Neutrophil to Lymphocyte Ratio Predicts SYNTAX Score in Patients With Non-ST Segment Elevation Myocardial Infarction

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SUMMARY

In this study we aimed to investigate whether there is an association between the neutrophil to lymphocyte ratio (NLR) and severity of coronary artery disease (CAD) in patients with non-ST segment elevation myocardial infarction (NSTEMI) using the SYNTAX score (SXscore). A total of 414 patients with NSTEMI who underwent coronary angiography were enrolled in the study. NLR was measured for all patients at presentation. The study population was then divided into tertiles based on the SYNTAX trial results. The low syntax group (n = 329) was defined as those with an SXscore ≤ 22, the intermediate syntax group (n = 58) was defined as an SXscore ≥ 23 and < 33, and the high syntax group (n = 27) as those with an SXscore ≥ 33. NLR was significantly lower in patients with a low SXscore compared to patients with an intermediate SXscore or high SXscore (3.7 ± 4 to 4.6 ± 2 and 7.9 ± 4, P < 0.001). Linear regression analysis revealed that NLR (coefficient β = 0.380, 95%CI: 1.165-1.917, P < 0.001) was significantly associated with the SXscore in patients with NSTEMI. Our results indicate that NLR is independently associated with the severity of CAD in patients with NSTEMI. (Int Heart J 2015; 56: 18-21)

Key words: Inflammation, Plaque burden, Acute coronary syndrome

N on-ST segment elevation myocardial infarction (NSTEMI) is one of the leading causes of death in patients with coronary artery disease (CAD). Patients with NSTEMI tend to have multivessel CAD and similar cardiovascular mortality compared to patients with STEMI. Several treatment strategies including intensive medical treatment and invasive procedures have been successful in decreasing the morbidity and mortality of NSTEMI. However, the severity of CAD in coronary angiography is the leading factor in determining the most useful treatment strategy. The SYNTAX score (SXscore) is an anatomic scoring system which quantifies the properties of a lesion including complexity, morphology, and location in the coronary vasculature. It has been shown that the SXscore may predict short and long-term mortality in patients with CAD intervention. The role of inflammation in the initiation and progression of coronary atherosclerosis is well described. Increased levels of inflammatory markers have been found in association with the severity of coronary atherosclerosis and prognosis in acute coronary syndromes. The neutrophil to lymphocyte ratio (NLR) is an indicator of baseline inflammatory response. Although the predictive value of NLR on the severity of CAD in patients with STEMI and stable CAD is well known, its role in NSTEMI is less clear. Therefore, the aim of the present study was to investigate whether there is an association between NLR and severity of CAD in patients with NSTEMI using the SXscore.

METHODS

Patient selection: A total of 414 patients (292 males, mean age, 63.8 ± 12 years) were consecutively selected from among patients with NSTEMI who underwent coronary angiography in the catheterization laboratory of the Kayseri Education and Research Hospital between July 2012 and November 2013. The control group consisted of 35 patients (22 males, mean age, 64.4 ± 8 years) without CAD who underwent coronary angiography for anginal symptoms or suspected CAD in non-invasive tests. NSTEMI was defined as having typical chest pain and a positive troponin-I level (defined in our clinical laboratory as > 0.01 ng/mL) without any evidence of ST segment elevation on 12-lead electrocardiogram. To diminish any confounders that might influence NLR, patients with a history of congestive heart failure, previous percutaneous coronary intervention, coronary artery bypass grafting surgery history, active infectious disease, inflammatory or immunologic disease, cirrhosis, peripheral arterial disease, chronic obstructive pulmonary disease, chronic kidney disease, malignancy, or cardiogenic shock on admission were excluded.

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Biochemical analysis: Fasting blood samples (12 hours) were collected on the day of admission to the hospital. All measurements were performed within 30 minutes after blood collection. Complete blood count (Cell-Dyn 3700 System; Abbot, Abbott Park, Illinois), fasting blood glucose, creatinine levels, and lipid profile were analyzed for all patients using a Beckman-Coulter AU 2700 (Australia Pty Ltd, Sydney, Australia). High-sensitivity C-reactive protein (hsCRP) level was analyzed using a BN-II nephelometer (Siemens, Marburg, Germany).

Coronary angiography: Quantitative coronary angiography was performed using the Judkins technique by 2 experienced interventional cardiologists unaware of the clinic and laboratory results of the patients. Significant CAD was defined as > 50% stenosis in at least 1 coronary artery. Each coronary lesion producing a ≥ 50% luminal obstruction in vessels ≥ 1.5 mm was separately scored and added to provide the vessel SX-score. The SX-score was calculated using dedicated software.

Statistical analysis: Statistical analysis was performed using the SPSS software version 15 (SPSS Inc., Chicago, Illinois, USA). Continuous variables are presented as the mean ± standard deviation and categorical variables as a percentage. The variables were investigated using the Kolmogorov-Smirnov test to determine whether or not they were normally distributed. Continuous variables were compared using 1-way analysis of variance and the post hoc Tukey test. The chi-square test was used for univariate analysis of the categorical variables. Linear regression analysis was performed to identify the significance of the relation between the SX-score and several variables. The effects of different variables on in-hospital MACE were calculated using univariate analyses for each variable. The variables for which the unadjusted P value was less than 0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model using backward elimination multivariate logistic regression analyses, and we eliminated potential risk markers using likelihood ratio tests. A 2-tailed P < 0.05 was considered significant.

RESULTS

The clinical characteristics and laboratory parameters of the patients with NSTEMI and controls are listed in Supplemental Table I. Left ventricular ejection fraction (49 ± 8% to 61 ± 3.5%, P < 0.001) was significantly lower in patients with NSTEMI compared with controls. Also NLR (4.1 ± 3.9 to 2 ± 0.8, P = 0.002), mean platelet volume (MPV, 9.3 ± 1.3 fl to 8.2 ± 1.8, P < 0.001), and C-reactive protein (CRP, 21 ± 29 mg/L to 5.5 ± 4 mg/L, P = 0.002) were significantly higher in patients with NSTEMI.

Patients with a low SX-score were younger (62.2 ± 12 years to 69.6 ± 9 years and 69.9 ± 11 years, P < 0.001), had lower triglyceride levels (176 ± 88 mg/dL to 210 ± 123 mg/dL, and 214 ± 128 mg/dL, P = 0.013) and lower CRP levels (18 ± 26 mg/L to 29 ± 36 mg/L and 34 ± 36 mg/L, P = 0.003) compared to patients with an intermediate or high SX-score. Also, MPV was lower in patients with a low SX-score compared to patients with an intermediate SX-score (9.1 ± 1.3 fl to 9.6 ± 1.4 fl, P = 0.032) in post-hoc analysis. NLR was significantly lower in patients with a low SX-score compared to patients with a high SX-score (3.7 ± 4 to 7.9 ± 4, P < 0.001, Supplemental Figure 1, Supplemental Table II). In addition, when the patients were divided into 3 tertiles according to NLR values, patients with the highest NLR tertile had significantly higher peak CK-MB when compared with patients with the lowest and intermediate NLR tertiles (75 ± 12 to 55 ± 6 and 47 ± 13, P < 0.001, respectively).

Linear regression analysis revealed that NLR (coefficient β = 0.380, 95%CI: 1.165-1.917, P < 0.001), age (coefficient β = 0.222, 95%CI: 0.100-0.245, P < 0.001) and LDL cholesterol level (coefficient β = 0.104, 95%CI: 0.004-0.052, P = 0.024, Table I) were significantly associated with SX-score in patients with NSTEMI. Supplemental Figure 2 shows the association between NLR and SX-score. Multivariate logistic regression analysis revealed age, SX-score, and NLR were independent predictors of in-hospital MACE in patients with NSTEMI (Table II).

DISCUSSION

Our results clearly demonstrate that patients with NSTEMI had higher NLR compared to controls with normal coronary arteries. Our results also show that there is a significant

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<th>Table I. Independent Correlates of Variables With SYNTAX Score in Linear Regression Analysis</th>
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<td><strong>Coefficients β</strong></td>
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<td>Age (years)</td>
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LDL indicates low density lipoprotein cholesterol; and NLR, neutrophil to lymphocyte ratio.
association between NLR and severity of CAD in patients with NSTEMI. In this study we showed that patients with a high SXscore had higher NLR compared to those with a low intermediate SXscore in NSTEMI. Non-ST segment elevation myocardial infarction is one of the most frequent presentations of patients with CAD. Although in-hospital mortality in patients with NSTEMI is lower than those with ST segment elevation, 6-month mortality is similar. Moreover, 4-year mortality in patients with NSTEMI is two-fold higher than patients with ST segment myocardial infarction. Therefore, risk stratification, management of patients with NSTEMI in the acute phase, and long-term follow-up are crucial to prevent increased mortality and morbidity in these patients.

The SXscore, a lesion-based angiographic scoring system, has been introduced to grade the complexity of coronary artery disease. Since the initial trial, several trials have demonstrated that the SXscore can be used to risk-stratify patients with complex coronary disease. These studies have shown that patients with a relatively high SXscore have worse cardiovascular outcomes, and that the score is an independent predictor of MACE for percutaneous coronary intervention (PCI). Therefore, SXscore can be used in the selection of optimal treatment by identifying those patients at highest risk of adverse events following PCI.

The role of inflammation in the initiation and progression of coronary atherosclerosis is well described. High levels of inflammatory markers have been found in association with the severity of coronary atherosclerosis, prognosis in acute coronary syndromes, and prognosis after coronary interventions.

NLR has been proposed as a prognostic marker and shown to be related with a pro-inflammatory state and resultant worse clinical outcomes in cardiovascular disease. NLR has been evaluated as a prognostic marker for several cardiovascular diseases including coronary artery ectasia, stable CAD, NSTEMI, and STEMI. NLR has also been shown in association with complexity of CAD in patients with stable CAD and acute coronary syndromes. In a recent study, Sahin, et al showed that NLR was significantly associated with severity of CAD in patients with STEMI. They also showed that NLR was an independent predictor for SXscore in patients with STEMI. Another study conducted by Kaya, et al showed that NLR was significantly associated with both the presence and severity of CAD in patients with stable CAD. In a more recent study, Altun, et al. showed that in patients with acute coronary syndrome, high sensitive troponin T and NLR were significantly correlated with the severity of CAD.

Similar to previous investigations, our study demonstrates that NLR, an indicator of systemic inflammatory response, is significantly associated with severity of CAD and may predict the SXscore in patients with NSTEMI. To our knowledge the present study is the largest study investigating the role of NLR on SXscore in patients with NSTEMI. The role of inflammation in the initiation and progression of atherosclerosis is well established. During the early stages of atherosclerotic plaque development, inflammatory monocytes are provoked to move into the vascular wall by several adhesion and chemoattractant molecules released from endothelial cells. These monocytes differentiate to macrophages to contribute to the formation of the lipid core in advanced stages of atherosclerotic plaque development. In mature atherosclerotic plaque, various inflammatory mediators play a role in the expression of proteolytic enzymes which may weaken the fibrous cap and result in plaque rupture. With this background in mind, we suggest that the inflammatory state, represented by NLR, contributes to the formation of coronary atherosclerosis in patients with NSTEMI.

Our study has several limitations. First, this is an observational, single-institution, cross-sectional study. However, our study is the first to evaluate the relation between SXscore and NLR in homogenous unselected NSTEMI patients, therefore mirroring a real world scenario. Second, additional markers of inflammation were not assessed in our study. Also, the lack of longitudinal data regarding the association of NLR and prognosis of NSTEMI is another limitation of the study.

In conclusion, NLR is a widely available parameter around the world. In patients with NSTEMI, NLR was higher in the high-SXscore group than in the low-SXscore group and was independently associated with SXscore. Also, there was a significant correlation between the SXscore and NLR ratio. Thus, we suggest that patients with NSTEMI who have more atherosclerotic involvement also have a higher NLR and we also suggest that a preprocedural NLR, which is an inexpensive and universally available marker, can be used for the risk stratification of patients with NSTEMI. Additionally, these results might play an important role in better understanding the role of inflammation in the pathogenesis of atherosclerosis and may lead to improved treatment strategies in patients with NSTEMI.

**Disclosure**

Conflict of interest: None
REFERENCES


Supplemental Files
Supplemental Table I, II
Supplemental Figure 1, 2
Please find supplemental files: https://www.jstage.jst.go.jp/article/jhj/56/1/56_14-175/_article/supplement