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Use of neutrophil/lymphocyte ratio as a marker in patients with suspicious diaphragmatic attenuation artifact

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ABSTRACT

Objective: This study aimed to evaluate whether neutrophil/lymphocyte (N/L) ratio assists in the diagnosis of coronary artery disease (CAD) in patients with suspected diaphragmatic attenuation artifact (DAA) on myocardial perfusion SPECT (MP-SPECT).

Material and Methods: A total of 255 patients undergoing coronary angiography between 2015-2020 due to unclear DAA of the inferior wall on MP-SPECT were included in this retrospective study. Patients were divided into two groups (CAD and non-CAD) according to angiographic images. Significant CAD was defined as ⩾50% stenosis of coronary arteries feeding the inferior wall. White blood cell count, biochemical parameters, and risk factors for CAD were compared between the two groups.

Results: There was no statistically significant difference between the two groups in terms of age (p = 0.055), gender (p = 0.482), and body mass index (p = 0.305). N/L ratio (OR = 1.397 p = 0.002 95% Cl = 1.128-1.732) and left ventricle ejection fraction (OR = 0.896 p = 0.023 95% Cl = 0.815-0.985) were independent risk factors for CAD in multivariate binary logistic regression analysis. Receiver Operating Characteristic (ROC) curve analysis showed that a cut-off value of ⩾2 for N/L ratio predicted the presence of CAD (sensitivity=63.5%, specificity=60.7%, AUC=0.668, 95% CI=0.596 – 0.740, p<0.001).

Conclusion: N/L ratio is a simple and accessible test and may increase the diagnostic accuracy of MP-SPECT for CAD in patients with suspicious diaphragmatic attenuation on MP-SPECT.

Keywords: neutrophil, lymphocyte, diaphragmatic attenuation, scintigraphy

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in the world (1). Numerous non-invasive methods have been developed to assist in the diagnosis of CAD. Myocardial perfusion single-photon emission tomography (MP-SPECT) is one of the methods with high sensitivity and specificity. However, image artifacts may occur in MP-SPECT due to the patient and technical problems. These artifacts reduce the sensitivity of MP-SPECT. The most common artifact associated with the left ventricular inferior wall in men is the diaphragmatic attenuation artifact (DAA). DAA can cause fixed perfusion defect interfering with a myocardial scar. It was reported that DAA was seen in 25% of MP-SPECT images (2). DAA can frequently occur due to elevation of the left diaphragm and, less often, the effect of the right ventricle. Generally, the elevation of the left diaphragm is seen in obese people and causes DAA. Pulmonary atelectasis and loss of pulmonary parenchyma can also cause diaphragm elevation. There are different methods used for the diagnosis of DAA (3). These methods can be listed as right lateral projection, electrocardiography (ECG) gated images, prone position images, and attenuation correction programs. Generally, prone position and ECG gated images are used (4). However, DAA frequently could not be distinguished despite these methods. Various cells and mediators play a role in the inflammatory process. The most important of these are neutrophils and lymphocytes. Neutrophils damage myocardial cells by releasing proteolytic enzymes such as Leukotriene B4, elastase, and neutrophil chemotactic activity. Many studies showed that these enzymes and low lymphocytes were responsible for acute coronary syndrome (ACS) and stable angina pectoris.

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In recent studies, the neutrophil/lymphocyte (N/L) ratio has been used as an inflammatory marker in atherosclerotic disease. N/L ratio was associated with CAD, mortality, low left ventricle ejection fraction (LVEF), and peripheral artery disease (5, 6).

To our knowledge, the role of the N/L ratio in the diagnosis of suspected DAA and myocardial ischemia differentiation is lacking in the literature. In this study, we evaluated whether the N/L ratio has a discriminative role for patients with suspicious inferior myocardial ischemia on MP-SPECT.

MATERIAL and METHODS

Study Design: This cross-sectional retrospective study was conducted at our institution. Two hundred and twenty-five patients who underwent coronary angiography with suspicious DAA on MP-SPECT between January 2015 and March 2020 were enrolled in this study. The study was designed in accordance with the Declaration of Helsinki and approved by Ethics Committee of Kahramanmaras Sutcu Imam University Faculty of Medicine (30.04.2019 decision no:7).

Participant Population: Data for patients who underwent MP-SPECT imaging between January 2015 and March 2020 were examined. During this time span, 2590 patients who could not be diagnosed by effort test, stress effort test, or who could not tolerate effort tests underwent MP-SPECT imaging. Of these 2590 patients, 269 patients had non-conclusive results due to suspicious DAA in the inferior wall of the left ventricle. Forty-four patients with previously known CAD, ACS, malignancy, suspected infection, hypertrophic cardiomyopathy, severe valve and rheumatologic disease were excluded. The remaining 225 patients were included in this study. Coronary angiographic images for all patients were examined by two physicians. The stenosis percentages for coronary arteries were calculated by the program used in the angiography unit. Stenosis of ⩾50% of the coronary arteries feeding the inferior wall was evaluated as CAD, and <50% stenosis of coronary arteries was assessed as non-CAD according to the American Heart Association classification for coronary artery segments. Age, height, weight, known diseases, and medication use of participants were explored.

Measuring Blood Samples: Blood samples were taken from patients through the antecubital vein at hospital admission. Routine blood tests, including red blood cell count (RBC), white blood cell count (WBC), and platelet count (PLT), were performed using an automated hematology analyzer (Sysmex XN-3100, Kobe, Japan). Biochemical markers, including fasting glucose, triglyceride (TG), high-density lipoprotein (HDL), LDL, total cholesterol (TC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine (CRE) were tested with an automated biochemical analyzer (Roche Cobas 6000, Germany)

Myocardial Perfusion Scintigraphy Design: Routinely, patients were examined with treadmill exercise stress (Bruce or modified Bruce protocol), or pharmacological stress with adenosine (140 mcg/kg) or dipyridamole (0.56 mg/kg). Radiopharmaceutical injection was performed within the 4th minute of maximal effort or pharmacological injection. Tc-99m-MIBI (Methoxyisobutilizonitrile) was used as a radiopharmaceutical. Patients in the supine position underwent 8mCi-22mCi activity for stress and rest protocol, respectively. SPECT was performed from right -45 degrees anterior oblique to 135 degrees according to 90-degree detector positioning with Siemens E. cam dual detector camera. ECG-gated images (8 times per second) were taken simultaneously. Radiopharmaceutical injection was performed approximately 3 hours later, and rest images were taken after 45 minutes after the injection. SPECT was performed in the prone position from -135 degrees to counterclockwise 180 degrees on patients with perfusion defects in the inferior wall. However, patients whose diaphragmatic attenuation wasn't recognized were included in the study. Transverse, vertical, coronal sections and GATED images were examined in all protocols. The SyngoMI system was used for processing images.

Statistical Analysis: Statistical Package for Social Sciences (SPSS) for Windows 21 program was used to analyze the data. Continuous variables are expressed as mean ± standard deviation and categorical variables as a percentage. The participants were divided into two groups as CAD and non-CAD. Kolmogorov-Simirnov test, skewness, and kurtosis were used for the assessment of normal distribution. Independent Student's t-test was used for continuous variables with normal distribution. The Chi-square test was performed on categorical variables. One-Way ANOVA was used in the comparison of more than two groups. Post-Hoc analysis was performed to find which group caused the difference. Multivariate binary logistic regression analysis was used to analyze independent predictors for the presence of CAD. Receiver Operating Characteristic (ROC) curve analysis was used to find the cut-off value for variables that predicted CAD. A 2-sided p-value of <0.05 was considered statistically significant.

RESULTS

One-hundred and ten (48.9%) patients were male, and the mean age of patients was 66.53 ± 9.66 years. Patients were divided into two groups as CAD and non-CAD, according to the presence of significant CAD on coronary angiography. The clinical and demographic characteristics of the patients are shown in **Table 1**. There were no statistically significant differences between the two groups in terms of DM, HT, smoking, age, and lipid profiles. The box plot graphic for the N/L ratio is shown between the two groups (**Figure 1A**). Age, sex, smoking, LVEF, DM, HT, and N/L ratio were entered into multivariate binary logistic regression analysis (**Table 2**). N/L ratio (OR = 1.397 p = 0.002 95% Cl = 1.128-1.732) and LVEF (OR = 0.896 p = 0.023 95% Cl = 0.815-0.985) were independent predictors for the CAD group (**Figure 1B**).

ROC curve analysis showed that a cut-off value of ⩾2 for N/L ratio predicted the presence of CAD (sensitivity=63.5%, specificity=60.7%, AUC=0.668, 95% CI=0.596 – 0.740, p<0.001). Furthermore, the participants were divided into four groups based on the presence of CAD and the cut-off value for N/L ratio. Comparison of these groups according to clinical and demographic characteristics is shown in **Table 3**. Creatinine (p= 0.047) and LVEF (p=0.036) had statistically significant differences between the four groups. Additionally, the diagnostic accuracy of the N/L ratio was 61.33%.

Table 1. Participant characteristics

	CAD	Non-CAD	p
Age	68.01±7.79	65.65±10.61	0.055
Male, n%	39 (45.9)	71(50.7)	0.482
DM, n%	37 (43.5)	44 (31.4)	0.067
HT, n %	50 (58.8)	70 (50)	0.198
Smoking, n%	33 (38.8)	41 (29.3)	0.140
LVEF, %	57.32±3.22	58.41±2.84	**0.009**
GFR, ml/min/1.73m2	77.72±21.61	81.66±20.01	0.167
BMI	30.01±5.00	29.30±4.99	0.305
HDL, mg/dl	44.72±9.64	44.60±11.13	0.933
LDL, mg/dl	121.38±42.63	123.96±45.13	0.672
TG, mg/dl	189.25±131.09	187.91±113.92	0.935
Glucose, mg/dl	146.52±73.37	129.12±60.07	0.067
Neutrophil count /uL	5558.24±1777.65	4505.14±1599.57	**<0.001**
Lymphocyte count/uL	2300.58±868.16	2445.71±824.92	0.211
N/L ratio	2.86±1.86	2.09±1.25	**0.001**

BMI; body mass index, CAD; coronary artery disease, DM ; diabetes mellitus, GFR; glomerular filtration rate, HDL ; high density lipoprotein cholesterol, HL; hyperlipidemia, HT; hypertension, LDL; low density lipoprotein cholesterol, LVEF; left ventricle ejection fraction, N/L ratio; Neutrophil/ Lymphocyte ratio

Table 2. Multiple binary logistic regression analysis of variables

Variables	B	Odd ratio	p Value	95% Cl
Age	0.024	1.024	0.134	0.993-1.057
Sex	0.379	1.461	0.213	0.805-2.654
Smoking	0.181	1.198	0.567	0.645-2.225
LVEF	-0.110	0.896	**0.023**	0.815-0.985
Hypertension	0.178	1.194	0.553	0.665-2.147
Diabetes Mellitus	0.509	1.663	0.094	0.916-3.020
N/L Ratio	0.335	1.397	**0.002**	1.128-1.732

Abbreviations: Cl; confidence interval, LVEF; left ventricular ejection fraction, N/L ratio; Neutrophil/ Lymphocyte ratio

Table 3. Participant characteristic according to cut off value for N/L ratio

Variables	N_L ratio ≥2 CAD+(n=54)	N_L ratio ≥2 CAD- (n=56)	N_L ratio< 2 CAD+(n=31)	N_L ratio< 2 CAD- (n=84)	P*
Male, n%	28(51,9)	29(51,8)	11(35,5)	42(50)	0,449
Age, year	68,90±7,19	66,41±11,87	66,45±8,63	65,11±9,72	0,169
BMI, kg/m²	29,27±4,76	28,95±5,35	31,29±6	29,54±4,76	0,192
HT, n%	32(59,3)	29(51,8)	18(58,1)	41(48,8)	0,618
DM, n%	24(44.4)	18(32,1)	13(41,9)	26(31)	0,329
Smoking, n%	22(40,7)	19(33,9)	11(35,5)	22(26,2)	0,342
TG, mg/dl	159;107	165;133	134;89	166;149	0,051
LDL, mg/dl	118,12±41,44	112,62±31,47	127,06±44,74	131,52±51,08	0,066
HDL, mg/dl	44,96±8,98	46,39±10,78	44,32±10,83	43,41±11,26	0,435
ALT, u/l	21,64±33,26	19,57±14,39	19±8,82	20,91±14,51	0,919
AST, u/l	20,53±13,47	20,71±9,30	20,77±8,17	21,61±12,43	0,945
Creatinine/dl	0,99±0,41	0.88±0,25	0,79±0,19	0,88±0,33	**0,047**
GFR, ml /min	74,08±22,25	80,28±19,28	84,07±19,17	82,58±20,55	0,073
Glucose, mg/dl	143,90±74,25	127,09±59,82	151,09±72,81	130,48±60,55	0,260
Hemogram, g/dl	13,43±1,55	13,41±1,89	13,10±1,50	13,57±1,66	0,620
LVEF, %	57,48±3,32	58,05±2,88	57,06±3,06	58,65±2,80	**0,036**

ALT; alanine transaminase, AST; Aspartate transaminase, BMI ; body mass index, DM; diabetes mellitus, HT; hypertension, GFR; glomerular filtration rate, HDL; high density lipoprotein, LVEF ; left ventricular ejection fraction, TG; triglyceride

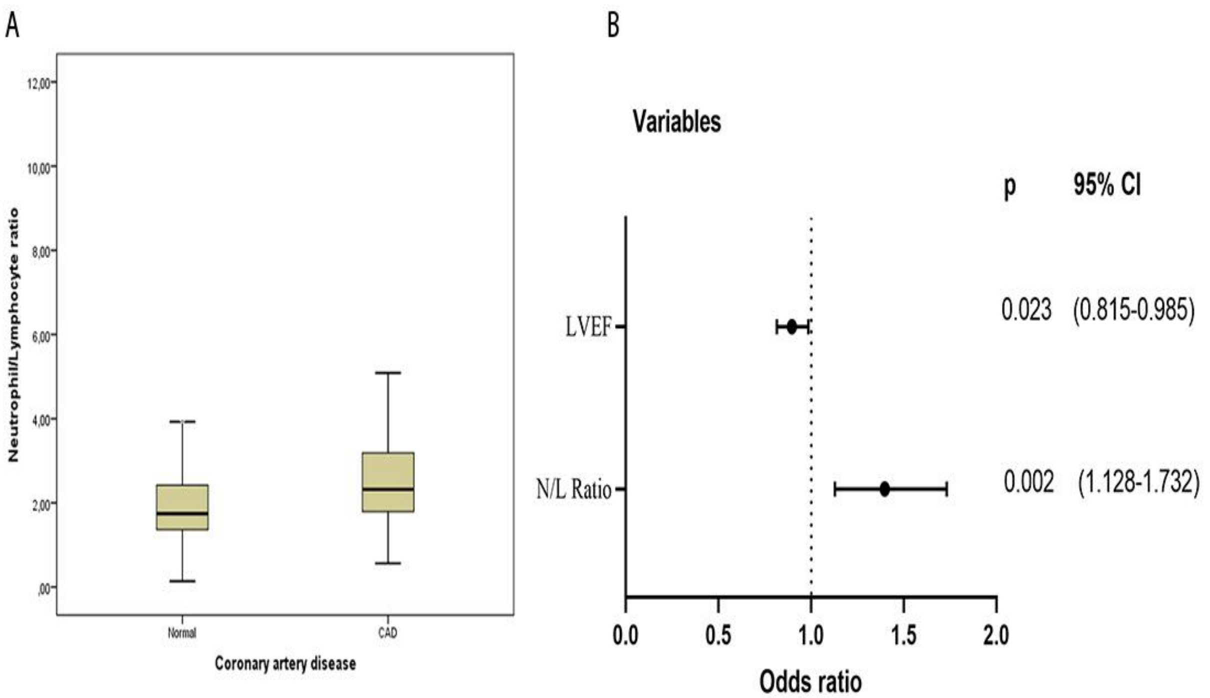

Figure 1. (A) Box plot showing the N/L ratio according to the presence of CAD, (B) Graph showing multivariate logistic regression analysis of statistically significant variables.

DISCUSSION

In this study, the N / L ratio, which is a simple laboratory test, was shown to help the diagnosis of CAD in patients with suspected diaphragmatic attenuation on MP-SPECT.

The purpose of diagnostic tests in clinical cardiology is to identify risky patients for CAD in the early period. MP-SPECT is a test that can provide important prognostic and diagnostic information. MP-SPECT has 90% sensitivity and specificity for the diagnosis of CAD. However, image artifacts reduce the sensitivity of the test. Diaphragmatic attenuation and breast attenuation are the most common image artifacts on SPECT (3-7). Gated ECG, prone images, and CT attenuation correction may be used for the recognition of these attenuations. Attenuation problems were significantly reduced through the use of these techniques. In a meta-analysis involving seventeen studies, the use of attenuation correction images increased the specificity of MP-SPECT (80% -90%) (8). PET and cardiac unique gamma cameras made of solid crystals developed in recent years, such as cadmium zinc telluride (CZT) and cesium iodide, increased sensitivity and specificity (9). In a meta-analysis performed in patients with coronary artery stenosis >50%, the sensitivity and specificity of conventional MP-SPECT studies were 86% and 74%, respectively. Myocardial perfusion images with Rb-82 PET had 92% sensitivity and 85% specificity in a study including 1442 patients (10). However, these methods are expensive and difficult to find. N/L ratio can help us to make the decision for coronary angiography despite artifact reducing methods in patients who were not able to be diagnosed due to DAA. Atherosclerotic heart disease, which is one of the most common causes of death in the world, is associated with multiple genetic and environmental risk factors. It was shown that neutrophils and lymphocytes, which are white blood cells, play a role in every stage of the atherosclerotic process from plaque onset to rupture of the plaque. Naruko et al. reported that the N/L ratio was associated with the progression of atherosclerosis and was an independent predictor of thin cap fibroatheroma (11). It was shown that atherosclerotic plaques in atherectomy specimens including neutrophil infiltration in patients with ACS tended to rupture vessels. Activated neutrophils release numerous proteolytic enzymes, and these enzymes are responsible for endothelial damage. Lymphocytes play a role in the inflammatory response with an inhibitory effect on atherosclerosis. Studies demonstrated that relative and absolute lymphocyte concentrations reduce in patients with cardiac events and a low lymphocyte count might be used as an early marker of physiologic stress and systemic collapse due to myocardial ischemia mediated by cortisol. Increased cortisol levels cause the reduction of lymphocyte counts (12). In our study, increasing neutrophil count was related to CAD. Before ACS occurred, the neutrophil count might increase and guide us for diagnosis of CAD. But the decrease in lymphocyte count was not found to be a factor affecting the N/L ratio. Studies showed that the N/L ratio was an independent risk factor for CAD mortality. When the N/L ratio was integrated into the Framingham risk score, the N/L ratio increased from the intermediate-risk score to the high-risk category.

A meta-analysis demonstrated that the N/L ratio is associated with CAD severity. GENSINI and SYNTAX scores were used to determine CAD severity in this study (13). In light of this information, the N/L ratio can be used for the diagnosis and severity of CAD. However, the cut-off value for the N/L ratio is controversial for CAD. A study found the cut-off the value of the N/L ratio was 2.7 for predicting the severity of CAD. (sensitivity= 72%, specificity= 61%) (14). In another study, including 172 patients, extensive CAD was identified with a 2.5 cut-off value for N/L ratio (sensitivity = 62%, specificity = 69%) (15). Our study did not determine the severity of CAD. However, increasing the cut-off value for the N/L ratio provided high specificity for CAD.

Increased neutrophil count and N/L ratio were associated with cardiac complications in patients admitted with ACS. In a study of 500 people, including stable coronary disease, the N/L ratio was an independent predictor of MACE (16). Patients who underwent coronary artery bypass grafting operation and percutaneous coronary intervention were also included in this study. In our study, patients without known CAD were included. We showed that the N/L ratio, a simple test, can help us diagnose CAD in patients undergoing MP-SPECT.

There are some limitations to the study. The study is from a single center, and the number of patients is inadequate. Prospective studies including many patients should support these results. N/L ratio may be affected by many factors such as dehydration, overhydration, depression, and anxiety in blood samples taken before coronary angiography. The histories of patients need to be examined rigorously in prospective studies.

CONCLUSION

N/L ratio is a simple and accessible test and may increase the diagnostic accuracy of MP-SPECT for CAD in patients with suspicious diaphragmatic attenuation on MP-SPECT.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

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