ORIGINAL ARTICLE

Assessment of neutrophil and neutrophil/lymphocyte ratio in coronary collateral developed patients with acute coronary syndrome

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SUMMARY

OBJECTIVE: *Inflammation-related markers provide diagnostic and prognostic information for coronary artery disease and acute coronary syndrome. We aimed to compare neutrophil count and neutrophil/lymphocyte ratio (NLR) in acute coronary syndrome patients with coronary collateral development in our study.*

METHODS: *A total of 426 patients (102 unstable angina pectoris (USAP), 223 non-ST-elevation myocardial infarction (non-STEMI), 103 ST-elevation myocardial infarction (STEMI) were compared regarding hemoglobin, platelet, lymphocyte, neutrophil count, and NLR.*

RESULTS: *Neutrophil count and NLR were significantly lower in USAP patients and higher in STEMI patients; 5.14± 1.79 vs. 7.21± 3.05 vs. 9.93±4.67 and 2.92±2.39 vs. 5.19±4.80 vs. 7.93±6.38, p <0.001. Other parameters, i.e., hemoglobin, platelet, and lymphocyte count, were not significantly different between the groups.*

CONCLUSIONS: *In our study, it was concluded that there may be a statistically significant difference in the number of neutrophil counts and NLR among the types of acute coronary syndromes with coronary collateral development.*

KEYWORDS: *Acute coronary syndrome. Collateral circulation. Neutrophils. Lymphocytes.*

INTRODUCTION

The mechanism responsible for coronary artery disease and acute coronary syndrome is inflammation[1]. The relationship between the degree of inflammation and the level of hematological markers has been studied in many diseases in the literature[1-3]. In the process of inflammation, blood cells continue to be the subject of studies because they involve the process of and also are affected by inflammation.

Coronary collateral circulation becomes visible after the presence of at least 90% stenosis in the main coronary artery. In a study conducted in patients with myocardial infarction, almost all patients showed the development of collateral flow in the first 24 hours[4]. There are many benefits of coronary collateral circulation, such as prevention of ischemia, reduction of infarction area, prevention of development of left ventricular aneurysm, improvement of left ventricular functions after infarction, reduction of coronary mortality and prolongation of survival[5]. Coronary angiography is the method used to determine collateral

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circulation, although it does not become visible before reaching 100 microns in size[6]. Coronary artery stenosis or occlusion has been shown to induce collateral circulation by affecting the balance between oxygen supply and demand[7]. Also, in cases with increased inflammation, it has been shown that coronary collateral circulation is less developed[8].

In coronary artery disease, acute coronary syndromes are characterized by exacerbation periods with a wide range of unstable angina pectoris, non-ST elevation myocardial infarction, and ST-elevation myocardial infarction. The relationship between the prognosis of the three groups and hematological markers is still the subject of research; their use in prognostic classification has the advantage of being widely available and cost-effective.

The level of NLR, which is associated with mortality in acute coronary syndromes, is the strongest prognostic predictor in hematological markers as a result of comprising two parameters used to assess the degree of inflammation[9-11]. NLR has also been studied in many clinical scenarios and it was used as a marker of chronic systemic inflammation. For example, in the literature, it may be used as an activity parameter in ulcerative colitis or as an indicator of the presence of Hashimoto's thyroiditis[12,13].

Our study aimed to compare neutrophil and neutrophil/lymphocyte ratio between the types of coronary collateral developed acute coronary syndromes.

METHODS

In our single-centered study, 426 patients who were admitted to Bolu Abant Izzet Baysal University Hospital and underwent coronary angiography with acute coronary syndrome between March 2015 and November 2018 were included.

The patients were divided into three groups: 102 patients with diagnosed USAP, 223 with diagnosed non-STEMI, and 103 with STEMI; all patients' emergency laboratory parameters were taken. Demographic data and laboratory parameters of the patients were recorded. Serum glucose, creatinine, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured using an automatic biochemical analyzer (Architect C8000, USA). Complete blood count (CBC) was determined using simultaneous optical and impedance measurements (Cell Dyn 3700; Abbott Diagnostics, Lake Forest, Illinois, USA). NLR was calculated by dividing the neutrophil count by the lymphocyte count.

The presence of hypertension was defined as systolic blood pressure > 140 mmHg, and/or diastolic blood pressure > 90 mmHg, or already receiving antihypertensive treatment. Diabetes was defined as fasting blood glucose > 126 mg/dl or related drug intake. Hyperlipidemia was defined as total cholesterol > 200 mg/dl or triglyceride > 150 mg/dl.

While USAP, non-STEMI, and STEMI were diagnosed according to the recommendations of the current guidelines; patients with acute chest pain and persistent (>20 minutes) ST-segment elevation were defined as STEMI. The patients with acute chest pain but no persistent ST-segment elevation (transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudo-normalization of T waves or normal ECG) and a hint for myocardial necrosis were defined as non-STEMI. USAP was defined as myocardial ischemia at rest or minimal exertion in the absence of cardiomyocyte necrosis.

The criteria for ST-segment elevation were as follows: 1) At least 1 mm ST-segment elevation in at least two successive leads, 2) 2.5 mm in men under 40 years of age, 2 mm in men over 40 years, and 1.5 mm ST-segment elevation in women in V2 and V3, 3) 0.5 mm ST-segment elevation in V7-V9 (at least 2 consecutive lines), 4) 0.5 mm ST-segment elevation in V3R and V4R (1 mm in men under 40).

Coronary angiography was performed by the femoral or radial route using the Seldinger technique and coronary angiography results were evaluated independently by at least two cardiologists. In our study, we included patients with acute coronary syndrome who had at least 95% stenosis in the coronary artery. Although different methods are used for angiographically identifying and classifying coronary collateral circulation, Rentrop classification is the most accepted classification and was used in our study[14]. According to this classification: Rentrop 0 shows the absence of collateral current; Rentrop 1 is the presence of weak collateral flow; Rentrop 2 is the presence of partial collateral; while Rentrop 3 shows the presence of complete collateral.

The exclusion criteria of the study were history of coronary bypass graft operation, presence of decompensated heart failure, severe valve disease, atrial fibrillation, cardiomyopathy or congenital heart disease, inflammatory disease, renal or hepatic failure, malignancy, active infection, and pregnancy.

The study was approved by the Local Ethics Committee of the Bolu Abant Izzet Baysal University Hospital, Turkey.

Statistical analyses

SPSS 18.0 Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA) was used for analysis. Quantitative variables are expressed as mean ± standard deviation (SD) and qualitative variables as numbers and percentages. The One-way ANOVA Test (with Post-Hoc Tukey HSD) was used for comparing variables in study groups. Post-Hoc Tukey Test was applied in group differences. The neutrophil to lymphocyte ratio (NLR) value was determined by the division of neutrophils by lymphocytes. Receiver operating curve (ROC) analysis was used to find the difference in neutrophil and NLR in the two groups of acute coronary syndrome (STEMI and without –STEMI). A two-tailed P value of <0.05 was considered significant.

RESULTS

A total of 426 patients (301 male, 125 female) were included in the study. There was no significant difference between the three groups regarding the demographic data (Table 1). Laboratory parameters were compared and no significant difference was found between creatinine, glucose, and lipid panels. Neutrophil count and NLR were significantly different; 5.14± 1.79 vs. 7.21± 3.05 vs. 9.93±4.67 and 2.92±2.39 vs. 5.19±4.80 vs. 7.93±6.38, p <0.001) (Table 2). No significant difference was found between the groups regarding the site of coronary lesions (Table 3).

In order to understand which group has mainly caused a significant difference between the study groups, the One-way ANOVA Test with Post-Hoc Tukey Test was applied. The differences in NLR and neutrophil count were caused by the differences between the USAP and non-STEMI (p<0.001), USAP and STEMI (p<0.001), and non –STEMI and STEMI (p<0.001) groups by Tukey Test.

A receiver operating curve (ROC) analysis was used to find the difference in neutrophil and NLR in the two groups of acute coronary syndrome (STEMI and without –STEMI). At the cut-off value of >7.22 u/mm^3, sensitivity and specificity of neutrophil were 71 % and 69 %, respectively (AUC = 0.738, 95% CI, 0.683-0.793). At the cut-off value of >3.87, sensitivity and specificity of NLR were 71% and 62%, respectively (AUC = 0.712, 95% CI, 0.655-0.770) (Figure 1).

DISCUSSION

In our study, we compared neutrophil count and NLR in patients with coronary collateral developed acute coronary syndromes and found that neutrophil and NLR were higher in STEMI patients than in non-STEMI and USAP patients.

Coronary artery disease and acute coronary syndromes are inflammatory diseases caused by atherosclerosis[15]. Therefore, inflammation-related

TABLE 1. GENERAL CHARACTERISTICS OF THE STUDY GROUPS

Baseline characteristics	USAP (n=102)	Non-STEMI (n=221)	STEMI (n=103)	p
	MEAN			
Age (mean ±SD) (years)	64 ±12	67±12	67±13	0.11
Body mass index (kg/m^2)	25±4	26 ± 4	25±3	0.43
Male/female	79/23	146/75	76/27	0.08
Hypertension (%)	67(65%)	139(63%)	53(51%)	0.07
Smoking(%)	42(41%)	81(37%)	35(34%)	0.56
Family history(%)	16(16%)	26(12%)	(88%)	0.21
Diabetes mellitus(%)	39(38%)	83(37%)	27(26%)	0.10
Acetylsalicylate (%)	35(34%)	70(32%)	29(28%)	0.63
Clopidogrel(%)	17(17%)	25(11%)	13(12%)	0.41
Statin(%)	25(24%)	46(21%)	13(13%)	0.08
Calcium channel blocker(%)	15(14%)	44(20%)	12(12%)	0.15
ACE inhibitor(%)	27(26%)	41(19%)	14(14%)	0.06
ARB (%)	21(21%)	36(16%)	18(17%)	0.64
Beta-blocker(%)	38(37%)	63(28%)	30(29%)	0.26

ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, SD: standard deviation.

TABLE 2. LABORATORY DATA OF THE STUDY COHORT

	USAP (n=102)	Non-STEMI (n=221)	STEMI (n=103)	p
	MEAN			
Creatinine (mg/dl)	1.0±0.3	1.0 ± 0.8	1.0± 0.3	0.50
Fasting plasma glucose (mg/dl)	130±42	138 ± 50	139±50	0.32
LDL-cholesterol (mg/dl)	113±44	115±41	118± 44	0.68
HDL-cholesterol (mg/dl)	42±9	45±11	43± 10	0.12
Triglyceride (mg/dl)	159±91	151± 92	157±102	0.76
Total cholesterol (mg/dl)	185±49	189±49	191± 51	0.74
Hemoglobin	13.6±1.6	13.5± 2.0	13.6± 1.9	0.84
Platelet counts (k/mm^3)	224±71	235±67	237±72	0.29
Lymphocyte (u/mm^3)	2.18±0.90	1.92±1.09	1.76±1.05	0.013*
Neutropil(u/mm^3)	5.14± 1.79	7.21± 3.05	9.93±4.67	<0.001*
NLR	2.92±2.39	5.19±4.80	7.93±6.38	<0.001*

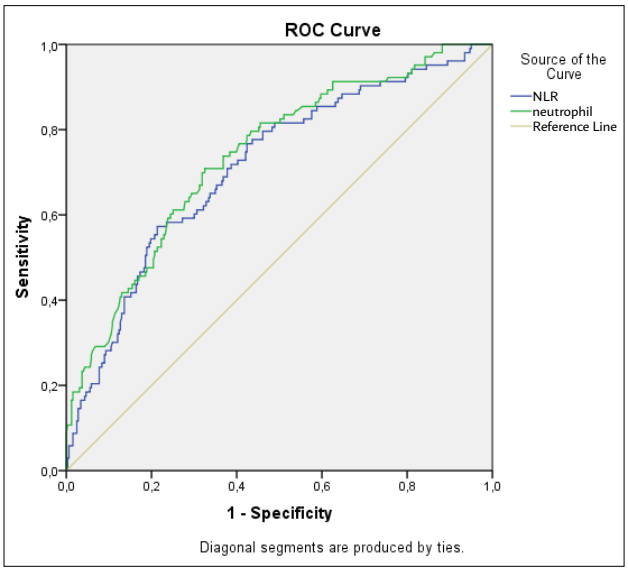
NLR: Neutropil to lymphocyte ratio; *One-way ANOVA test with Post HocTukey HSD; *Difference is statistically significant P < 0.05 levels

TABLE 3. CORONARY ANGIOGRAPHIC LABORATORY FINDINGS OF THE STUDY WORKING

Coronary artery	USAP (n=102)	Non-STEMI (n=221)	STEMI (n=103)	p
LMCA	12(12%)	18(8%)	8(8%)	0.098
LAD	86(84%)	193(87%)	90(87%)	0.281
CX	62(60%)	158(71%)	77(75%)	0.305
RCA	91(91%)	195(88%)	96(93%)	0.015

LMCA: left main coronary artery, LAD: left anterior descending, CX: circumflex, RCA: right coronary artery.

FIGURE 1. ROC CURVE ANALYSIS OF NEUTROPIL AND NLR FOR PREDICTION OF STEMI.



At the cut-off value of >7.22 u/mm3, sensitivity and specificity of Neutropil were 71 % and 69 %, respectively (AUC = 0.738, 95% CI, 0.683-0.793). At the cut-off value of >3.87, sensitivity and specificity of NLR were 71% and 62%, respectively (AUC = 0.712, 95% CI, 0.655-0.770). AUC: Area under the curve, CI: Confidence interval.

markers provide diagnostic and prognostic information for both coronary artery disease and acute coronary syndrome[16].

NLR is an inexpensive marker that can be easily calculated from peripheral blood tests and gives diagnostic and prognostic information in many diseases.

Lymphocytes have inflammation-suppressing properties and low levels of lymphocytes in cardiac diseases have been associated with poor prognosis[17-19]. As an example of this, Blum et al. found that it is possible to associate lymphopenia with low ejection fraction and high myocardial loss. In another study, low lymphocyte count in USAP patients was reported as an independent risk factor for major adverse coronary events[19].

On the contrary, high levels of pro-inflammatory and pro-atherogenic substances secreted by activated neutrophils are associated with a poor prognosis of cardiovascular disease[20,21]. Examples of this condition include restenosis associated with the infiltration of neutrophils in balloon-injured arteries[22]. Sezer et al.[21] showed a direct correlation between reperfusion injury and neutrophil count in patients with acute coronary syndrome. In parallel with our study, Biasucci et al.[23] found that the neutrophil count was higher in acute MI patients than in USAP and stable coronary artery disease patients.

NLR can be easily calculated by peripheral blood test and is a parameter that includes both neutrophil and lymphocyte count. In many studies comparing white blood cell count and all subtypes in acute coronary syndrome, NLR has been shown to be the most potent predictive value for both death and MACE (Major Adverse Cardiac Event)[9-11]. For example, Núñez et al.[24] showed that the NLR-maximum level calculated in the first 96 hours of STEMI patients was a marker for mortality.

In the study of Erturk et al.[1], the NLR among the types of acute coronary syndromes was the highest in STEMI and the lowest in USAP, similar to what we found in our study. Our study was the first to show the presence of the highest-burden of inflammation in STEMI with NLR elevation among the types of acute coronary syndromes with coronary collateral development.

It was concluded that NLR is correlated with the degree of coronary artery calcification in males, not only in acute coronary syndromes, and also in asymptomatic healthy group[25]. The NLR in patients with stable coronary artery disease is a parameter that predicts the functional severity of coronary artery stenosis evaluated by Fractional Flow Reserve (FFR)[2].

In contrast to previous studies, Kurtul and Ozturk[26] showed the presence of good coronary collateral circulation was independently associated with increased in-hospital mortality. In their study, which emphasized the benefits of good collateral development, they presented several possible mechanisms to interpret these results. The most likely mechanism is that these patients have high-risk factors and more severe clinical features affecting mortality.

In another study, patients were classified according to coronary angiography results as acute coronary syndrome, stable angina pectoris, and normal coronary arteries groups. The NLR value between the groups was found to be related to both the severity and progression of coronary artery disease; for the patients with high NLR, in-hospital and long-term adverse cardiac events were found[3].

CONCLUSION

In our study, we compared the neutrophil counts and NLR by classifying acute coronary syndrome with coronary collateral development patients as USAP, non-STEMI, and STEMI. Even in patients with acute coronary syndrome who developed collaterals, we found that NLR and neutrophil values were significantly higher in the STEMI group, which was known to have the highest inflammation burden in comparison with non-STEMI and USAP groups. Despite the disadvantage of having ambiguous cut-off values, NLR and neutrophil counts are important biomarkers that can be used in diagnosis and prognosis in acute coronary syndromes with cheap, fast, and easy application. Being single centered is the limitation of our study.

Conflict of interest

None

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Author's Contribution

Conception and design of the research: Mansiroglu AK, Sincer I, Gunes Y; Acquisition of data: Mansiroglu AK, Sincer I; Analysis and interpretation of the data: Sincer I, Gunes Y; Statistical analysis: Sincer I; Writing of the manuscript: Mansiroglu AK; Critical revision of the manuscript for intellectual content: Gunes Y;

All authors checked the final version of the manuscript.

RESUMO

OBJETIVO: *Marcadores relacionados a inflamação fornecem informações de diagnóstico e prognóstico para doença arterial coronariana e síndrome coronariana aguda. Nosso objetivo foi comparar o número de neutrófilos e razão neutrófilos/linfócitos (RNL) em pacientes com síndrome coronariana aguda com desenvolvimento de circulação colateral.*

MÉTODOS: *Um total de 426 pacientes [102 com angina de peito instável (APIN), 223 com infarto do miocárdio sem supradesnível de ST (IMSS), 103 com infarto do miocárdio com supradesnível de ST (IMCS)] foram comparados em relação a hemoglobina, plaquetas, linfócitos, neutrófilos e RNL.*

RESULTADOS: *O número de neutrófilos e RNL estavam significativamente mais baixos em pacientes com APIN e mais altos nos pacientes com IMCS; 5,14± 1,79 vs. 7,21± 3,05 vs. 9,93±4,67 and 2,92±2,39 vs. 5,19±4,80 vs. 7,93±6,38, p <0,001. Os outros parâmetros (hemoglobina, contagem de linfócitos e plaquetas) não foram significativamente diferentes entre os grupos.*

CONCLUSÃO: *No nosso estudo, concluiu-se que pode haver uma diferença significativa no número de neutrófilos e RNL entre os tipos de síndromes coronarianas agudas com desenvolvimento de circulação colateral.*

PALAVRAS-CHAVE: *Síndrome coronariana aguda. Circulação colateral. Neutrófilos. Linfócitos.*

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