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Original Research Article

Association between neutrophil to lymphocyte ratio and severity of coronary artery disease

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ABSTRACT

Background: Atherosclerosis is a chronic systemic inflammatory disease. Neutrophil-to-lymphocyte ratio (NLR) is systemic inflammatory marker that is correlated with poor cardiovascular outcome. The aim of this study was to investigate the association between neutrophil to lymphocyte ratio (NLR) and severity of coronary atherosclerosis.
Methods: A total of 324 patients undergoing coronary angiography were included in the study. All the patients were included in study were divided into two groups based on the result of coronary angiography report. While 226 patients had abnormal coronary angiography (case) (78 female, mean age: 60.6±12.6 years), 98 patients had normal coronary angiography (control) (60 female, mean age: 57.2±10.9 years). NLR was calculated as the ratio of neutrophil count to lymphocyte count.
Results: Although age distribution was similar between the two groups
($p = 0.073$), female gender was significantly higher in the normal coronary angiography group ($p < 0.001$). Smoking history has shown a significant higher in cases compared to the normal coronary angiography ($p=0.001$). Patients with abnormal coronary angiography had significantly higher NLR when compared to patients with normal coronary angiography ($p<0.001$). NLR was significantly correlated with Gensini score. In logistic regression analyses, NLR was an independent predictor of CAD. An NLR of 2.34 or higher predicted the CAD with a sensitivity of 66% and specificity of 70%.
Conclusions: There is significant association between severity of coronary artery disease and neutrophils to lymphocyte ratio. This study suggests that the NLR is an independent predictor of coronary heart disease that may be useful for cardiac risk stratification in patients with coronary artery disease.

Keywords: Coronary artery disease, Coronary angiography, Gensini Score, Neutrophil-lymphocyte ratio

INTRODUCTION

Atherosclerosis is a complex inflammatory disease.[1] Inflammation plays a major role at all stages of coronary artery disease (CAD).[2] Coronary artery diseaseis the leading cause of morbidity and mortality throughout the world.[3,4] White blood cell count and its subtypes have been studied as inflammatory biomarkers to predict adverse cardiovascular outcomes.[5,6] Neutrophil to lymphocyte ratio (NLR) has recently emerged as new prognostic marker.[7] A number of studies have suggested that NLR was associated with adverse outcomes in patients undergoing coronary angiography, in those with stable and unstable CAD and also in patients undergoing percutaneous coronary intervention or coronary artery bypass grafting.[8-10] The relationship between NLR and CAD has been shown in several studies, but there are only few data available with severity of coronary atherosclerosis measured using Gensini scores. In the present study, we evaluated the association between NLR and severity of coronary atherosclerosis using the Gensini Score in patients undergoing coronary angiography.

METHODS

The present study is a single-center, observational study and was conducted at super speciality hospital, BMCRI, Bangalore, India, during Aug 2015 to April 2017. The study population consisted of 234 eligible consecutive patients who underwent coronary angiography for suspected or known coronary atherosclerosis. Exclusion criteria were clinically significant valvular heart disease, significant congestive heart failure, hematological disease, cancer, severe renal or liver disease, ongoing infection or systemic inflammatory conditions, and autoimmune disease. All participants gave an informed consent and the study was approved by local ethics committee.

Clinical variables and cardiovascular risk factors patients enrolled in the study underwent detailed clinical examination for the assessment of the cardiac status and history of smoking, family history of CAD, previous myocardial infarction, hypertension, diabetes mellitus, and noncardiac diseases.

Arterial hypertensionwas considered in patients with repeated blood pressure measurements >140/90mmHg or active use of antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose levels more than 126mg/dL in multiple measurements or active use of antidiabetic medications. Smokingwas defined as current smoking. The family history of CAD was considered as a history of CAD or sudden cardiac death in a first degree relative before the age of 55 years for men and 65 years for women. Acute coronary syndrome (ACS) was defined as presentation with symptoms of ischemia in association with qualifying electrocardiographic changes or positive cardiac enzymes.

Laboratory measurement

Blood samples (venous) were collected before the day of coronary angiography for analysis of the following parameters using standard techniques

- White blood cell, neutrophils and lymphocyte counts, total cholesterol, high - density lipoprotein cholesterol, low-density lipoprotein cholesterol. Triglycerides (TG), hemoglobin.
- NLR was calculated by dividing Neutrophil count to lymphocyte count.
- The whole blood samples for hematological indices were analyzed on an automated blood cell counter
- Biochemical parameters were analyzed using automated analyzer.

Coronary angiography and severity of coronary atherosclerosis

Coronary angiography was performed by Judkins technique through femoral artery access. Each angiogram was evaluated by 2 interventional cardiologists who were blinded to the study plan and to each other. A thorough review of each index coronary angiogram established lesion location and percentage of stenosis among all the coronary lesions. The CAD was defined as the presence of significant stenosis, at least 50% of the vessel diameter, in any of the main coronary arteries, in accordance with the American college of cardiology/American heart association lesion classification.[11]

The Gensini scoring system was used to determine the severity of CAD.[12] This method defines narrowing of the lumen of the coronary arteries as 1 for 1% to 25% stenosis, 2 for 26% to 50%, 4 for 51% to 75%, 8 for 76% to 90%, 16 for 91% to 99%, and 32 for total occlusion.

The score is then multiplied by a factor representing the importance of the lesion's location in the coronary artery system. For the location scores, 5 points were given for left main lesion; 2.5 for proximal left anterior descending (LAD) or left circumflex (LCX) artery;1.5 for the mid-segment LAD and LCX;1 for the distal segment of LAD and LCX, first diagonal branch, first obtuse marginal branch, right coronary artery, posterior descending artery, and intermediate artery; and 0.5 for the second diagonal and second obtuse marginal branches.

Coronary angiography revealed that there was coronary Stenosis-abnormal CAG in 226 patients (case) and normal coronary arteries in remaining 98 (control group).

Statistical analysis

Statistical analysis was performed using the SPSS 23.0 statistical package for windows. Continuous data were expressed as mean ±standard deviation (SD), while the categorical data by percentage. Student t-test used to compare the parametric variables, correlation analysis was performed by the Pearson correlation test.

RESULTS

The study population consisted of 324 consecutive patients undergoing elective coronary angiography (CAG). All members of the study population were divided into two groups according to the results of CAG. While 226 patients had abnormal CAG, 98 patients had normal CAG. Baseline characteristics and clinical data are shown in (Table 1). Although age distribution was similar between two groups (p=0.073), female gender was significantly higher in the normal CAG group (p<0.001). While diastolic blood pressure was significantly higher in the normal CAG group (p = 0.005), smoking status was significantly higher in the abnormal CAG group (p = 0.001).

The laboratory findings and NLR values are shown in (Table 1). Patients with abnormal CAG had significantly higher NLR when compared to patients with normal CAG (p<0.001). Patients with abnormal CAG had

significantly higher creatinine and significantly lower high-density lipoprotein (HDL), when compared to patients with normal CAG. In correlation analysis, NLR was significantly correlated with GENSINI score (Table 2).

Table 1. Baseline characteristics and clinical data of the study population.

	Case n=226	Control group n=98	P-value
Age (years)	60.6 ± 12.6	57.2 ± 10.9	0.073
Female gender	78 (34%)	60 (58%)	<0.001
Coronary risk factor			
Family h/o cad, n (%)	45 (20)	12 (13)	0.535
Smoking	120 (53)	30 (29)	0.001
Hypertension			
Systolic	135.9 ± 23.0	141.3 ±18.9	0.051
Diastolic	74.5 ± 11.9	78.2 ± 18.9	0.005
Diabetes	120 (53)	22 (22)	0.500
Biochemical parameters			
Total cholesterol, mg/dl	209.5 ± 506	208.4 ± 498	0.256
LDL	132.6 ± 39.2	126.2 ± 34.6	0.565
HDL	40.3 ± 9.2	45.9 ± 12.2	0.001
TG	180.0 ± 65.0	177.6 ± 60.0	0.557
Glucose-fasting	121.5 ± 42.6	119 ± 43.9	0.752
Creatinine	0.98 ± 0.30	0.87 ± 0.35	<0.001
Haematological parameters			
Haemoglobin(g/dl)	14.02 ± 1.6	13.95 ±1.3	0.354
WBC count (cumm)	9.06 ± 2.43	7.01 ± 1.89	0.001
Neutrophil count	6.20 ± 2.85	4.62 ± 2.01	<0.001
Lymphocyte count	2.03 ± 0.75	2.45 ±0.81	<0.001
Platelet count(cumm)	220.4 ± 48.3	234.4 ± 65.8	0.233
NLR	3.7 ± 2.6	2.2 ± 1.7	<0.001

Table 2: Correlation of neutrophil-to-lymphocyte ratio with severity of coronary artery disease.

	Gensini score	
	r	**p**
Neutrophil-to-lymphocyte ratio	0.413	0.001

Table 3: Logistic regression analysis to determine the independent predictors of abnormal coronary angiography.

	Odds ratio	95% confidence interval	P-value
Age (year)	1.023	0.993 – 1.054	0.134
Neutrophil-to-lymphocyte ratio	1.514	1.145 – 2.002	0.004
High-density lipoprotein	0.951	0.920 – 0.983	0.003
Creatinine	2.537	0.858 – 7.503	0.092

We included NLR, age, HDL, and creatinine into multivariate analysis to determine the independent predictors of CAD. In logistic regression analyses, NLR and HDL were independent predictors of CAD (Table 3). ROC analysis was performed to determine the cut-off value of NLR to predict the CAD. A NLR of 2.3 or higher predicted the CAD with a sensitivity of 66%and specificity of 70% (Figure 1).

DISCUSSION

In the present study, we demonstrated that patients with abnormal CAG had significantly higher NLR compared to patients with normal CAG. Moreover, NLR was correlated with severity of CAD. NLR was an independent predictor of CAD.

It is clear that inflammation plays a pivotal role in atherosclerosis.[13] It causes not only cardiovascular disease, but also numerous chronic diseases such as cancers, diabetes mellitus, hypertension, connective tissue disease, and chronic kidney disease.[14-18]

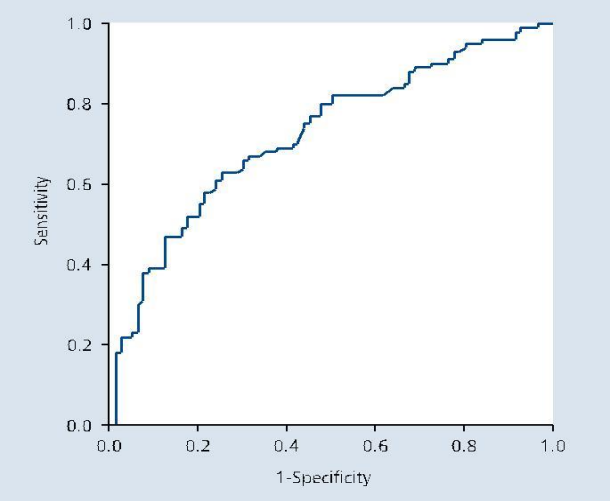

Figure 1: Receiver operating characteristic analysis for neutrophil-to-lymphocyte ratio to predict abnormal coronary angiography (area under curve is 0.726).

In the initiation of atherosclerotic plaque formation, inflammatory molecules are released from endothelial cells of vessels and cause vascular damage. Besides the early phase of atherosclerosis, inflammatory molecules also play an important role in the formation of thrombosis due to plaque rupture in ACS.[19,20] Therefore, it is not surprising that inflammatory markers increase in patients with cardiovascular disease. Although numerous inflammatory markers including CRP, tumour necrosis factor alpha (TNF-a), interleukin (IL)-1, and IL-6 are known as indicators of inflammatory process, recent studies have shown that WBC count and its subtypes are also useful for predicting the inflammatory process in cardiovascular diseases.[21] Leukocytes play an important role in inflammatory processes, and neutrophils are the most abundant type of WBC.

The NLR, which can be derived from the WBC count, is a common, cheap, and reproducible test worldwide. Previous studies have shown that NLR is associated with poor clinical outcomes in various cardiovascular diseases. In a study that included 300 patients who were admitted to hospital with ACS, higher NLR was associated with higher 30-day in-hospital mortality.[22]

Another study reported by Cho et al showed that use of combination of NLR and haemoglobin provided valuable information for early risk stratification in patients with ST elevation myocardial infarction (STEMI). Patients with higher NLR and anaemia had higher mortality rate at six months compared to patients with lower NLR and without anaemia. After coronary artery bypass surgery, NLR is useful to predict saphenous vein graft disease. Recently published trials established that NLR was associated with increased mortality and poor prognosis in ACS, especially STEMI. Previous studies have shown that severity of CAD is correlate with higher NLR value. Kaya et al showed that NLR is a predictor of severe atherosclerosis, which may be useful for cardiac risk stratification in patients with CAD. They showed significant correlation between NLR and GENSINI score.

In another study, Sönmez et al showed that NLR is a strong clinical laboratory value that is associated with the presence and complexity of CAD. Papa et al demonstrated that lower HDL was independent prognostic factor for mortality in patients with stable CAD. Yan et al showed fasting glucose as a significant determinant of Gensini score in nondiabetic participants. In a recent study, Kocaman et al showed that NLR was independently related with increased age, glucose, and serum uric acid levels.[23-25] As shown in previous studies, we found that glucose, HDL, and NLR are independently related with severity of atherosclerosis.

The main limitations of this study are the limited number of study participants, and participants were from 1 center rather than multiple centers and cross-sectional study design. We evaluated atherosclerosis only by coronary angiography. Angiography also has its limitations since only the lumen is displayed and the information it provides about the coronary plaque burden is not extensive. Therefore, further studies with intravascular ultrasound and coronary computerized tomography may provide more accurate information on the amount of coronary atherosclerosis. Another limitation of this study was that, it provides no information regarding cause or effect relationship between NLR and atherosclerosis. Although we found significant associations, further studies are needed to investigate clinical significance of NLR on atherosclerosis.

CONCLUSION

Patients with CAD had significantly higher NLR compared to patients with normal CAG. Moreover, NLR was correlated with severity of CAD. NLR of 2.34 or higher was an independent predictor of CAD. NLR seem to be simple parameters to evaluate severity of CAD in patients undergoing elective CAG, and it could be part of cardiovascular evaluation before coronary angiography.

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