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Relation between neutrophil-to-lymphocyte ratio and severity of coronary artery stenosis

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ABSTRACT. This study aimed to investigate the relation between the neutrophil-to-lymphocyte ratio (NLR) and the severity of coronary artery stenosis. A total of 219 patients were included in the study, comprising 51 coronary artery atherosclerosis (CAC) patients, 92 stable angina pectoris (SAP) patients, and 76 acute coronary syndrome (ACS) patients. Based on the results of coronary angiography, all patients were divided into two groups according to the Gensini scores: the low-score group (N = 142) and the high-score group (N = 77). The NLR was computed from the ratio of neutrophils and lymphocytes from the complete blood count. The association between the NLR and severity of coronary artery disease was assessed using correlation analysis and logistic regression. The NLR was higher in ACS patients than in SAP and CAC patients ($P < 0.05$). In addition, the NLR was higher in the high-score group than in the low-score group ($P < 0.05$). Correlation analysis showed that the NLR was significantly correlated with the Gensini score. After multivariate analysis, high NLRs were independent predictors of high Gensini scores, together with age and high-density lipoprotein. A cutoff NLR of 2.385 predicted high Gensini scores with a sensitivity and specificity of 64 and 63%, respectively. The study suggests that the NLR is an independent

predictor of coronary heart disease that may be useful for predicting the severity of coronary artery stenosis.

Key words: Neutrophil-to-lymphocyte ratio; Coronary artery disease; Gensini score

INTRODUCTION

Atherosclerosis is the major cause of cardiovascular disease that still accounts for most of the mortality worldwide (Lopez et al., 2006). Recent studies on atherosclerotic plaques show that atherosclerosis is a complex pathophysiology wherein the inflammatory process plays an important role in the onset and progression of the disease (Libby et al., 2009). It is well known that elevated levels of inflammatory markers are associated with increasing rates of cardiac events in patients with coronary artery disease (CAD) (Hatmi et al., 2010). As a representative indicator of inflammation in the body, the neutrophil-to-lymphocyte ratio (NLR) has been newly used as a biological sign to predict coronary heart disease (Gibson et al., 2010). A series of studies show that a high NLR is an independent risk factor for the progression of atheromatous plaque lesions, in-stent restenosis, cardiac death after percutaneous coronary intervention or coronary artery bypass surgery, and development of cardiac events in acute coronary syndrome (ACS) (Gibson et al., 2007; Muhmmed Suliman et al., 2010; Guasti et al., 2011; Kalay et al., 2012; Turak et al., 2012). The relation between NLR and CAD has been shown in several studies; however, most of these studies focus on the significance of this relation in diagnosing ACS or predicting the outcome instead of the severity of coronary stenosis. In this study, we evaluated the relation between the NLR and severity of coronary stenosis using the Gensini score in patients undergoing coronary angiography.

MATERIAL AND METHODS

Study population

The study population consisted of 288 consecutive patients who underwent coronary angiography for suspected or known coronary atherosclerosis between January 2012 and December 2012. All patients recruited in this study underwent coronary angiography due to chest pain with objective signs of ischemia. The exclusion criteria were Gensini score = 0 (N = 22), previous coronary artery bypass grafting (N = 6), percutaneous coronary intervention (N = 17), significant congestive heart failure (N = 9), hematological disease (N = 5), cancer (N = 1), severe renal or liver disease (N = 3), ongoing infection or chronic inflammatory disease (N = 5), and autoimmune disease (N = 1). Finally, the study population consisted of 219 patients, comprising 51 coronary artery atherosclerosis (CAC) patients, 92 stable angina pectoris patients (SAP), and 76 ACS patients. All participants gave informed consent, and the study was approved by the local Ethics Committee. Evaluations were visually performed by two experienced cardiologists. Patients' laboratory and clinical characteristics, such as age, gender, previous diabetes mellitus, hypertension, hypercholesterolemia, smoking, family history of cardiovascular disease, height, and weight, were accessed through the medical records. Arterial hypertension was considered in patients with repeated blood pressure measurements >140/90 mmHg or current use of antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose levels >126 mg/dL on multiple measurements or current use of antidiabetic medications. Smoking

was defined as current smoking. Family history of CAD was considered to be 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. ACS was defined as presentation with symptoms of ischemia in association with qualifying electrocardiographic changes or positive cardiac enzymes.

Gensini score

Coronary angiography was performed using the Judkins technique through a coronary intensive care unit (Vivid 7; GE Medical System, Norway). Each angiogram was evaluated by two interventional cardiologists who were blinded to the study plan and to each other. A thorough review of each index coronary angiogram established the lesion location and percentage of stenosis of the coronary lesions. CAD was defined as the presence of significant stenosis of 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. The Gensini scoring system was used to determine the severity of coronary artery stenosis (Gensini, 1983). 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 location in the coronary artery system. For the location scores, 5 points were given for a left main lesion; 2.5 for the 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 the 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. The 219 patients with coronary stenosis were divided into two groups according to the Gensini scores: the low-score group (N = 142; Gensini score 1-50) and the high-score group (N = 77; Gensini score >50).

Laboratory data

On admission, venous blood was obtained from all patients. Levels of neutrophils, lymphocytes, platelets, red blood cells, and white blood cell (WBC) were measured as part of the automated complete blood count before starting any medication. The NLR was calculated as the ratio of the neutrophils and lymphocytes, both obtained from the same automated blood sample at admission. All measurements were performed 30 min after blood collection using an automatic blood counter (Sysmex K-1000; Block Scientific, USA). Plasma levels of triglyceride, low-density lipoprotein, high-density lipoprotein (HDL), uric acid (UA), and creatinine (Cr) were measured using an automated chemistry analyzer (Abbott Aeroset, USA) with commercially available kits (Abbott, USA).

Statistical analysis

Continuous variables are reported as means ± SD. Categorical variables are expressed as percentages. To compare parametric continuous variables, the independent sample *t*-test or the Mann-Whitney U-test was used. One-way analysis of variance or the Kruskal-Wallis test was used to compare the three groups. The chi-square test was used to compare the categorical variables. Multivariate logistic regression analysis was used to identify the independent predictors of high Gensini scores. All variables showing significance values <0.05 in uni-

variate analysis were included in the multivariate model, and results are shown as an odds ratio (OR) with 95% confidence intervals (CI). The receiver-operating characteristic (ROC) analyses were used to determine the cutoff NLR in the prediction of high Gensini scores. Association between variables was tested using the Spearman or Pearson correlation coefficient, when appropriate. Two-tailed P values <0.05 were considered to be statistically significant. All statistical studies were carried out with the SPSS program (version 17.0; SPSS, IBM, USA).

RESULTS

The study population consisted of 219 patients with coronary stenosis (mean age: 62.45 ± 10.23 years). Baseline demographic, biochemical, and hematological characteristics of the three kinds of patients are outlined in Table 1. According to age, gender, and coronary risk factors, the proportion of male patients and smoking cases were higher in ACS patients than in CAC and SAP patients ($P < 0.05$). Smoking and diabetes cases were higher in SAP patients than in CAC patients ($P < 0.05$). The biochemical and hematological characteristics showed that UA, WBC, neutrophil, and NLR were higher in ACS patients than in CAC and SAP patients ($P < 0.05$), whereas HDL levels and lymphocyte levels were lower in ACS patients ($P < 0.05$). Compared with CAC patients, SAP patients showed a lower HDL level ($P < 0.05$) and ACS patients showed a higher Cr level. When the patients were divided into two groups, we observed that age, proportion of male patients, levels of UA, Cr, neutrophils, and NLR were higher in the high-Gensini-score group than in the low-Gensini-score group, whereas lymphocyte and HDL levels were lower in the high-Gensini-score group ($P < 0.05$, Table 2). In the correlation analysis between the NLR and Gensini score, significant correlations were found between them. After multivariate analysis, high NLR was an independent predictor of severe atherosclerosis (OR: 1.246, 95%CI = 1.054-1.471, $P < 0.05$) together with age (OR: 1.055, 95%CI = 1.021-1.089, $P < 0.01$) and HDL (OR: 0.155, 95%CI = 0.030-0.809, $P < 0.05$; Table 3). Using a cutoff NLR of 2.385, severe atherosclerosis was predicted with a sensitivity of 63.6% and specificity of 62.7% (ROC area under curve: 0.658, 95%CI = 0.583-0.733, $P < 0.05$; Figure 1).

Table 1. Baseline characteristics of different kinds of patients.

Variables	CAC patients (N = 51)	SAP patients (N = 92)	ACS patients (N = 76)	P value
Age (years)	62.04 ± 9.41	61.42 ± 9.38	64.20 ± 12.20	0.217
Male [N, (%)]	24 (47.10)	54 (58.70)	59 (77.60)[bc]	0.001
Smoking [N, (%)]	7 (13.70)	30 (32.60)[a]	42 (55.30)[bc]	<0.001
Hypertension [N, (%)]	33 (64.70)	61 (66.30)	49 (64.50)	0.965
Diabetes [N, (%)]	4 (7.80)	21 (22.80)[a]	15 (17.10)	0.076
TC (mM)	4.87 ± 1.04	4.96 ± 1.09	4.78 ± 1.11	0.540
TG (mM)	1.96 ± 2.14	1.98 ± 1.26	1.71 ± 1.04	0.484
HDL (mM)	1.18 ± 0.26	1.09 ± 0.19[a]	0.96 ± 0.20[bc]	<0.001
LDL (mM)	3.01 ± 0.93	3.07 ± 0.89	3.15 ± 0.99	0.677
UA (μM)	305.89 ± 83.31	327.23 ± 90.30	359.68 ± 101.00[ac]	0.004
Cr (μM)	72.91 ± 16.95	76.06 ± 15.63	80.33 ± 19.82[a]	0.060
WBC ($x10^9$/L)	6.06 ± 1.65	6.41 ± 1.69	7.63 ± 2.70[ac]	<0.001
RBC ($x10^{12}$/L)	4.23 ± 0.44	4.32 ± 0.51	4.25 ± 0.57	0.537
PLT ($x10^9$/L)	176.65 ± 46.12	175.98 ± 52.68	188.05 ± 64.03	0.325
N (%)	59.58 ± 11.30	59.98 ± 8.99	67.70 ± 10.04[ac]	<0.001
L (%)	29.40 ± 9.26	29.40 ± 8.20	22.34 ± 8.00[ac]	<0.001
NLR	2.56 ± 2.11	2.34 ± 1.19	3.64 ± 1.94[ac]	<0.001

CAC = coronary artery atherosclerosis; SAP = stable angina pectoris; ACS = acute coronary syndrome; TG = triglyceride; TC = total cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; UA = uric acid; Cr = creatinine; WBC = white blood cell count; RBC = red blood cell count; PLT = platelet; N = neutrophil; L = lymphocyte; NLR = neutrophil-to-lymphocyte ratio. [a]$P < 0.05$ compared with CAC patients. [b]$P < 0.01$ compared with CAC patients. [c]$P < 0.05$ compared with SAP patients.

Table 2. Baseline characteristics of the two Gensini score groups.

Variables	Low-Gensini-score group (N = 142)	High-Gensini-score group (N = 77)	P value
Age (years)	61 ± 10	66 ± 10	0.001
Male [N, (%)]	79 (56)	59 (77)	0.002
HDL (mM)	1.11 ± 0.23	1.00 ± 0.19	<0.001
UA (μM)	320 ± 88	364 ± 99	0.001
Cr (μM)	75 ± 16	81 ± 20	0.008
N (%)	61 ± 10	66 ± 10	0.001
L (%)	29 ± 9	24 ± 8	0.002
NLR	2.5 ± 1.6	3.4 ± 2.0	0.001

For abbreviations, see legend to Table 1.

Table 3. Multivariate logistic regression analysis to assess predictors of high Gensini score.

Variables	Odds ratio (95%CI)	P value
Age (years)	1.055 (1.021-1.089)	0.001
HDL (mM)	0.155 (0.030-0.809)	0.027
NLR	1.246 (1.054-1.471)	0.010

95%CI = 95% confidence interval. For other abbreviations, see legend to Table 1.

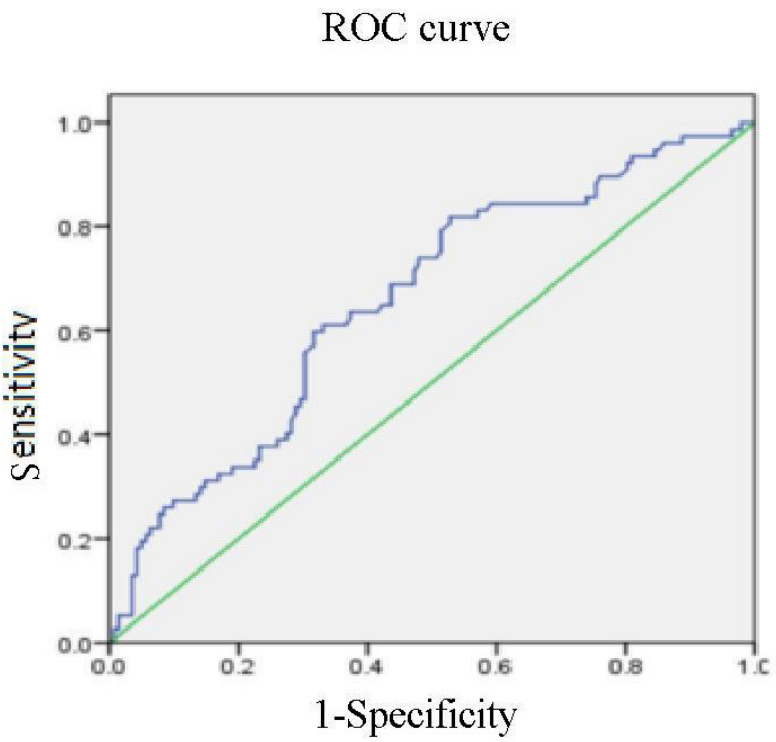

Figure 1. Receiver-operating characteristic (ROC) curve analysis of neutrophil-to-lymphocyte ratio for predicting high Gensini scores.

DISCUSSION

The NLR has been proposed as a new prognostic marker in patients with CAD. In our study, we demonstrated that the NLR is higher in severe CAD. Moreover, the NLR is higher in patients with higher Gensini scores. Furthermore, we found that the NLR is an independent risk factor for high Gensini scores. There is an association between the NLR and Gensini score in patients with CAC. Additionally, our study showed that NLRs >2.385 predicted high Gensini scores. Coronary angiography is the gold standard for the clinical judgment of CAD, whereas the Gensini score is a quantitative indicator for the estimation of the severity of coronary artery stenosis on the basis of coronary angiography (Gensini, 1983). To the best of our knowledge, the present study is the first to evaluate the relation between the NLR and severity of coronary artery stenosis in patients with CAC regardless of whether CAD could be diagnosed.

Coronary artery stenosis caused by coronary atherosclerotic plaque formation is the important pathophysiological basis of myocardial ischemia in CAD patients. Although cell proliferation secondary to endothelial damage has been recognized as the trigger for the formation of atherosclerotic lesions, many factors have been currently shown to be involved in the inflammatory process at the onset and progression of this event (Libby et al., 2009; Zanardo et al., 2011). Previous studies showed that WBC count and its subtypes are indicators of systemic inflammation and have an important role in modulating the inflammatory response in the atherosclerotic process (Horne et al., 2005). Neutrophils are purported to play an active role in the initiation and evolution of coronary arterial plaques (Baetta and Corsini, 2010). Evidently, certain biological characteristics of nascent coronary plaques serve as potent stimuli for neutrophil activation and homing to the evolving lesion (Mayadas et al., 2009). These plaque-infiltrating neutrophils are capable of accelerating the atherosclerotic process, and correspondingly, experimental depletion of neutrophils can decelerate the process (Drechsler et al., 2010; Soehnlein, 2012). Multiple studies have proposed that neutrophilia may be a chronic, adaptive response to myocardial ischemia (Horne et al., 2005). Lymphocytes also play a crucial role in modulating the inflammatory response in the atherosclerotic process (Sahin et al., 2013). Leukocytosis affects CAD through multiple pathological mechanisms, including inflammation, oxidative damage to the endothelial cells, microvasculature, and hypercoagulability (Ates et al., 2011).

The NLR is a combination of two independent markers of inflammation: neutrophils as a marker of the ongoing nonspecific inflammation and lymphocytes as a marker of the regulatory pathway (Nunez et al., 2008; Azab et al., 2010). A higher NLR indicates a higher level of inflammation (Imtiaz et al., 2012). The NLR reveals information that is not evident from the total leukocyte count. The NLR was also associated with arterial stiffness and coronary calcium score (Park et al., 2011). Unlike many other inflammatory markers and bioassays, the NLR is an inexpensive and readily available marker that provides an additional level of risk scores in predicting the severity of coronary artery stenosis.

Limitations

This is an observational, single-institution study with a relatively small sample size and was thus subject to various unaccounted confounders inherent in such analysis. Additionally, the diagnostic value is not very significant, both in sensitivity and specificity. Therefore, these findings must be confirmed with a study involving a larger number of patients.

CONCLUSION

Our study showed that the NLR may provide additional prognostic value in patients with coronary atherosclerotic disease, and that increased NLR is associated with severe coronary artery stenosis. The determination of the NLR for the preliminary diagnosis of the severity of CAD during hospitalization may be useful. We think that the significant findings of our analysis can serve as a guide for future clinical practice.

Conflict of interests

The authors declare no conflicts of interest.

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