

Original Research Article

Association between neutrophil to lymphocyte ratio with the severity of coronary artery diseases

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ABSTRACT

Background: Coronary artery disease is a type of heart disease where the arteries of the heart cannot deliver enough oxygen-rich blood to the heart. This study aimed to evaluate the association between neutrophil to lymphocyte ratio (NLR) with the severity of coronary artery diseases.

Methods: This cross-sectional study was conducted in the Department of Cardiology, Chittagong Medical College Hospital, Chattogram, Bangladesh during the period from 1 July 2020 to 31 June 2021. 160 patients undergoing elective coronary angiography with the symptoms of coronary artery disease were enrolled in this study. A purposive sampling technic was used. The association between NLR and Gensini score was assessed using Pearson's or Spearman's correlation analysis as appropriate. All data were processed, analyzed and disseminated by using MS Excel and SPSS version 23.0 program as per necessity.

Results: The mean (\pm SD) Gensini score of our participants was 42.75 (\pm 29.50) and the mean (\pm SD) NLR (Neutrophil-lymphocyte ratio) was 2.38 (\pm 1.11). In this study, the AUROC for NLR was found as 0.851 with a P-value of <0.001 , indicating a statistically significant association of NLR with the severity of CAD. The scatter dot diagram showed the correlation between NLR and Gensini score. Both the variables were positively correlated and the degree of correlation was found statistically significant ($r=0.44$; $p<0.001$) by Pearson's correlation test. The multivariate logistic regression analysis showed that a high level of NLR had an independent association with severe CAD (with OR being 3.308) along with dyslipidemia.

Conclusion: High blood NLR is associated with the severity of CAD and it may be useful for predicting angiographically severe disease.

Keywords: Association, Neutrophil, Lymphocyte, Severity, CAD, Coronary angiography

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of morbidity and mortality throughout the world accounting for more than 17 million deaths globally each year. It contributes to 30% of all deaths and 80% of those occur in

low-income and middle-income countries. This figure is expected to grow to 23.6 million by the year 2030. CAD alone caused 7 million deaths worldwide in 2010. It is an increase of 35% since 1990.¹ Burden of CAD is increasing everywhere even in some high-income countries where it was previously declining.² CAD is growing by epidemic proportions day by day in Bangladesh.³ The exact

prevalence of CAD in Bangladesh is not known but recent data indicates the CAD prevalence is 1.85% to 3.4% in the rural population and it is 19.6% in the urban population.⁴ Classification of CAD is typically done as stable ischemic heart disease (SIHD) and acute coronary syndrome (ACS). ACS is further classified into ST-elevation MI (STEMI), and Non-ST elevation ACS (NSTEMI).⁵ Atherosclerosis plays a dominant role in the pathophysiology of CAD. Studies have shown that CAD and atherosclerosis are closely associated with inflammation.⁶ As a complex inflammatory disease, atherosclerosis plays an important role in the onset, progression and complications of CAD.⁷ It has been found that elevated levels of inflammatory biomarkers are associated with increased rates of cardiac events in CAD patients.⁸ Recently, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a new addition to this inflammatory marker.⁹ The states of lymphopenia are associated with atherosclerosis progression, and the decrease in lymphocytes may be caused by apoptotic processes triggered during atherosclerotic lesions.¹⁰ On the other hand, the quantitative increase in neutrophils is also related to the atherogenic process, acting through lipid-mediated inflammation and secreting chemokines and cytokines. Neutrophil regulates intercellular adhesion molecule-1 and expresses myeloperoxidase, a protein that contributes to the formation of free radicals. It promotes greater low-density lipoprotein oxidation, exacerbating the pathological process.¹¹ Neutrophil activated by cholesterol crystals can expel Neutrophil Extracellular Trap (NET) which can destabilize plaque. NOD-like receptor protein 3 (NLRP3) inflammasome, a cytosolic multiprotein complex in the myeloid cell is activated by cholesterol crystals that mediate the release of two key cytokines IL-1 and IL-18.¹² Both of these are a predictor of a future cardiovascular event and key mediators in plaque development, progression and destabilization.¹³ Increased neutrophil count was shown to be associated with the presence and severity of coronary atherosclerosis.¹⁴ The objective of this current study was to evaluate the association between neutrophil to lymphocyte ratio with the severity of coronary artery diseases in patients undergoing elective coronary angiography.

METHODS

This was a cross-sectional study that was conducted in the Department of Cardiology, Chittagong Medical College Hospital (CMCH), Chattogram, Bangladesh during the period from 1 July 2020 to 31 June 2021. In total 150 patients undergoing elective coronary angiography due to symptoms related to coronary artery disease during the study period and fulfilling the inclusion and exclusion criteria were enrolled in this study as study subjects. The study was approved by the ethical committee of the mentioned hospital. Properly written consent was taken from all the participants before data collection. As per the inclusion criteria of this study, patients scheduled for elective CAG for their symptoms related to CAD and willing to participate in the study by giving written informed consent were included. On the other hand,

according to the exclusion criteria of this study, patients with evidence of any acute or chronic infection and inflammatory status and patients with systemic disease and medical treatment that can affect the WBC counts, patients with a history of using glucocorticoid therapy within the past three months and cases with congenital heart disease were excluded. Moreover, patients with valvular heart diseases, cardiomyopathy, first 4 weeks of ACS and previous history of revascularization and a history of chronic renal or hepatic disease were rejected. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count from the differential count of the CBC report. Analysis of the coronary angiograms was performed visually by 2 independent clinical observers (one of them is an experienced cardiologist). The severity of the CAD was assessed by using the vessel score and Gensini score.¹⁵ After collection, data were recorded in the form of an Excel worksheet. At the end of the data collection period, the Excel master sheet was fed into SPSS 23.0 software for processing and analysis. Significance levels were analyzed by student's t-test between two parameters and analysis of variance (ANOVA) test when parameters were more than two. The association between NLR and Gensini score was assessed using Pearson's or Spearman's correlation analysis as appropriate. The odds ratio (OR) and 95% confidence interval were calculated, p value <0.05 was considered significant.

RESULTS

In this study, among the total 160 participants, 74% were male whereas the rest 26% were female. So, the male-female ratio of the participants was 2.9:1.

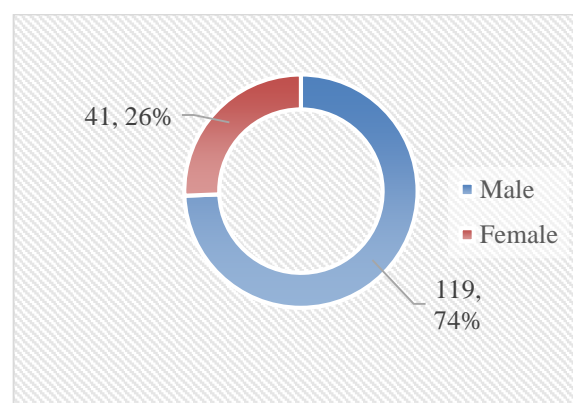


Figure 1: Distribution of the study patients by gender (n=160).

Age of the patients ranged from 30-78 years with a mean (\pm SD) of 51.7 (\pm 10.9) years. The majority of the patients (74.3%) were male with a male-to-female ratio of 2.9:1. Total WBC count, neutrophil count, lymphocyte count, NLR, serum creatinine, random blood sugar, serum LDL-C, serum HDL-C and Gensini score of the patients have been described in Table 1. It depicts that, the mean (\pm SD) NLR was 2.38 (\pm 1.11).

Table 1: Investigation profile of the studied patients (n=160).

Parameters	Mean (±SD)	Minimum-Maximum
Total WBC count, (×10 ⁹ /l)	9.50 (±2.1)	4.40-14.50
Neutrophil count, (×10 ⁹ /l)	5.86 (±1.81)	2.21-11.20
Lymphocyte count, (×10 ⁹ /l)	2.76 (±0.92)	1.04-5.39
NLR	2.38 (±1.11)	0.65-5.27
Random blood sugar, mmol/l	6.7 (±2.3)	4.0-15.0
LDL-C, mg/dl	114.7 (±26.9)	63.0-196.0
HDL-C, mg/dl	38.6 (±6.1)	26.0-80.0
Creatinine, mg/dl	1.00 (±0.21)	0.60-1.60

NLR: Neutrophil to lymphocyte ratio, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol.

As per the angiographic evaluation, among our total participants (n=160), 27 (16.9%) patients had no significant stenosis in any of the major coronary arteries. The mean (±SD) Gensini score was 42.75 (±29.50).

Table 2: Coronary angiographic findings of the patients (n=160).

CAG parameters	N (%)
Significant CAD	
Absent	27 (16.9)
Present	133 (83.1)
Number of vessels involved in CAD	
No significant vessel involved	27 (16.9)
Single vessel	42 (26.2)
Double vessel	40 (25.0)
Triple vessel	51 (31.9)
Gnesini score	
Mean (±SD)	42.75 (±29.50)
Range	0-120.00
Stenosis severity	
Normal	27 (16.9)
Gensini score <30	27 (16.9)
Gensini score ≥30	106 (66.2)

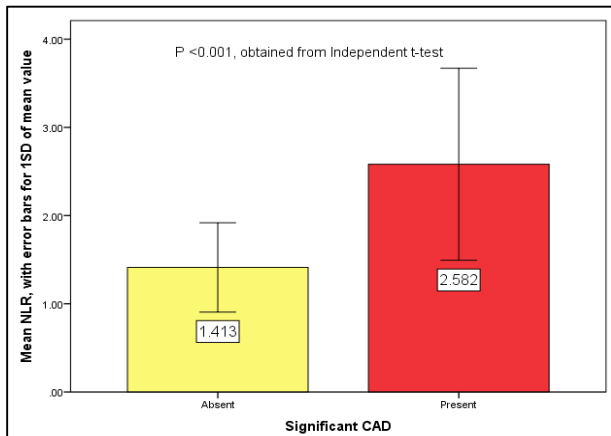


Figure 2: Relationship of NLR value with CAD.

The majority of the patients with significant coronary stenosis had Gensini score ≥30 indicating moderate to severe stenosis. Among them, the majority of the patients

had triple vessel disease (31.9%), followed by single vessel disease in 42 (26.2%) patients and double-vessel disease in 40 (25.0%) patients. In this study, the mean (±SD) NLR (Neutrophil-lymphocyte ratio) of our participants was 2.38 (±1.11).

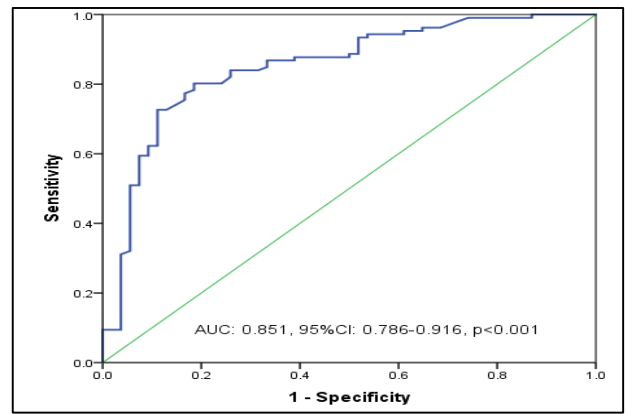


Figure 3: The receiver–operating characteristic (ROC) curve analysis of NLR for predicting severe CAD.

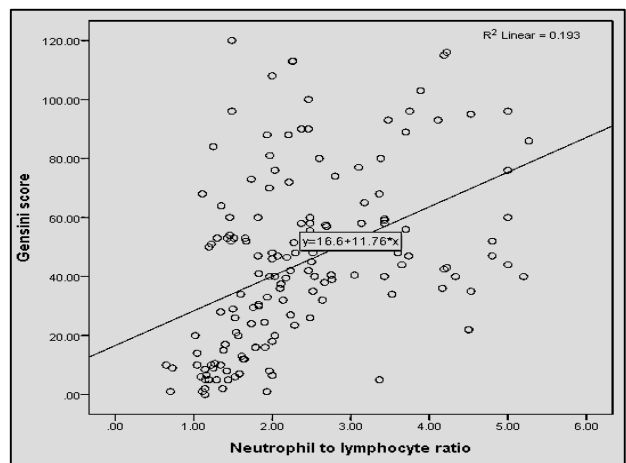


Figure 4: Scatter dot plot showing the correlation between NLR and Gensini score.

In this study, the AUROC for NLR was found as 0.851 with a P-value of <0.001, indicating a statistically

significant association of NLR with the severity of CAD. The cut-off value of NLR 1.94 had a sensitivity of 80.4% and a specificity of 81.5% for the detection of moderate to severe stenosis (Gensini >30). The scatter dot diagram showed the correlation between NLR and Gensini score. Both the variables were positively correlated and the degree of correlation was found statistically significant ($r=0.44$; $p<0.001$) by Pearson's correlation test. To further evaluate the correlation between NLR and angiographic severity of CAD a multivariate logistic regression analysis was performed. Variables that were found to have a significant association in univariate analysis were entered into the model. It showed a high level of NLR had an independent association with severe CAD (with OR being 3.308) along with dyslipidemia.

DISCUSSION

This study aimed to evaluate the association between neutrophil to lymphocyte ratio (NLR) with the severity of coronary artery diseases. Regarding the demographic and clinical presentation of the patients undergoing elective CAG present study has found that the majority of patients (74.3%) were male with a mean age of around 51 years. The study showed that 61.3% of patients were smokers, 55.6% of the patients had hypertension, 41.9% had diabetes mellitus, and 37.5% had dyslipidemia. Similar demographic and risk factors distribution were also reported by other studies conducted in another tertiary hospital in Bangladesh.^{4,16} In the current study correlation

coefficient between NLR and Gensini score was $r=0.44$ ($p<0.001$). This positive correlation was in agreement with other similar studies. The study conducted by Kaya et al.¹⁷ found a similarly significant relationship between NLR and Gensini score ($r=0.422$, $p<0.001$). In another similar study including patients with chronic stable angina correlation coefficient between NLR and Gensini score was 0.65¹⁶. Moreover, the Gensini score had statistically significant correlations with NLR ($r=0.20$, $p=0.011$) in the study of Uysal et al.¹⁸ All of these studies confirmed that NLR has the potential of being a highly useful predictor of severe disease in patients with CAD. In the present study those with moderate to severe CAD had significantly higher NLR values; mean, 2.58 (± 1.10) when compared with the patients with mild CAD, NLR mean 1.85 (± 0.87) or control group with no significant stenosis, mean 1.41 (± 0.50); $p=0.010$). In the study of Kaya et al those in the severe CAD had significantly higher NLR values mean, 4.1(± 3.0); when compared with the mild atherosclerosis group, median, 2.4 (± 1.2); $p=0.010$) and the control group mean, 1.9 (± 0.6); $p<0.001$).^{17,18} Similar to the positive correlation with Gensini score present study also demonstrated a significant positive association between the number of vessels involved and NLR ($p<0.005$). In the present study, the patients with no vessel involvement had the least mean NLR, and the patients with DVD and TVD had the higher mean NLR. In the study of Iraniard et al, the patients with single-vessel CAD had the least neutrophil and the highest lymphocyte counts, and the patients with triple-vessel CAD had the highest neutrophil and the least lymphocyte counts.¹⁹

Table 3: Multivariate logistic regression analysis of determinants of severe CAD.

Variables of interest	B	SE	OR	95% CI for OR		P value
				Lower	Upper	
Diabetes	-0.384	0.528	0.681	0.242	1.917	0.467
Dyslipidemia	1.258	0.585	3.519	1.118	11.079	0.032
NLR	1.196	0.356	3.308	1.645	6.653	0.001

OR: Odds ratio; CI: Confidence interval.

In this study in multivariate logistic regression analysis, NLR was found to have an independent association with severe CAD with an OR of 3.308. In the multiple logistic regression analysis of the study of Uysal et al, high levels of NLR (OR:1.450; 95% CI:1.080 to 1.945; $p=0.013$) were revealed as independent predictors of severe atherosclerosis.¹⁸ Datta et al reported from their multivariate logistic regression analysis, after adjustment of factors, age >50 years, hypertension, dyslipidemia and NLR were found the independent predictors of severe CAD with ORs being 3.27, 3.71, 4.95, and 5.73 respectively.¹⁶ In the ROC curve analysis, it was revealed that using a cut-off level of 1.94, NLR predicted severe CAD with a sensitivity of 80.4% and specificity of 81.5% (AUC: 0.851; 95% CI:0.786-0.916; $p<0.001$). Similarly, in the study of Uysal et al the ROC curve analysis revealed that NLR had good discriminating power to differentiate severe atherosclerosis with a sensitivity of 74% and

specificity of 53% using a cut-off level of 2.54 (AUC:0.627; 95% CI:0.545 to 0.704; $p=0.004$).¹⁸ All the findings of this current study may be helpful in further similar studies.

Limitations

Small sample size from only one hospital and randomization was not done. The other inflammatory biomarkers of the patients were not evaluated in the study. Assessment of the severity of CAD was performed by visual estimation of coronary angiography. Moreover, the study was conducted over a very short period.

CONCLUSION

As per the findings of this current study, we can conclude that high blood neutrophil to lymphocyte ratio (NLR) is

associated with the severity of coronary artery diseases (CAD) and it may be useful for predicting angiographically severe disease. For patients undergoing elective coronary angiography (CAG) with an NLR level of more than 1.94, physicians should pay more attention to appropriate management. Along with previous international recommendations, the present study supports the use of NLR as a simple, inexpensive, and easily obtainable biomarker to predict individuals at risk for advanced CAD. A further large-scale multicenter study from Bangladesh is necessary to validate the present research findings.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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