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Original Article

Correlation of Neutrophil to Lymphocyte Ratio with in Hospital Mortality in Patients of Acute Coronary Syndrome

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ABSTRACT

Objective: To study the correlation of Neutrophil to Lymphocyte Ratio (NLR) with in-hospital mortality in patients of Acute Coronary Syndrome (ACS).

Study Design: Analytical cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi, Pakistan, from Jul-Dec 2022.

Methodology: One hundred and sixty patients regardless of gender and presented with ACS were included in this study. Their venous blood samples were taken, at the time of admission and were analyzed by the CBC analyzer (Mandray BC 6200) at pathology laboratory and who were delineated into high NLR (>5.25) and low NLR (≤5.25) groups. Their in-hospital morbidity and mortality outcomes were noted. Chi-squared test was applied to compare qualitative variables. Independent samples t-test was applied to compare mean values. Receiver Operating Characteristic (ROC) curve of NLR for predicting in-hospital mortality was plotted, and *p*-value of <0.05 was considered as statistically significant.

Results: Out of n=160 patients, 88(55.0%) were in low NLR group, while 72(45.0%) were in high NLR group. In-hospital mortality was statistically higher in the high NLR group 17(23.6%) vs low NLR group, 3(3.4%), *p*<0.001). The area under the ROC curve of NLR for predicting in-hospital mortality was 0.75(0.64-0.84). The best cut-off value of NLR to predict in-hospital mortality was 6.70 (72.9% sensitivity, 70% specificity)

Conclusion: Patients in high NLR group have statistically higher in-hospital mortality. NLR is a sensitive and specific predictor of in-hospital mortality. Patients in the high NLR group also had lower mean EF, and higher mean troponin levels.

Keywords: Acute Coronary Syndrome, In-hospital Mortality, Neutrophil to Lymphocyte Ratio

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INTRODUCTION

Coronary Artery Disease (CAD) is a major cause of mortality all around the world and contributes to 7 million deaths annually.[1] Common risk factors include smoking, diabetes, hypertension, hyper-lipidemia, male gender, poor nutritional practices and family of CAD. Acute Coronary Syndrome (ACS) is a manifestation of CAD, commonly due to plaque disruption in the coronary arteries.[2] It is an umbrella term encompassing unstable angina (UA), non-ST Elevation Myocardial Infarction (NSTEMI) and ST Elevation Myocardial Infarction (STEMI). Since long, in-flammation is considered to play an important role in CAD and atherosclerosis.[3] Complete Blood Count (CBC) is a routine test done in all patients suffering from ACS. A number of CBC parameters have been studied for their possible role in predicting cardiovascular outcomes. For example, recent studies have shown that increased monocyte count can predict the extent of intra-coronary thrombus burden in patients suffering from STEMI[4,5] while, mean platelet volume to platelet ratio can serve as a prognostic tool for adverse cardio-vascular outcomes in acute Myocardial Infarction (MI).[6] White Blood Cells (WBCs) may have an important patho-physiological role in CAD and ACS by mechanisms such as inflammation, vascular injury, plaque development, disruption and thrombosis.[7] Leu-kocytes are frequently raised at the time of ACS along with variations in circulating levels of neutrophils and lymphocytes causing changes in Neutrophil to Lymphocyte Ratio (NLR). Studies have revealed that amongst all hematological indices, NLR has the greatest predictive value of death in MI patients deemed high risk and is also a powerful predictor of long term mortality in patients hospitalized with STEMI.[8,9] Furthermore, it was also found that out of all the parameters in hemogram, NLR strongly correlates with in-hospital mortality in patients of NSTEMI,

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independently of hypertension, diabetes, smoking, and obesity.[10]

CBC is a routine inexpensive test performed in all patients of ACS and it can easily yield NLR values. We believe that it is worthwhile to evaluate the possible association of NLR with in-hospital mortality in patients of ACS which in turn might pave way to establish NLR as an important prognostic marker in ACS. Thus, the study's purpose was to determine the correlation of neutrophil to lymphocyte ratio (NLR) with in-hospital mortality in patients of ACS.

METHODOLOGY

This study was conducted at Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi, Pakistan, from July to December 2022. It was an Analytical cross-sectional study done after ethical approval from Institutional Ethical Review Board (IERB), (Ltr# 9/2/R&D/2022/185). Patients were informed and consent was taken. Non-probability consecutive sampling was used to collect data.

Total n=160 sample was calculated using WHO sample size calculator, taking 11.8% prevalence of mortality in ACS patients,[11] keeping 95% confidence level and 5% margin of error.

Inclusion Criteria: Males and females aged more than 18 years presented with ACS were part of our study.

Exclusion Criteria: Patients with no follow up, patients with coexisting chronic kidney disease, chronic liver disease and hematological malignancies, patients referred to another medical facility, sepsis being the cause of mortality and patients who underwent cardiac arrest or Cardiopulmonary Resuscitation (CPR) outside the hospital were excluded.

ACS was defined as a subgroup of CAD including unstable angina, NSTEMI and STEMI.[12] Neutrophil to Lymphocyte Ratio (NLR) is a marker of inflammation obtained by dividing neutrophils to lymphocytes count. Normal range of NLR in adult population with no comorbid is 0.78 to 3.53.[13]

Patient's name, age, gender, co-morbidities, symptoms, duration of symptoms, ECG findings, diagnosis, biochemical investigations, list of medications, coronary angiographic findings and coronary interventions were noted. Venous blood samples were taken, at the time of admission and were analyzed by the CBC analyzer (Mandray BC 6200) at pathology laboratory of AFIC & NIHD to determine neutrophil and lymphocyte values. NLR values were obtained by dividing the Neutrophil count to Lymphocyte count. The patients were divided into high NLR (>5.25) and low NLR (≤5.25) groups.[13] They were followed-up during their hospital stay, to determine their in-hospital outcomes (morbidity and mortality), day of mortality and cause of mortality during hospital admission. Day of discharge was noted in case of patients who were alive at the time of discharge.

Statistical Package for Social Sciences (SPSS) version 24:00 was utilized for statistical analysis. Means and standard deviations of quantitative data were calculated; while frequencies and percentages were calculated for qualitative data. ROC curve of NLR group for predicting in-hospital mortality was plotted. Independent samples t-test and Chi Square test were applied to compare study variables among NLR groups and p-value <0.05 was considered as statistically significant.

RESULTS

Total n=160 patients were part of the study, out of which 138(86.3%) were males and 22(13.8%) were females. Cases of STEMI were 100(62.5%) while 60(37.5%) cases were of NSTEMI or unstable angina. 88(55.0%) patients were in the low NLR group, while 72(45.0%) were in the high NLR group, and in-hospital mortality of ACS was 20(12.5%). Patients in the high NLR group were older as compared to the other group, (63.93±10.56 years vs 60.22±11.23 years; p=0.85). No statistically significant difference was observed between the two groups (high NLR group and low NLR group) in terms of mean symptoms duration (10.26±14.41 hours vs 14.95±20.29 hours (p>0.05), day of mortality (4±5 days vs 2±2 days, p>0.05) and day of discharge (5±4 days vs 4±4 days; p>0.05) and mean ejection fraction (40.51±10.41% vs 43.13±8.52%; p>0.05).

Table-I shows the comparison of clinical, electrocardiographic and angiographic parameters between the two groups. It was seen that patients in the high NLR group, in comparison to their counter-parts were more likely to have hypothyroidism (6.9% vs 0.0%, p=0.04), had higher rates of STEMI (73.6% vs 53.4%, p=0.01), and were more frequently administered Tirofiban alongside ACS protocol (70.8 % vs 42.0 %, p< 0.001) and differences between the groups were statistically significant.

Furthermore they were also likely to undergo PCI, (86.1% vs 73.9%; p=0.08), which was not found statistically significant.

Table-I: Comparison of Clinical, Electrocardiographic and Angiographic Parameters Between Low and High NLR Groups (n=160)

Variables		Low NLR (≤ 5.25) Frequency (%) Total=88	High NLR(>5.25) Frequency (%) Total=72	*p*-value
Gender	Male	75 (85.2)	63 (87.5)	0.85
	Female	13 (14.8)	9 (12.5)	
Symptoms	Chest pain	67 (76.1)	55 (76.4)	1.00
	Dyspnea	45 (51.1)	39 (54.2)	0.82
	Apprehension	47 (53.4)	36 (50.0)	0.78
	Sweating	46 (52.3)	41 (56.9)	0.66
Comorbids	Hypertension	46 (52.3)	40 (55.6)	0.79
	Diabetes	38 (43.2)	35 (48.6)	0.59
	Obesity	19 (21.6)	17 (23.6)	0.90
	COPD	19 (21.6)	14 (19.4)	0.89
	Hyperthyro-idism	3 (3.4)	1 (1.4)	0.76
	Hypothyroi dism	0 (0.0)	5 (6.9)	0.04
Diagnosis	STEMI	47 (53.4)	53 (73.6)	0.01
	NSTEMI or Unstable Angina	41 (46.6)	19 (26.4)	
ST changes	ST Elevation	44 (50)	49 (68.1)	0.22
	ST Depression	29 (33.0)	14 (19.4)	
	T wave inversions	11 (12.5)	6 (8.3)	
	LBBB	3 (3.4)	2 (2.8)	
	RBBB	1 (1.1)	1 (1.4)	
Infarct related artery	LAD	48 (54.5)	46 (63.9)	0.43
	LCX	13 (14.8)	10 (13.9)	
	RCA	27 (30.7)	16 (22.2)	
Total diseased vessels	SVCAD	25 (28.4)	32 (44.4)	0.16
	DVCAD	26 (29.5)	17 (23.6)	
	TVCAD	29 (33.0)	20 (27.8)	
	TVCAD+LMS	8 (9.1)	3 (4.2)	
Interventions done	PCI	65 (73.9)	62 (86.1)	0.08
	TPM	3 (3.4)	6 (8.3)	0.31
	PPM	1 (1.1)	2 (2.8)	0.86
	CABG	13 (14.8)	6 (8.3)	0.31
	Medical treatment only	11 (12.5)	4 (5.6)	0.22
Antithrombo-tic therapy	ACS protocol	51 (58.0)	21 (29.2)	<0.001
	ACS protocol plus tirofiban	37 (42.0)	51 (70.8)	

*NLR= Neutrophil to lymphocyte ratio, COPD= Chronic obstructive pulmonary disease, STEMI= ST Elevation Myocardial Infarction, NSTEMI= Non-ST Elevation Myocardial Infarction, LBBB= Left bundle branch block, RBBB= Right bundle branch block, LAD= Left anterior descending artery, LCX= Left circumflex artery, RCA= Right coronary artery, SVCAD= Single vessel coronary artery disease, DVCAD= Double vessel coronary artery disease, TVCAD= Triple vessel coronary artery disease, LMS= Left main stem, PCI= Percutaneous coronary intervention, TPM= Temporary pacemaker, PPM= Permanent pacemaker, CABG= Coronary artery bypass graft, ACS= Acute coronary syndrome.

Table-II showed the biochemical data of the two NLR groups. It was observed that mean troponin levels and mean ALT levels were higher in the high NLR group in comparison to their counterparts, (14838.75 ± 19124.39 ng/L vs 6326.97±12058.28 ng/L, p=0.01) and (51.80 ± 71.22 U/L vs 33.20 ± 16.3 U/L, *p*=0.01)

Table-II: Biochemical data of low and high NLR groups (n=160)

Variables	Low NLR (≤ 5.25) (Mean ±SD) Total=88	High NLR (>5.25) (Mean ±SD) Total=72	*p*-value
Hemoglobin (g/dl)	14.14±1.15	14.26±1.24	0.50
MCV (f L)	85.25±5.95	83.99±10.5	0.34
TLC(×10³/µL)	11.77±11.86	13.76±4.75	0.18
Troponin (ng/L)	6326.97±12058.28	14838.75±19124.39	0.01
Urea(mg/d L)	44.64±18.00	44.72±21.00	0.98
Creatinine (mg/d L)	1.07±0.23	1.28±1.540	0.21
Sodium (mmol/L)	137.37±2.92	137.06±2.73	0.50
Potassium (mmol/L)	4.30±0.47	4.26±0.43	0.56
ALT (U/L)	33.20±16.3	51.80±71.22	0.01
Bilirubin (mg/dL)	0.63±0.19	0.68±0.23	0.09
ALP(U/L)	88.44±19.13	102.20±84.90	0.14

MCV= Mean Corpuscular Volume, TLC= Total Leucocyte Count, ALT= Alanine Aminotransferase, ALP= Alkaline Phosphatase

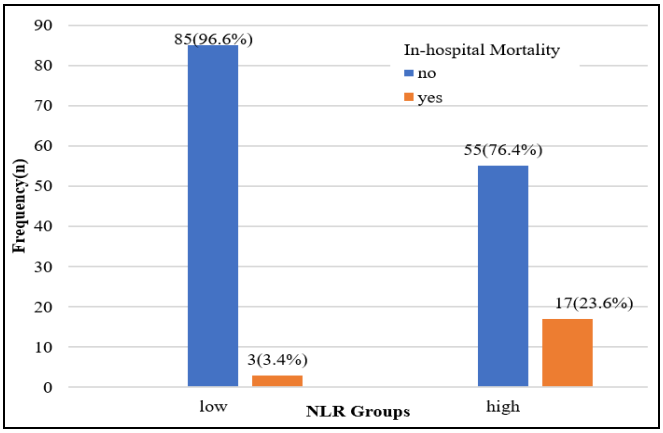

Figure-1: In-hospital Mortality in low and High NLR Groups (n=160)

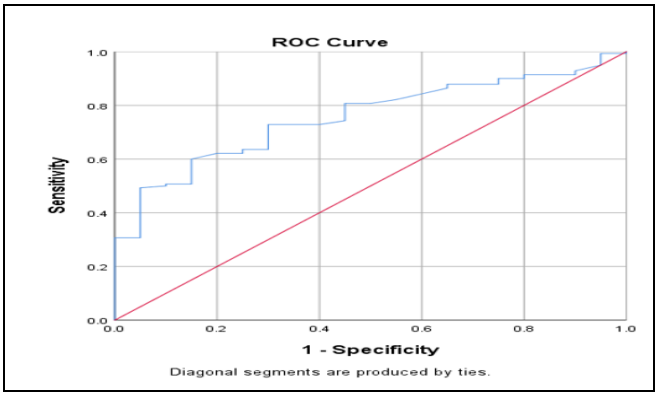

Figure-2: ROC Curve Showing NLR as a Prognostic Tool of In-Hospital Mortality. ((AUC)= 0.755(0.664-0.846) (n=160)

Figure-1 showed the difference in hospital mortality outcomes between the two NLR groups.

Figure-2 depicted ROC Curve of NLR. Area under the ROC curve of NLR for predicting in-hospital mortality was 0.75 (0.66-0.84). Best cut-off value for NLR to predict in-hospital mortality was 6.70 (72.9 % Sensitivity and 70% Specificity).

Table-III compares the mortality and morbidity out-comes. In our study, it was observed that patients in the high NLR group, in comparison to their counter-parts were statistically more likely to have mitral regurgitation (18.1% vs 5.7%; *p*=0.02). They also more commonly had ventricular arrhythmias (12.5% vs 3.4%; *p*=0.06), but the difference did not hold statistical weightage. The in-hospital mortality was significantly higher in the high NLR group as compared to their counterparts, (17(23.6%) vs 3(3.4%); *p*<0.001).

Table III: Mortality and Morbidity Outcomes of Low and High NLR Groups (n=160)

Mortality and Morbidity Outcomes		Low NLR (≤ 5.25) Frequency(%) Total=88	High NLR (>5.25) Frequency(%) Total=72	*p*-value
Survivors		85(96.6)	55(76.4)	<0.001
Non survivors		3(3.4)	17(23.6)	
Causes of Mortality	Cardiogenic shock	0(0.0)	9(52.9)	0.19
	Heart Failure	1(33.3)	4(23.5)	
	Arrhythmias	2(66.7)	4(23.5)	
Morbidity Outcomes	Ventricular Arrhythmias	3(3.4)	9(12.5)	0.06
	Atrial fibrillation	11(12.5)	6(8.3)	0.27
	Sinus tachycardia	9(10.2)	14(19.4)	0.15
	Heart blocks	3(3.4)	7(9.7)	0.18
	Sinus Bradycardia	8(9.1)	4(5.6)	0.58
	Mitral Regurgitation	5(5.7)	13(18.1)	0.02
	Aortic Regurgitation	1(1.1)	0(0.0)	1.00
	Aortic Stenosis	1(1.1)	0(0.0)	1.00
	Tricuspid Regurgitation	8(9.1)	6(8.3)	1.00
	Pericardial effusion	1(1.1)	5(6.9)	0.13

DISCUSSION

ACS is a common cardiac emergency. A MEDLINE systematic review of observational studies found that among patients admitted for cardio-vascular diseases (CVDs), the prevalence of ACS can be up to 22.3%14 and 30-day mortality rates can approach as high as 30%.[15] Despite being a potentially fatal disease, early diagnosis, identification of patients at risk of adverse cardiovascular outcomes and sub-sequently appropriate treatment can improve patient outcomes. NLR is a significant predictor of mortality including cases of STEMI[9] as well as NSTEMI.[10] Since CBC is a routine inexpensive test done in all patients presenting with ACS, we designed our study to evaluate the role of NLR in predicting in-hospital mortality in ACS, as well as to study the difference in mortality outcomes between High NLR and Low NLR groups.

The overall in-hospital mortality was 20(12.5%) while the all-cause mortality was 20.4% in a study conducted by Fanta *et al*.,[16] We found that there was a statistically significant difference of in-hospital mortality between high NLR and low NLR group [17(23.6%) vs 3 (3.4%), *p*<0.001]. The higher mortality rate in the high NLR group in our research was similar to the study conducted by Khan *et al* (14.6%).[17] The difference of in-hospital mortality rates between high and low NLR groups in the research of Bajari *et al* was 11.1% vs 1.1% respectively.[13] We found in our study that patients in the high NLR group more frequently had ventricular arrhythmias in comparison to the low NLR group (12.5% vs 3.4 %; *p*=0.06), but the difference was not significant statistically, similar to the findings of Ghaffari *et al*.,[18] and Bajari *et al*.,[13] also found that ventricular arrhythmias were more common in the high NLR group. It was revealed that the likelihood of Tirofiban administration was statistically higher in the high NLR group of current study.

The role of NLR as a predictive marker of in-hospital mortality in ACS, using ROC curve was studied, and found that NLR is a good predictor of in-hospital mortality, keeping cut-off value of NLR as 6.70 (72.9 % Sensitivity and 70% Specificity, AUC 0.75), while in the study conducted by Bajari *et al* [13], cut-off values of NLR to predict mortality was >5.25 (sensitivity of 89.36%, specificity of 75.07%, AUC = 0.843), while Avici *et al*.,[10] used NLR cutoff value of 3.62, and found that it had 84.2% sensitivity and 66.3% specificity, for predicting in-hospital mortality. It is worth mentioning that their study only included NSTEMI patients, while our study included STEMI, NSTEMI and unstable angina patients. Similarly, Li *et al*.,[19] conducted a study recently on the impact of NLR on mortality in unstable angina, and found that keeping an NLR cut-off value of 2.76 predicts cardiovascular mortality (69.2% sensitivity, 64.8% specificity).

LIMITATIONS OF STUDY

This was a single center study, and the study was limited to assess mortality outcomes during the same hospital admission, hence 30 day and 6-month mortalities were not assessed and compared with NLR.

CONCLUSION

NLR is an easy approach to acquire laboratory-based investigations derived from CBC, which can predict in-hospital mortality in patients of ACS. It was demonstrated that the in-hospital mortality rates, mitral regurgitation and likelihood of Tirofiban administration was statistically higher in the high NLR group. Further work is needed to assess the role of NLR in predicting mortality in the setting of ACS over longer periods of time. Being a cost effective, readily available biochemical parameter, NLR has the potential to serve as a prognostic marker in ACS.

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Conflict of Interest: None

Authors' Contribution

Following authors have made substantial contributions to the manuscript:

IAK & SKS: Concept, study design, critical review, drafting the manuscript, approval of the final version to be published

AAC & SAK: Data analysis, data interpretation, critical review, approval of the final version to be published

ZA, SSK & FKT: Concept, data acquisition, drafting the manuscript, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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