The relationship of coronary flow to neutrophil/lymphocyte ratio in patients undergoing primary percutaneous coronary intervention

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ABSTRACT

Purpose: It has been known that inflammatory mechanisms play an important role in the coronary artery disease. Our aim in this study was to investigate the relationship between the neutrophil/lymphocyte (N/L) ratio and coronary flow velocity after primary percutaneous coronary intervention (PCI) in patients presenting with ST-segment elevation myocardial infarction (STEMI).

Methods: Two hundred and ten patients who had undergone primary PCI were included. The coronary flow velocities were evaluated using the recorded PCI procedures by Thrombolysis in Myocardial Infarction (TIMI) flow grades and corrected TIMI frame counts (cTFC) values. A value of >40 for the final cTFC was accepted as an index of insufficient coronary blood flow. The white blood cell subtypes and counts were determined in the blood samples obtained at the clinics.

Results: In 165 (78%) of the investigated patients, reperfusion was found to be sufficient (Group I) while in 45 (22%) of them (Group II) insufficient reperfusion was observed (Group II). In-hospital mortality was 7.2% (n=12) in Group I, whereas it was 17.7% (n=8) in Group II (P=0.033). Similarly, one-year mortality was higher in Group II (26.6%, n=12) than in Group I (13.3%, n=22) (P=0.031). N/L ratio was determined to be higher in Group I than in Group II (8.3±6.1 *vs.* 6.2±5.0; P=0.034). Also, N/L ratio was found as an independent predictor of severe no-reflow development (TIMI 0-1) and of one-year mortality (P=0.01 and P=0.047, respectively).

Conclusions: N/L ratio has been found to be an independent indicator for no-reflow development in patients who have undergone PCI for acute STEMI. This simple and low-cost parameter can provide useful information for the relevant risk evaluation in these patients.

KEY WORDS Inflammation; acute ST-segment elevation myocardial infarction (acute STEMI); neutrophil/lymphocyte ratio (N/L ratio)

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Introduction

It has been known for some time that inflammatory processes play a major role in coronary artery disease (1,2). This pathophysiology provides the basis for estimating some inflammatory indicators as predictors in the progression of coronary artery disease. Acquisition of prognostic information through white blood cell (WBC) counts in cardiac patients had been shown in earlier studies (3,4). Recently, neutrophil/lymphocyte (N/L) ratio has been shown to provide a reliable inflammatory index to be used in the coronary artery disease for prognostic stratification (5,6).

Coronary no-reflow phenomenon was described as the inability to obtain normal coronary flow (TIMI 3) or electrocardiographic ST segment resolution after coronary intervention. Many studies showed that it was related to poor prognosis and increased mortality (7-10). It continues to be one of the major fears of invasive cardiologists during primary percutaneous coronary intervention (PCI) despite recent advances in the procedural techniques and medications. Some researchers pay attention to the relation of this phenomenon with increased inflammatory status (11-13). Therefore, we aimed to evaluate the relationship between development of no-reflow and N/L ratio.

Methods

In this study, 210 consecutive patients with ST-segment elevation

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myocardial infarction (STEMI) who underwent primary PCI within 12 hours after diagnosis were included. Mean age was 58±12 years and 75% of them were male. The definition of STEMI was based on the criteria of the classic symptoms of coronary ischemia and detection of a 1-mm ST-segment elevation in the inferior leads, or a 2-mm ST-segment elevation in the anterior chest leads occurring in two contiguous leads, or on the presence of a new (or presumably new) left bundle branch block. Patients with active infection or previously proven systemic inflammatory disease, known malignancy, advanced stage liver or renal disorders were excluded from the study.

Angiographic analyses

The recorded angiographic parameters were analyzed by two experienced interventional cardiologists, blinded to the clinical data of the patients. The coronary angiograms were acquired at 15 frames/second with a digital angiographic system (ACOM. PC; Siemens AG, Germany). Data were then converted to the most common filming speed of 30 frames/second by multiplying with a factor of two. TIMI flow grades, TFC values and the degree of stenosis were measured by Quantitative Coronary Arteriography. TIMI flow grades and corrected TIMI frame counts (cTFC) values were measured by previously described methods (14). cTFC was regarded as 100 for flows not reaching the distal reference point (15).

At the completion of primary PCI, determination of a cTFC value of >40 in the concerned artery was taken to indicate insufficient reperfusion, while a value <40 was accepted to indicate sufficent reperfusion (14). Accordingly, the patients were subdivided into Group I (i.e., those who regained sufficient reperfusion) and Group II (i.e., those who could not). Further, those who had coronary flow indices of 'TIMI 0 and 1' were accepted to have severe no-reflow status.

The patients' clinical and follow-up information was obtained during the patients' visits to the clinic or by telephone interviews conducted 12 months after index PCI.

Laboratory analyses

From all patiens included in the study, blood samples were taken via the antecubital vein after arriving the emergency department. Automated cell counts and subtyping had been performed in these blood samples and N/L ratios were automatically calculated by loading all the data to the statistical program used.

Statistical analyses

All data were loaded to the SPSS 15 program. Subsequently, normal distribution of the data was tested using the Kolmogorov-Smirnov test. Datas were logarithmically transformed before analysis when distribution of the data was not normal. Group means for continuous variables were compared using independent-samples t test Comparison of categorical values was carried out by the chi-square test. Any correlation between the data was tested by the Pearson correlation analysis. Logistic regression analysis was used to test the indicative significance of the data on the final coronary flow velocity. The forward selection technique was preferred in the elimination of variables. While the continuous data were expressed with 'mean ± SD (standard deviation)', the categorical data were expressed with percentage values and a P value of <0.05 was accepted as statistically significant.

Results

Of the 210 patients, 165 (Group I, mean age 57.8±12.9 years, 76% males) had sufficient coronary flow while 45 (Group II, mean age 62±13.4 years, 67% males) had insufficient flow on the basis of final reperfusion sufficiency. The basal characteristics of the patients have been summarised in Table 1.

Total blood counts of the patients with respect to neutrophils, eosinophils, monocytes ve basophils were similar. However, the lymphocyte ratio in Group I were higher than in Group II (18.6±11.4% *vs.* 14.2±9.6%, P=0.007) and N/L ratio was lower in Group I (6.2±5.0 *vs.* 8.3±6.1, P=0.017) (Figure 1). The N/L ratio of all patients included in the study was 6.5±5.2.

Although incidences of diabetes mellitus were similar in both groups, the glucose level of Group II patients was significantly higher (221.1±143.8 *vs.* 175.8±90.7 mg/dL, P=0.048). The diameters of the stents used for PCI in the two groups were similar (3.1±0.3 mm in Group I and 3.3±0.6 mm in Group II, P=0.114), but the lengths of the stents used in Group I were 16.3±4.3 mm compared to 18.1±4.0 mm in Group II (P=0.024). Lastly, the pain-to-balloon time in Group I patients had been significantly shorter than in Group II (4.12±1.1 *vs.* 4.9±1.6 hours, P<0.001). Both in-hospital mortality and one-year mortality was higher in Group II (P=0.033 and P=0.031, respectively).

Significant positive correlation was demonstrated between serum N/L ratio and final cTFC values in all patients (r=0.161, P=0.019) (Figure 2). Significant correlation was also demonstrated between final cTFC value and age, pain-to-balloon time, initial cTFC value, post-wire flow, high sensitive C-reactive protein (hs-CRP) concentrations, and lympchocyte counts (Table 2).

According to the multivariate logistic regression analyses made, N/L ratio above 7.5 (OR: 5.072; 95% CI: 1.443-17.828; P=0.011) and serum glucose level (OR: 1.007; 95% CI: 1.001-1.014; P=0.022) were observed to be independent predictors for the development of no-reflow phenomenon. Also, patient's age (OR: 1.104; 95% CI: 1.035-1.179; P=0.003), serum glucose level (OR: 1.008; 95% CI: 1.002-1.013; P=0.005) and serum

Table 1. Baseline characteristics.

	Group I final cTFC ≤40 [n=165]	Group II final cTFC>40 [n=45]	P
Age [years]	57.8±12.9	62±13.4	0.065
Men [%]	125 [75.7]	30 [66.6]	0.132
Hypertension [%]	76 [46.0]	26 [57.7]	0.186
Diabetes mellitus [%]	38 [23.0]	11 [24.4]	0.842
Smoke [%]	92 [55.7]	20 [44.4]	0.177
High-sensitivity C-reactive protein [mg/L]	39.3±49.9	54.4±61.4	0.103
Total cholesterol [mg/dL]	176.6±41.2	172.0±47.3	0.496
Serum glucose [mg/dL]	175.8±90.7	221.1±143.8	0.048
Hemoglobin [g/L]	14.0±1.8	13.7±2.0	0.261
Platelet [mm^3]	247.9±75.6	249.1±75.3	0.863
White blood cell count [$10^3/\mu L$]	12.47±4.8	12.3±3.7	0.790
Neutrophil/lymphocyte ratio	6.2±5.0	8.3±6.1	0.017
Glycoprotein IIb/IIIa antagonist [%]	19 [12]	10 [22]	0.065
Pain-to-balloon time [hours]	4.12±1.1	4.9±1.6	<0.001
Infarct-related coronary artery			0.404
Left anterior descending artery	73 [44]	19 [42]	0.907
Circumflex coronary arter	21 [12]	3 [7]	0.385
Right coronary artery	71 [43]	23 [51]	0.425
Primary percutaneous coronary intervention			
Stent length [mm]	16.3±4.3	18.1±4.0	0.024
Stent diameter [mm]	3.1±0.3	3.3±0.6	0.114
In-hospital mortality [%]	12 [7.2]	8 [17.7]	0.033
1-year mortality [%]	22 [13.3]	12 [26.6]	0.031

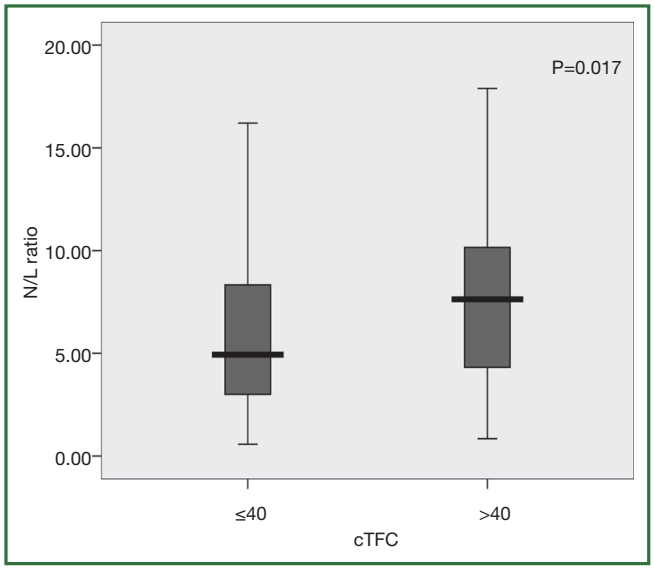

Figure 1. Neutrophil/lymphocyte ratio of the patients according to cTIMI frame counts.Student t test test was used to compare neutrophil/lymphocyte ratios between groups after logarithmic transformation.

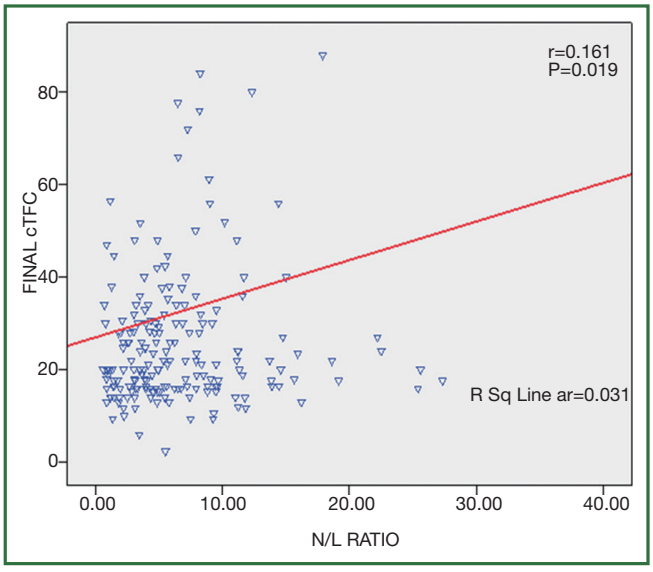

Figure 2. Correlation of final cTFC with neutrophil/lymphocyte ratio (r=0.161, P=0.019). Pearson correlation was used to assess the relation between final cTFC and neutrophil/lymphocyte ratio.

Table 2. Corelation of Final cTFC and other paramethers.

	Correlation coefficient	P
Age	0.165	0.017
Creatinin	0.096	0.167
Pain-to-balloon time	0.240	0.026
Stent diameter	0.147	0.780
Stent length	0.104	0.215
Serum glucose	0.028	0.689
High-sensitivity C-reactive protein	0.183	0.034
White blood cell count	−0.040	0.566
Lymphocytes	−0.197	0.004
Neutrophils	0.034	0.627
Neutrophil/lymphocyte ratio	0.161	0.019
Hemoglobin	−0.080	0.246
Mean platellet volume	0.010	0.888
TIMI flow at the beginning	−0.295	0.008
cTFC at the beginning	0.228	0.001
Post wire TIMI flow	0.301	0.050

Table 3. Effects of various variables on no-reflow and mortality in multivariate logistic regression analyses.

Dependent variables	Covariates	Adjusted OR	95% CI	P
No-reflow	N/L ratio >7.5	5.072	1.443-17.828	0.011
	Serum glucose	1.007	1.001-1.014	0.022
In-hospital mortality	Age	1.104	1.035-1.179	0.003
	Serum glucose	1.008	1.002-1.013	0.005
	Serum creatinin	4.692	1.841-11.959	0.001
1 year mortality (%)	N/L ratio >7.5	2.707	1.013-7.239	0.047
	Age	1.079	1.034-1.125	<0.001
	Serum Glucose	1.005	1.001-1.009	0.009
	Serum Creatinin	2.294	1.066-4.939	0.034

Multivariate logistic-regression analysis that included potential confounders (N/L ratio, age, serum glukoz, serum creatinin, male gender, mean platelet volume, hemoglobin, hypertension, smoking) for No-reflow, in-hospital mortality and 1 year mortality.

creatinine level (OR: 4.692; 95% CI: 1.841-11.959; P=0.001) were found to be independent predictive indices of in-hospital mortality. Patient's age (OR: 1.079; 95% CI: 1.034-1.125; P<0.001), serum glucose level (OR: 1.005; 95% CI: 1.001-1.009; P=0.009), serum creatinine level (OR: 2.294; 95% CI: 1.066-4.939; P=0.034), and N/L ratio above 7.5 (OR: 2.707; 95% CI: 1.013-7.239; P=0.047) were determined to be independent predictive indices for mortality within one year (Table 3).

The ROC statistical analyses made showed that N/L ratio above 7.5 had 70% specificity with 72% sensitivity for the development of no-reflow status (Figure 3). When the patients were regrouped on the basis of this cut-off ratio, it was found that in the patients with N/L ratios above 7.5 the final cTFC values were higher than the patients with N/L ratios below 7.5 (39.6±31.2 *vs.* 29.1±21.2, P=0.023). Further, 30-day and 1-year mortality incidences and the incidence of no-reflow were higher in the group with high N/L ratios (Table 4).

Discussion

Up-to-date cardiology guidelines recommend mechanical techniques to restore coronary flow and reestablish myocardial perfusion in patients presenting with STEMI (16). Despite improvements in the techniques and materials used, the

performance of primary PCI fails to normalize the coronary flow and myocardial perfusion in some of these patients. This phenomenon described as no-reflow is associated with an increased mortality as well as morbidity (17,18).

The aim during primary PCI is to achieve TIMI 3 flow in the occluded artery. However, this target is semi-quantitative and not objective. It cannot provide an objective discrimination between flows of TIMI 2 and 3. TIMI frame count is a quantitative and objective method to evaluate the coronary flow. In earlier works, the final cTFC values achieved by PCI had been demonstrated to be reliable indices of myocardial perfusion and size of the myocardial infarct (19,20). In our work, the coronary flow was evaluated by cTFC and cTFC value of >40 was taken as an indication of insufficient perfusion (14).

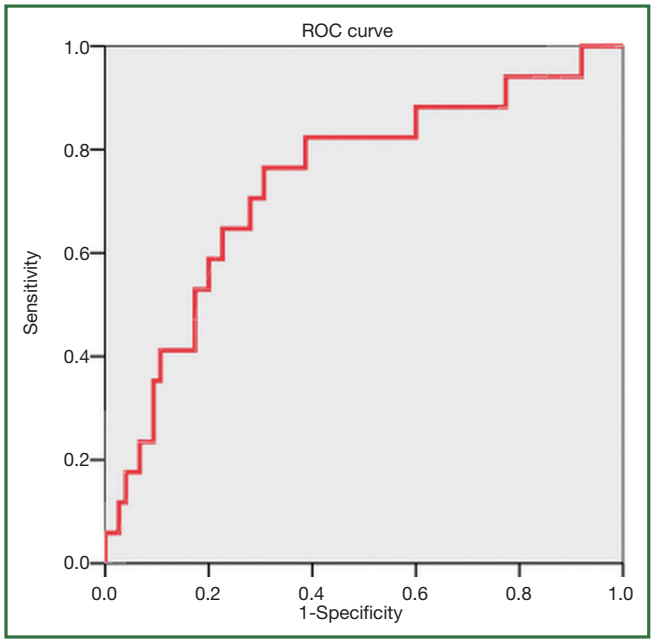

Figure 3. ROC analysis of N/L ratio data for severe no-reflow (AUC=0.737).

Studies have suggested possible mechanisms for no-reflow phenomenon such as endothelial ischemic damage, microvascular obstruction, leukocyte occlusions, mechanical compression due to interstitial oedema, reactive oxygen radicals and coagulation (21,22). Research also demonstrated the relationship of inflammation to no-reflow. Akpek *et al.* reported that N/L ratio and CRP had a significant and positive correlation with no-reflow in STEMI patients treated with PCI (12). Oduncu *et al.* showed that in STEMI patients treated with PCI, basal CRP levels were higher in patients developing no-reflow, while previous use of statins decreased the incidence of no-reflow (13). In our study, patients with insufficient final coronary flow had significantly elevated N/L ratios (8.3±6.1 *vs.* 6.2±5.0, P=0.017) and decreased lymphocyte ratio (14.2±9.6% *vs.* 18.6±11.4%, P=0.007). In addition, a significant correlation was present between final coronary flow and N/L ratio, and neutrophil and lymphocyte counts which suggested a relationship between the inflammatory response and leukocyte occlusions. Further, the possible contribution of duration of occlusion to the development of no-reflow has been demonstrated (23). In our study, a significant positive correlation between pain-to-balloon time and final cTFC has been determined. This suggests that a longer occlusion period will cause further microvascular damage and therefore worse final flow rates.

The results presented here showed that N/L ratio above

Table 4. Clinical and angiographic parameters according to N/L ratio (high or low).

	N/L ratio <7.5 (n=139)	N/L ratio ≥7.5 (n=71)	P
Spontaneous recanalization (%)	55 (39.5)	26 (36.6)	0.677
cTFC at the beginning	81.2±30.7	82.6±29.5	0.629
TIMI flow at the beginning (%)			
0	85 (61.2)	45 (63.4)	0.753
1	10 (7.2)	7 (9.8)	0.503
2	29 (20.8)	14 (19.7)	0.846
3	15 (10.8)	5 (7.1)	0.381
Postwire cTFC	72.1±34.6	73.3±33.1	0.773
cTFC after balloon angioplasty	35.4±25.7	44.2±32.1	0.149
Stenosis at the beginning (%)	95.7±14.0	97.2±10.6	0.481
Final cTFC	29.1±21.2	39.6±31.2	0.023
Severe No-reflow (TIMI 0-1) (%)	6 (4.3)	11 (15.4)	0.005
cTFC >40 (%)	20 (14.4)	21 (29.6)	0.009
In-hospital mortality (%)	9 (6.4)	11 (15.4)	0.035
1 year mortality (%)	15 (10.7)	19 (26.7)	0.003

7.5 was an independent predictor for severe no-reflow (TIMI 0-1) development and mortality within one year. N/L ratio above 7.5 had 70% specificity with 72% sensitivity for the development of no-reflow phenomenon. Akpet *et al.* reported a cut-off value of 3.3 for the N/L ratio with 74% specificity and 83% sensitivity for no-reflow development (12). The different results may arise from the disparities in the methodology used or in the baseline clinical characteristics of the patients. In the literature, clinical value of N/L ratio was evaluated not only in no-reflow phenomenon but also in different STEMI patient groups. Sahin *et al.* found that N/L ratio of STEMI patients with a high Syntax score (>18) was also higher in comparison to N/L ratio of patients with a relatively lower Syntax score (<11) (6.5±3.9 *vs.* 4.0±2.9) (24). While Zazula *et al.* reported high N/L ratios of 6.9±5.7 in STEMI patients (25), Nunez *et al.* determined N/L ratios of 3.7 (2.4-6.7) in the same patient group (26).

Taking the cut-off value obtained in our study, patients with high N/L ratios had an increased incidence of worse final cTFC, severe no-reflow, and 30-day and 1-year mortality. In recently published studies, it was also shown that high N/L ratio was associated with increased mortality and major adverse cardiac events in patients with STEMI (5,27-29). Han *et al.* found that high N/L ratio in STEMI patients undergoing PCI was an independent predictor for 12-month MACE (29). Similarly, Muhammed Suliman *et al.* reported that mortality was higher among acute coronary syndrome patients with high N/L ratios (27). In our study, N/L ratio above 7.5 was an independent predictor for mortality within 1 year. Age, serum creatinine and glucose levels were also determined to be independent predictors for in-hospital and 1-year mortality.

C-reactive protein is a nonspecific acute phase reactant released from the liver into the bloodstream. CRP levels have been shown to be elevated during acute coronary syndromes (30,31). Ndrepepa *et al.* showed that CRP was an independent predictor for no-reflow development in STEMI patients treated with PCI (32). On the other hand, Niccoli *et al.* found similar final cTFC values and clinical no-reflow incidences irrespective of high or low CRP levels in a total of 60 patients treated with primary PCI or rescue PCI (33). In our study, hs-CRP levels in the patient group with insufficient final coronary flow were higher than those with sufficiently restored coronary flow, but the difference was not statistically significant (54.4±61.4 *vs.* 39.3±49.9, P=0.103). On the other hand, a significant positive correlation between final cTFC value and hs-CRP level was determined (r=0.183, P=0.034).

Conclusions

The results presented here demonstrated that raised N/L ratios in STEMI patients treated with primary PCI were related to the final coronary flow velocity and increased mortality. High N/L ratio was determined to be an independent predictor of no-reflow development and mortality within one year. Since N/L ratio depends on a simple and low-cost analysis, we believe that it will be useful in risk evaluation of patients treated with primary PCI.

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