Use of the neutrophil to lymphocyte ratio for prediction of in-stent restenosis in bifurcation lesions

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Abstract. – OBJECTIVE: Percutaneous coronary interventions (PCI) are the preferred treatment for coronary artery disease, even though the development of in-stent restenosis (ISR) continues to be an important complication. Neutrophil to lymphocyte ratio (NLR) is indicative of the inflammatory process and can predict the short- and long-term prognosis of cardiovascular diseases. We investigated the relationship between ISR development and neutrophil-lymphocyte ratio (NLR) in bifurcation lesions in stable coronary artery disease (CAD) patients.

PATIENTS AND METHODS: We analyzed the clinical and angiographic data of 181 consecutive stable CAD patients who had undergone successful PCI to the true bifurcation lesion from January 2010-December 2012. Patients were divided into two groups based on the development of ISR (group 1, ISR –; group 2, ISR +).

RESULTS: NLR_{after} ($p < 0.001$) and NLR_{Δ} ($p < 0.001$) were significantly higher in group 2. NLR_{Δ} was found to be significant independent predictor of ISR in the multivariate logistic regression analysis. A NLR_{Δ} level > 0.58 mg/dL had 81.8% sensitivity and 93.5% specificity for the prediction of ISR, as identified by the ROC curve. A NLRafter level > 3.43 predicted ISR with 45.5% sensitivity and 95.8% specificity. The comparison of ROC curve analysis demonstrated that NLRΔ was the strongest independent predictor of ISR ($p = 0.001$).

CONCLUSIONS: As a result, although drug eluting stent implantation is known to be recommended in the bifurcation lesion PCI in worldwide, we want to emphasize the usage of the NLR values in the prediction of ISR. So, we think that NLR_{Δ} levels may be a useful marker for the prediction of ISR in patients who undergo bifurcation PCI.

Introduction

Percutaneous coronary interventions (PCI) are the preferred treatment for coronary artery disease, even though the development of in-stent restenosis (ISR) continues to be an important complication[1]. While both clinical and angiographic factors contribute to the development of ISR, inflammation and pro-inflammatory molecules also play an important role[2,3]. Neointimal proliferation underlies the pathophysiological development of ISR and is triggered by the pro-inflammatory molecules released due to endothelial damage, particularly during the thrombogenic and proliferative phases of ISR[4].

Recent studies have shown that a white blood cell count that includes the neutrophil to lymphocyte ratio (NLR) is indicative of the inflammatory process and can predict the short- and long-term prognosis of cardiovascular diseases[5]. Although the relationship between various inflammatory biomarkers, including NLR, and the development of ISR has been investigated[6-8], no study has evaluated the effectiveness of the NLR change (NLR_{Δ}), defined as the NLR value before (NLR_{before}) and after (NLR_{after}) PCI intervention, in prediction of ISR in bifurcation lesions, which are at high risk for the development of ISR. In this study, we investigated the relationship between ISR development and NLR_{Δ} in bifurcation lesions in patients with stable coronary artery disease (CAD).

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Patients and Methods

We analyzed the clinical and angiographic data of 247 consecutive stable CAD patients who had undergone successful PCI to the true bifurcation lesion from January 2010-December 2012. During one-year of follow up, secondary angiography performed in 203 patients due to anginal symptoms and/or positive tests detecting ischemia. Clinical and angiographic data were compared between the first and second procedure in patients who underwent secondary coronary angiography. We excluded patients who had acute coronary syndrome, active infection, chronic inflammatory disease, malignancy, heart failure defined as left ventricular ejection fraction (LVEF) < 40%, renal dysfunction defined as serum creatinine levels > 1.5 mg/dl, chronic liver disease, chronic obstructive pulmonary disease, hematologic disease, acetylsalicylic acid (ASA) or clopidogrel resistance.

Due to the problems of reimbursement conditions of the drug eluting stent (DES) and/or the policy of health insurance system in our country during the years of the study, DES could not be performed to the bifurcation lesions of the most patients in our clinic. Therefore, risks of the alternative treatment modalities [Coronary artery bypass grafting and bare metal stents (BMS)] were explained to the patients, then further treatment was made. Thus, we excluded the patients who received a DES because of the study design. The patients to whom final balloon kissing angioplasty could not be performed were also excluded. During follow up, the patients with acute or sub-acute stent thrombosis were excluded. After applying these criteria, we assessed the remaining 181 patients.

Patients' baseline clinical and demographic data, and previous medical treatments were recorded. Hypertension was defined as blood pressure ≥ 140/90 mm/Hg or treatment with anti-hypertensive medications. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL or treatment with oral anti-diabetic drugs or insulin. Smokers were defined as current cigarette users or patients who had quit smoking within 1 month of the procedure. Heart failure was defined by transthoracic echocardiography in patients with LVEF < 40%. Pre- and post-operative complete blood cell count, white blood cell subgroups count, fasting blood glucose, urea, creatinine, high density lipoprotein, triglycerides, low-density lipoprotein, aspartate aminotransferase, and alanine aminotransferase

values were noted. True bifurcation lesions were defined as described previously[9].

All PCI procedures were performed by experienced interventional cardiologists who were blinded to the study design using the femoral artery approach recommended by the current guidelines[10] with 7-Fr sheath and 7-Fr guiding catheters. During PCI, the coronary bifurcation stenting technique, stent diameter, stent length, stent type, and pre- or post-dilatation decisions were left to the physician's discretion based on the current literature[11-15]. Before PCI, 300-mg ASA (p.o.), 300-mg clopidogrel (p.o.) and 100 U/kg unfractionated heparin (i.v.) (ACT > 250 sn) were administered to all patients.

Successful PCI was defined as > 20% reduction in stenosis and TIMI 3 flow in the main and side branch without any major complication (10). Stent thrombosis was classified according to Academic Research Consortium's definition in 2006[16]. ISR was defined as ≥ 50% in-stent late lumen loss 5 mm proximal to distal in the main branch or side branch[17].

Statistical Analysis

All analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were calculated as means ± standard deviation; categorical variables were defined as percentages. The Kolmogorov-Smirnov test was used to evaluate a normal distribution. An independent-samples t-test was used to compare continuous variables between the two groups. Non-parametric values were compared with the Mann-Whitney U test. The χ^2 test was used to compare categorical data. The effects of different variables on ISR were calculated using univariate analyses for each variable. The variables for unadjusted p-values < 0.10 were identified in multivariate logistic regression analysis as potential risk markers and included in the initial model. We reduced the model using backward elimination multivariate logistic regression analyses, and we eliminated potential risk markers using likelihood-ratio tests. A receiver operator characteristic (ROC) curve was constructed to determine the predictive value of NLR on ISR. A p-value < 0.05 was considered to indicate significance.

Results

In our study, we assessed 181 patients (male, 111 [61.6%]; female, 70 [38.4%]) who under-

went PCI for the true bifurcation lesion. Patients were divided into two groups based on the development of ISR (group 1, ISR –; group 2, ISR +). Clinical and hematological characteristics are shown in Table I. Although the NLR$_{before}$ was not different between the groups (group 1 = 2.40 ± 0.99 vs. group 2 = 2.38 ± 0.72, p = 0.869), the NLR$_{after}$ was significantly different (group 1 = 3.41 ± 0.96 vs. group 2 = 2.64 ± 0.46, p < 0.001) and the NLR$_{\Delta}$ was significantly higher in group 2 (1.02 ± 0.53 vs. 0.26 ± 0.30, p < 0.001)

The stenting technique, follow-up period and placement of the bifurcation lesion did not differ significantly between the two groups. In contrast, we found significant differences in the main and side branch inflation pressure (p = 0.034 and p = 0.024, respectively), main and side branch stent length (p = 0.011 and p = 0.015, respectively), main and side branch stent diameter (p = 0.015 and p = 0.009, respectively), and pre-intervention main and side branch lesion degrees (p = 0.028 and p = 0.018, respectively) between the two groups (Table II).

The predictors of ISR in the multivariable logistic regression analyses are presented in Table III. Because NLR$_{after}$ and NLR$_{\Delta}$ were both inflammatory markers, they were not considered together in the multivariate model. Therefore, two multivariate models including NLR$_{\Delta}$ (NLR$_{\Delta}$, model 1) and NLR after (NLR$_{after}$, model 2) were separately constructed. Among these, NLR$_{\Delta}$ was found to be significant independent predictor of ISR in the multivariate logistic regression analysis.

A NLR$_{\Delta}$ level > 0.58 mg/dL had 81.8% sensitivity and 93.5% specificity for the prediction of ISR, as identified by the ROC curve. The area under the ROC curve (AUC) was 0.918 (95% confidence interval [CI] = 0.868-0.953, p < 0.001). A NLR$_{after}$ level > 3.43 predicted ISR with 45.5% sensitivity and 95.8% specificity (AUC, 0.771; 95% CI = 0.703-0.830, p < 0.001). The ROC curve comparison of these two markers is shown in Figure 1. The comparison of ROC curve analysis demonstrated that NLR$_{\Delta}$ was the strongest independent predictor of ISR (difference between areas = 0.147, 95% CI = 0.059-0.234, p = 0.001).

Table I. Clinical and hematological characteristics of the according to development of in-stent restenosis.

Variables	Group 1 ISR NO (n=93)	Group 2 ISR YES (n= 88)	p value
Age	56.4 ± 12.4	55.3 ± 10.0	0.547
Sex male n (%)	51 (54.8)	60 (68.2)	0.066
HT n (%)	57 (61;3)	46 (52.3)	0.223
HPL n (%)	68 (73.1)	62 (70.5)	0.692
DM n (%)	21 (22.6)	34 (38.6)	**0.019**
Smoking n (%)	33 (35.5)	37 (42.0)	0.368
Family history n (%)	58 (62.4)	49 (55.7)	0.363
Statin n (%)	54 (58.1)	48 (54.5)	0.636
BB n (%)	54 (58.1)	47 (53.4)	0.531
ACEI-ARB n (%)	46 (49.5)	45 (51.1)	0.823
CCB n (%)	28 (30.1)	25 (28.4)	0.803
OAD n (%)	20 (21.5)	26 (29.5)	0.217
Insulin n (%)	6 (6.5)	8 (9.1)	0.509
Glucose	118.5 ± 47.4	135.1 ± 68.5	0.059
HDL	37.9 ± 6.9	36.9 ± 8.8	0.412
LDL	95.8 ± 30.1	100.3 ± 33.5	0.338
TG	148.6 ± 98.6	147.9 ± 105.4	0.961
Pre- interventional neutrophil count	5.04 ± 1.45	4.82 ± 1.79	0.350
Post-interventional neutrophil count	6.61 ± 2.31	9.99 ± 4.10	**< 0.001**
Pre- interventional lymphocyte count	2.19 ± 0.42	2.07 ± 0.45	0.083
Post-interventional lymphocyte count	2.55 ± 0.89	2.93 ± 0.93	**0.005**
NLR$_{before}$	2.38 ± 0.72	2.40 ± 0.99	0.869
NLR$_{after}$	2.64 ± 0.46	3.41 ± 0.96	**< 0.001**
NLR$_{\Delta}$	0.26 ± 0.30	1.02 ± 0.53	**< 0.001**
LVEF	50.6 ± 9.1	47.9 ± 7.3	**0.029**

HT: Hypertension; HPL: Hyperlipidemia; DM: Diabetes Mellitus; BB: Beta- Blocker; ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blockers; CCB: Calcium Channel Blockers; OAD: Oral Anti-diabetics; HDL: High Density Lipoprotein; LDL: low Density Lipoprotein; TG: Triglyceride; NLR: Neutrophil Lymphocyte Ratio.

Table II. Angiographical and procedural characteristics of study population.

Variables	Group 1 ISR (+) (n = 93)	Group 2 ISR (–) (n = 88)	p value
Bifurcation localizations, (%)			
LAD-Diagonal	74 (79.6)	62 (70.5)	0.319
Cx-OM	14 (15.1)	22 (25.0)	
RCA-PL-PDA	5 (5.4)	4 (4.5)	
Bifurcation area angles (°)			
Main branch-main branch angle	152.7 ± 16.2	149.4 ± 12.3	0.118
Main branch- side branch angle	149.2 ± 13.6	152.1 ± 17	0.205
Bifurcation angle	59.3 ± 19	60.2 ± 16.4	0.718
Carina angle	30.2 ± 13.9	28.2 ± 14.9	0.346
Bifurcation technique, (%)			
Minicrush	43 (46.2)	34 (38.6)	0.358
Flower petal	15 (16.1)	9 (10.2)	
Culotte	5 (5.4)	9 (10.2)	
T and protrusion	12 (12.9)	16 (18.2)	
Provisional	18 (19.4)	20 (22.7)	
Main branch inflation pressure (atm)	12.9 ± 3.0	12.0 ± 2.4	0.034
Side branch inflation pressure (atm)	12.7 ± 2.7	11.8 ± 2.3	**0.024**
Main branch stent length (mm)	18.9 ± 5.9	21.1 ± 5.3	**0.011**
Main branch stent diameter (mm)	3.4 ± 0.4	3.3 ± 0.4	**0.015**
Side branch stent length (mm)	14.2 ± 4.2	15.9 ± 4.6	**0.015**
Side branch stent diameter (mm)	2.9 ± 0.4	2.8 ± 0.3	0.009
Pre-intervention main branch stenosis degree %	81.5 ± 6.4	83.9 ± 8.5	**0.028**
Pre-intervention side branch stenosis degree %	67.1 ± 13.4	71.9 ± 13.7	**0.018**
Follow-up time (month)	9.6 ± 3.4	8.9 ± 3.9	0.224
Syntax score	16.6 ± 3.3	17.3 ± 3.9	0.184

LAD: Left Anterior Descending Arter; CX-OM: Circumflex- Obtus Marginalis; RCA: right CoronaryArtery; PL: Posterolateral; PDA: Posterior Descending Artery.

Table III. Significant predictors of stent restenosis in the multivariable logistic regression analyses.

Variables	Model 1 (NLR$_\Delta$)		Model 2 (NLR$_{after}$)	
	OR (95% CI)	p value	OR (95% CI)	p value
NLRΔ	13.03 (5.62-30.20)	**< 0.001**	–	–
NLR$_{after}$	–	–	6.98 (3.19-15.27)	**< 0.001**
DM	1.84 (0.56-6.02)	0.313	2.26 (0.89-5.71)	0.084
Age	0.99 (0.95-1.04)	0.947	0.98 (0.94-1.01)	**0.327**
Sex	0.50 (0.16-1.54)	0.229	0.59 (0.24-1.46)	**0.259**
LVEF	0.93 (0.88-0.99)	**0.043**	0.95 (0.90-1.00)	0.075
Main branch inflation pressure (atm)	1.01 (0.83-1.24)	0.864	0.98 (0.82-1.16)	0.818
Side branch inflation pressure (atm)	0.90 (0.72-1.12)	0.369	0.82 (0.68-0.98)	**0.034**
Main branch stent length (mm)	1.17 (1.04-1.31)	**0.006**	1.11 (1.02-1.20)	**0.010**
Side branch stent length (mm)	1.11 (0.96-1.28)	0.142	1.05 (0.95-1.16)	0.321
Main branch stent diameter (mm)	0.09 (0.01-0.51)	**0.007**	0.13 (0.03-0.49)	**0.002**
Side branch stent diameter (mm)	0.46 (0.10-2.11)	0.322	0.20 (0.05-0.75)	**0.017**
Pre-intervention main branch stenosis degree %	1.05 (0.96-1.15)	0.265	1.08 (1.01-1.15)	**0.015**
Pre-intervention side branch stenosis degree %	1.06 (1.01-1.11)	**0.015**	1.05 (1.01-1.09)	**0.005**

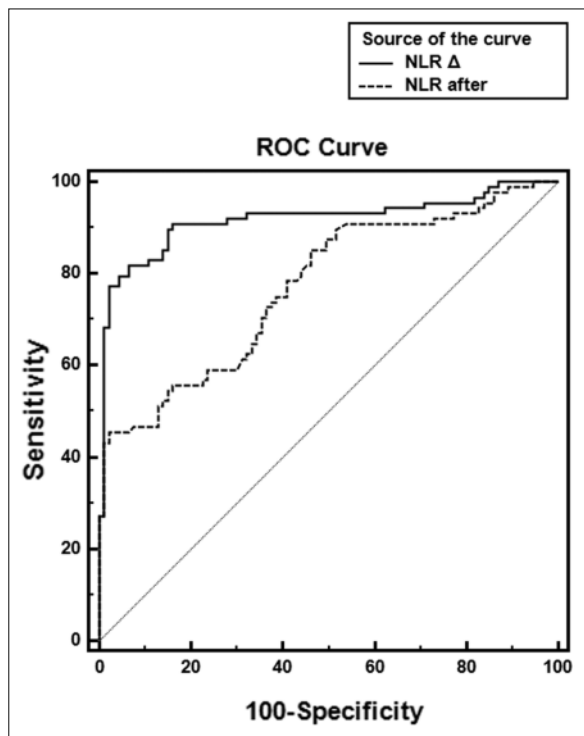NLR: Neutrophil to Lymphocyte Ratio; DM: Diabetes Mellitus; LVEF: Left Ventricular Ejection Fraction.

Figure 1. The pairwise comparisons of the ROC curves of the NLRΔ and NLRafter for prediction of the in-stent restenosis [difference between areas = 0.147, 95% CI = 0.059-0.234, $p = 0.001$]. NLR: Neutrophil to lymphocyte ratio.

Discussion

The primary finding of our study is that the NLR_Δ level was a better independent predictor than NLR_{after} level for the development of the ISR in patients who underwent PCI for bifurcation lesions. We did not find a relationship between the NLR_{before} levels and the development of ISR.

Restenosis can be generally defined as a healing response that occurs due to induced damage during transluminal coronary arterial revascularization[18]. Bifurcation lesions seen by coronary angiography constitute 20% of all lesions. However, since bifurcation lesions and stenting techniques are more complex than non-bifurcation lesions, they have lower probabilities of success and a high rate of ISR. Currently, bifurcation lesions constitute 15-20% of coronary lesions that undergo PCI[19,20]. Although bifurcation stenting with BMS results in significant technical success and patency rates in the acute phase, the restenosis rate ranges from 25-62% in both the main and side branch in these patients[15,19,21] In our study, the development rates of ISR were similar to those reported in the literature.

When lumen enlargement occurs, plaque compression or distal embolization of the plaque is seen during the PCI. Moreover, medial dissections and arterial wall injury accompany these processes[22]. Inflammation caused by barotrauma to the vessel wall during PCI is considered a mechanical model of plaque rupture, which increases the risk of future adverse coronary events, including ISR[23,24]. In addition to barotrauma and plaque rupture in the balloon and stent applications, vascular wall trauma caused by stent struts contributes to inflammation and a proliferative response[25-28]. Depending on endothelial damage during the PCI, increases in adhesive molecules and chemotactic factors are followed by the accumulation of inflammatory cells and pro-inflammatory molecules, such as interleukin-1 and -6, which mediate the development of neo-intimal proliferation[4]. Previous studies showed that even though angiographic and clinical factors may contribute, inflammation and the inflammatory response play the most important important role in the development of ISR[1].

As an inflammatory marker, pre-interventional C-reactive protein (CRP) levels were shown to predict ISR[6] and post-interventional CRP levels were associated with major cardiac events[29,30]. Furthermore, primary and secondary prevention studies showed that CRP levels predicted future cardiac events[31,32]. NLR has emerged as a less costly, more accessible inflammatory marker than CRP[33] and studies that evaluated NLR counts found these values to be associated with cardiovascular mortality during heart failure and stable CAD[34,35]. NLR was also indicated as a sensitive marker of inflammation associated with cardiovascular events in other studies[5,35-37].

Bifurcation lesions have a greater plaque burden and are also more complex interventional procedures; therefore, these lesions are associated with a greater inflammatory response than non-bifurcation lesions[19,38]. Although few studies have investigated the association between NLR and ISR, the role of NLR_{after} and NLR_Δ has not been assessed. Turak et al[8] examined the relationship between NLR_{before} and the development of ISR, and found that high NLR_{before} levels were independent predictors of ISR. However, that study included only acute coronary syndrome patients, which is caused by inflammatory processes. Our results showed that NLR_{before} levels did not predict the development of ISR in patients who underwent bifurcation PCI with the diagnosis of stable CAD.

NLR counts are influenced many factors such as obesity, smoking, gender and alchool consumption[39]. NLR and other inflammatory markers (CRP, interleukin-6, tumour necrosis factor-α) are prognostic indicators of cardiovascular diseases, and the significance is quite stronger especially when used in combination[40,41]. Gaspardone et al[42] showed that the severity of post-interventional inflammatory response using CRP values was significantly correlated with cardiovascular events in patients who underwent PCI. In our study, we evaluated the degree of inflammatory response using NLR values and found that the NLR_{after} level was an independent predictor of the development of ISR. Due to the study design, we evaluated the NLR changes, between the pre- and postoperative NLR levels, in CAD patients who undergo bifurcation PCI, so we believe that NLR_Δ is an adequate marker for the prediction of ISR and does not need further combination. Moreover, NLR_Δ values may be a biochemical indicator of plaque volume, changing plaque morphology, and endothelial trauma caused by stents and/or balloon applications in CAD patients who underwent bifurcation PCI.

Our study included only stable CAD patients treated with BMS. Though DES implantation is recommended in patients who underwent PCI for bifurcation lesions, we could not use DES for our study group due to economic considerations. Moreover, we could not use intravascular ultrasound to objectively visualize plaque structure, endothelial trauma and changes in plaque volume.

Conclusions

Although DES implantation is known to be recommended in the bifurcation lesion PCI in worldwide, we want to emphasize the usage of the NLR values in the prediction of high risk patients for ISR in the current study. So, we think that NLR_Δ levels may be a useful marker for the prediction of ISR in patients who undergo bifurcation PCI.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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