

Relation of neutrophil-to-lymphocyte ratio with coronary artery disease severity in patients undergoing coronary angiography

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Abstract

Background and Aims: Inflammation plays important role in atherosclerosis. Recently, neutrophil-to-lymphocyte ratio(NLR) has emerged as new inflammatory marker in identification of coronary artery disease(CAD). We aimed to evaluate correlation of NLR with CAD severity and propose suitable cut-off NLR for predicting CAD.

Methods: This cross-sectional study included 147 patients undergoing coronary angiography for angina with ischemic ECG changes. CAD severity was assessed by SYNTAX score and categorized into low, intermediate and high SYNTAX group. Neutrophil and lymphocyte count determined by BeneSphera analyser and NLR was calculated. Statistical analysis was performed using chi-square, ANOVA, Pearson's correlation test and logistic regression analysis.

Results: In 147 patients [mean age 61.27±12.87year (25-86 years);68% male],NLR ranged from 1.0 to 9.66[median 2.53(1.96-3.73 IQR), mean 3.21±1.86].The NLR (mean ± SD) in low, intermediate and high SYNTAX group were 2.35±1.27, 3.04±1.541, 4.72±2.07 respectively (p<0.0001).High SYNTAX group more frequently had diabetes mellitus, dyslipidemia, smoker, alcohol consumer, were older, and had significantly high neutrophil count, NLR values and low lymphocyte count. In univariate analysis, diabetes mellitus, NLR, neutrophil and lymphocyte count were predictors of high SYNTAX score. In the multiple logistic regression analysis, NLR >3[OR=17.36, 95% CI 6.7-44.5, p=0.001] was identified as independent predictor of high SYNTAX score. In ROC analysis, NLR ≥ 1.785 was best suitable cut-off to identify presence of CAD with sensitivity of 97.4% and specificity of 83.3%.

Conclusion: NLR correlated positively with presence and severity of CAD as assessed by SYNTAX score

Key Words: Neutrophil lymphocyte ratio, Coronary artery disease, SYNTAX score

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Introduction

Coronary artery disease (CAD) is leading cause of morbidity and mortality throughout world despite modern therapeutic advances.¹ CAD has a complex pathophysiology and inflammation plays fundamental role in initiating and progression of atherosclerosis.²

The relationship between various inflammatory markers and CAD has been established long ago.³ White blood cell (WBC) and subtypes are well known inflammatory markers that play a crucial role in pathogenesis of atherogenesis and atherothrombosis.⁴ Inflammatory markers, including WBC count, high neutrophil count and low blood lymphocyte count are associated with worse cardiovascular consequences in patients with CAD and these markers have been used for prediction of cardiovascular events in asymptomatic patients.⁵

Neutrophil-to-lymphocyte ratio (NLR) integrates two risk predicting parameters into one and have more value than individual parameter alone in prediction of coronary atherosclerotic burden.⁶ NLR is inexpensive and easily available and has been recently researched as a predictor of CAD severity.⁷ Irrespective of other biomarker levels, an elevated NLR was found to independently increase long term risk of mortality not only in patients with stable CAD but also in acute coronary syndrome (ACS) patients.⁸ There are no data available regarding this in Nepalese population.

The aim of this study is to explore the correlation of NLR with presence and severity of CAD in patients at risk undergoing coronary angiography (CAG).

Methods

This prospective, cross-sectional study was conducted at B. P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal from August 2019 to July 2020. All consecutive patients aged ≥ 20 years visiting emergency department or cardiology outpatient unit for typical angina and ECG showing signs of ischemia and/ or biomarker evidence of myocardial injury (elevated troponin I or creatine kinase-MB (CK-MB)) who underwent CAG were enrolled. Based on clinical history, patients having any known systemic infection, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, chronic inflammatory disease, hematopoietic system disorder, malignancy and/or treatment with chemotherapy, acute infection and history of using glucocorticoid therapy within the past three months were excluded. Patients were recruited as per medical ethics and informed written consent was taken from each patient. Institutional Review Committee had approved the study protocol before recruitment of patients.

The general objective of this study is to explore the correlation of NLR with presence and severity of CAD in patients at risk undergoing coronary angiography (CAG), and specific objective is to propose a suitable cut-off NLR values for predicting CAD.

Sample size was estimated based on the prevalence of CAD as 5% as shown by a previous study.⁹ Using Z value of 1.96 for confidence interval of 95% with 80% power and precision of 10%, the estimated sample size was 147 patients.

All patients underwent thorough detailed medical history, clinical evaluation, blood sampling, electrocardiography (ECG), echocardiography. Complete blood count and differential count, fasting blood sugar (FBS), post-prandial blood sugar (PPBS), glycosylated hemoglobin (HbA1c), renal function tests, lipid profile, troponin I and CK-MB of all patients were performed by standard methods. Neutrophil and lymphocyte count was analyzed by using BeneSphera analyser during emergency or outpatient department visit. Baseline NLR was measured by dividing neutrophil count to lymphocyte count.

All patients also underwent CAG as per American College of Cardiology /American Heart Association (ACC/AHA) guidelines.¹⁰ The coronary angiography films were reviewed by two on duty cardiologists. SYNTAX score which is angiographic index was used in grading the complexity of CAD and ranged from 0 to 83. Each coronary lesion with a diameter stenosis of at least 50%, in vessels at least 1.5 mm, was scored. The online latest updated version (2.1) was used for the calculation of the SYNTAX scores (www.syntaxscore.com).^{11,12} CAD severity was graded into three grades according to SYNTAX score. Low SYNTAX group was defined as those with SYNTAX score less than 22, Intermediate SYNTAX group as those having a SYNTAX score between 23 and to 32, and the high SYNTAX group as those with SYNTAX score above 32.

Case definition of CAD was based on the WHO European Acute Myocardial Infarction Registry criteria.¹³ Hypertension was defined as per 2017 ACC/ AHA task force guideline.¹⁴ Diabetes was defined as per 2017 American Diabetes Association guidelines.¹⁵ Dyslipidemia was defined as per 2017 American Association of Clinical Endocrinologists guidelines.¹⁶ Smokers were defined as anyone who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes.¹⁷

The collected data was entered in Microsoft excel 2007 and uploaded into Statistical Package for Social Sciences version 17 (SPSS Inc; Chicago, IL, USA). Values were expressed as number, percentage, mean \pm standard deviation or median (IQR). The chi-square test was used for comparison of categorical variables, Student's t-test was used to compare parametric continuous variables and Mann-Whitney U test or Kruskal-Wallis test was used to compare nonparametric continuous variables. Normal distribution was assessed by Kolmogorov-Smirnov test. Correlation analysis was performed by Pearson or Spearman's correlation test to document

the strength of correction. Multiple logistic regression analysis was used to identify the independent predictors of high SYNTAX score (>32). All variables showing significance values of less than 0.1 on univariate analysis was included in multiple logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off level of NLR to predict the CAD. Sensitivity, specificity of NLR was calculated to predict the coronary artery disease and logistic regression analysis was performed to determine the potential predictors of severe CAD. A value of $p < 0.05$ was considered statistically significant.

Results

Out of 147 patients [mean age 61.27 ± 12.87 year (25-86 years); 68% male], 59 (40.1%) had low SYNTAX score, 49 (33.3%) had intermediate SYNTAX score and 39 (26.6%) had high SYNTAX score. Common risk factors observed in CAD patients were hypertension (58.5%), diabetes mellitus (44.9%), smoking (39.5%), dyslipidemia (12.2%) and family history of IHD (4.1%). Intermediate and high SYNTAX score groups were older and had more diabetes mellitus, dyslipidemia, hypertension, smoker and alcohol consumer. Neutrophil counts and lymphocyte count differed significantly among SYNTAX scores groups ($p < 0.0001$) but mean WBC counts did not differ significantly although their counts were relatively high in intermediate and high SYNTAX score group. Similarly, there was no difference in LDL, serum creatinine and left ventricular ejection fraction (LVEF %) among SYNTAX score groups. The baseline characteristics of the three groups are presented in Table 1.

Table 1: Baseline Characteristics of Syntax Score groups

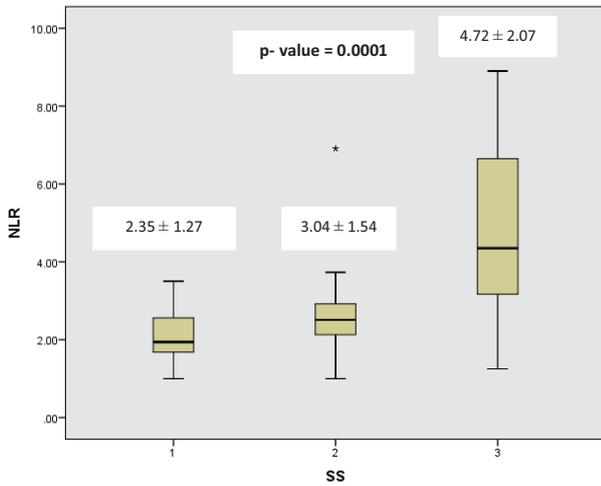
Variables	SYNTAX 1-22 (n=59)	SYNTAX 22-32 (n=49)	SYNTAX >32 (n=39)	p-value
Age, \pm SD years	58.12 \pm 13.019	62.96 \pm 12.29	64.05 \pm 12.66	0.07 ^a
Male, n (%)	38 (64.4)	36(73.4)	27(69.2)	0.69*
Diabetes mel- litus, n (%)	22(36.67)	22(38.77)	22(56.4)	0.17*
Hypertension, n (%)	30(50.8)	34(69.4)	22(56.4)	0.14*
Smoking, n (%)	22(36.7)	17(34.7)	19(48.7)	0.37*
Alcohol, n (%)	12(20.3)	12(24.4)	13(33.3)	0.45*
Family h/o CAD, n (%)	3(5)	1(2)	3(7.8)	0.17*
Dyslipidemia, n (%)	7(11.9)	6(12.2)	5(12.8)	0.99*
Creatinine, mg/dl	1.03 \pm 0.48	1.036 \pm 0.31	1.02 \pm 0.35	0.96 ^a
LDL, mg/dl	141.39 \pm 39.55	143.86 \pm 40.83	135.81 \pm 39.96	0.74 ^a
LVEF %	38.75 \pm 15.31	39.55 \pm 11.98	38.16 \pm 13.01	0.77 ^a
WBC Count/ cumm	9689.83 \pm 3378	9971 \pm 3483	10352 \pm 3234	0.75 ^a
Neutrophil/ cumm	5870.38	6668.36	7679.52	0.0001 ^a
Lymphocyte/ cumm	2795.51	2464.23	1890	0.0001 ^a

NLR	2.35±1.276	3.04±1.54	4.724±2.071	0.0001 ^μ
Aspirin use, n (%)	18(30.5)	18(36.7)	17(43.6)	0.41*
Statin, n (%)	18(30.5)	18(36.7)	16(41.0)	0.55*
B-Blocker, n (%)	11(18.6)	13(26.5)	15(38.5)	0.09*
ACEIs/ARB, n (%)	7(11.9)	10(20.4)	13(33.3)	0.036

p <0.05 considered as significant; SD: Standard deviation; NLR: neutrophil lymphocyte ratio, LDL: low density lipoprotein; WBC: white blood count; *chi-square test; μ ANOVA test

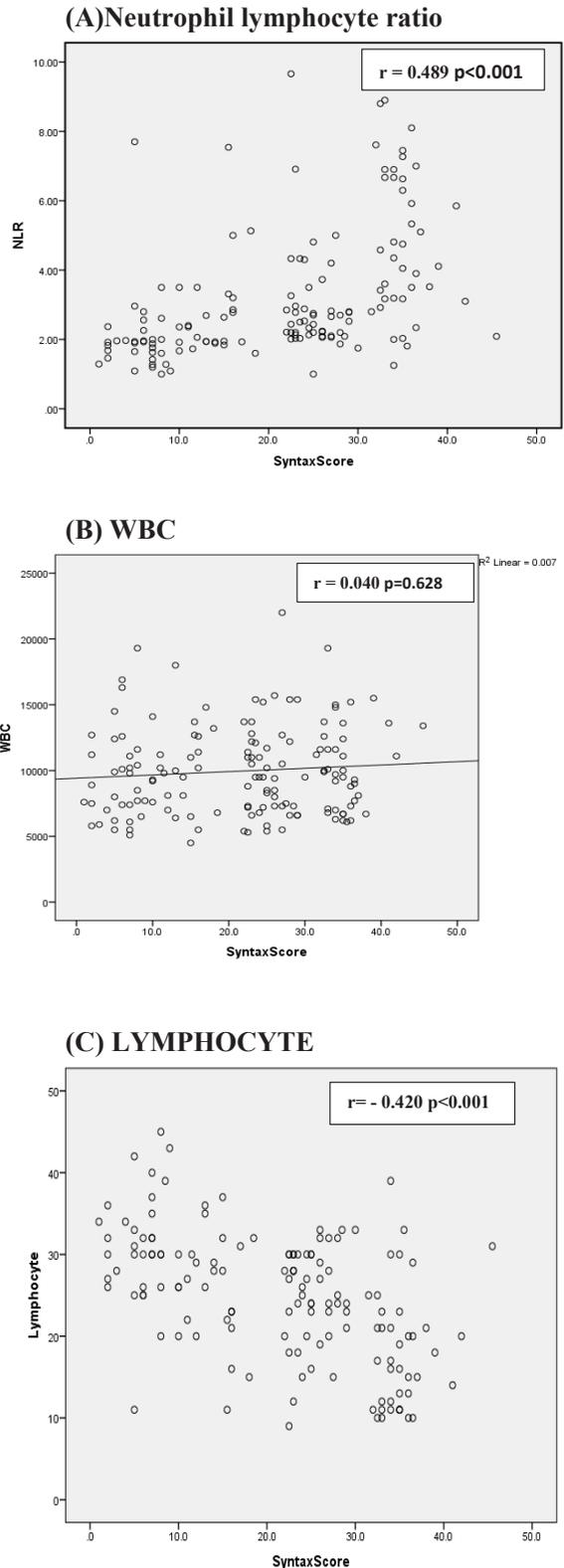
Out of 147 patients, 4.7% (n=7) of patients were diagnosed as chronic coronary syndrome and rest 95.3% (n=140) patients were diagnosed as acute coronary syndrome in present study. The NLR value [median (IQR) and mean] among 147 patients was 2.53 (1.96-3.73 IQR) and 3.21±1.86 respectively with minimum of 1.0 and maximum of 9.66. Thirty-eight patients (25.85%) had NLR below 2, 57 patients (38.78%) had NLR between 2 to 3 and 52 patients (35.37%) had NLR above 3. Mean NLR were 2.35 ± 6.98, 3.04 ± 1.54 and 4.796 ± 2.051 in low, intermediate and high SYNTAX score groups respectively (p-value =0.0001) (Figure 1).

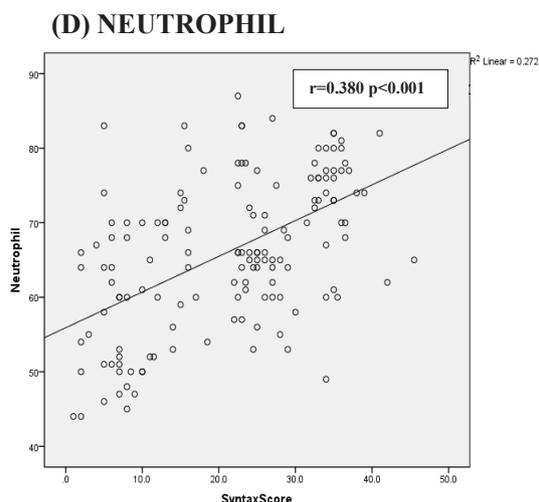
Figure 1: Comparison of mean NLR values among Low, Intermediate and High Syntax Score Groups



A positive significant correlation was found between high SYNTAX score >32 and NLR (r= 0.489 & P<0.0001) by Pearson’s Correlation test. Positive correlation was also found for neutrophil count (r= 0.380 & p<0.001) and WBC count (r= 0.040 & P=0.628). However, negative correlation was found between high syntax score and lymphocyte count (r= - 0.420 & P<0.001) (Figure 2).

Figure 2: Correlation between High Syntax Score (> 32) and WBC, its subtypes and NLR





Predictors of coronary artery disease severity

Univariate logistic regression analysis showed that diabetes mellitus, neutrophil count, lymphocyte count and NLR were predictive markers for high SYNTAX score (Table 2). In multivariate logistic regression analysis, only diabetes mellitus and NLR >3 were identified as independent predictors of high SYNTAX score. Among all the variables NLR >3 was found to be strongest predictor of CAD showing odds ratio of 17.36 (95% CI for OR: 6.77 – 44.49 p= 0.001) (Table 2).

Table 2: Univariate and multivariate logistic regression analysis of risk factors and laboratory parameters

A) Univariate Logistic Regression Analysis				
Predicting Variables	Syntax Score>32	Odds Ratio	95% CI	p-Value
Age group > 60yrs	58.9% (n=23)	1.28	0.613-2.70	0.50
Male Gender	69.2%(n=27)	1.07	0.48-2.37	0.85
Diabetes Mellitus	56.4%(n=22)	1.88	0.89-3.94	0.09
Hypertension	56.4%(n=22)	0.89	0.424-1.88	0.76
Smoking	48.7%(n=19)	1.68	0.80-3.53	0.68
Dyslipidemia	12.8%(n=5)	1.07	0.36-3.23	0.89
Creatinine	1.02±0.35	0.97	0.47-2.03	0.95
LDL	58.9% (n=23)	0.88	0.417-1.85	0.73
LVEF< 35%	48.7%(n=19)	0.96	0.47-2.05	0.97
WBC count	56.4%(n=22)	1.20	0.57-2.51	0.62
Neutrophil count	-----	Exp(B)=0.884	0.88-0.93	<0.001
Neutrophil > 66% (>50 th percentile)	84.6%(n=33)	7.7	2.97-19.91	<0.001
Lymphocyte count	-----	Exp(B)=1.17	1.10-1.24	<0.001

Lymphocyte > 26% (>50 th percentile)	15.4%(n=6)	0.107	0.04-0.27	<0.001
NLR	-----	Exp(B)=0.54	0.43-0.69	<0.001
NLR < 2	5.1%(n=2)	9.20	2.11 – 40.55	<0.001
NLR 2-3	15.4%(n=6)	4.21	1.90 – 12.70	<0.001
NLR>3	79.5%(n=31)	16.05	6.45 – 39.95	<0.001

B) Multivariate Logistic Regression Analysis			
Predicting Variables	Odds Ratio	95% CI for exp(B)	p-value (Significance)
Diabetes Mellitus	2.362	0.95 - 5.88	0.065
NLR >3	17.36	6.77 – 44.49	0.001

p <0.1 considered as significant; CI: confidence Interval; NLR: neutrophil lymphocyte ratio, LDL: low density lipoprotein; WBC: white blood count

Receiver Operative Curve (ROC) analysis

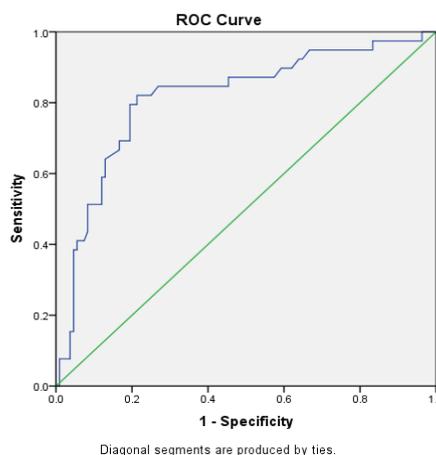
Among WBC and its subtypes, NLR was found to have highest area under curve (AUC) at 0.815 (95% Confidence Interval: 0.73-0.89, p <0.001) (Figure 2). In ROC analysis, NLR ≥ 1.785 was best suitable cut-off to identify the presence of CAD with a sensitivity of 97.4% and specificity of 83.3% (Table 3, Figure 3).

Table 3: Receiver Operative Curve (ROC) analysis of laboratory parameters

Variables	Area Under Curve	95% CI	p- value
WBC count	0.539	0.43 – 0.64	0.47
Neutrophil count	0.796	0.71 – 0.875	<0.001
Lymphocyte count	0.798	0.710 - 0.88	<0.001
NLR	0.815	0.733 – 0.89	<0.001

p <0.01 considered as significant; CI: Confidence Interval; NLR: neutrophil lymphocyte ratio

Figure 3: ROC (Receiver Operative Curve) analysis of predictive power of NLR for high SYNTAX score



Discussion

Our study demonstrated that NLR and neutrophil count correlated with coronary artery disease severity measured by SYNTAX score in patients undergoing coronary angiography and NLR was identified as independent predictor of a high SYNTAX score. Present study also showed that NLR of 1.785 or higher predicted CAD with a sensitivity of 97.4% and specificity of 83.3%.

Atherogenesis represents an active, inflammatory process rather than simply passive injury with infiltration of lipids.¹⁸⁻²⁰ Multiple studies have demonstrated a strong and consistent relationship between various inflammatory biomarkers and coronary artery disease.^{6,8,21} WBC count is an independent predictor of cardiovascular events and all-cause mortality without traditional cardiovascular risk factors.^{6,22-24} Neutrophil-to-lymphocyte ratio is a combination of two independent inflammatory biomarkers, could reveal more information that was not evident from the total leukocyte count.⁶ A higher neutrophil-to-lymphocyte ratio level suggested a higher inflammatory level.²⁵

Contrary to prior studies, in our study mean WBC counts did not differ significantly between SYNTAX scores groups although their counts were relatively high in intermediate and high SYNTAX score group.³ Our study reported significantly high NLR values, high neutrophil count and low lymphocyte count in patients with high SYNTAX score which was similar to previous studies.^{22,23,26-28} A positive significant correlation was also found between NLR, neutrophil count with high SYNTAX score and negative correlation found between lymphocyte count and high SYNTAX score which was comparable to prior studies.^{26,29}

NLR was reported as strongest predictor of CAD among all other studied variables, with odds ratio of 1.495 (95% CI: 0.942–2.371; $p=0.048$) and NLR value of 2.13 or higher predicted CAD with sensitivity and specificity of 83.64% and 63.46% in an Indian study.²⁶ Another study from China also reported NLR as independent predictor of presence of CAD and proposed a cut-off NLR value of more than 2.04 (AUC=0.63, 95% CI 0.59-0.67) with sensitivity of 69% and a specificity of 69%.³⁰ Similarly, study from Turkey also reported that among all other systemic inflammatory markers only NLR was the predictor of CAD showing odds ratio of 1.576 (confidence interval: 1.198–2.072, $p=0.001$) and proposed NLR of 2.3 or higher predicted CAD with sensitivity of 66% and specificity of 70%.²⁹ Another Turkish study proposed a cut-off NLR value of more than 1.95 (AUC=0.68, 95% CI 0.60-0.76) with sensitivity of 69% and a specificity of 69%.²³ These studies were comparable to present study.

Limitations

Firstly, our sample size was small and study was restricted to a single center and don't represent whole Nepalese population. Secondly, we did not have outcome related data. Thirdly, we did not assess cardiovascular risk factors such as carotid intima media thickness, ankle-brachial index and also did not measure other inflammatory markers like CRP in our study population. These factors may contribute to increased inflammatory process.

Conclusion

Neutrophil lymphocyte ratio is a simple inexpensive laboratory value that is strong predictor of presence of CAD in population at risk and correlated positively with CAD severity. This study also suggested NLR value of 1.785 or more as best suitable cut-off value in predicting presence and severity of CAD with a sensitivity of 97.4% and specificity of 83.3%.

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