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Original Article

Neutrophil-lymphocyte ratio and severity of atherosclerotic disease in stable coronary artery patients with chronic total occlusion

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Abstract

Aim: Neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation that correlates with coronary artery disease. The Syntax score is an angiographic tool used in grading the complexity of coronary artery disease (CAD). The aim of this study is that NLR is associated with a greater CAD complexity in patients with stable angina pectoris with chronic total occlusion.

Materials and Methods: A total of 495 patients who underwent coronary angiography and who had stable angina pectoris with chronic total occlusion in at least 1 vessel were included in the study. The syntax score was used to determine coronary complexity.

Results: Patients with CAD were evaluated by grouping according to 2 different criteria as pointed in the European Society of Cardiology (ESC) revascularization guide. When the syntax S is divided into 3 groups (Syntax score 1-22, 23-32,> 32) according to their score values, or 2 groups (Syntax score 1-21 and> 22 or 1-31 and> 31) according to their Syntax score values, NLR was higher in high Syntax score groups than in low groups ($p < 0.05$). Patients with CAD were further divided into 3 groups according to Syntax score values (Syntax score 1-22, 23-32, >32) or 2 groups according to Syntax score values (Syntax score 1-21 and >22 or 1-31 and >31) as pointed in ESC revascularization guideline, high Syntax score group having a higher NLR than low group ($p<0.05$). However, when the patients were divided into 3 groups according to the Syntax score, it was seen that there was no statistical difference in terms of NLR values between the high group and the middle group or the middle group and the low group of the Syntax score.

Conclusion: In this study, it has been demonstrated that NLR can be used for the determination of the complexity of the disease in patients with stable angina pectoris with chronic total occlusion. However, in determining the degree of complexity in the patients with stable angina, discrimination of the patients close to each other may not be sufficient.

Keywords: Inflammation; syntax score; stable angina

INTRODUCTION

Atherosclerosis is a multifactorial disease that depends on many variables that contribute to pathogenesis, such as age, genetics, hypertension, diabetes, lipid disorders, and other causes that cause endothelial damage, such as smoking. (1,2). Studies have shown that inflammation, and therefore neutrophils, have contributed significantly at all stages of atherosclerosis. (3). Neutrophil/lymphocyte ratio (NLR) is an index that reflects both the acute state of inflammation with neutrophilia and post-stress with lymphopenia. Studies that have been evaluated with other inflammatory markers are a good determiner of inflammation. (4). Recently, complete blood count (CBC) is one of the most commonly ordered laboratory tests before the coronary angiography (CAG). CBC and NLR is an easy, inexpensive, routine examination technique and usually result within 30 minutes. NLR is a blood cell count index with an easily measurable laboratory variable that indicates the inflammatory condition and it is important for predicting cardiovascular risk. (5,6).

Chronic coronary total occlusion (CTO) is defined by the loss of distal vascular blood flow due to complete occlusion of the epicardial coronary vessels and the absence of distal opacification or minimal contrast imaging in angiography. More than 3 months are required for this lesion formation. (7). The prevalence of CTO, which is the endpoint of atherosclerotic coronary artery disease, is between 30-50% among the patients undergoing catheterization. (8-10). Syntax score (SS) is an angiographic calculation method used to determine the complexity of atherosclerotic diseases by evaluating the anatomy of the coronary artery. SS guides in determining the procedure, especially in patients undergoing revascularization, and provides information on predicting cardiac major events, including death (11,12).

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We hypothesized that NLR is associated with a greater complexity of atherosclerotic coronary artery disease (CAD) identified by SS in stable angina pectoris (SAP) patients with CTO.

MATERIALS and METHODS

A total of 495 patients with indications of coronary angiography, because they come with stable character chest pain and / or positive results from stress tests (positive stress test result and/or ischemia on myocardial SPECT) are included in our study. Our study patients were selected from individuals who underwent consecutive coronary angiography with a preliminary diagnosis of coronary diseases from 2011 to 2017. Some important information was obtained from the physician's report which includes physical findings, patients' history, and risk factors. We recorded variables such as age, gender, tobacco use, diabetes, hypertension, and hyperlipemia. Patients who had previous coronary artery bypass grafting (CABG), acute coronary syndrome (ACS), renal and liver failure, ongoing inflammatory diseases, malignancy, autoimmune diseases, and hematological diseases were excluded. Measurements of white blood cell (WBC), lymphocyte, and neutrophil counts were made as a part of the automated complete blood count at baseline (on admission, before angiography). NLR result was obtained from the division of the neutrophil count by the lymphocyte count.

Patients were divided into 3 groups according to SS (SS 1-22, 23-32,> 32) as recommended in the European Society of Cardiology (ESC) revascularization guidelines. (13). The latest version (2.1) available for SS calculation used (www.syntaxscore.com) (11,14).

Statistical analyses

All the analyzes were performed using the SPSS V 17.0 (version 17.0; SPSS, Chicago, Illinois) statistics program for Windows. Unless otherwise stated, data are processed as mean ± standard deviation. If nonparametric values between the two groups will be compared, the Mann-Whitney U test, if the parametric values between the two groups are compared, independent sample t-test was used. In the comparison of categorical variables, the chi-square test was performed. One-way analysis of variance (ANOVA) was used to calculate the significance of the difference between groups.

Pearson correlation coefficient was computed to evaluate the correlation between two continuous variables. When significant differences were detected, logistic regression analysis including independent variables was initiated. Significance of two-tailed p-value was taken as ≤0.05.

According to the Helsinki Declaration, written informed consent was obtained from all participants, which was approved by our corporate ethics committee.

RESULTS

The number of study patients was 495, which were diagnosed with CTO in the coronary artery in CAG and accepted with SAP were included in our study. Baseline demographic and laboratory variables are shown in Table 1. The mean age of the patients was 63.5 ± 9.5 years and 32.9% were women, 55.2% had hypertension and 30.1% had diabetes mellitus.

Table 1. Comparison of baseline clinical, demographical and laboratory parameters between the low and the high Syntax scores or the low, the moderate and the high Syntax scores

	SYNTAX 1-22 (n=224)	SYNTAX 23-32 (n=188)	SYNTAX >32 (n=83)	*p	SYNTAX 1-21 (n=224)	SYNTAX >22 (n=271)	p	SYNTAX 1-31 (n=412)	SYNTAX >32 (n=83)	p
Age, years	62.9±9.8	63.1±9.3	65.7±8.8	0.07	62.9±9.8	63.9±9.2	0.1	63±9.6	65.7±8.8	0.01
Male, n (%)	78.1	79.3	71.1	0.4	78.1	76.8	0.4	78.6	71.1	0.2
Diabetes mellitus, n (%)	32.6	28.2	27.7	0.6	32.6	28	0.5	30.6	27.7	0.6
Hypertension, n (%)	53.6	52.1	66.3	0.2	53.6	56.5	0.7	52.9	66.3	0.07
Creatinine, mg/dL	0.95±0.23	0.94±0.22	1.01±0.23	0.08	0.95±0.23	0.96±0.23	0.6	0.95±0.22	1.01±0.23	0.03
BUN	20.1±8.7	20.6±9.6	26.4±11.8	0.01	20.1±8.7	22.5±10	0.6	20.3±9.1	26.4±11.8	0.01
Albumin	4.0±0.3	4.0±0.3	3.9±0.3	0.05	4.0±0.3	4.0±0.3	0.9	3.9±0.3	3.9±0.3	0.5
Total kolesterol	220±74	209±40	232±54	0.5	220±74	216±45	0.7	216±64	232±54	0.5
LDL	131±40	132±39	144±46	0.5	131±40	135±41	0.7	131±39	144±46	0.4
WBC, 103/mL	7.88±2.22	7.88 ± 2.02	7.78±1.86	0.9	7.88±2.22	7.85±2	0.9	7.88±2.15	7.78±1.86	0.8
Hemoglobin	14.3±1.6	14.1±1.6	13.8±1.5	0.05	14.3±1.6	14.0±1.6	0.4	14.2±1.6	13.8±1.5	0.09
Platelet	225±59	234±56	231±60	0.2	225±59	233±57	0.6	229±58	231±60	0.3
MPV	9.6±1.2	9.7±1.8	9.7±2	0.7	9.6±1.2	9.7±1.8	0.2	9.7±1.5	9.7±2	0.3
RDW	14.9±4.1	14.6±3.7	14.9±4.2	0.8	14.9±4.1	14.7±3.8	0.5	14.8±4	14.9±4.2	0.9

LDL; low density lipoprotein WBC; White blood count

The study patients were divided into 3 groups according to their SS (low 1-21, moderate 22-31, high>31). Baseline characteristics of patients, WBC counts, CRP were not different within the groups. The group with high SS values was older than the moderate and low score groups (p<0.05 for other groups). The group with high SS had a higher NLR than the low group (p<0.05). Whereas the low SS group had the lowest NLR values among the other SS groups (p<0.05) (Table 2). The low SS group had higher lymphocyte values than the high SS group. However, it was similar between the low group and the moderate group and between the moderate group and the high group. The group with high SS had significantly elevated serum creatinine values than the other two groups (p<0.05 for all).

If study patients are separated into two groups according to SS (low ;1-21, high;> 21 or low; 1-31, high >32), the high SS groups had more NLR values than the low SS groups (group 1-21; 2.35±1.18 vs group >22; 2.60 ± 1.25 p=0.04 and group 1-31; 2.43±1.20 vs group >32; 2.74±1.3 p=0.02) (Table 2).

When evaluated with univariate analysis, age, creatinine, lymphocyte count and NLR index were predictors with high SS groups. When multiple logistic regression analysis is performed, only BUN detected as an independent predictor of high SS (Table 3).

Table 2. Comparison of neutrophil / lymphocyte and CRP (inflammatory marker) between the low and the high Syntax scores or the low, the moderate and the high Syntax scores

	SYNTAX 1-22 (n=224)	SYNTAX 23-32 (n=188)	SYNTAX >32 (n=83)	*p	SYNTAX 1-21 (n=224)	SYNTAX >22 (n=271)	p	SYNTAX 1-31 (n=412)	SYNTAX >32 (n=83)	p
Neutrophil, 103/mL	4.9±1.88	5.0±1.7	4.96±1.5	0.8	4.9±1.88	4.99±1.64	0.2	4.96±1.8	4.96±1.5	0.5
Lymphocyte, 103/mL	2.28±0.75	2.17±0.69	2.06±0.71	0.06	2.28±0.75	2.14±0.7	0.05	2.23±0.77	2.06±0.71	0.07
NLR	2.35±1.18	2.54±1.18	2.74±1.30	0.04	2.35±1.18	2.60±1.25	0.04	2.43±1.20	2.74±1.3	0.02
CRP (median)	2.1	1.1	1.8	0,2	2.18	1.45	0.4	1.30	1.80	0.1

NLR; neutrophil-lymphocyte ratio CRP; C-reactive protein

Table 3. Independent predictors of low and the high Syntax scores

Variable	Univariate Analysis		Multivariate Analysis	
	Odds Ratio, 95% CI	p Value	Odds Ratio, 95% CI	p Value
Age	1.036 (1.005-1.067)	0.021		
Creatinine	2.768 (1.213-6.319)	0.016		
BUN	1.035 (1.012-1.059)	0.003	1.028 (1.006-1.050)	0.012
Hemoglobin	0.886 (0.768-1.023)	0.09		
Neutrophil-lymphocyte ratio	1.126 (0.997-1.272)	0.04	**1.057 (1.020-1.089)**	**0.137**

DISCUSSION

This study investigates the relationship between NLR and the severity and complexity of coronary disease calculated by SS in SAP with CTO who underwent coronary angiography. We showed in our study that NLR was slightly higher in the high SS group.

The basic pathophysiology mechanism for ischemia in patients with CAD is the development of atherosclerotic plaque. Previous studies claim that WBC cells such as neutrophils and lymphocytes are markers of the inflammatory condition and have an important role in triggering and maintaining the atherosclerotic process (15). NLR, an index indicating the inflammatory status, is calculated by CBC. NLR was used with other inflammatory markers and was found to be a good indicator of inflammatory status (4,16).

When the literature is analyzed, it is seen that there is a relationship between CAD and high WBC. While neutrophilia may be a chronic, adaptive response in myocardial ischemia due to coronary diseases, lymphocytes also play an important role in controlling the inflammatory response in this process. An increase in the count of neutrophils and a decrease in the lymphocyte count are more common in the acute phase of the ischemic process (15,16). However, neutrophilia and low lymphocyte levels are not significant in patients diagnosed with stable coronary artery disease, such as stable angina pectoris. (17,18). Previous clinical studies have shown that high NLR levels increase cardiovascular mortality and adverse outcomes in patients with stable and unstable CAD (19-22).

Demir et al showed that NLR was significantly higher in CTO patients, this suggests that high NLR predicts CTO

in patients with stable clinics. But the study included a small patient population and did not divide the patients into groups according to their Syntax score (23). Kaya et al and Sonmez et al demonstrated that the linkage of NLR with the severity and complexity of atherosclerosis in stable CAD patients (17,24). In our study, there was a statistical significance difference between very high and low when we divided the patients into 3 groups according to SS. However, when all SS groups were evaluated in WBC and neutrophil counts, no significant difference was found between them. (1-22 to 23-32, 23-32 to >32). Similarly, there was no statistically significant difference between WBC and neutrophil counts when the 2 groups were divided into the low score and high score according to the patients' SS (SS groups 1-21 to >22 and 1-31 or >32). Similar to these studies, although there was no statistical difference in neutrophil counts, the lymphocyte counts were significantly lower and the NLR ratios were significantly lower. Neutrophilia with lymphopenia is observed in the early stages of ACS patients. (25-28). The presence of lymphopenia may suggest chronic inflammation. Sönmez et al and Kaya et al revealed that a higher baseline NLR value is independently associated with the presence of greater coronary complexity of CAD. We performed a multivariant analysis, only BUN was detected as an independent predictor of a high SS. This finding is compatible with studies in the literature that say the NLR provides important information about inflammation in renal dysfunctions (29). However, in multivariant analysis, we could not find a statistical relationship between NLR and SS in CTO in SAP patients. The reason for these results might be the fact that our patient group has taken the CTO group as the subgroup of stable CAD. It is necessary to pass at least 3 months from the onset of the disease for this patient group to occur. During this period, inflammation has decreased relatively and the marker property of NLR in determining coronary complexity of CAD determination may have been lost. Our study, contrary to the literature findings, suggests that NLR is not an adequate marker in determining coronary complexity of CAD instable angina over the long run.

CONCLUSION

This study is the first study of the research of the relationship between NLR and the severity and complexity of CAD in large population patients with SAP with CTO. The small differences between the ratios in the groups support this low grade of inflammation in SAP with CTO and in these patients, NLR may not be sufficient to determine the severity and complexity of CAD in contrast to previous studies. But the NLR in determining the severity and complexity of CAD is more important than the WBC counts in the patients with SAP with CTO. Even if the NLR is not an independent risk factor, it may be effective in showing the complexity in the coronary artery before the procedure. In such cases, it may indicate to be more careful and prepared.

Competing interests: The authors declare that they have no competing interest.

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