14,15]:

- **STEMI**[10,7]**:**
  1. **Symptoms** of Characteristic squeezing, pressure or burning chest pain radiating to left shoulder, lower jaw, back, upper abdomen or either limb with or without symptoms of palpitations, shortness of breath, nausea / vomiting and diaphoresis.
  2. **ECG**, to be performed by Fukuda me C110 machine at the standard paper speed of 25mm/second with 0.1mV/mm voltage representation standardization and interpreted by me and verified by the cardiology consultants team, showing new ST-segment elevation at the j-point persistent for more than 20-minutes in at least two adjacent leads of two mm or more in males or 1.5 millimeter or more in females in V2-V3 leads and/or of one millimeter or more in another adjacent precordial or limb leads or new onset LBBB.
  3. **Cardiac Markers:** Elevated highly sensitive serum troponin levels with cut off of more than 16 ng/l for women and more than 34 ng/l for men measured in the MTI, Khyber teaching hospital laboratory by ROCHE analyzer Machine taken at the time of admission, then after 6-hours and finally after 12-hours. 10% of the samples was randomly selected to be sent to ISO-Certified authentic clinical laboratory with the same machine for counter checking.
- **NSTEMI**[11]**:**
  1. **Symptoms** of Characteristic squeezing, pressure or burning chest pain for more than 20-min duration radiating to left shoulder, lower jaw, back, upper abdomen or either limb with or without symptoms of palpitations, SOB, nausea / vomiting and diaphoresis.
  2. **ECG** showing ST-segment depression of 0.5mm or more at the J-point in at least 2 adjacent leads performed by Fukuda me C110 machine at the standard paper speed of 25mm/second with 0.1mV/mm voltage representation standardization and interpreted by me and verified by the cardiology consultants' team.
  3. **Cardiac Markers:** Elevated highly sensitive serum troponin levels with cut off of more than 16 ng/l for women and more than 34 ng/l for men measured in the MTI, Khyber teaching hospital laboratory by ROCHE analyzer Machine taken at the time of admission, then after 6-hours and finally after 12-hours. 10% of the samples was randomly selected to be sent to ISO-Certified authentic clinical laboratory with the same machine for counter checking.
- **Unstable Angina** [14,15]**:**
  1. **Symptoms** of Characteristics squeezing, pressure or burning chest pain radiating to left shoulder, lower jaw, back, upper abdomen or either limb with or without symptoms of palpitations, SOB, nausea/vomiting and diaphoresis occurring at rest and continuous for more than 20 min.
  2. **Electrocardiography** showing ST-segment depression of 0.5mm or more at the J-point in at least 2 adjacent leads performed by Fukuda me C110 machine at the standard paper speed of 25mm/second with 0.1mV/mm voltage representation standardization and interpreted by me and verified by the cardiology consultants' team.
  3. **Cardiac Markers:** Highly sensitive serum troponin levels below the cut off level of 16 ng/l for women and 34 ng/l for men measured in the Khyber teaching hospital laboratory by ROCHE analyzer Machine taken at the time of admission, then after 6-hours and finally after 12-hours. 10% of the samples was randomly selected to be sent to ISO-Certified authentic clinical laboratory with the same machine for counter checking.

It is described as the number of ACS having higher NLR (>4.7) died during first one week from the time of admission in hospital.

MATERIAL AND METHODS

This study was conducted in Cardiology unit, MTI KTH, Peshawar. The duration of study was six months from 28th May 2019 to 27th November 2019. A total of 185 patients were included in the study. Those cases presenting with ACS with high neutrophil to lymphocyte ratio (NLR >4.7), age 40–70 years and both male and female were included in

the study. Those with Infection or sepsis was excluded by detecting C-reactive protein and blood culture, any type of Hematological disorder diagnosed by medical record or by special smear examination, past history of STEMI or NSTEMI as diagnosed on medical records and past history of Arrhythmias, Current use of immunosuppressant (corticosteroids) assessed on the basis of drug history were excluded from the study. All patients who present to Cardiology Unit, with ACS (as per operational definition) were parts of the study. The patients were described clearly the purpose of study. Informed written consents were taken from volunteers.

Detailed history taken from all cases and examined clinically. Aseptic measures done, 10cc of oxalated blood was taken from every subject and had handed over to the haematology unit of the hospital for determination of NLR and to label the patient as having high NLR. All patients with high NLR were followed over a period of one weeks to detect in hospital mortality.

All cases were managed as per departmental and international criteria under the competent and experienced cardiologist supervision. The whole lab test examination has supervised by competent and experienced hematologist. exclusion criteria have strictly followed to control confounders and bias. The demographic data of the patients and the clinical data has described in a pre-designed proforma.

Through statistical software SPSS version 20, data has been analyzed. Mean±Standard deviation was calculated for continuous variable, i.e., age, BMI. Frequency and percentages were calculated for categorical variables like gender and in hospital mortality. In-hospital mortality was stratified among age, sex, BMI, DM history, HTN and smoking to observe the modification effect using chi square test (p<0.05). All results have described in the tabulated and graphic form.

RESULTS

Mean age was 55.61±6.65 years, mean weight was 73.23±6.64 kg, mean height was 1.71±0.13 m, Mean BMI was 25.28±4.32 kg/m^2. Male were 130 (70.3%) and female were 55 (40.0%), Diabetes was present in 111 (60.0%) and non-diabetics were 74 (40.0%), Hypertension was present in 122 (65.9%) and was not present in 63 (34.1%), Smoking history was positive in 81 (43.8%) and was negative in 104 (56.2%), Only 27 (14.6%) of patient died in hospital and 158 (85.4%) survived in hospital, ≤45 years old were 15 (8.1%) and >45 years old were 170 (91.9%), Of BMI ≤27.00 were 126 (68.1%) while >27.00 were 59 (31.9%) (Table-2)

Stratification of gender against the mortality showed that 17 (13.1%) of 130 male and 10 (18.2%) of 55 female died in hospital and the remaining 113 (86.9%) male and 45 (81.8%) of female were not died. This difference was not significant as the p value for this was 0.377 (Table-3).

Stratification of BMI against the mortality showed that 20 (15.9%) of 126 patient of <27.00 kg/m^2 group and 7 (11.9%) of 59 patients of >27.00 kg/m^2 group died in hospital and the remaining 106 (84.1%) of <27.00 kg/m^2 group and 52 (88.1%) of >27.00 kg/m^2 group were not died. This difference was not significant as the p value for this was 0.465 (Table-3).

Stratification of age against the mortality showed that in 15 patients of age ≤45 years old only 1 (6.7%) died and the remaining 14 (93.3%) did not died. In 170 of age >45 years, 26 (15.3%) died in hospital and the remaining 144 (84.7%) did not died. This difference was also not significant as the p value for this was 0.321 (Table-3).

Stratification of diabetes history against the mortality showed that 21 (18.9%) of 111 diabetics and 6 (8.1%) of 74 nondiabetics died in hospital and the remaining 90 (81.1%) diabetic and 68 (91.9%) of nondiabetics were not died. This difference was significant as the p value for this was 0.035 (Table-3).

Stratification of hypertension history against the mortality showed that 18 (14.8%) of 122 hypertensive and 9 (14.3%) of 63 non-hypertensive died in hospital and the remaining 104 (85.2%) of hypertensive and 54 (85.7%) of non-hypertensive did not die. This difference was not significant as the p value for this was 0.932 (Table-3)

Stratification of smoking against the mortality showed that in 81 positive history of smoking, 8 (9.9%) died in hospital and 73 (90.1%) did not died. In 104 non-smoker 19 (18.3%) died in hospital and the remaining 85 (81.7%) did not died. This difference was also not significant as the p value for this was 0.103 (Table-3).

Table-1: Mean and standard deviation of age

Descriptive Statistics					
	n	Minimum	Maximum	Mean	Std. Deviation
Age (years)	185	40.00	70.00	55.6108	6.64879
Weight (kg)	185	55	88	73.23	6.642
Height (m)	185	1.36	2.14	1.7157	0.13392
BMI (kg/m^2)	185	16.00	38.13	25.2875	4.3232

Table-2: Frequency and percentage of baselines

		Frequency	Percent
Gender	Male	130	70.3
	Female	55	29.7
Diabetes	Yes	111	60.0
	No	74	40.0
Hypertension	Yes	122	65.9
	No	63	34.1
Smoking	Yes	81	43.8
	No	104	56.2
Mortality	Yes	27	14.6
	No	158	85.4

Table-3: Stratification of different variables against mortality

		Mortality		*p*-value
		Yes	No	
Gender	Male	17	113	0.377
	Female	10	45	
Age Group	≤45 years	1	14	0.321
	>45 years	26	144	
BMI groups	≤27.00 kg/m^2	20	106	0.465
	>27.00 kg/m^2	7	52	
DM	Yes	21	90	0.035
	No	6	68	
HTN	Yes	18	104	0.932
	No	9	54	
Smoking	Yes	8	73	0.103
	No	19	85	

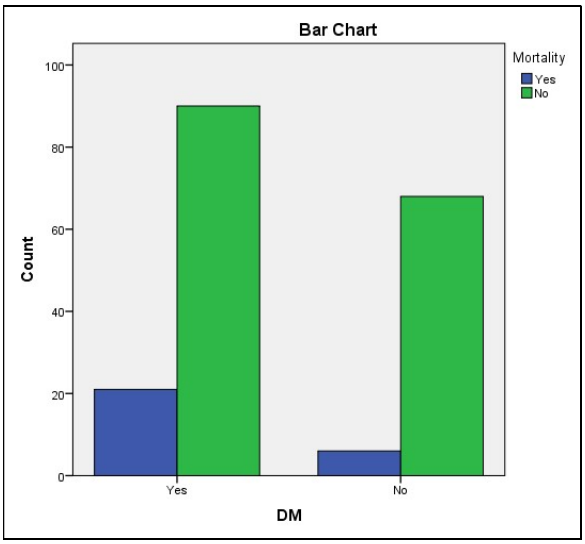

Figure-1: Bar chart of mortality and diabetes

DISCUSSION

It has been reported that the neutrophil-to-lymphocyte ratio (NLR) in the peripheral blood is an easily assessable factor. An ELEVATED neutrophil count might indicate inflammation, and decrease lymphocyte count shows of physiologic stress.[6] Additionally, in past studies, the CV deaths in hospitalized patients and long-term demise in ST elevated MI were revealed to be related to neutrophil to lymphocyte ratio.[7] However, the output of separate studies had different.[8] White blood cell counts are simple and universally available markers of inflammation. Several studies observed that Acute MI cases and more recently with unstable angina and NSTEMI who has elevated white blood cell counts have higher mortality and recurrent myocardial infarction.[9] Of all leukocyte parameters NLR was the strongest predictors of adverse outcome.[10]

The prevalence of in hospital mortality in our study is found to be 27 (14.6%) of patient died in hospital and 158 (85.4%) survived in hospital of patients with ACS and high NLR. The reported prevalence of in-hospital death among patients with ACS and having high NLR is 8.7% founded by Bassand *et al.*[11] in a foreign study, and 8.36% Rafique *et al* in local study.[12] These studies coincide with our results. Another study by Soylu et al showed that, ACS patients with high neutrophil to lymphocyte ratio group has more in-hospital deaths as compared to low or moderate neutrophil to lymphocyte ratio groups (35.8%, 7.5% and 1.9%, $p<0.001$).[13] This study showed more than two times higher incident of mortality of ACS with NRL patient as compared to our result despite the definition of ACS was kept similar compared to other studies[14, 15].

The rate of mortality in our study was significantly associated with the diabetes (18.9% of 8.1% nondiabetics died in hospital, *p*-value 0.035) only among the factors analysis which were gender, BMI, age, hypertension, diabetes and smoking. The association of diabetes was significant with p value

of 0.035. All other were not associated with in hospital mortality (p value >0.05). Many studies have shown the poor prognostic impact of high neutrophil to lymphocyte ratio[16,17] but there is scanty of study to further correlate the diabetes, hypertension, smoking, BMI or with the Major adverse event in patients with myocardial infarction and high neutrophil to lymphocytes ratio.

The limitation of the study included the population restricted to Khyber teaching hospital which is large hospital and many patients are referred from periphery which also delay the presentation to cardiac care unit and thus may have increased mortality. Furthermore, observer bias in the laboratory during observing the neutrophil and lymphocyte and also have occurred which leads to the inclusion of another patient.

CONCLUSION

There is high rate of in hospital mortality in patient with high neutrophil to lymphocytes ratio. The mortality rate further increases when the patients is diabetics. Other variables like, gender, age, smoking, hypertension and BMI don't have effect on in hospital mortality in such patient. Further studies are recommended to reject or further strengthen this result.

AUTHORS' CONTRIBUTION

SK: Study design, data nalysis, data interpretation, proof rading, write-up. HUR: Data collection, ethical issues, write-up. AK: Data collection

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