Relation of neutrophil -to- lymphocyte ratio with the presence and complexity of coronary artery disease: an observational study

Koroner arter hastalığı varlığı ve karmaşıklığı ile nötrofil lenfosit oranı ilişkisi:
Gözlemsel bir çalışma

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ABSTRACT

Objective: The neutrophil -to- lymphocyte ratio (NLR) is a new predictor for cardiovascular risk and mortality. The SYNTAX score is an angiographic tool used in grading the complexity of coronary artery disease (CAD). However, its relation with CAD severity and complexity is not yet known. We hypothesized that NLR would be associated with a greater complexity of CAD as assessed using the SYNTAX score.

Methods: This cross-sectional observational study included 106 patients who had undergone coronary angiography for stable angina pectoris and 69 patients who had normal coronary angiogram. Baseline NLR was measured by dividing neutrophil count to lymphocyte count. The patients were classified two groups as CAD (-) (n=69) and CAD (+) (n=106), then patients in CAD (+) group were divided into 3 groups according to SYNTAX scores (SYNTAX score 1-22, 23-32, >32) as pointed in European Society of Cardiology (ESC) revascularization guideline. Statistical analysis was performed using the Mann-Whitney U and Kruskal-Wallis tests, and multiple logistic regression analysis was used to identify the independent predictors of complexity of CAD-SYNTAX score.

Results: Patients with CAD had a significantly higher value of NLR [1.6 median (1.2-3.3 IQR) vs. 2.3 median (1.8-3.0 IQR) p<0.001]. The group with high SYNTAX scores (>32) more frequently had diabetes mellitus (DM), hypercholesterolemia (HL), were of older age, and also had significantly elevated NLR values [2.4 (1.3-2.6), 2.6 (2.3-3.9), 2.0 (1.5-2.6) p=0.006]. In univariate analysis, age, DM, HL, creatinine, neutrophil count and NLR were predictors of high SYNTAX score. In the multiple logistic regression analysis, only NLR [odds ratio (OR)=2.1, 95% confidence interval (CI) 1.2-3.8, p=0.09], was identified as independent predictor of a high SYNTAX score.

Conclusion: NLR is a strong clinical laboratory value that is associated with presence and complexity of CAD. *(Anadolu Kardiyol Derg 2013; 13: 662-7)*

Key words: Neutrophil -to- lymphocyte ratio, complexity, coronary artery disease, regression analysis, sensitivity, specificity

ÖZET

Amaç: Nötrofil lenfosit oranı (NLO) kardiovasküler risk ve mortalite için yeni bir öngördürücüdür. SYNTAX skoru koroner arter hastalığı (KAH) karmaşıklığını derecelendirmede anjiyografik bir yöntemdir. NLO ile KAH varlığı ve karmaşıklığı arasındaki ilişki henüz ortaya konmamıştır. Biz SYNTAX skorunu kullanarak NLO ile KAH varlığı ve karmaşıklığı arasında daha güçlü bir ilişki olabileceği tezini öne sürdük.

Yöntemler: Bu enine kesit gözlemsel çalışmaya 106 koroner anjiyografisi yapılmış stabil angina pectoris hastası ve 69 normal koronere sahip hastalar dahil edildi. Bazal NLO nötrofil sayısının lenfosit sayısına oranı olarak hesaplandı. Hastalar KAH olan ve olmayan şeklinde iki gruba ayrıldı. KAH grubu SYNTAX skoruna göre Avrupa Kardiyoloji Cemiyeti miyokardiyal girişim kılavuzuna dayanarak 3 gruba ayrıldı (SYNTAX skor 1-22, 23-32, >32). İstatistiksel analiz Mann-Whitney U ve Kruskal-Wallis testleri ile yapıldı, ayrıca KAH karmaşıklığının bağımsız öngördürücülerini belirlemek amacı ile çoklu lojistik regresyon analizi kullanıldı.

Bulgular: KAH olan grup olmayan gruba göre daha yüksek NLO değerlerine sahipti [1,6 median (1,2- 3,3 IQR) vs. 2,3 mediyan (1,8-3,0 IQR) p<0.001]. SYNTAX skoru >32 olan grup daha yaşlı, diyabet ve hiperlipidemi oranları fazlaydı. NLO değerleri anlamlı olarak yüksekti [2,4 (1,3-2,6), 2,6 (2,3-3,9), 2,0 (1,5-2,6) p=0,006]. SYNTAX >32 univaryant öngördürücüleri olarak yaş, diyabet, kreatinin, hiperlipidemi, nötrofil ve NLO değerleri belirlendi. SYNTAX >32 multivaryant öngördürücüsü olarak sadece NLR değeri anlamlı tespit edildi (odds ratio=2,1, %95 güven aralığı 1,2-3,8, p=0,09).

Sonuç: NLR koroner arter hastalığı varlığı ve karmaşıklığı ile ilişkili güçlü bir klinik parametredir. *(Anadolu Kardiyol Derg 2013; 13: 662-7)*

Anahtar kelimeler: Nötrofil lenfosit oranı, koroner arter hastalığı, karmaşıklık, regresyon analizi, duyarlılık, özgüllük

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Introduction

Atherosclerosis is a chronic low-grade inflammatory disease, and inflammatory marker can be shown in circulation (1, 2).

White blood cell (WBC) count and subtypes are well known measurements as inflammatory markers (3-5) in cardiovascular disease and its index as the ratio between neutrophils and lymphocytes (NLR) count have recently emerged as inflammatory biomarkers to predict cardiovascular outcomes in patients with coronary artery disease (CAD) (6-10). The SYNTAX score is an angiographic tool used in grading the complexity of CAD. The SYNTAX score provides important information with respect to favor revascularization strategy and the prognostic significance of CAD.

However NLR's relation with severity and complexity of CAD is not yet known.

Therefore. in the light of these findings we hypothesized that NLR would be associated with a greater complexity of CAD as assessed using the SYNTAX score. We evaluated this hypothesis in patients with stable angina.

Methods

Study design

This study was designed as a cross-sectional observational study.

Patient selection

The study population included 106 consecutive nonanemic patients who were referred or applied to our faculty outpatient clinic for elective coronary angiography who had objective signs of ischemia (treadmill exercise, dobutamine stress echo and myocardial SPECT) for stable angina pectoris and 69 patients who had normal coronary angiogram between March 2011 and May 2012. Overall, 106 patients who had coronary lesion with a diameter stenosis of at least 50% were included CAD (+) group, and 69 patient who had normal coronary anatomy were included CAD (-) group. Patients with CAD were further divided into 3 groups according to SYNTAX score values (SYNTAX score 1-22, 23-32, >32) as pointed in European Society of Cardiology (ESC) revascularization guideline (11).

Patients presenting with acute myocardial infarction (AMI), coronary artery bypass surgery (CABG), end-stage renal disease, malignancy, any prior blood transfusions, presence of thalassemia traits, and menorrhagia were excluded from the study. In addition, we excluded the patients with coronary ectasia and slow coronary flow, as well as those patients with WBC count >13.000 cells per uL or <4.000 cells per uL and high body temperature >38º were excluded from the study.

The ethical implications regarding the study were approved by the local Ethics Committee and informed consent was obtained from each patient.

Study protocol

Baseline variables

Baseline demographic, clinical and laboratory data were obtained from patients' charts and were recorded. For each patient, height, weight and body mass index (BMI) were calculated. Hemoglobin (Hb), WBC, platelet, lymphocyte and neutrophil counts were measured as part of the automated complete blood count (CBC) using a Sysmex XT-1800i (USA) hematology analyzer.

NLR (Neutrophil -to- Lymphocyte Ratio)

Baseline NLR was measured by dividing Neutrophil count to lymphocyte count.

SYNTAX score

The SYNTAX score is an angiographic index used in grading the complexity of CAD. Each coronary lesion with a diameter stenosis of at least 50%, in vessels at least 1.5 mm, was scored. The online latest updated version (2.1) was used for the calculation of the SYNTAX scores (www.syntaxscore.com) (12, 13).

Statistical analyses

The statistical analyses were performed using software (SPSS 15.0, SPSS Inc, Chicago, Ill, USA). Continuous variables are expressed as mean±SD or median (interquartile range) when appropriate. Categorical variables are expressed as percentages. To compare parametric continuous variables, Student's t-test or analysis of variance was used; to compare nonparametric continuous variables, the Mann-Whitney U test or the Kruskal-Wallis test was used. To compare categorical variables, the Chi-square-test was used. Multiple logistic regression analysis was used to identify the independent predictors of high SYNTAX score (>32). All variables showing significance values of less than 0.1 on univariate analysis (age, sex, DM, hypertension, hypercholesterolemia, creatinine, WBC, neutrophil and NLR) were included in the model. A receiver operating characteristic (ROC) analysis was performed to define the diagnostic value of NLR in prediction of high SYNTAX score. Two-tailed p values of less than 0.05 were considered to indicate statistical significance.

Results

Baseline characteristics

The baseline characteristics of the groups are presented in Table 1. In 175 patients (mean age 59.2±11.9, 59% male), NLR ranged from 0.56 to 7.74 (median 2.07, mean 2.29±1.1). Patients with CAD had a significantly higher value of NLR (1.6 median (1.2- 3.3 IQR) vs. 2.3 median (1.8-3.0 IQR) p<0.001).

NLR values and complexity of CAD

When SYNTAX scores were divided into low (1-22), moderate (23-32), and high (>32) score groups, those with low SYNTAX

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Table 1. Baseline characteristics of groups (coronary artery disease and without coronary artery disease)

Variables	CAD (-) (n=69)	CAD (+) (n=106)	*p
Age, years	56 (47-62)	62 (53-70)	<0.001#
Female n (%)	40 (58)	36 (34)	<0.001
BMI, kg/m^2	29.1±3.1	30.2±3.4	0.132
Diabetes mellitus, n (%)	19 (27)	52 (50)	0.01
Hypertension, n (%)	31 (45)	63 (59)	0.12
Hypercholesterolemia, n (%)	22 (31)	54 (51)	0.028
Family history, n (%)	4 (6)	8 (7)	0.87
Creatinine, mg/dL	0.9±0.6	0.9±0.3	0.65
LDL, mg/dL	127±33	131±37	0.55
WBC, 10^3/mL	7.2±1.9	7.7±2.1	0.1
Neutrophil, 10^3/mL	3.7 (2.9-4.9)	4.4 (3.4-5.8)	0.006#
Lymphocyte, 10^3/mL	2.2±0.7	2.0±0.7	0.11
NLR	1.6 (1.2-3.3)	2.3 (1.8-3.0)	<0.001#
Hemoglobin, g/dL	12.4±1.8	12.6±1.8	0.60
Platelet, 10^3/mL	252±69	243±67	0.40
Aspirin use, n (%)	15 (21%)	22 (20%)	0.63
B-blocker, n (%)	10 (14%)	13 (12%)	0.35
ACE inhibitor use, n (%)	31 (45%)	63 (59%)	0.12
Statin use, n (%)	20 (29%)	50 (48%)	0.03

Results are expressed as mean±SD or frequency (within group percentage) and median (Interquartile range).

*unpaired Student's t- and Chi-square tests

#Mann-Whitney U test

ACE - angiotensin converting enzyme, BMI - body mass index, NLR - neutrophil -to-lymphocyte ratio, WBC - white blood cell count

Table 2. Baseline characteristics of SYNTAX score groups

Variables	SYNTAX 1-22 (n=62)	SYNTAX 23-32 (n=23)	SYNTAX >32 (n=21)	*p
Age, years	60±10	64±12	66±12	0.09
Male, n (%)	40 (64)	14 (61)	15 (71)	0.79
BMI, kg/m^2	28.1±3.2	29.2±3.6	31.2±3.3	0.10
Diabetes mellitus, n (%)	20 (32)	12 (52)	12 (57)	0.04
Hypertension, n (%)	35 (56)	9 (40)	11 (52)	0.81
Hypercholesterolemia, n (%)	20 (32)	11 (47)	12 (57)	0.60
Creatinine, mg/dL	0.9±0.2	0.8±0.3	1.0±0.5	0.14
LDL, mg/dL	123±44	132±33	139±45	0.64
WBC, 10^3/mL	7.5±2.1	7.7 ±2.5	8.0±2.4	0.69
Neutrophil, 10^3/mL	4.0 (3.1-5.0)	4.2 (3.0-5.0)	4.9 (3.8-7.0)	0.18
Lymphocyte, 10^3/mL	2.1±0.6	2.2±1.0	1.8±0.5	0.16
NLR	2.0 (1.5-2.6)	2.4 (1.3-2.6)	2.6 (2.3-3.9)	0.006#
Hemoglobin, g/dL	12.5±1.6	12.5±1.9	12.9±1.8	0.69
Platelet, 10^3/mL	244±67	231±72	255±73	0.54
Aspirin use, n (%)	7 (11)	5 (21)	7 (33)	0.05
B-blocker, n (%)	8 (13)	2 (9)	2 (9)	0.63
ACE inhibitor use, n (%)	35 (56)	9 (39)	11 (52)	0.81
Statin use, n (%)	22 (35)	11 (47)	12 (57)	0.06

Results are expressed as mean±SD or frequency (within group percentage) and median (interquartile range).

*ANOVA, Kruskal-Wallis and Chi-square tests

#Kruskal Wallis df/Chi-square - 2/10.226

ACE - angiotensin converting enzyme, BMI - body mass index, NLR - neutrophil -to- lymphocyte ratio, WBC - white blood cell count

score group were younger whereas moderate and high score groups more frequently had DM (p<0.05 for all). Those with high SYNTAX score group had the highest NLR values, whereas those with low SYNTAX score group had the lowest NLR values (p<0.05) (Table 2). The group with high SYNTAX scores more frequently had DM, hypercholesterolemia, were of older age, and also had significantly elevated NLR values (p<0.05 for all) (Table 2, Fig. 1). The patients with high (>32) and moderate-to-low SYNTAX scores (<32) were compared in the univariate analysis. Variables found to be statistically significant in univariate analyses were entered into multiple logistic regression analysis.
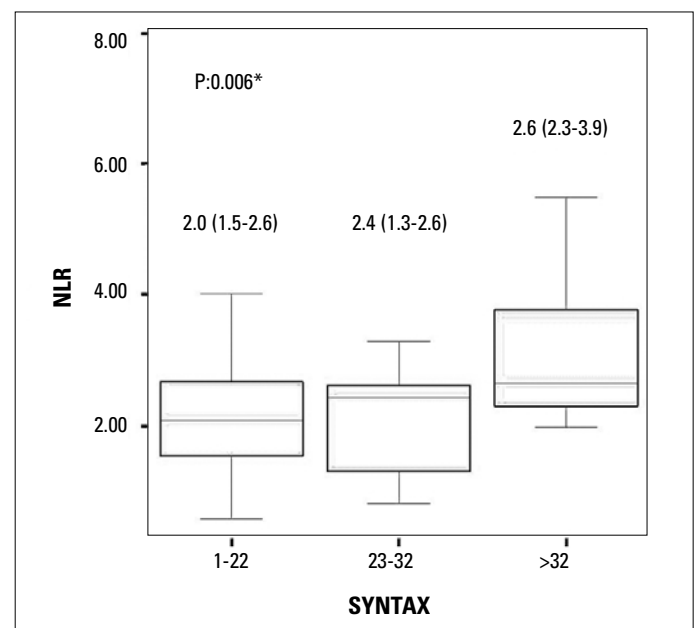
Predictors of CAD complexity

In univariate analysis, age, DM, HL, creatinine, neutrophil count and NLR were predictors with high SYNTAX score group (SYNTAX>32) (Table 3). In multiple logistic regression analysis, only NLR [odds ratio (OR)=2.1, 95% confidence interval (CI) 1.2-3.8, p=0.09], was identified as independent predictor of a high SYNTAX score (Table 3).

Figure 1. NLR values in SYNTAX score groups
Data are presented median and interquartile range (IQR), *Kruskal-Wallis test
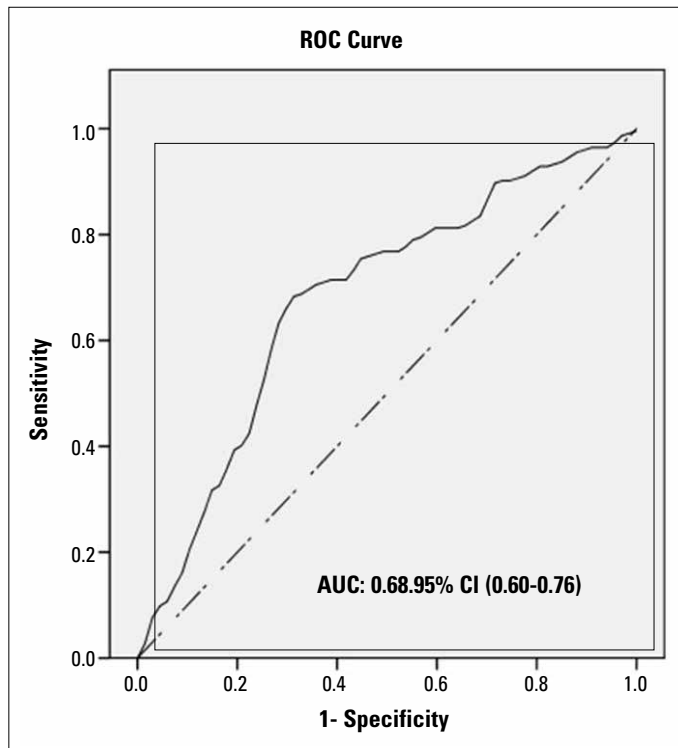NLR - neutrophil -to- lymphocyte ratio

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Figure 2. Diagnostic accuracy of NLR in prediction of severe and complex CAD-high SYNTAX score
*ROC analysis
AUC - area under curve, CAD - coronary artery disease, CI - confidence interval, NLR - neutrophil -to- lymphocyte ratio

In ROC analysis, a cut-point of 1.95 identified patients with angiographic CAD (+) (area under curve=0.68, 95% CI 0.60-0.76). An NLR value of more than 1.95 demonstrated a sensitivity of 69%, a specificity of 69% (Fig. 2).

Discussion

In this study, we found a relation of NLR with the presence and complexity of coronary artery disease. Our findings indicate that high- levels of NLR are predictive of a greater complexity of CAD.

There is no doubt in cardiovascular medical science that atherosclerosis is a chronic inflammatory disease (1, 2). The low-grade inflammation with (2, 14, 15) inflammatory marker and oxygen radicals released by aggregated and activated neutrophils can be shown in circulation especially in coronary sinus (14-16). NLR is a CBC index, which shows inflammatory status. In the light of recent data and studies, WBC count and index as NLR are independent predictors of short and term mortality in patients with AMI (7, 10, 14-17). NLR is an independent predictor of cardiac mortality in stable CAD patients (9) and predictor of mortality in patients undergoing percutaneous coronary intervention (6). Baseline leukocyte counts were higher in CAD patients who have stable angina pectoris, unstable angina, AMI than in patients who had no significant CAD (9, 10).

The SYNTAX score is an angiographic index used in grading the complexity of CAD and ranges from 0 to 83. The lover scores mean

Table 3. Independent predictors of high SYNTAX score (>32) in multiple logistic regression analysis

Variables	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Age	--	0.07	1.0 (0.9-1.1)	0.2
Male	0.6 (0.2-2.2)	0.5	--	--
Diabetes mellitus	0.4 (0.2-1.1)	0.1	1.4 (0.4-5.2)	0.4
Hypertension	1.2 (0.5-3.3)	0.6	--	--
Hypercholesterolemia	0.4 (0.2-1.1)	0.1	0.4 (0.2-1.5)	0.2
Creatinine	--	0.09	2.2 (0.4-12)	0.3
WBC	--	0.4	--	--
Neutrophil	--	0.06	1.1 (0.7-1.8)	0.7
NLR	--	0.01	2.1 (1.2-3.8)	0.009

CI - confidence interval, NLR - neutrophil -to- lymphocyte ratio, OR - odds ratio, WBC - white blood cell count

less complex CAD, inversely higher scores indicate more complex CAD. Metzler et al. (18) pointed that SYNTAX score reflects only the coronary anatomy not patient characteristics and treatment strategy. And also, this score has been shown to predict cardiac mortality and major adverse cardiovascular events in patients undergoing percutaneous revascularization (11,18, 19). However, NLR and other inflammatory markers like hs-CRP are not yet included any clinical and angiographic scoring system including GRACE, SYNTAX, TIMI, STS, Euroscore (18, 20, 21).

Işık et al. (22) have revealed an association between red cell distribution width (RDW) and the complexity of CAD. RDW and NLR have been associated with an increased risk of adverse cardiac events. We have revealed that a higher baseline NLR value is independently associated with the presence of a greater coronary complexity of CAD as assessed by the SYNTAX score. Inflammation might explain the higher NLR values in patients with complex CAD. It has been reported that elevated inflammatory markers (14, 15), RDW (22) and WBC counts (5, 23) are associated with the extent and severity of CAD. However, we did not measure other inflammatory markers in the present study.

Contrary to prior studies (5, 23-25), in our study WBC and neutrophil counts did not differ significantly between SYNTAX scores groups (1-22, 23-32, >32), although their counts were relatively high in moderate and high score groups. Our data showed similar findings with prior studies when assessing WBC and neutrophil count between CAD (-) and CAD(+) groups. Besides, Amaro et al. (25) evaluated only relationship of severity of CAD with Gensini score instead of complexity of CAD by SYNTAX score. Additionally, this finding can simply be explained that we excluded WBC count >13.000 cells per uL or <4.000 cells per uL. Secondly, our population accounts for patients with stable angina, because prominent neutrophilia with lymphopenia is seen in the setting of acute coronary syndrome (3, 26-28). Suliman et al. (26) pointed that NLR is a dynamic variable owing to neutrophil and lymphocytes counts

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after AMI demonstrate significant variation. However, we found in the present study that NLR value is not dynamic and is more useful indicator reflecting severity and complexity of CAD than WBC count in the setting of stable CAD. This condition may be related with low-grade inflammation.

Study limitations

Major limitation of the study was small number of patients. Secondly, this was a cross-sectional observational study; therefore, we did not research correlation with short and long-term events. Thirdly, we did not measure and assess predictive value of other inflammatory markers. Lastly, strict including and excluding criteria were used. The results of present study are not yet generalizable to all patients in clinical practice.

Conclusion

The main finding of the present study was that the NLR is a robust inexpensive, clinical and routinely calculable value that is associated with the severity and complexity of CAD.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - H.U.; Design - O.S., G.E.; Supervision - H.U., Ö.G.; Resource - E.A.; Data collection&/or Processing - O.S., E.A., E.E., G.E.; Analysis &/or interpretation - O.S.; Literature search - O.S., A.T.; Writing - O.S., A.T.; Critical review - O.S.; A.B., G.E.; Other - A.B.

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