

# Frequency of High Neutrophil to Lymphocyte Ratio and Its Common Clinical Outcome among Patients with Non-ST Elevation Myocardial Infarction

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## Abstract:

NSTEMI can be defined as angina pectoris and elevated creatine kinase enzyme (CK-MB), and troponin T or I, with at least Pain, occurring at rest and usually lasting >20 minutes (if not interrupted by nitroglycerin administration) or being severe and described as frank pain, and of new onset (i.e., within 1 month) or occurring with a crescendo pattern (i.e., more severe, prolonged, or frequent than previously). The risk of new-onset Atrial fibrillation (AF) is highest during the first 2 months after the acute MI (16% event rate). The Purpose of the current study to determine the frequency of high neutrophil to lymphocyte ratio and its common clinical outcome among patients with non-ST elevation myocardial infarction at Cardiology Unit, Lady Reading Hospital, Peshawar from Sep 17, 2020 to Mar 16, 2021. The current study result show that 250 patients with non-ST elevation myocardial infarction were observed, in which Male to female ratio was 1.45:1. The study included age ranged from 30 up to 71 years. Average age was 53.14 years  $\pm$  11.39SD. High neutrophil to lymphocyte ratio (HNLR) was found in 74 (29.60%). From the recent study we conclude that High neutrophil to lymphocyte ratio was observed and compared to other national and international studies. Male were found in majority than females. **KEY WORDS:** Frequency, neutrophil, left ventricular failure, myocardial infarction, lymphocyte, ST elevation

## INTRODUCTION

Coronary artery diseases are a leading cause of death worldwide. Each year 1.3 million people got unstable angina or Non-ST Elevation Myocardial Infarction (NSTEMI).<sup>1</sup> Indo-Pakistani populations have one of the highest risks of coronary artery disease (CAD) in the world. The

findings indicate that one in five middle-aged adults in urban Pakistan may have underlying CAD. Moreover, women are at greater risk than men.<sup>2</sup>

NSTEMI can be defined as angina pectoris and elevated creatine kinase inoenzyme (CK-MB), and / or troponin T or I, with at least one of three features: (1) Pain, occurring at rest and usually lasting >20 minutes (if not interrupted by nitroglycerin administration); (2) being severe and described as frank pain, and of new onset (i.e., within 1 month); (3) occurring with a crescendo pattern (i.e., more severe, prolonged, or frequent than previously).<sup>1</sup>

There are multiple risk factors for NSTEMI. Age, Male gender, Family history of coronary artery diseases and ethnicity are non-modifiable while cigarette smoking, blood lipid abnormalities, diabetes mellitus, hypertension, obesity and alcohol consumption are modifiable risk factors. Smoking remains the number one preventable cause of cardiovascular diseases worldwide.<sup>3</sup> Patient with NSTEMI is at greater risk of cardiac morbidity and mortality especially in first week of presentation. They are also exposed to many types of arrhythmias including ventricular tachycardia and ventricular fibrillation.<sup>4</sup> The risk of new-onset Atrial fibrillation (AF) is highest during the first 2 months after the acute MI (16% event rate).<sup>5</sup> Coronary artery disease is one of the most common cause of complete atrioventricular block.<sup>6</sup> Sudden cardiac death from ventricular fibrillation during acute myocardial infarction is a leading cause of total and cardiovascular mortality.<sup>7</sup>

There are few predictors of short-term mortality, new onset AF and ST segment deviation in NSTEMI, of which neutrophil to lymphocyte ratio (NLR) is the strongest white blood cell predictors of adverse outcome. White blood cell counts are simple and universally available markers of inflammation. Several studies observed that patients with acute myocardial infarction and more recently with unstable angina and NSTEMI who has elevated white blood cell counts have higher mortality and recurrent myocardial infarction. Other studies evaluated the relation between white blood cell subtypes and adverse coronary outcome. Of all leukocyte parameters NLR was the strongest predictor of adverse outcome. One study showed high NLR (>4.7) in 19.1% patients with NSTEMI with a significant higher in hospital death (8.7%), six months mortality (14.4%) and 4-year (29.8%) mortality in frequency of new onset AF and ST segment deviation is more, 13% and 39.8% respectively in patient with higher NLR (>4.7) as compared to low NLR (<3%).<sup>8</sup> Another study showed that admission NLR is an independent predictor of in hospital and 6-month mortality in patients with ACS.<sup>9</sup>

In this part of the world and especially in Pakistan, where proper facilities are limited and cardiac care centers are usually overburdened, little attention has been given so far to neutrophil to leukocyte ratio among patients of NSTEMI. Additionally, there is no local statistics about NLR in our population presenting with NSTEMI and this current study is designed in view to generate local statistics of NLR and its clinical outcome. Also, this study will be first of its kind in our local population and based upon results of this study, crucial decisions can be made by consultants in the management of patients with high NLR and higher authorities in opening further areas of research work incorporating NLR in NSTEMI and its association with the common clinical outcome.

## **MATERIALS AND METHODS**

The study design was case study, done in Cardiology Unit Lady reading hospital Peshawar and duration of study was 06 months from Sep 17, 2020 to Mar 16, 2021.

Sample Size was taken as 250 with  $p= 19.1\%^8$ ,  $d=5\%$  and Confidence interval=95%  $n=250$ . After approval from research and ethical committee, all patients who present to cardiology Unit, Lady Reading Hospital Peshawar with Non-ST Elevation Myocardial Infarction as per operational definition were included in the study. The purpose of the study was explained to the patients. Informed written consent was taken from those who agreed to participate in the study. Demographic characteristics were recorded in the Performa.

All patients were subjected to detailed history and clinical examination. Under strict aseptic conditions, 10cc of oxalated blood was obtained from each patient and was sent to the hematology department of the hospital for determination of Neutrophil to lymphocyte ratio and to label the patient as having high NLR or normal NLR. Among those patients in whom the high NLR is detected, were followed over a period of two weeks to detect in hospital mortality, Atrial Fibrillation and ST segment Deviation. All the patients were managed as per ward protocols under supervision of an expert cardiologist having minimum of five years of experience. All the laboratory investigations were done under supervision of an expert hematologist having minimum of 5 years of experience. Data were analyzed by using a statistical software SPSS version 16.0 Mean  $\pm$ Standard deviation was calculated for continuous variable like age.

Frequency and percentage were calculated for categorical variable like gender, high NLR and its common clinical outcome (in hospital mortality, Atrial Fibrillation and ST segment Deviation). High NLR and its common clinical outcome were stratified among age and gender to see the effect modifications. All results were presented in the form of tables and graphs

Inclusion Criteria were all NSTEMI patients admitted to cardiology department of Lady Reading Hospital, Peshawar, and Patients of age 30 years and above and of either gender.

Exclusion Criteria were 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, Second NSTEMI was excluded by past medical record, and past history of AF. The above-mentioned conditions act as confounders and if included, introduce bias in the study results.

### **OPERATION DEFINITIONS:**

Non-ST Elevation Myocardial Infarction (NSTEMI) was defined by the presence of any two of the following features:

1. Left side chest pain by Visual analogous score of more than 3 lasting for more than 20 minutes, not interrupted by nitroglycerin administration.
2. Electrocardiogram showing ST segment depression of more than one millimeter or T wave inversion in any lead.
3. Cardiac enzymes CK MB of more than 75 or Troponine I of more than 1 performed in the hematology laboratory.

**High NLR:** It was considered in patients in whom the NLR is more than 4.7 at time of diagnosis of NSTEMI and was measured by an expert pathologist in the hospital laboratory.

**Common Clinical Outcome:**

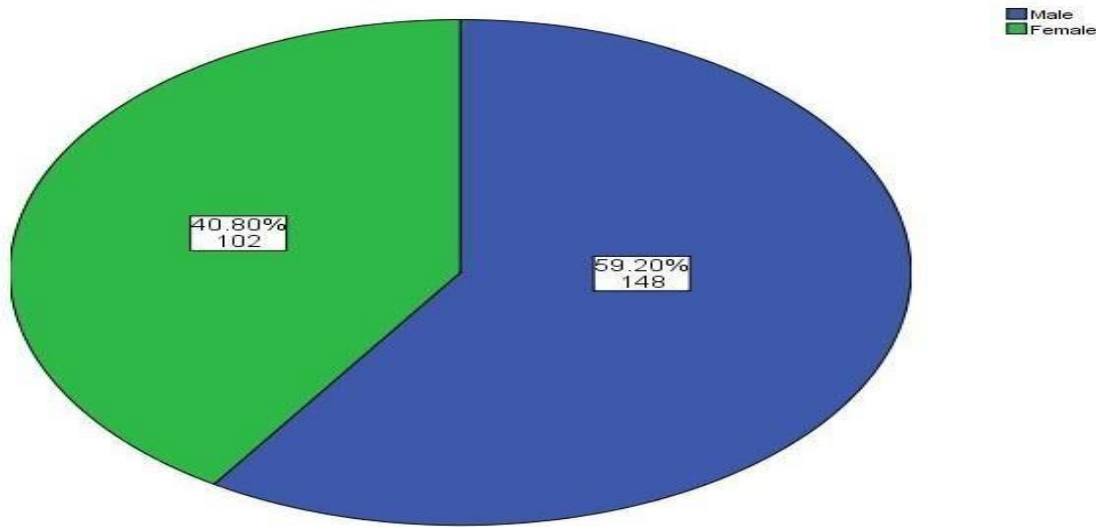
**In Hospital Mortality:** It was defined as the number of NSTEMI patients having higher NLR (>4.7) died during first two weeks from the time of admission in hospital.

**ST Segment Deviation:** was defined as down sloping of ST segment of one or more than one millimeter from baseline in any electrocardiographic lead as compared to previous till the end of 2 weeks of NSTEMI with high NLR.

**Atrial Fibrillation:** It was defined as new onset of rapid and irregular atrial fibrillatory waves at a rate of 350 to 600 impulses/mint with irregularly irregular QRS complexes on the basis of electrocardiogram (ECG) till the end of two weeks of NSTEMI with high NLR.

**RESULTS**

In this study, 250 patients with non-ST elevation myocardial infarction were observed, in which 148(59.20%) were male and 102(40.80%) were female patients. Male to female ratio was 1.45:1. (Figure 1).



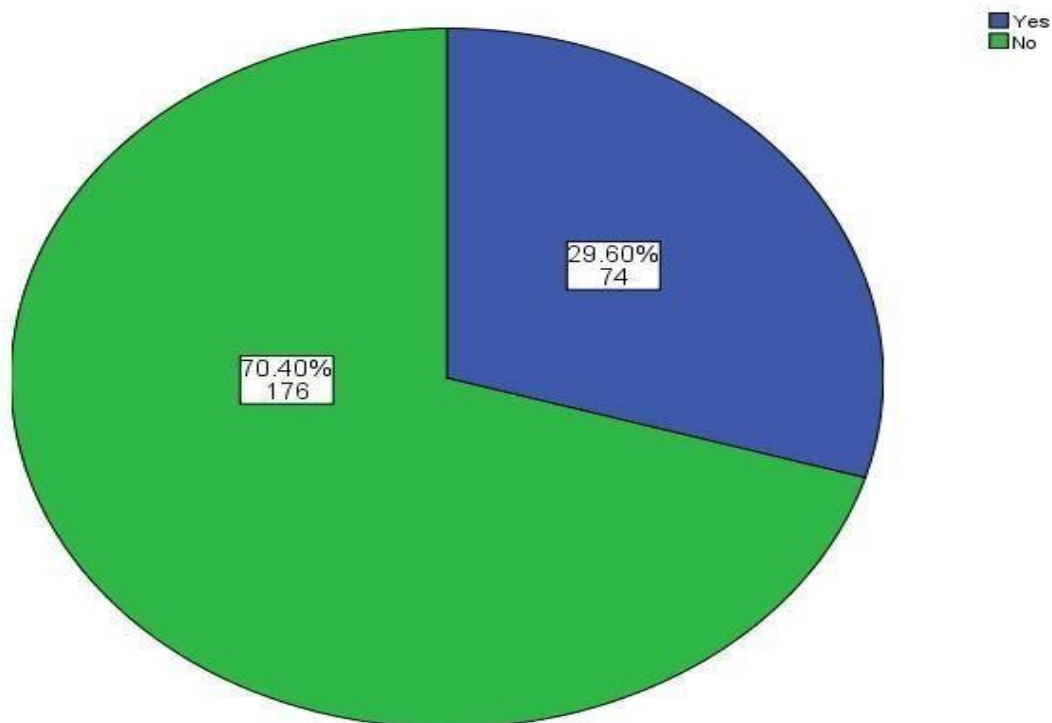
**FIGURE NO: 1. GENDER WISE DISTRIBUTION OF THE PATIENTS**

Patient's age was divided in three categories, out of which most presented with age of more than 55 years were 109(43.60%) while 41(16.40%) patients were in the age range of less than or equal to 40 years, 100(40.00%) were of age range 41-55 years. The study included age ranged from 30 up to 71 years. Average age was 53.14 years  $\pm$  11.39SD. (Table 1).

**Table NO: 1 AGE WISE DISTRIBUTION OF THE PATIENTS**

	Frequency	Percent	Mean±SD
≤40	41	16.4	
41 – 55	100	40.0	
≥56	109	43.6	
Total	250	100.0	53.14 years ± 11.39SD

High neutrophil to lymphocyte ratio (HNLR) was found in 74(29.60%) patients while 176(70.40%) patients have not high neutrophil to lymphocyte ratio. (Figure 2)



**FIGURE NO: 2. DISTRIBUTION OF HIGH NEUTROPHIL TO LYMPHOCYTE**

**RATIO**

Distribution of common clinical outcome in patients with non-ST elevation myocardial infarction shows that ST Segment Deviation was found in majority of cases which is 55(22.0%), followed by Atrial Fibrillation in 20(8.0%) while 19(7.6%) patients have mortality. (Table 2)

**TABLE NO: 2DISTRIBUTION OF COMMON CLINICAL OUTCOME**

		Count	%
Mortality	Yes	19	7.6%
	No	231	92.4%
ST Segment Deviation	Yes	55	22.0%
	No	195	78.0%
Atrial Fibrillation	Yes	20	8.0%
	No	230	92.0%

Age wise distribution of high neutrophil to lymphocyte ratio and its common clinical outcome among patients with non-ST elevation myocardial infarction shows that old age is more prone as that of younger age. HNLN was found in majority of the patients having age more than 55 years which was 45.95% followed by patients having 41-45 years of age 40.54% and 13.51% HNLN was found in age less than 40 years. Similar pattern has been followed approximately by the clinical outcomes but all of them were statistically insignificant when stratify over age. (Table 3).

**Table No.3 AGE WISE DISTRIBUTION OF HIGH NEUTROPHIL TO LYMPHOCYTE RATIO AND CLINICAL OUTCOME**

			age (in years)			p-value
			≤ 40	41 - 55	≥56	
High Neutrophil to Lymphocyte Ratio	Yes	Count	10	30	34	0.714
	No	Column N %				

Mortality	Yes	Count	24.39%	30.0%	31.19%	0.37
	No	Column N %				
	Yes	Count	31	70	75	
	No	Column N %				
	Yes	Count				
	No	Column N %	75.61%	70.0%	68.81%	
		Count				
		Column N %	1	8	10	
		Count				
		Column N %	2.44%	8.0%	9.17%	
ST Segment Deviation Atrial Fibrillation		Count	40	92	99	0.90
		Column N %				
		Count				
		Column N %	97.56%	92.0%	90.83%	
		Count	8	22	25	
		Column N %	19.51%	22.0%	22.94%	
		Count	33	78	84	
		Column N %				
		Count				
		Column N %	80.49%	78.0%	77.06%	
		Count	2	8	10	0.68
		Column N %				
		Count				
		Column N %	4.88%	8.0%	9.17%	
		Count	39	92	99	
		Column N %				
		Count				
		Column N %				
		Count				
		Column N %				

			age (in years)			p-value
			≤ 40	41 - 55	≥ 56	
High Neutrophil to Lymphocyte Ratio	Yes	Count	10	30	34	0.714
	No	Column N %				

Mortality	Yes	Count	24.39%	30.0%	31.19%	0.37
	No	Column N %				
	Yes	Count	31	70	75	
	No	Column N %				
	Yes	Count				
	No	Column N %	75.61%	70.0%	68.81%	
	Count					
	Column N %					
	Count		1	8	10	
	Column N %					
	Count		2.44%		9.17%	
	Column N %					
Count		40	8.0%	99		
Column N %						
Count		97.56%	92.0%	90.83%		
Column N %						
Count		8	22			
Column N %						
ST Segment Deviation				25	0.90	
		19.51%	22.0%	22.94%		
		33	78	84		
		80.49%	78.0%	77.06%		
Atrial Fibrillation		2	8	10	0.68	
		4.88%	8.0%	9.17%		
		39	92	99		
		95.12%	92.0%	90.83%		

The majority of males i.e., 48(32.43%) presented with non-ST elevation myocardial infarction have HNLR while 26(25.49%) HNRL were found in female patients. Similarly, 10(6.76%) mortality found in male and 09(8.82%) were found in female. The rest of clinical outcomes were a little bit high in male as that of female but all of them were statistically insignificant.



**TABLE NO: 4. GENDER WISE DISTRIBUTION OF HIGH NEUTROPHIL TO LYMPHOCYTE RATIO AND CLINICAL OUTCOME**

			Gender		p-value		
			Male	Female			
High Neutrophil to Lymphocyte Ratio	Yes	Count	48	26	0.237		
		Column N %					
	No	Count	32	25			
		Column N %	32.43%	25.49%			
	Mortality	Yes	Count	10		9	0.544
			Column N %	6.76%		8.82%	
		No	Count	138		93	
			Column N %	93.24%		91.18%	
ST Segment Deviation		Yes	Count	31	24	0.628	
			Column N %	20.95%	23.53%		
	No	Count	117	78			
		Column N %	79.05%	76.47%			
Atrial Fibrillation	Yes	Count	11	9	0.690		
		Column N %	7.43%	8.82%			
	No	Count	137	93			

	92.57%	91.18%	
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## DISCUSSION

In the current study, we evaluated the leukocytic response to non-STEMI and examined its possible association with in-hospital mortality and post-infarction complications. We demonstrated that 12-24 hours following non-STEMI the numbers of white blood cells, mostly in the form of neutrophils, are higher than known normal values. Increased neutrophil count was associated with higher in-hospital mortality. Myocardial infarction (MI), which is common in male gender and elderly population, is related with increased cardiovascular mortality and morbidity. Because of the economic, social, and health burden impact, early and precise detection of PAOD is crucial for both general and high-risk populations<sup>10</sup>. Many observational studies have presented a white blood cell (WBC) count as a predictor of coronary artery disease (acute myocardial infarction), stroke, and cardiovascular mortality and morbidity that is independently related with several coronary risk factors.

NLR has been found to be an independent predictor of short-term mortality in patients with acute coronary syndrome<sup>11-14</sup>. Also, the relation of elevated NLR with higher mortality and morbidity in patients with severe PAD including critical limb ischemia has been shown in recent studies<sup>19</sup>. The strong independent predictive effect of high NLR on survival was reported in patients undergoing high-risk vascular surgery such as abdominal aortic aneurysm repair, lower limb revascularization, coronary artery bypass graft, and carotid endarterectomy in a large observational study<sup>15</sup>.

NLR has been found as a novel potential indicator which determines individuals at risk for future cardiovascular events in recent studies<sup>16</sup>. Currently, there are numerous models predicting incident CVD in the general population but many lack external validation. Including NLR may help to improve the performance of CVD risk prediction model. Therefore, future research should explore on comparing existing CVD risk models with those including NLR<sup>17</sup>. A systemic review and meta-analysis suggest that high NLR was associated with CAD, ACS, stroke, and composite cardiovascular events. Therefore, NLR should be considered when assessing the cardiovascular risk in the population.<sup>18</sup> NLR is also associated with a wide variety of diseases including CVDs, and a decrease in NLR following smoking cessation is suggestive of decreased risk of CVD.<sup>19</sup> Due to the importance represented by recent studies regarding NLR in the prognosis for cardiovascular diseases and its association with other inflammatory diseases, establishing a laboratory reference specific for the NLR is promising. Differences in demographic classifications, such as classifications by age group and gender, should be considered<sup>20 21</sup>. Simple calculation of NLR from a complete blood cell count by clinicians treating patients with CVD may add some information to the overall assessment of future risk of adverse

Outcomes, keeping in mind that this could be modified by the Duffy antigen variant<sup>22</sup>.

Out of 250 patients in our study, 74 (29.6%) patients showed a high NLR (>4.7). In these patients there was a significant frequency of In Hospital Mortality, which was 20.27%. Munir et al and Azab et al showed in their study a trend to higher mortality (8.7%) in patients with high NLR which is consistent with our results. Azab et al studied the relation of Atrial Fibrillation and high NLR in NSTEMI patients and showed a frequency of 13%, which was statistically significant. Barron et al investigated that frequency of Atrial Fibrillation increases with raising of leukocyte counts.

## CONCLUSION

We demonstrated that an increased NLR was related with higher cardiovascular mortality in patients, who were admitted for non-ST elevation myocardial infarction. Even after adjustment of various risk factors, age and NLR > 3, it is concluded that High NLR is a good predictor of short-term complications like in hospital mortality, Atrial Fibrillation and ST Segment deviation in patients with Non-ST Segment elevation Myocardial Infarction. Thus, a single CBC analysis may help to identify Non-STEMI patients at risk for mortality and heart failure.

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