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The Role of Neutrophil to Lymphocyte Ratio and its Common Clinical Outcomes Among Patients with Non-ST Elevation Acute Coronary Syndrome

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Abstract

Objectives: **To evaluate the admission neutrophil-to-lymphocyte ratio (NLR) for risk stratification for in-hospital outcomes and complications in non-ST-elevation acute coronary syndrome (non-ST-ACS) patients.**

Methods: **We recruited consecutive patients with non-ST-ACS. The NLR was obtained and stratified as low, intermediate, and high-risk based on <3.0, 3.0−6.0, and >6.0, respectively. The new ST-T changes, arrhythmias, contrast-induced nephropathy (CIN), and mortality were recorded.**

Results: **Median NLR was 3 [2.1−5.3] for 346 patients with 19.9% and 30.6% in high- and intermediate-risk group. New ST-T changes were observed in 3.5% (12) out of which 8, 3, and 1 patient in low, intermediate, and high-risk group (p = 0.424), respectively. Arrhythmias were observed in 5.8% (20) with 7, 5, and 8 patients in low, intermediate, and high-risk group (p = 0.067), respectively. CIN was observed in 4.9% (17) with 5, 5, and 7 in low, intermediate, and high-risk group (p = 0.064), respectively. In-hospital mortality was recorded in 1.4% (5) with 2 and 3 patients in high and low-risk group (p = 0.260), respectively.**

Conclusion: **A significant number of non-ST-ACS patients fall in the high-risk category of NLR. Although, the association between NLR and in-hospital mortality and adverse events was not statistically significant but relatively higher rates of events were observed in high risk group.**

Keywords: Atherosclerotic cardiovascular diseases (ASCVD), Neutrophil to lymphocyte ratio (NLR), Non-ST-elevation acute coronary syndrome (non-ST ACS), Prognosis, Pakistan

1. Introduction

Human stressors and lifestyle have changed so the pattern of diseases and their effects have made the healthcare systems of every country insufficient to provide emergency care to people [1]. Amongst the major causes of death and disability are cardiovascular diseases (CVD), especially in South Asians (SA), the Global Burden of Disease (GBD) study, around 10.8 million deaths in Asia are due to CVD making up 35% of the total deaths in this region [2]. According to an estimation the prevalence rate of CVD per 100,000 individuals in Pakistan is reported to be around 3850.8 corresponding to the death rate of 152.2 per 100,000 individuals for the year 2019 [3].

A feared complication of myocardial ischemia is the sudden loss of life and along with disability which further adversely affects daily life and increases the financial burden over the family; so such a disease should be prevented firstly, then risk stratified and treated on a priority basis to save myocardium and to save a working youth of Pakistan [4]. Atherosclerotic cardiovascular diseases

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(ASCVD) has a spectrum of presentations like stable ischemic heart disease (SIHD) and acute coronary syndrome (ACS) [5] which is further categorized as "ST-segment elevation myocardial infarction (STEMI)" and "non-ST ACS". Management strategies and recommendations for STEMI are well established [6,7], however, management of non-ST ACS widely varies from patient to patient. Hence, the identification of high-risk patients who could possibly benefit from invasive and aggressive management can be vital to combating the increasing burden of disease in our region [8].

Among the different risk stratifying methods, Neutrophil to Lymphocyte Ratio (NLR) is an emerging parameter that is cheap and easily available through patients' baseline and routine investigation of complete blood count [9]. The NLR has been extensively studied in heart diseases particularly in atherosclerotic coronary artery disease (CAD), despite all emerging therapeutics and procedures, high NLR portrays poor prognosis regarding recurrent events, low ejection fraction (EF), extensive myocardial damage, slow recovery, and more procedural complications like contrast-induced nephropathy (CIN), slow flow [10–12].

Hence, in this study, our aim was to evaluate the role of admission NLR for risk stratification for in-hospital outcomes and complications in a contemporary cohort of non-ST ACS patients presented at the largest cardiac care center in Pakistan.

List of abbreviations

ACS	acute coronary syndrome
ASCVD	atherosclerotic cardiovascular diseases
CAD	coronary artery disease
CIN	contrast-induced nephropathy
CRP	C-reactive protein
CVD	cardiovascular diseases
EF	ejection fraction
GBD	Global Burden of Disease
I/R	ischemia-reperfusion MACE = major cardiovascular events
MLR	monocyte-to-lymphocyte ratio
NLR	neutrophil-to-lymphocyte ratio
NSTEMI	non-ST elevation myocardial infarction
SIHD	stable ischemic heart disease
ST-ACS	ST-elevation acute coronary syndrome
STEMI	ST-segment elevation myocardial infarction

2. Methodology

After approval from the ethical review board of the hospital, consecutive patients diagnosed with non-ST ACS (either Non-STEMI or unstable angina) were recruited for this cross-sectional study. This study was conducted at the "National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan" between June 2021 and March 2022. In accordance with the "Declaration of Helsinki", verbal consent for participation was obtained from all the recruited patients. Inclusion criteria were; patients diagnosed with non-ST ACS, between 18 and 80 years of age, either sex, and presented to the hospital within two days of the onset of symptoms. Exclusion criteria were; patients with a history of trauma, surgery, or neoplasm the last 30 days prior to admissions, patients currently using immunosuppressants (including corticosteroids), and patients who refused to give consent for participation in the study.

The non-ST ACS was diagnosed by a consultant cardiologist based on reported presenting symptoms of "centrally diffused chest pain for more than 20 min duration", "chest heaviness, pressure over chest radiating to jaw or arms", or "shortness of breath (respiratory rate >18 breaths per minute)" along with ECG finding of "ST depression of 1 mm or more, transient ST elevation, and/or prominent T-wave inversions". The non-ST ACS was further confirmed through troponin-I value, "if less than the normal reference range of the essay" it was considered as unstable angina, and "if above the normal reference range of the essay" it was considered as non-ST elevation myocardial infarction (NSTEMI).

A blood sample of 2–3 ml was drawn immediately upon arrival by trained nursing personnel and collected in EDTA (Ethylene Diamine Tetra Acetate) containers for immediate dispatch to a clinical laboratory located within the premise of the emergency department. Total and differential leukocytes were analyzed by automated machines. The NLR, a ratio of neutrophils to the number of lymphocytes, was obtained and stratified as low, intermediate, and high-risk based on NLR ratio of <3.0, 3.0 to 6.0, and >6.0, respectively.

All the patients were managed by consultant cardiologists as per the standard treatment protocols and hospital policies. The researcher was a silent observer and has no influence on the treatment and management decision-making of the patients. The hospital course of all the patients' were observed and any event of new ST-T changes, atrial fibrillation, contrast-induced nephropathy (CIN), and mortality were recorded. ST-T changes included ST depression ("ST depression of 1 mm or more in all leads except in aVR"), ST elevation ("1 mm or more"), and T wave inversion ("downward deflection of any size"). A "variable R–R interval with normal QRS, LBB or RBB morphology but absent or unidentifiable P wave" on 12 lead ECG was taken as atrial fibrillation, and "a rise in creatinine of >0.5 mg or >20% decline in estimated glomerular filtration rate (eGFR)" was taken as CIN.

The "IBM SPSS" version 21 was used for the analysis of data. Patients were stratified based on NLR as low, intermediate, and high-risk categories, and demographic variables, clinical characteristics, and hospital course were compared among the three groups. The summary statistics computed were mean ± standard deviation (SD)/median [interquartile range (IQR)] and frequency (%) and appropriate ANOVA (analysis of variance)/Kruskal–Wallis test or Chi-square test were performed at $p \leq 0.05$ level of significance.

3. Results

In this study we observed a total of 346 patients with non-ST ACS, 67.1% (232) of that were male and mean age of the study sample was 57.67 ± 10.64 years. Older patients (>70 years) were 10.1% (35) of the sample and 23.4% (81) were 20–50 years of age. Presenting complaint was chest pain in 88.7% (307) with median duration of 24 [IQR: 6–48] hours and 25.7% (89) reported shortness of breath (SOB) with median duration of 24 [IQR: 7–48] hours. A majority, 90.5% (313), had NSTEMI, 74.6% (258) had ST-T changes on admission ECG, 1.2% (4) had atrial fibrillation, and median TIMI (thrombolysis in myocardial infarction) score was 3 [IQR: 2–4]. Hypertension was the commonly observed co-morbid condition observed in 69.7% (241) followed by diabetes in 51.7% (179), smoking in 10.7% (37), heart failure in 10.1% (35), and hyperlipedemia in 7.8% (27). Median NLR was 3 [IQR: 2.1–5.3] with 19.9% (69) with NLR>6.0, 30.6% (106) between 3.0 and 6.0, and remaining 49.4% (171) with NLR<3.0. The distribution of NLR was found to be associated with SOB symptoms and low ejection fraction, the demographic and clinical characteristics of patients stratified by admission NLR are presented in Table 1.

During the hospital course, new ST-T changes were observed in 3.5% (12) out of which 8 patients had NLR<3.0, 3 had NLR between 3.0 and 6.0, and 1 patient had NLR>6.0 ($p = 0.424$). Arrhythmias were observed in 5.8% (20) out of which 8 patients NLR>6.0, 5 had NLR between 3.0 and 6.0, and remaining 7 patients had NLR<3.0 ($p = 0.067$). The contrast induced nephropathy was observed in 4.9% (17) of the patients with 7 patients with NLR>6.0, 5 with NLR between 3.0 and 6.0, and 5 with NLR<3.0 ($p = 0.064$). In-hospital mortality was recorded in 1.4% (5) out of which 2 patients had NLR>6.0 and 3 patients had NLR<3.0 ($p = 0.260$). The in-hospital outcomes and complications of patients stratified by admission NLR are reported in Table 2.

Area under the curve (AUC) on the ROC analysis for NLR was 0.414 [95% CI: 0.268 to 0.561; $p = 0.314$] for in-hospital new ST-T changes, 0.630 [95% CI: 0.495 to 0.756; $p = 0.051$] for in-hospital arrhythmias, 0.651 [95% CI: 0.517 to 0.784; $p = 0.036$] for CIN, and 0.592 [95% CI: 0.325 to 0.860; $p = 0.478$] for in-hospital mortality.

4. Discussion

This study was conducted to evaluate the potential role of NLR for risk stratification of patients with non-STE ACS who are prone to develop complications and adverse events during their hospital course. Nearly 1/5th (19.9%) of the patients were categorized as high-risk individuals with NLR of more than 6.0 and over 30% of the individuals were labeled as intermediate-risk groups with NLR between 3.0 and 6.0. The distribution of most of the clinical and demographic characteristics were not statistical significant among the three risk strata except for the SOB symptoms and ejection fraction. The distribution of NLR was found to be associated with SOB symptoms and low ejection fraction. In-hospital arrhythmias were higher (but not statistically significant) in patients with NLR of >6.0 (11.6%) compared to the patients in intermediate (4.7%) and low-risk (4.1%) group. Similarly, we observed higher (but not statistically significant) incidence of CIN (10.7%) in high-risk groups compared to intermediate (4.7%) and low-risk (2.9%) group. In-hospital mortality was found to be 2.9% in high-risk group compared to 0.0% and 1.8% in intermediate and low-risk group. NLR showed a moderate degree of predictive value for in-hospital arrhythmias (AUC = 0.630) and CIN (0.651) but it has low predictive for in-hospital new ST-T changes (AUC = 0.414) in mortality (ACU = 0.592).

In contrast to our observation, the NLR was reported to have a significant role in prediction of outcomes of the patients with NSTEMI. A study by Avci BŞ et al. [13] reported NLR to be an independent predictor of in-hospital mortality with AUC of 0.783 [0.68–0.88] and a cutoff value of 3.625 was 84.2% sensitive and 66.3% specific in identifying in-hospital mortality. In addition to in-hospital mortality, NLR has been found to be a good prognostic marker for short- and long-term adverse major cardiovascular events (MACE). In study by Wang Z et al. [14], the NLR was found to be a significant and important predictor of MACE at one-year follow-up of patients with NSTEMI undergone elective PCI with AUC value of 0.72 (0.625–0.814) and adjusted

Table 1. Demographic and clinical characteristics of patients with non-ST ACS stratified by admission neutrophil to lymphocyte ratio (NLR).

	Neutrophil to Lymphocyte ratio (NLR)			P-value
	Low risk (NLR<3.0)	Intermediate risk (NLR: 3.0 to 6.0)	High risk (NLR>0.6)	
Total (N)	**171**	**106**	**69**	–
Sex				
Male	66.7% (114)	64.2% (68)	72.5% (50)	0.515
Female	33.3% (57)	35.8% (38)	27.5% (19)	
Age (years)	57.42 ± 10.11	57.25 ± 11.22	58.96 ± 11.06	0.531
20−50 years	22.2% (38)	26.4% (28)	21.7% (15)	0.435
51−60 years	45% (77)	39.6% (42)	33.3% (23)	
61−70 years	24.6% (42)	21.7% (23)	33.3% (23)	
>70 years	8.2% (14)	12.3% (13)	11.6% (8)	
Chest pain (CP)	90.6% (155)	89.6% (95)	82.6% (57)	0.192
CP duration (hours)	24 [IQR:12−48]	24 [IQR:5−48]	24 [IQR:5−48]	0.015
Shortness of breath (SOB)	21.6% (37)	22.6% (24)	40.6% (28)	0.007
SOB duration (hours)	48 [IQR:24−48]	24 [IQR:4−36.5]	24 [IQR:4.5−48]	0.045
Diagnosis				
Unstable angina	12.3% (21)	8.5% (9)	4.3% (3)	0.151
NSTEMI	87.7% (150)	91.5% (97)	95.7% (66)	
Admission ECG findings				
ST-T changes	73.1% (125)	71.7% (76)	82.6% (57)	0.222
Atrial fibrillation	0.6% (1)	1.9% (2)	1.4% (1)	0.596
TIMI Score	3 [IQR:2−4]	3 [IQR:2−4]	3 [IQR:2−4]	0.630
Co-morbid conditions				
Hypertension	70.2% (120)	68.9% (73)	69.6% (48)	0.974
Diabetes mellitus	50.3% (86)	50.9% (54)	56.5% (39)	0.670
Hyperlipidemia	7.6% (13)	7.5% (8)	8.7% (6)	0.953
Smoking	10.5% (18)	12.3% (13)	8.7% (6)	0.753
Heart failure	8.8% (15)	11.3% (12)	11.6% (8)	0.714
Prior myocardial infarction	26.9% (46)	19.8% (21)	23.2% (16)	0.400
Ischemic heart disease	33.9% (58)	28.3% (30)	24.6% (17)	0.316
CVA/stroke	1.2% (2)	0.9% (1)	1.4% (1)	0.954
Admission neutrophils	62 ± 9.54	76.72 ± 4.59	86.35 ± 3.21	<0.001
Admission lymphocyte	34.07 ± 8.16	18.9 ± 2.78	9.4 ± 2.67	<0.001
NLR	2.1 [IQR:1.7−2.2]	3.8 [IQR:3.7−4.8]	8.5 [IQR:7.2−11.3]	<0.001
Ejection fraction				
20−40%	31% (53)	40.6% (43)	53.6% (37)	0.006
40−55%	39.2% (67)	38.7% (41)	34.8% (24)	
55−65%	29.8% (51)	20.8% (22)	11.6% (8)	

NSTEMI = non-ST elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction, CVA = cerebral vascular accident, NLR = neutrophil to lymphocyte ratio, IQR = interquartile range.

Table 2. In-hospital outcomes and complications of patients with non-ST ACS stratified by admission neutrophil to lymphocyte ratio (NLR).

	Neutrophil to Lymphocyte ratio (NLR)			P-value
	Low risk (NLR<3.0)	Intermediate risk (NLR: 3.0 to 6.0)	High risk (NLR>0.6)	
Total (N)	**171**	**106**	**69**	–
In-hospital new ST-T changes	4.7% (8)	2.8% (3)	1.4% (1)	0.424
In-hospital arrhythmias	4.1% (7)	4.7% (5)	11.6% (8)	0.067
Bradyarrhythmia	62.5% (5)	20% (1)	37.5% (3)	0.298
Atrial fibrillation	37.5% (3)	60% (3)	37.5% (3)	0.675
VT/VF	25% (2)	20% (1)	50% (4)	0.738
PVCs	0% (0)	0% (0)	25% (2)	0.166
Contrast induced nephropathy	2.9% (5)	4.7% (5)	10.1% (7)	0.064
Need for dialysis	0% (0)	1.9% (2)	1.4% (1)	0.218
Hospital stay (days)	3 [IQR:2−4]	3 [IQR:2−4]	3 [IQR:2−4]	0.313
In-hospital mortality	1.8% (3)	0% (0)	2.9% (2)	0.260

VT/VF = ventricular tachycardia/ventricular fibrillation, PVCs = premature ventricular contractions, IQR = interquartile range.

OR of 1.307 [1.034–1.651]. Jun SJ et al. [15] reported a similar observation for MACE of 180 days of early invasive PCI for NSTEMI patients, in this study use of hemoglobin and NLR in combination provided a significant improvement to the risk stratification of patients. Similarly, in addition to NLR, monocyte-to-lymphocyte ratio (MLR) has been also reported to be and important predictor and combination of NLR and MLR can further improve the risk stratification of NSTEMI patients [16,17]. In a meta-analysis, Dentali F et al. [18] provided that the high admission NLR in NSTEMI patients is associated with higher risk of mortality with and OR of 6.41 [2.65–15.50]. Similarly, in another systematic review and meta-analysis by Dong CH et al. [19], OR of 1.26 [1.13–1.41] is reported for the prediction of medium to long-term against elevated NLR.

The NLR is its significance not only for the prediction of mortality but it is observed to be a strong predictor of various post procedure complications, such as CIN [20]. In our study NLR has moderate predictive power, when considered CIN, with an AUC of 0.651 [0.517–0.784]. Similar to our observations, Kurtul A et al. [20] also reported NLR as an important predictor of CIN with AUC of 0.787 [0.726–0.848] and on multivariable analysis, NLR>3.46 was found to be an independent predictor of CIN with adjusted OR of 2.63 [1.15 to 6.06] in addition to Estimated glomerular filtration rate and high sensitivity C-reactive protein (CRP).

Admission NLR can be also used for the prediction of complexity and burden of coronary artery diseases (CAD). In a study by Elamragy A et al. [21] Admission NLR >7.1 was found to be 100% sensitive and 94% specific in predicting severe CAD in patients with NSTEMI. Similarly, in another study, NLR was found to be associated with SYNTAX score but after adjustment for TIMI (Thrombolysis in Myocardial Infarction) score, the association between SYNTAX score and NLR become less evident [22].

The association of elevated NLR with poor long- and short outcomes can be postulated from ischemia-reperfusion (I/R) injury because of high absolute neutrophils generating MPO and relative deficiency of protective lymphocytes; several pathophysiological studies have proven no-reflow phenomena related to neutrophil activated microthrombi obstructing flow in microcirculation despite wide open epicardial major vessel and leading to adverse remodeling and depressed ventricular functions [23,24].

Our study have several limitations. Major one is observation single center experience with relatively small sample size. Lack of extensive clinical and laboratory workup to determine the cause of raise of NLR. Hence, further extensive studies are needed to ascertain the role of NLR for risk stratification in our population.

5. Conclusion

A significant number of non-ST ACS patients fall in the high-risk category of NLR. Although, the association between NLR and in-hospital mortality and adverse events was not statistically significant but relatively higher rates of events were observed in high risk group. As suggested in literature, use of NLR in combination with other readily available laboratory parameters such as hemoglobin and monocyte can improve the accuracy of prediction of adverse outcomes in non-ST ACS patients.

Author contributions

CONCEPTION: JJ, KIB. **LITERATURE REVIEW:** JJ, MTS, AMB, FA, VK. **METHODOLOGY**: JJ, MTS, PT, FA. **SOFTWARE**: JJ, PT, AA, VK. **ANALYSIS AND/OR INTERPRETATION**: JJ, PT, AA, VK. **INVESTIGATION**: JJ, KIB, MTS, AMB, PT, FA, AA, VK. **RESOURCES:** JJ, KIB, MTS, AMB, PT, FA, AA, VK. **DATA COLLECTION AND/OR PROCESSING:** MTS, AMB, FA, VK. **WRITER-ORIGINAL DRAFT**: JJ, AMB, PT, FA, AA, VK. **WRITING- REVIEW & EDITING:** JJ, KIB, AMB. **VISUALIZATION**: JJ, AA. **SUPERVISION**: KIB, AMB. **PROJECT ADMINISTRATION**: JJ, AA, VK. **FUNDINGS**: JJ, KIB.

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None to declare.

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