Relationships Among Markers of Inflammation, Neutrophil-to-Lymphocyte Ratio, and Syntax Severity Score in the Early Phase of Acute Coronary Syndrome

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ABSTRACT

Objective: The aim of the present study was to examine a possible association between inflammation, as indicated by High-sensitivity C-reactive protein (HsCRP) and neutrophil/lymphocyte ratio (NLR), and the complexity and severity of coronary artery disease assessed using syntax severity score (SSS) in patients with acute coronary syndrome (ACS).

Methods: Patients with symptoms suggestive of ACS who were admitted within 6 h of onset and who underwent coronary angiography were enrolled in the study. According to NLR, we divided patients into two groups: group 1 (NLR≤2.7) and group 2 (NLR>2.7). According to SSS, patients were divided into two groups: group 1 including low scores and group 2 including intermediate and high scores. Statistical analysis was performed using chi-square test and Mann–Whitney U test.

Results: A total of 87 patients (65 males and 22 females) with acute myocardial infarction (AMI; 57 ST-se AMI and 30 non-ST-se AMI) were included in this study. Patients were classified into low (NLR≤2.7, n=63) and high (NLR>2.7, n=24) NLR groups. Univariate a>nalysis demonstrated that SSS was significantly higher in high NLR group than in low NLR group (23.6±12.7 versus 13.9±8.7, p<0.001). Similar to NLR, significant correlation was revealed among HsCRP, troponin levels, and SSS that indicated their predictive value in the severity of AMI.

Conclusion: In present study, we showed NLR to be an independent predictor of hemodynamically significant coronary artery stenosis as measured using SSS.

Keywords: Neutrophil-to-lymphocyte ratio, syntax severity score, acute coronary syndrome

Introduction

Atherosclerosis, a major cause of cardiovascular disease, appears to be a chronic inflammatory process and may result in the development of unstable atherosclerotic plaque. The formation of atherosclerotic plaque, its rupture, and consecutive thrombus formation leads to occlusion of the affected coronary artery followed by necrosis of the subtended myocardial tissue. These events are clinically referred as acute coronary syndrome (ACS), including ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina pectoris. Peripheral blood mononuclear cells (PBMCs) increase after acute myocardial infarction (AMI) and subsequently infiltrate the infarct region. Increased PBMC count correlated with left ventricular remodeling, suggesting that PBMCs play a significant role in the development of left ventricular remodeling after AMI (1, 2). Recently, an elevated white blood cell (WBC) count, particularly neutrophil/lymphocyte ratio (NLR), has been shown to be a marker of increased risk of death in patients with myocardial infarction (3). Previous studies have revealed a strong relationship between C-reactive protein (CRP) and the clinical presentation and outcome in patients with ACS (4, 5). Additionally, some authors have shown elevated CRP levels in patients with unstable coronary artery disease (CAD), and the severity of this elevation has been correlated with the severity of coronary atherosclerosis, myocardial damage, and relative prognosis (6-8). The measurement of early NLR at the time of admission to emergency

can predictive the severity of coronary artery lesion in patients with myocardial infarction. The SYNTAX severity score (SSS) is a new angiographic tool that can be used to characterize coronary vasculature and predict outcomes of coronary intervention based on the anatomical complexity of CAD (9). SSS is an independent predictor of long-term mortality and morbidity in several patient types including ACS patients (10). Thus, the aim of the present study was to reveal a possible association between inflamation, as indicated by serum NLR, and the complexity and severity of CAD assessed using SSS in patients with ACS.

Materials and Methods

In this prospective study, we enrolled 87 consecutive patients (57 ST-se AMI and 30 nonST-se AMI) with ACS who were referred to an emergency department (Bezmialem Vakıf University Hospital) documented in an electronic database. This study and all experimental procedures were approved by the ethical committee of Bezmialem Vakıf University. Written informed consent was obtained from each participant.

Inclusion criteria were onset of chest discomfort in the prior 6 h with pozitif troponin (troponin I>0.06) and electrocardiographic changes consisting of transient ST-segment depression (≥0.05 Mv) or T wave inversion(≥0.1 mV); pozitif troponin and ST-segment elevation; ischemic symptoms suggestive of ACS with no elevation in troponin, no ECG changes indicative of ischemia (eg., ST segment depression, transient elevation, or a new T wave inversion). Patients with active inflammatory conditions, malignancies, autoimmune diseases, use of immunosuppressive drugs, and known hematological disorders, as well as those SYNTAX score of 0 were not included in this study. According to NLR, patients were divided into two tertiles as group 1 (NLR≤2.7) and group 2 (NLR>2.7) and possible difference between the groups was studied. SSS was evaluated as low SYNTAX score (≤22), intermediate SYNTAX score (23-32), and high SYNTAX score (≥33). Patients were divided into two groups as group 1 consisting of low scores and group 2 consisting of intermediate and high scores.

Patients with clinical evidence of cancer, chronic inflammatory disease, or any systemic infection were excluded.

Laboratory Measurements
Venous blood samples were collected from all patients at the time of admission to the emergency department. Serum WBC count, HsCRP, and cardiac markers such as the MB fraction of creatine kinase (CK-MB) and troponin I were measured. Blood samples were collected in EDTA tubes (two tubes, each containing 3 mL of blood) within 10 min after admission to emergency department from the antecubital vein while the patient was in the supine position. Plasma was obtained by the centrifugation of blood at 3,000 rpm for 10 min at 4±2°C by a cooling centrifuge. Complete blood counts were performed using an autoanalyzer (Siemens Advia 120 hematology analyzer; Siemens, Eschborn, Germany).

SYNTAX Score Calculation
Coronary angiography was performed using the Judkins technique. The complexity of CAD was determined using SYNTAX score. The SYNTAX score takes into account features such as bifurcations, total occlusions, thrombus, calcification, and small vessels. Each coronary lesion with a luminal obstruction greater than 50% in vessels ≥1.5 mm were separately scored and summated to provide the overall SYNTAX score. This was calculated using dedicated software that integrates the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion and morphologic features of each single lesion (11, 12). The latest online updated version (2.11) was used for calculation of the SYNTAX score (www.syntaxscore.com). The SYNTAX score was classified into the following groups: low SYNTAX score (<22), intermediate SYNTAX score (23-32), and high SYNTAX score (≥33).

All angiographic variables pertinent to SYNTAX score were computed by two experienced cardiologists blinded to the procedural data and clinical outcomes.

Statistical analysis
Data were analyzed using the Statistical Package for the Social Sciences software version 15.0 for Windows (SPSS Inc.; Chicago, IL, USA). Categorical variables were presented as frequency and percentage. The $\chi 2$ test and Fisher's exact test were used to compare categorical variables. The assessment of the distribution of continuous variables was performed using the Kolmogorov–Smirnov test. Student's t-test was used for variables with normal distribution, and the values were presented as mean±standard deviation. Mann–Whitney U test was used to analyze continuous variables without normal distribution, and the values obtained were presented as median (50th) values and interquartile ranges (25th and 75th). One-way analysis of variance and Kruskal–Wallis test were used for parametric and nonparametric variables to compare tertiles, respectively. The independent association of the risk of severe RMS was evaluated with multivariate logistic regression analysis. Parameters with a p-value of <0.1 in univariate analysis were included in the model. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A two-tailed p-value of 0.05 was considered statistically significant.

Results

A total of 87 patients (65 males and 22 females) with AMI (57 ST-se AMI and 30 non-ST-se AMI) were included in this study. The results of our study demonstrated that the group consisted of patients with high NLR composed of 60.3% of ST-se MI and 39.7% non-ST-se MI and the group consisted

of patients with low NLR composed of 70.8% of ST-se MI and 29.2% of non-ST-se MI. No differences were observed among the groups with regard to ST segment elevation (p=0.363).

No differences in comorbidity and demographic features were observed among the groups.

The elevated levels in leukocyte, lymphocyte, and neutrophil counts were observed in the high NLR group (Table 1). The results of our study showed that patients with high NLR had a longer duration of hospital stay and higher levels of cardiac markers (Table 1). A positive correlation was observed between high NLR and SSS (p=0.001) and demonstrated in Figure 1. The associations between high NLR and CK-MB (p=0.009) and troponin (p=0.049) were observed and demonstrated in Figure 2 and Table 1. Furthermore, an assosiation between troponin levels and SSS was observed (p= 0.008) (Figure 3). Although patients with high NLR were shown to have a longer duration of hospital stay, no differences was observed between NLR levels and duration of hospital stay (p=0.136).

Discussion

Some studies reported that many scoring systems and biochemical parameters are available for patients with ACS (13, 14). However, as most of them are time consuming and not cost-effective, their availability is limited; therefore, new parameters that can predict severity and ACS prognosis in the early phase are being tested. In our study, we used markers, such as NLR and HsCRP, to assess the inflammation status of the patients and SSS system, whihc has been gaining popularity in recent years, to specify the severity of ACS (15).

Inflammatory parameters were investigated to assess their potential predictive role in ACS (16).

Inflammation plays an important role not only in the initiation and progression of atherosclerosis but also on plaque
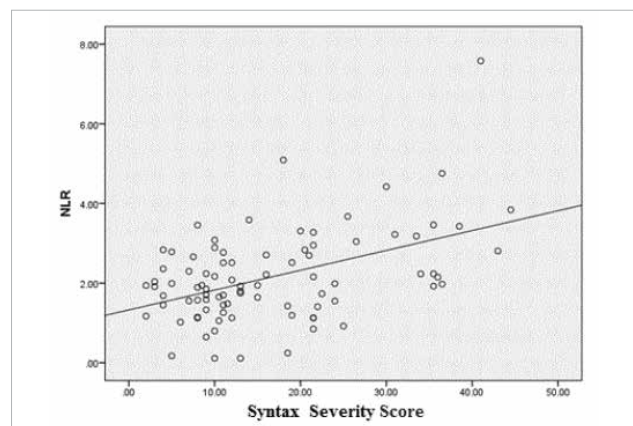

Figure 1. The associaton between neutrophil/lymphocyte ratio (NLR) and syntax severity score (SSS)

Figure 2. Mean troponin I levels of the groups

Figure 3. The associaton between troponin I levels and syntax severity score (SSS)

Table 1. Demographic and clinical parameters in NLR≤2.7 and NLR>2.7

	NLR≤2.7 (n=63)	NLR>2.7 (n=24)	p
Baseline characteristics			
Age (years)	49.62±9.06	52.73±15.38	0.264
Male % (n)	71 (45)	83 (20)	0.304
Hypertension % (n)	68 (43)	54 (13)	0.484
Diabetes mellitus % (n)	50 (32)	45 (11)	0.250
Smoking % (n)	57 (36)	62 (15)	0.566
SSS	13.9±8.76	23.6±12.7	0.001
Biochemical tests			
WBC (× 10^9 Cells/L)	11.14±2.70	12.11±3.24	0.161
Neutrophils	56.71±17.52	71.11±5.16	0.001
Lymphocytes	38.63±12.95	20.92±3.22	0.001
Hs-CRP	0.61±0.45	1.07±0.94	0.029
Troponin I	3.36±7.46	6.15±8.97	0.041
CKMB	48.40±76.80	66.48±52.13	0.009
Length of Stay	3.75±2.51	5.13±4.39	0.136

Results are n (%), mean±standard deviation, or median (interquartile range).

NLR: neutrophil/lymphocyte ratio; SSS: syntax severity score; hs-CRP: high-sensitive C-reactive protein; WBC: white blood cell
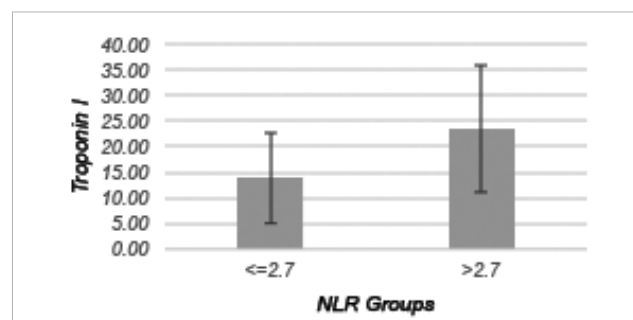
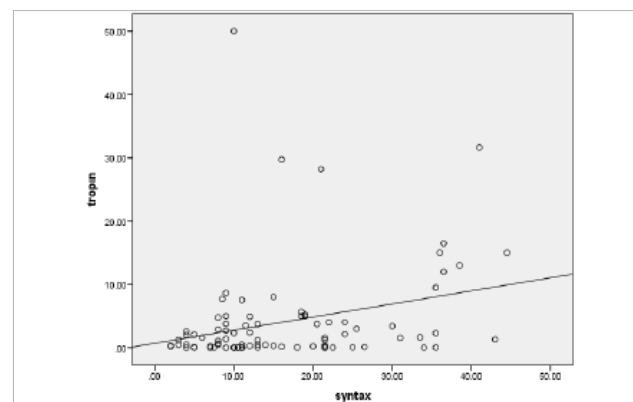rupture, an event that leads to acute vascular events (17). In fact, several markers of inflammation including CRP, TNF-α, and cytokines were found to be associated with the presence of cardiovascular diseases (18). In our study, we have encountered that levels of hsCRP as an inflammatory indicator is strongly correlated with SSS, and it could have been predicted that severity score of ACS may be high grade in presence of high inflammatory status. In a study that investigated the changes in WBC in case of inflammatory conditions, it was shown that neutrophil count increased by 300% in the circulation within the first 6 h following inflammation, whereas lymphocyte count decreased by 85% (19). In parallel with results of that study, some studies reported that NLR rate is a more useful inflammatory parameter than the sole evaluation of neutrophil or lymphocyte counts in many atherosclerotic diseases, such as ACS, acute ischemic stroke, and pulmonary embolism, in which inflammation plays a role in the pathogenesis (20, 21). In the present study, only NLR rate was used as an inflammatory indicator. We observed that NLR rates correlated with troponin levels in the blood samples obtained within the first hours of acute MI in patients who applied to the emergency department due to chest pain, and we found a statistically significant outcome. In similar studies, controversial outcomes have been obtained on the relationship of troponin levels with prognosis and worse clinical progression (22, 23). However, similar to NLR, we showed that troponin level strongly correlated with severity of ACS and complexity of CAD, which are measured using SSS.

Neutrophils, which infiltrate coronary plaques and become activated in the early phase of acute MI, lead to tissue deterioration by increasing the levels of free oxygen radicals and proteolytic enzymes such as myeloperoxidase. It has negative effects on heart failure and long-phase mortality rates due to all these negative characteristics (24). We showed that early phase NLR rates obtained in the first hours after acute MI also correlated with SSS and concluded that NLR rate is an important parameter in measuring the severity of AMI. It was previously reported that elevated NLR rates may also predict increased risk for stable CAD and development of restenosis as well as ACS (25, 26). Recent studies suggested that increased rate of NLR also plays an important role in the development of mitral valve disease and non-CAD cardiac events, such as atrial fibrillation, beside coronary artery disease (27, 28). In the present study, we observed that elevated rates of NLR also increase the duration of hospital stay; however, no statistically significant outcome was found.

Conclusion

This is a prospective cohort study that evaluated the prognostic value of NLR rate in patients with ACS at an emergency department. Based on the obtained data in our study, we concluded that high NLR rate is an independent predictor of severity and complexity for coronary atherosclerosis and cardiac

markers, such as troponin and CK-MB levels, in patients with ACS. Clinicians should bear in mind that NLR rate can be useful as a low-cost, easily available, easily applicable, and repeatable test in predicting the severity of acute MI in patients who apply to emergency departments due to chest pain and that patients with high rates of NLR may need an emergency and aggresive treatment.

References

1. Weber M, Dill T, Arnold R, Rau M, Ekinci O, Müller KD, et al. N-terminal B-type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris. Am Heart J 2004; 148: 612-20 [CrossRef]

2. Koenig W. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. Int J Cardiol 2013; 168: 5126-34. [CrossRef]

3. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008; 102: 653-7. [CrossRef]

4. Prospero BO, David JS, Edward FT, Matthew WW, Bruton ES, Harold LD. Relation of leukocytosis to C-reactive protein and interleukin-6 among patient undergoing percutaneous coronary intervention. Am J Cardiol 2005; 4: 538-42.

5. Libby P, Simon DI. Inflammation and thrombosis: the clot thickens. Circulation 2001; 103: 1718-20. [CrossRef]

6. Avanzas P, Quiles J, Lopez de Sa E, Sánchez A, Rubio R, García E, et al. Neutrophil count and infarct size in patients with acute myocardial infarction. Int J Cardiol 2004; 97: 155-6. [CrossRef]

7. Folsom AR, Chambless LE, Ballantyne CM, Coresh J, Heiss G, Wu KK, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. Arch Intern Med 2006; 166: 1368-73. [CrossRef]

8. Thompson A, Gao P, Orfei L, Watson S, Di Angelantonio E, Kaptoge S, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet 2010; 375: 1536-44. [CrossRef]

9. Zahorec R. Ratio neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001; 102: 5-14.

10. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. Eurointervention 2005; 1: 219 -27.

11. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. Circ Cardiovasc Intervent 2009; 2: 302-8. [CrossRef]

12. Serruys PW, Onuma Y, Garg S, Garg S, Sarno G, van den Brand M, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009; 5: 50-6. [CrossRef]

13. Genereux P, Palmerini T, Caixeta A, Cristea E, Mehran R, Sanchez R, et al. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. Circ Cardiovasc Interv 2011; 4: 553-61. [CrossRef]

14. Poludasu S, Cavusoglu E, Khan W, Marmur JD. Neutrophil to lymphocyte ratio as a predictor of long-term mortality in African Americans undergoing percutaneous coronary intervention. Clin Cardiol 2009; 32: E6e10.

15. Bhutta H, Agha R, Wong J, Tang TY, Wilson YG, Walsh SR. Neutrophil-lymphocyte ratio predicts medium-term survival following elective major vascular surgery: a crosssectional study. Vasc Endovascular Surg 2011; 45: 227e31.

16. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009; 360: 961-72. [CrossRef]

17. Carter AM. Inflammation, thrombosis and acute coronary syndromes. Diab Vasc Dis Res 2005; 2: 113-21. [CrossRef]

18. Madjid M, Casscells SW, Willerson JT. Biomarkers of inflammation as surrogate markers in detection of vulnerable plaques and vulnerable patients. Cardiovascular Medicine. 3rd edn. Springer-Verlag London Limited, London, pp. 641-51.

19. Danesh J, Kaptoge S, Mann AG, Sarwar N, Wood A, Sara BA, et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two newprospective studies and a systematic review. PLoS Med 2008; 5: e78 [CrossRef]

20. Jilma B, Blann A, Pernerstorfer T, Stohlawetz P, Eichler HG, Vondrovec B, et al. Regulation of adhesion molecules during human endotoxemia. Am J Respir Crit Care Med 1999; 159: 857-63. [CrossRef]

21. Azab B, Zaher M, Weiserbs KF, Torbey E, Lacossiere K, Gaddam S, et al. Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction. Am J Cardiol 2010; 106: 470e6.

22. Cho KH, Jeong MH, Ahmed K, Hachinohe D, Choi HS, Chang SY, et al. Value of early risk stratification using hemoglobin level and neutrophil-to-lymphocyte ratio in patients with STelevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol 2011; 107: 849e56.

23. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 2009; 361: 2538-47. [CrossRef]

24. Wallace TW, Abdullah SM, Drazner MH, Das SR, Khera A, McGuire DK, et al. Prevalence and determinants of troponin T elevation in the general population. Circulation 2006; 113: 1958-65. [CrossRef]

25. Guasti L, Dentali F, Castiglioni L, Maroni L, Marino F, Squizzato A, et al. Neutrophils and clinical outcomes in patients with acute coronary syndromes and/or cardiac revascularisation. A systematic review on more than 34,000 subjects. Thromb Haemost 2011; 106: 591-9. [CrossRef]

26. Kaya H, Ertas F, İslamoglu Y, Kaya Z, Atılgan ZA, Çil H, et al. Association between neutrophil to lymphocyte ratio and severity of coronary artery disease. Clin Appl Thromb Hemost 2014; 20: 50-4. [CrossRef]

27. Yildiz A, Yuksel M, Oylumlu M, Polat N, Akyüz A, Acet H, et al. The Utility of the Platelet-Lymphocyte Ratio for Predicting No Reflow in Patients With ST-Segment Elevation Myocardial Infarction. Clin Appl Thromb Hemost 2015; 21: 223-8. [CrossRef]

28. Acet H, Ertaş F, Akıl MA, Oylumlu M, Polat N, Yıldız A, et al. New inflammatory predictors for non-valvular atrial fibrillation: echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio. Int J Cardiovasc Imaging 2014; 30: 81-9. [CrossRef]

29. Polat N, Yıldız A, Yüksel M, Bilik MZ, Aydın M, Acet H, et al. Association of Neutrophil-Lymphocyte Ratio With the Presence and Severity of Rheumatic Mitral Valve Stenosis. Clin Appl Thromb Hemost 2014; 20: 793-8. [CrossRef]