Neutrophil to Lymphocyte Ratio Predicts Long-Term Clinical Outcomes in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Background and Objectives: A higher neutrophil to lymphocyte ratio (NLR) has been associated with poor clinical outcomes in various cardiac diseases. However, the clinical availability of NLR in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) has not been known. We evaluated the availability of NLR to predict clinical outcomes in patients with STEMI undergoing primary PCI.
Subjects and Methods: We analyzed 326 consecutive STEMI patients treated with primary PCI. The patients were divided into tertiles according to NLR: NLR≤3.30 (n=108), 3.31<NLR≤6.52 (n=108) and NLR>6.53 (n=110). We evaluated the incidence of major adverse cardiac events (MACE), a composite of all causes of death, non-fatal MI, and ischemic stroke at the 12-month follow-up.
Results: The high NLR group was associated with a significantly higher rate of 12-month MACE (19.1% vs. 3.7%, p<0.001), 12-month death (18.2% vs. 2.8%, p<0.001), in-hospital MACE (12.7% vs. 2.8%, p=0.010) and in-hospital death (12.7% vs. 1.9%, p=0.003) compared to the low NLR group. In the multivariable model, high NLR was an independent predictor of 12-month MACE {hazard ratio (HR) 3.33 (1.09-10.16), p=0.035} and death {HR 4.10 (1.17-14.46), p=0.028} after adjustment for gender, left ventricular ejection fraction, creatinine clearance, angiographic parameters and factors included in the Thrombolysis in Myocardial Infarction risk score for STEMI. There was a significant gradient of 12-month MACE across the NLR tertiles with a markedly increased MACE hazard in the high NLR group (log rank test p=0.002).
Conclusion: The NLR is a useful marker to predict 12-month MACE and death in patients with STEMI who have undergone primary PCI. **(Korean Circ J 2013;43:93–99)**

KEY WORDS: Neutrophils; Lymphocytes; Myocardial infarction.

Introduction

It has been demonstrated that inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein (CRP) and interleukin-6 are significantly associated with cardiovascular disease.[1)2)] Inflammation also promotes coronary atherosclerotic plaque rupture and thrombosis.[3)] Above all, white blood cell (WBC) count and its subtypes are widely known as classic inflammatory biomarkers to predict cardiovascular outcomes.[4)] In addition, the neutrophil to lymphocyte ratio (NLR) has been evaluated as a prognostic biomarker for various cardiovascular diseases.[5–8)] This ratio has also been studied in patients with acute coronary syndrome, non ST-segment

elevation myocardial infarction (STEMI).[9)10)] Moreover, a high NLR was a prognostic marker for poor clinical outcomes in patients with STE-MI.[11)] However, the previous study evaluated the prognostic value of NLR in STEMI patients who were mainly treated with thrombolysis or rescue angioplasty.[11)] The aim of this study was to evaluate the association between the NLR and long-term clinical outcomes in patients with STEMI undergoing primary percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

Subjects and Methods

Subjects

We enrolled patients with STEMI undergoing primary PCI within 12 hours of symptom onset at Inje University Busan Paik Hospital from January 2005 to December 2009. Initially 412 patients were eligible for this study. Eighty six patients were excluded, and finally 326 patients were included in the current analysis (Fig. 1). STEMI was defined as cumulative ST-segment elevation of at least 1 mm or new onset left bundle branch block or new Q wave in two or more contiguous electrocardiogram leads, with at least one of the following: acute onset of typical ischemic chest pain lasting for at least 30 minutes; and elevated serum levels of creatine kinase-MB or troponin, at least twice the upper limit of normal values. Patients with medical conditions known to affect the total and differential WBC counts, such as hematologic disorder, acute or chronic infection or inflammatory conditions, COPD, current steroid therapy and/or history of steroid use 3 month before the admission, and a history of cancer and/or treatment with radiation or chemotherapy were excluded from the current study. Additionally, patients who did not have differential WBC data, who had an infarct-related lesion that was unsuitable for stent implantation, and who were lost to follow-up were excluded. Informed consent was obtained from all patients. This study was approved by the local institutional review board and was conducted in accordance with the Declaration of Helsinki.

Percutaneous coronary intervention and medications

Coronary lesions were treated using standard PCI techniques. Selection of the type of DES and the decision to use of glycoprotein IIb/IIIa antagonists or an intra-aortic balloon pump were left to the discretion of the operator. Post-dilatation with additional balloons was performed to achieve optimal stent apposition and acceptable angiographic or intravascular ultrasound results. All patients received a single loading dose of 300 to 600 mg clopidogrel and 300 mg aspirin immediately after arrival at the hospital. A 75 mg clopidogrel was continued for at least 12 months after PCI, and 100 mg aspirin was prescribed indefinitely. In addition, 200 mg cilostazol per day was prescribed to some patients, and the additional administration of cilostazol was also left to the discretion of the operators. All patients received heparin to maintain an activated clotting time of ≥250 seconds during the procedure.

Neutrophil to lymphocyte ratio

White blood cell and differential counts were measured at the time of admission before the patients were transferred to the catheter laboratory. The total numbers of WBCs, neutrophils, and lymphocytes were determined using an automated blood cell counter (XE-2100, Sysmex Inc., Japan). The patients were divided into tertiles according to the NLR (NLR ≤3.30; 3.31<NLR≤6.52; and NLR >6.53).

Clinical outcomes and definitions

The primary endpoint of this study was the 12-month cumulative incidence of major adverse cardiovascular events (MACE), which was composite of all causes of death, non-fatal MI, and ischemic stroke. The secondary endpoint was the incidence of each component of MACE at 12 months. Non-fatal MI was diagnosed by increase in the serum creatine kinase-MB or troponin levels to more than twice the upper limit of normal values during follow-up. Stroke was defined as the development of disabling neurological symptoms and objective findings which were confirmed by a neurologist and by imaging technique. The patient's clinical and follow-up information was obtained during the patient's visits to the clinic or telephone interviews conducted 12 months after index PCI.

Fig. 1. Study flow diagram. CABG: coronary artery bypass graft, BMS: bare metal stent, WBC: white blood cell.

Statistical methods

Continuous data are presented as the means±standard deviation. Differences in continuous variables between the groups were
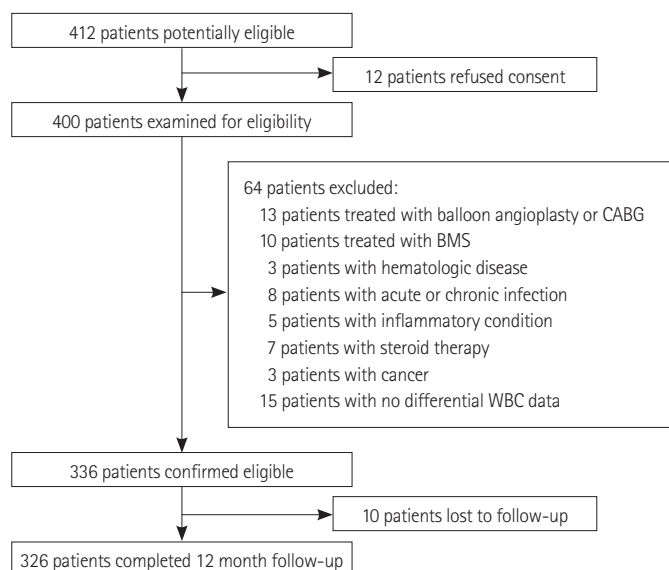
determined by an analysis of variance or Student's t-test. Categorical data are presented as frequencies. Differences in categorical variables were analyzed by Pearson's chi-square test or Fisher's exact test. The association between NLR and clinical outcomes was evaluated with the Cox proportional hazards model using a stepwise multivariate analysis. Covariates for the Cox model were: NLR, gender, left ventricular ejection fraction, creatinine clearance, angiographic parameters (multivessel disease, left main disease, presence of ch-

ronic total occlusion) and factors included in the Thrombolysis in Myocardial Infarction (TIMI) risk score for STEMI {age, hypertension, diabetes, previous coronary artery disease, systolic blood pressure (SBP), heart rate, anterior ST-segment elevation or left bundle branch block, Killip classification, body weight <67 kg, and symptom to balloon time >4 hours}. The discriminative abilities of NLR, WBC count, neutrophil count and relative lymphocyte count for predicting 12-month MACE were compared using the area under the re-

Table 1. Baseline characteristics according to the neutrophil to lymphocyte ratio

Clinical characteristics	Low (n=108)	Medium (n=108)	High (n=110)	p	
				Overall	Low vs. High
Age (years)	59.7±12.0	61.6±12.7	64.2±12.0	0.025	0.006
Men, n (%)	79 (73.1)	85 (78.7)	83 (75.5)	0.636	0.757
Body mass index (kg/m²)	24.4±2.9	23.6±2.6	22.9±3.1	0.003	0.001
Hypertension, n (%)	37 (34.3)	39 (36.1)	46 (41.8)	0.486	0.267
Diabetes mellitus, n (%)	22 (20.4)	29 (26.9)	35 (31.8)	0.157	0.065
Dyslipidemia, n (%)	25 (23.1)	23 (21.3)	19 (17.3)	0.435	0.314
Previous MI, n (%)	5 (4.6)	5 (4.6)	3 (2.7)	0.730	0.497
Previous PTCA, n (%)	5 (4.6)	6 (5.6)	4 (3.6)	0.761	0.747
Smoking, n (%)	65 (60.2)	59 (54.6)	45 (40.9)	0.013	0.005
Systolic blood pressure (mm Hg)	125.8±23.7	122.3±30.6	114.1±29.9	0.008	0.002
Left ventricle ejection fraction (%)	51.3±11.5	47.8±10.5	45.5±11.8	0.001	<0.001
Atrial fibrillation, n (%)	3 (2.8)	5 (4.6)	10 (9.1)	0.141	0.083
Anterior infarction, n (%)	65 (60.2)	52 (48.1)	64 (58.2)	0.171	0.784
Cardiogenic shock, n (%)	7 (6.5)	18 (16.7)	26 (23.6)	0.001	0.001
Killip classification, n (%)				0.001	<0.001
Class I	75 (69.4)	68 (63.0)	51 (46.4)		
Class II	20 (18.5)	25 (23.1)	20 (18.2)		
Class III	8 (7.4)	8 (7.4)	18 (16.4)		
Class IV	5 (4.6)	7 (6.5)	21 (19.1)		
Neutrophil-lymphocyte ratio	1.92±0.84	4.87±0.94	11.86±9.34	<0.001	<0.001
WBC count (×10³/μL)	10.96±8.38	13.36±11.69	13.80±4.47	0.036	0.002
Peak CK-MB (ng/mL)	146.4±117.4	194.0±110.0	195.7±113.8	0.002	0.002
Peak troponin-I (ng/mL)	40.2±37.4	53.1±40.2	63.2±40.4	<0.001	<0.001
C-reactive protein (mg/dL)	2.1±5.6	2.9±5.0	3.7±6.1	0.232	0.102
Creatinine clearance (mL/min)*	72.9±27.6	70.4±32.3	62.1±30.4	0.024	0.007
Symptom-balloon time (min)	244.0±143.7	322.8±137.7	448.1±248.4	<0.001	<0.001
Gp IIb/IIIa inhibitor, n (%)	12 (11.1)	17 (15.7)	26 (23.6)	0.044	0.020
Use of IABP, n (%)	15 (13.9)	22 (20.4)	33 (30.0)	0.015	0.005
No. of used stent, n	1.21±0.48	1.22±0.46	1.21±1.00	0.990	0.971
Final TIMI flow, n (%)				0.036	0.005
TIMI 0	0 (0.0)	1 (0.9)	1 (0.9)		
TIMI 1	4 (3.7)	5 (4.6)	6 (5.5)		
TIMI 2	8 (7.4)	13 (12.0)	24 (21.8)		
TIMI 3	96 (88.9)	89 (82.4)	79 (71.8)		

Values are given as numbers (%) or mean±SD. *Creatinine clearance calculated by Cockcroft and Gault method. MI: myocardial infarction, PTCA: percutaneous transluminal coronary angioplasty, CK-MB: creatine kinase-MB, Gp IIb/IIIa inhibitor: glycoprotein IIb/IIIa inhibitor, IABP: intra-aortic balloon pump, TIMI: Thrombolysis in Myocardial Infarction

ceiving-operating characteristics curve. The final discriminative ability of the multivariate model was analyzed using Harrell's C-statistics. Same covariates as those for Cox model were used for Harrell's C-statistics. Survival curves were generated using the Kaplan-Meier method, and the difference between curves was assessed by the log-rank test. A $p \leq 0.05$ was considered statistically significant. All statistical analysis was performed using SAS 9.2 (SAS Inc., Cary, NC, USA).

Results

Patients

A total of 326 patients with STEMI who received primary PCI with DES within 12 hours of symptom onset was enrolled in the current study. The mean age was 61.9±12.3 years, and 75.8% of the patients were men. Mean and median values of NLR according to NLR tertiles were: 1.92±0.84 and 1.86; 4.87±0.94 and 4.90; and 11.86±9.34 and 9.64, respectively. The baseline clinical and procedural characteristics are shown in Table 1. Overall, there was a positive association between clinical features associated with high risk of poor outcomes and increased level of NLR. The High NLR group was older and had lower body mass index, lower initial blood pressure, lower left ventricle ejection fraction, higher Killip class, higher cardiac enzyme levels, decreased renal function and higher initial serum glucose levels. These patients also had longer symptom to balloon time and worse final TIMI flow.

Twelve month clinical outcomes according to neutrophil to lymphocyte ratio

A total of 23 (7.1%) and 37 (11.3%) MACE were documented during hospitalization and at the 12 month follow-up, respectively. Clinical outcomes in the hospital and 12 months after primary PCI

according to NLR tertiles are listed in Table 2. The high NLR group had a higher rate of 12-month MACE and death compared to the low NLR group. Furthermore, the high NLR group had a higher rate of in-hospital MACE and death compared to the low NLR group. Medium NLR group had a higher rate of 12-month MACE (p=0.066) and death (p=0.050) compared to the low NLR group, although statistical significance was borderline. In-hospital MACE (p=0.498) and death (p=0.280) rates were not different between the medium and low NLR group. The high NLR group had a higher tendency of 12-month MACE (p=0.130) or death (p=0.120) compared to the medium NLR group.

Univariate and multivariate analysis for clinical events

In the univariate analysis, 12-month MACE rate was significantly higher in the high NLR group (vs. low NLR group), female group (p= 0.022), patients with left ventricular ejection fraction below 35% group (vs. above 35%, p=0.000), patients with creatinine clearance below 59 mL/min which was median value (vs. above 59 mL/min, p=0.000), multivessel disease (p=0.009), left main disease (p=0.012), chronic total occlusion (p=0.011), patients whose age were above 75 and between 65-74 years old (vs. below 65 years old, p=0.000 and 0.001, respectively), patients whose SBP were below 100 mm Hg (vs. above 100 mm Hg, p=0.010), heart rate above 100 per min (vs. below 100 per min, p=0.042), Killip class II-IV (vs. class I, p=0.015) and body weight below 67 kg (vs. above 67 kg, p=0.006). Twelve-month all causes of death rate was also higher in the high and medium NLR group (p=0.041 and 0.002, respectively), female group (p= 0.027), patients with left ventricular ejection fraction below 35% group (p=0.000), patients with creatinine clearance below 59 mL/ min (p=0.000), multivessel disease (p=0.010), left main disease (p= 0.047), chronic total occlusion (p=0.005), patients whose age were above 75 and between 65-74 years old (p=0.000 and 0.005, respec-

Table 2. Clinical outcomes during hospitalization and at twelve month follow-up according to the neutrophil to lymphocyte ratio

Variable	Low (n=108)	Medium (n=108)	High (n=110)	p	
				Overall	Low vs. High
12 months, n (%)					
MACE	4 (3.7)	12 (11.1)	21 (19.1)	0.001	<0.001
Death	3 (2.8)	11 (10.2)	20 (18.2)	0.001	<0.001
Nonfatal MI	1 (0.9)	0 (0.0)	1 (0.9)	1.000	1.000
Ischemic stroke	0 (0.0)	1 (0.9)	0 (0.0)	0.663	1.000
In-hospital, n (%)					
MACE	3 (2.8)	6 (5.6)	14 (12.7)	0.014	0.010
Death	2 (1.9)	6 (5.6)	14 (12.7)	0.006	0.003
Nonfatal MI	1 (0.9)	0 (0.0)	0 (0.0)	0.663	0.495
Ischemic stroke	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000

Values are given as numbers (%). MACE: major adverse cardiac events, MI: myocardial infarction

Table 3. Prognostic value of several variables for 12-month major adverse cardiac event and all causes of death

Variables	Hazard ratio (95% confidence interval)			
	No adjustment	p	Adjustment*	p
MACE				
Low NLR*				
Medium NLR	3.09 (0.99-9.58)	0.051	3.45 (0.98-12.10)	0.053
High NLR	5.54 (1.90-16.13)	0.002	3.79 (1.13-12.64)	0.030
LVEF >35 (%)*				
LVEF ≤35 (%)	6.19 (3.10-12.35)	0.000	3.16 (1.37-7.31)	0.007
CCr >59 (mL/min)*				
CCr ≤59 (mL/min)	7.69 (3.38-17.51)	0.000	3.46 (1.26-9.54)	0.016
Death				
Low NLR*				
Medium NLR	3.79 (1.06-13.60)	0.041	3.54 (0.87-14.48)	0.078
High NLR	6.99 (2.08-23.53)	0.002	3.91 (1.02-15.04)	0.047
LVEF >35 (%)*				
LVEF ≤35 (%)	7.03 (3.47-14.23)	0.000	3.29 (1.39-7.73)	0.007
CCr >59 (mL/min)*				
CCr ≤59 (mL/min)	8.81 (3.44-20.07)	0.000	3.27 (1.09-9.77)	0.034

Adjusted for NLR, gender, left ventricular ejection fraction, creatinine clearance and factors included in Thrombolysis in Myocardial Infarction risk score for ST-segment elevation myocardial infarction (age, hypertension, diabetes, previous coronary artery disease, systolic blood pressure, heart rate, anterior ST-segment elevation or left bundle branch block, Killip classification, body weight <67 kg, and symptom to balloon time >4 hours). *Reference group. NLR: neutrophil to lymphocyte ratio, MACE: major adverse cardiac events, LVEF: left ventricular ejection fraction, CCr: creatinine clearance

tively), patients whose SBP were below 100 mm Hg (p=0.013), Killip class II-IV (p=0.010) and body weight below 67 kg (p=0.006). In the multivariate Cox regression analysis, a high NLR (low NLR as the reference), a lower left ventricular ejection fraction (above 35% as the reference) and lower creatinine clearance (above 59 mL/min as the reference) were found to be a significant and independent predictor of 12-month MACE and death after adjusting for NLR, gender, left ventricular ejection fraction, creatinine clearance, angiographic parameters, and factors included in the TIMI risk score for STEMI (Table 3). Furthermore, a lower left ventricular ejection fraction (above 35% as the reference) was the only significant and independent factor to predict in-hospital MACE {hazard ratio (HR) 3.43, 95% confidence interval 1.19-9.83, p=0.022} and death (HR 3.42, 95% confidence interval 1.07-10.97, p=0.039). There was a significant gradient of 12-month MACE across the NLR tertiles, with a markedly increased MACE hazard in the high NLR group (log rank test p=0.002) (Fig. 2).

Discriminative ability of neutrophil to lymphocyte ratio

The area under the curve of the NLR for 12-month MACE (0.696, p<0.001) was greater than those of the WBC count (0.616, p= 0.023), neutrophil count (0.628, p=0.012), and lymphocyte count (0.653, p=0.005). Higher Harrell's C-statistics was noted if multivariate model included NLR tertiles (0.846) as covariate rather than
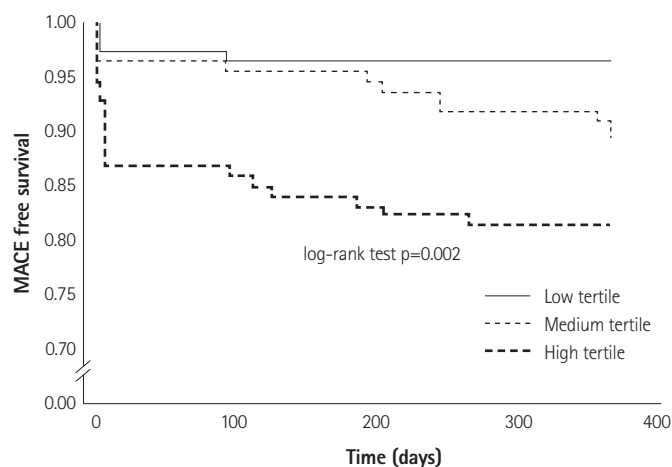

Fig. 2. Major adverse cardiovascular events (MACE) free survival curves according to the tertiles of neutrophil to lymphocyte ratio.

WBC count (0.830), neutrophil count (0.830) and lymphocyte count (0.837) tertiles. The combination of NLR with TIMI risk score was able to further stratify the risk of 12-month MACE, especially in high TIMI risk score (Fig. 3).

Discussion

In this consecutive series of patients recruited from real-world clinical practice, NLR measured at the time of admission was able
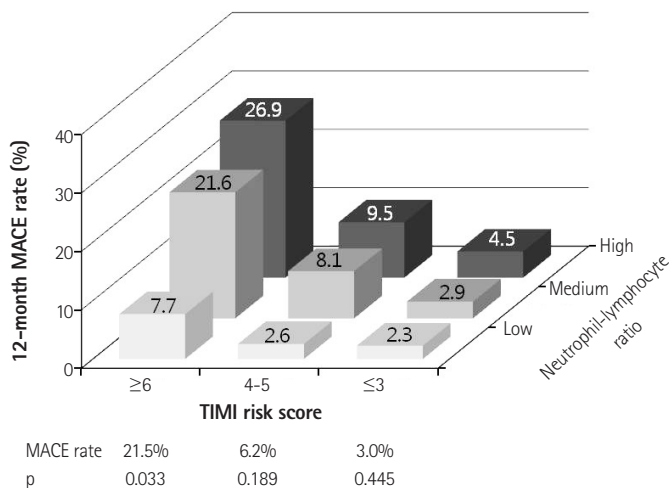
Fig. 3. Major adverse cardiovascular events (MACE) at 12-months stratified by neutrophil to lymphocyte ratio and Thrombolysis in Myocardial Infarction (TIMI) risk score.

to predict 12-month MACE in patients with STEMI who underwent primary PCI with DESs. The results of this study demonstrated the following. First, the high NLR group had the highest rate of in-hospital MACE and death as well as the greatest rate of 12-month MACE and death. Second, a high NLR was a predictor of 12-month MACE and death after adjusting for multiple cardiovascular risk factors. Third, the predictive ability of NLR for 12-month MACE was greater than those of WBC count, neutrophil count, and lymphocyte count.

Several studies have reported that WBC counts provide independent and additional predictive value to short-term mortality risk stratification in patients with acute myocardial infarction.[12][13] Proposed mechanisms responsible for this association include leukocyte-mediated no-reflow, leukocyte-mediated hypercoagulable state and indirect cardiotoxicity mediated through proinflammatory cytokines.[14][15] The prognostic significance of different WBC subtypes varies in patients with acute myocardial infarction.[16-22] Elevated neutrophil count predicts a larger infarction size, worse angiographic outcomes and poor short-term prognosis in patients with STEMI.[16][17] Neutrophils produce several inflammatory mediators (such as elastase, myeloperoxidase and acid phosphatase) as well as substances that cause acute myocardial injury or further tissue damage after STEMI.[18][19] In contrast, lymphopenia is related to high risks of adverse outcomes and mechanical complications after acute myocardial infarction.[20][21] Furthermore, lymphopenia and decreased CD4 counts with inverted CD4/CD8 ratio are strongly correlated with low ejection fraction, high degree of myocardial necrosis and mortality in patients with acute myocardial infarction.[22] However, CD4 counts and CD4/CD8 ratio are not easily and immediately obtainable blood tests in routine clinical practice. The NLR integrates for two WBC subtypes with opposite actions in terms of vascular inflammation. Hen-

ce, this ratio can be more predictive than either parameter alone. Several studies have found that high NLR is associated with adverse clinical outcomes in patients with coronary artery disease.[9-11] The NLR at the time of admission was found to be an independent predictor of in-hospital and 6-month mortality in patients with acute coronary syndrome.[9] NLR is also an independent predictor of 1- and 6- month and 4-year mortalities in patients with non-STEMI.[10] Moreover, maximal NLR is a useful marker to predict subsequent mortality among patients admitted for STEMI and has a superior discriminative ability compared to maximal WBC counts.[11] These findings are reasonable considering that the NLR combines two independent inflammatory markers which predict clinical outcomes in opposite directions.

To the best of our knowledge, this is the first study that identifies an association between NLR and 12-month adverse clinical outcomes in patients with STEMI undergoing primary PCI with DES. The results of this study are in agreement with recently published data that showed an association between higher NLR and poor clinical outcomes in patients with SEMI undergoing primary PCI. In the previous study, NLR and hemoglobin levels were combined to provide valuable information for risk stratification, and follow-up period was relatively shorter than ours.[23] Moreover, NLR was more useful for predicting 12-month MACE compared to WBC, neutrophil or lymphocyte counts in the current study. These findings coincide with evidence demonstrating the role of inflammation in the pathogenesis of STEMI and its complications along with the differential roles of neutrophils and lymphocytes. NLR can be easily calculated from WBC subtype counts, which are routinely performed at admission and is universally available. Because of its broad availability and low cost, NLR can be of great utility as a prognostic marker to risk-stratify patients with STEMI who undergo primary PCI.

C-reactive protein is also known to be a good prognostic marker for cardiovascular events. However, CRP was not a good predictor for 12-month MACE, and the area under the curve of CRP was much smaller (data are not shown) compared to that of NLR in this study. The fact that data of high sensitivity CRP was mixed with that of conventional CRP over the study period may be one of the causes of the findings. Inconsistent sampling times may be another possible explanation.

This study has a few limitations. First, this was a retrospective and non-randomized single center study that included a relatively small number of patients. Therefore, the possibility of selection bias and/or residual confounding from unknown or unmeasured covariates cannot be excluded. Further studies with a larger sample size may be needed. Second, NLR was measured only at time of admission to evaluate its prognostic impact. The short life of neutrophils (around 7 hours) and brief steady kinetic state of neutrophils may have af-

fected the study results. However, a previous study showed that there is a significant correlation between long-term mortality and any NLR (initial, last in the index admission, maximum, or average NLR).[10] Third, left ventricular ejection fraction of low NLR group was preserved compared to those of medium or high NLR groups. Thus this finding may have a considerable effect on results of the current study. Finally, the clinical availability of NLR was not compared to that of other inflammatory markers, such as fibrinogen or myeloperoxidase.

In conclusion, the results of this study demonstrate that the NLR, inexpensive and immediately obtainable blood index, is a useful and powerful marker to predict 12-month MACE and death in patients with STEMI who have undergone primary PCI with DESs.

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