acta medica

ORIGINAL ARTICLE

Neutrophil to lymphocyte ratio may predict coronary artery disease in geriatric patients

Muhammet Cemal KIZILARSLANOGLU[1], [MD]
Mehmet Emin KUYUMCU[1], [MD]
Mustafa Kemal KILIC[1], [MD]
Esat CINAR[2], [MD]
Ozgur KARA[1], [MD]
Gunes ARIK[1], [MD]
Burcu KIZILARSLANOGLU[3], [MD]
Meltem HALIL[1],
Yusuf YESIL[1], [MD]
Burcu Balam YAVUZ[1], [MD]
Mustafa CANKURTARAN[1], [MD]
Servet ARIOGUL[1], [MD]

1 Hacettepe University Faculty of Medicine, Department of Internal Medicine, Division of Geriatrics, Ankara, Turkey

2 Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Geriatrics, Ankara, Turkey

3 Hacettepe University Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey

* *Corresponding Author: Muhammet Cemal Kizilarslanoglu, MD, Hacettepe University School of Medicine, Department of Internal Medicine, Division of Geriatrics, 06100, Sihhiye, Ankara-TURKEY*

e-mail: drcemalk@yahoo.com.tr

Received 23 May 2015; accepted 31 August 2015; published online 24 December 2015

ABSTRACT

Objective: Neutrophil/lymphocyte ratio (NLR) is a new, inexpensive and easily applicable indicator and one of the markers showing inflammation that plays an important role in the pathogenesis of coronary artery disease (CAD). There is currently no data showing the association between NLR and CAD in geriatric patients. Herein, we aimed to determine this relationship in this study.

Materials and Methods: This is a cross-sectional study involving 507 patients of whom 239 were diagnosed with CAD while 268 were not. The patients' demographic characteristics, illnesses, laboratory parameters and NLRs at the time of admission were investigated.

Results: Mean age, gender rate, and comorbidities of the patients were similar between two groups. NLR was higher in patients with CAD than controls (2.34 vs. 2.03, p=0.003, respectively). Receiver operating characteristic (ROC) curve analysis suggested that optimum NLR cut-off point for CAD was 1.96 with 66.5% sensitivity and 48.8% specificity, 54.1% positive predictive values and 61.7% negative predictive values (AUC=0.575). Multivariate regression analysis revealed that NLR (OR: 1.208, 95% CI: 1.008–1.447, p = 0.041) and cigarette smoking (OR: 2.281, 95% CI: 1.037–5.019, p=0.040) were independently correlated with CAD.

Conclusion: It has been shown that geriatric patients with CAD have higher NLR, and this new marker may be an independent correlate for CAD in geriatric patients.

Key words: Coronary artery disease; neutrophil to lymphocyte ratio; elderly; geriatric; neutrophils; lymphocytes

Introduction

Atherogenesis is an active inflammatory process triggered by endothelial injury [1]. The effect of inflammation in CAD is well established and it has a major role in the initiation and progression of CAD [2]. To show this inflammatory effect, various markers such as high sensitive C reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), fibrinogen, white blood cell (WBC) count and its subtypes, interleukins [3] have been used. A new marker to detect inflammation is blood neutrophil to lymphocyte ratio (NLR).

NLR is a novel, inexpensive and easily applicable marker that shows inflammation. Studies showing association of NLR with coronary artery diseases such as acute coronary syndrome, stable CAD, and other diseases such as; malignancies, chronic renal impairment, Alzheimer's disease, metabolic syndrome, coronary artery ectasia are available in literature [4-14]. Association between NLR and cardiovascular mortality and morbidity has been stated previously in some studies [15-16]. But there is a lack of data for this novel marker's use as a predictor for CAD in geriatric patients.

In light of this knowledge, in this recent study, we aimed to show the association of NLR and CAD in geriatric patients.

Material and Methods

Study design

In this retrospective, cross-sectional study, 507 patients (239 patients with CAD and 268 without CAD) were included. All the patients underwent comprehensive geriatric assessment including medical history, nutritional, mood and cognitive status of the patients. The patients with CAD were comprised of patients who fit one or more of the following in medical history: previous heart attack, positive and documented treadmill test, electrocardiographic findings of previous myocardial infarction, history of stable or unstable angina pectoris, documented CAD with radionuclide imaging or coronary angiography with computerized tomography or percutaneous intervention.

Patients with chronic renal failure, any malignancies, Alzheimer's disease, severe liver failure, active infections, uncontrolled inflammatory diseases such as rheumatologic disorders and diabetes mellitus were excluded from the study.

Biochemical parameters of the patients including fasting plasma glucose, creatinine, calcium, blood urea nitrogen, plasma levels of cholesterol, albumin, liver function tests, vitamin B12 and folate were evaluated.

Erythrocyte sedimentation rate (ESR), ferritin and C-reactive protein (CRP) levels that were used as inflammation markers were also evaluated to show any relationships with NLR.

Complete blood count (CBC) analysis of the patients results were done at their first admittance to our outpatient clinic and NLR (by dividing absolute neutrophil count to absolute lymphocyte count) was calculated by using CBC analysis if there wasn't any excluding criteria mentioned above.

This study protocol was approved by Local Ethics Committee of Hacettepe University School of Medicine and also conducted in accordance with Helsinki Declaration.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 15.0 version program was used for statistical analysis and $p<0.05$ was considered as statistical significance. The numerical parameter evaluation was done by Kolmogrov Smirnov and Shapiro Wilks tests and histograms to determine which parameters were normally distributed and skew distributed. Mean ±SD was used for the numerical parameters that were normally distributed and median (minimum-maximum) was used for skew distributed numerical parameters. Categorical parameters were shown as numbers and frequencies.

For comparing two groups with normally distributed numerical parameters,, Independent Student-T test was used. Mann-Whitney U test was used when numerical parameters were not normally distributed.

Chi-square test was performed to compare the differences between groups for categorical variables.

Receiver operating characteristic (ROC) curve analysis was performed to determine significant cut-off values of NLR, ESR, WBC, CRP and ferritin values for predicting CAD development. The sensitivity, specificity, positive predictive values and negative predictive values were presented in all the mentioned parameters.

The parameters which had $p<0.2$ values after evaluation of univariate analysis and had possible effect on development of CAD were included in multivariate analysis. Binary logistic regression analysis was performed to identify significantly independent correlated factors for CAD.

Results

A total of 507 geriatric patients; 239 in CAD group and 268 in control group; were evaluated in this study. The mean ages of the patients were similar in two groups. There were no differences between groups in demographic, clinic and biochemical parameters, except Mini Mental Status Examination (MMSE) score, creatinine and ALT levels (shown in Table 1). Creatinine level was higher in CAD group than control (0.96 mg/dl vs. 0.89 mg/dl, $p=0.02$, respectively). MMSE score and ALT level were lower in CAD group than control (26 vs. 27, $p<0.001$ and 19 U/L vs. 20 U/L, $p=0.02$, respectively), but these results did not have clinical importance.

After comparison of acute phase reactants and other parameters between two groups, it was found that median of NLR was higher in CAD group than control (2.34 vs. 2.03, $p=0.003$). Other results were shown in Table 1. Furthermore, when compared to control group, median for ferritin levels was lower in CAD group (57 vs. 67, $p=0.035$).

The receiver operating characteristic curve analysis suggested that the optimum NLR cut-off point for CAD was 1.96 with 66.5% sensitivity, 48.8% specificity, 54.1% positive predictive values and 61.7%

Table 1. Comparison of baseline demographic, clinical, biochemical parameters, acute phase reactants and NLR in patients with and without CAD

Parameters	CAD group N = 239	Control group N = 268	P value
Age, years	73±7	72 ±6	0.08
Sex (Male), n (%)	104 (43.5)	99 (36.9)	0.13
BMI (kg/m^2)	26.5 ±3.8	26.4 ±3.3	0.83
HT, n (%)	166 (69.5)	178 (67.2)	0.58
Smoking, n (%)	75 (31.4)	68 (25.4)	0.15
MMSE, score	26 ±4	27 ±3	<0.01
TC (mg/dL)	209 ±49	213 ±44	0.32
LDL-cholesterol, mg/dL	124 ±43	148 ±31	0.23
Triglyceride, mg/dL	137 ±65	134 ±71	0.61
HDL-cholesterol, mg/dL	57 ±14	59 ±15	0.32
FBG, mg/dL	95 ±18	95 ±13	0.54
BUN, mg/dl	19 ±6	18 ±6	0.24
Creatinine, mg/dL	0.96 ±0.33	0.89 ±0.25	0.02
AST, U/L	22 ±9	23 ±11	0.56
ALT, U/L	19 ±9	20 ±9	0.02
Hemoglobin, g/dl	13.7 ±1.2	13.9 ±1.3	0.18
WBC, /µl	6548 ±1378	6406 ±1346	0.24
PLT, /µl	240037 ±66991	249146 ±60430	0.11
NLR, median (min.-max.)	2.34 (0.76 – 8.20)	2.03 (0.73 – 6.17)	<0.01
ESR, mm/h	17 ±11	16 ±12	0.37
CRP, mg/dl	0.54 ±0.47	0.51 ±0.46	0.45
Ferritin, ng/mL, median (min-max)	57 (3–789)	67 (3–667)	0.03

BMI = Body mass index; WBC = white blood cell; PLT = platelets; BUN = blood urine nitrogen; FBG = fasting plasma glucose; TC = total cholesterol; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HT = hypertension; MMSE = Mini–mental state examination; MPV = Mean platelet volume; CAD = Coronary artery disease; NLR = neutrophil-lymphocyte ratio; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein

negative predictive values (AUC=0.575). The same analysis for other inflammatory markers is presented in Table 2 and Figure 1.

The results of the multivariate logistic regression analysis of the possible correlates for CAD are summarized in Table 3 and this analysis revealed that NLR (OR: 1.208, 95% CI: 1.008–1.447, p = 0.041) and cigarette smoking (OR: 2.281, 95% CI: 1.037–5.019, p=0.040) were independently correlated for CAD.

Discussion

In this study, it was shown that NLR was significantly higher in CAD group than control group and there was an association between NLR and CAD in our geriatric patients. The results of this study suggest that the inflammatory process may be diagnosed in geriatric patients by using a simple and inexpensive test like NLR. This study is the first study showing this relationship in geriatric patients with CAD.

The role of inflammation in CAD is well described in literature. Inflammatory cells, inflammatory proteins, and inflammatory responses from vascular cells play a cornerstone role in the pathogenesis of atherosclerosis, including the initiation and progression of atheroma [17]. To show this inflammatory effect, numerous markers such as CRP, ESR, WBC, interleukins etc. were used. Recently, a new marker called NLR is used to understand the effect

Table 2. Results of ROC curve analysis of NLR and other markers of inflammation in CAD.

Parameters	Cut-off	AUC	Sensitivity %	Specificity %	NPV %	PPV %
NLR	1.96	0.575	66.5	48.8	61.7	54.1
ESR, mm/h	9	0.539	69.1	39.9	58.2	51.6
CRP, mg/dl	0.208	0.523	88.2	18.7	63.0	49.9
WBC, /µl	7100	0.528	34.7	73.7	55.0	55.0
Ferritin, ng/mL	25.5	0.557	25.3	85.7	56.4	61.3

NLR = neutrophil-lymphocyte ratio; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; MPV = Mean platelet volume; CAD = Coronary artery disease; AUC = Area of under curve

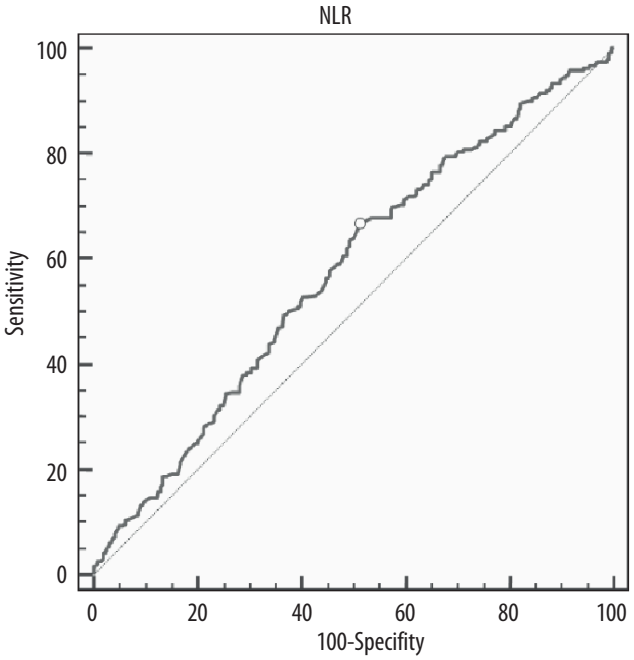

Figure 1A. ROC curve analysis for NLR is shown in this figure.

of inflammation. The illnesses expressing inflammatory pathogenesis such as CAD, malignancies, Alzheimer's disease, pancreatitis and others have been investigated by authors to explain the effect of NLR. The results of these studies show that NLR is a good, inexpensive and reliable marker that shows inflammation, but there is no consensus about what the cut-off point of NLR should be in such diseases when trying to predict the inflammation.

In addition to its predictive effect for showing inflammatory process in CAD patients, this new marker has been studied to determine whether it has effects on the prediction of prognosis of CAD. It has been shown that NLR is a systemic inflammatory marker which predicts mortality and morbidity in patients with high risk CAD and myocardial infarction [12]. It is linked with increased risk of ventricular arrhythmias during percutaneous coronary intervention (PCI) and higher long-term mortality in patients undergoing PCI irrespective of indications of PCI [18]. In a study by Shen *et al.*, 551 ST elevation myocardial infarction (STEMI) patients treated with percutaneous coronary intervention (PCI) were included and they proposed to show the effect of NLR on long term survival and found that NLR was a strong predictor for long term mortality after PCI in patients with STEMI [5]. In addition to this study, the positive relationship between NLR and six month mortality

Table 3. Results of multiple logistic regression analysis of the possible correlates for CAD

Parameters	β	95% CI		p values
		Lower	Upper	
NLR	1.208	1.008	1.447	0.041
Smoking	2.281	1.037	5.019	0.040
Hemoglobin, g/dl	0.888	0.759	1.038	0.135
Platelet, /µl	1.000	1.000	1.000	0.958
Creatinine, mg/dl	1.850	0.857	3.993	0.117
Gender (Male)	1.145	0.711	1.845	0.578
Age, years	1.012	0.981	1.044	0.458
ALT, U/L	0.987	0.965	1.009	0.241

ALT = alanine aminotransferase; MPV = Mean platelet volume

rate was shown in another study designed with acute coronary syndrome patients by Tamhane et al. [19]. In another study by Ergelen et al., they investigated the importance of NLR in patients undergoing percutaneous intervention for STEMI [16]. It was found that higher NLR was associated with long-term mortality rate and in-hospital mortality rate in this study. A study conducted by Papa et al. showed that NLR could be used as a predictor to show mortality rate in patients with stable CAD [20]. This marker is also found to be associated with arterial stiffness and coroner calcium score [21]. In our study, we could not investigate the effect of NLR on mortality or other prognostic factors, because it was designed cross sectionally. On the other hand, in light of our findings, prospective studies aiming to determine the prognostic effect of NLR on prognosis in this group of patients may be designed in the future.

Although there are numerous studies showing the relationship between NLR and acute or chronic stable CAD, there was no study specifically designed to indicatie the significance of NLR for geriatric patients with CAD. Thus, our study has shown that there is positive relationship between NLR and CAD in geriatric patients. The patients with CAD have higher NLR than control patients (2.34 vs. 2.03, p=0.003). In our study, ALT and ferritin values were lower and creatinine level was higher in CAD group when compared to the control group, but in our opinion, because all these parameters were in their normal range, these results do not have clinical importance. After ROC curve analysis, it was suggested that the optimum NLR cut-off point for CAD was 1.96 (66.5% sensitivity, 48.8% specificity, 54.1% positive predictive values and 61.7% negative predictive values, AUC=0.575). In literature, the real cut-off value of NLR is not known for geriatric patients with CAD. So, further prospective studies are needed to establish the real cut-off value of NLR in geriatric patients with CAD and other diseases. Another important point of our study is that when we used multivariate analysis to show the relationships between risk factors and CAD, NLR and smoking were found to independently correlate with CAD in geriatric patients.

There are several limitations of our study. Firstly, we used a cross-sectional design that does not show a causal relationship. Secondly, patients were evaluated only once, so laboratory measurement errors may easily have affected the accuracy of the data. Thirdly, the relationship between elevated NLR and co-morbid conditions may have been confounded by some unmeasured covariates (although patients with active infection, renal impairment, Alzheimer's disease and diabetes mellitus were excluded from the study). Another limitation is that in the present study, the CAD group was selected according to medical history, so, elapsed time after the diagnosis of the coronary condition may have an effect on NLR by lowering the level of NLR as compared the first acute phase of coronary event.

In conclusion, in our study we found that elderly people with CAD have a higher NLR than the control group. It is the first study investigating NLR in geriatric patients with CAD. Also, it was shown that NLR was an independent correlate for CAD in the elderly. Further prospective studies are needed to establish a causal relationship between NLR and CAD in geriatric population.

REFERENCES

[1] **Zazula AD, Precoma-Neto D, Gomes AM, Kruklis H, Barbieri GF, Forte RY,** *et al.* An assessment of neutrophils/lymphocytes ratio in patients suspected of acute coronary syndrome. Arq Bras Cardiol 2008; 90: 31-36.

[2] **Ross R.** Atherosclerosis—an inflammatory disease. N Engl J Med 1999; 340: 115-126.

[3] **Hansson GK.** Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352: 1685-1695.

[4] **Kuyumcu ME, Yesil Y, Ozturk ZA, Kizilarslanoglu C, Etgul S, Halil M,** *et al.* The Evaluation of Neutrophil-Lymphocyte Ratio in Alzheimer's Disease. Dement Geriatr Cogn Disord 2012; 34: 69-74.

[5] **Shen XH, Chen Q, Shi Y, Li HW.** Association of neutrophil/lymphocyte ratio with long-term mortality after ST elevation myocardial infarction treated with primary percutaneous coronary intervention. Chin Med J (Engl) 2010; 123: 3438-3443.

[6] **Okyay GU, Inal S, Onec K, Er RE, Pasaoglu O, Pasaoglu H,** *et al.* Neutrophil to lymphocyte ratio in evaluation of inflammation in patients with chronic kidney disease. Ren Fail 2013; 35: 29-36.

[7] **Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G,** *et al.* Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. Am Heart J 2007; 154: 995-1002.

[8] **Koh YW, Kang HJ, Park C, Yoon DH, Kim S, Suh C,** *et al.* Prognostic significance of the ratio of absolute neutrophil count to absolute lymphocyte count in classic Hodgkin lymphoma. Am J Clin Pathol 2012; 138: 846-854.

[9] **Kishi Y, Kopetz S, Chun YS, Palavecino M, Abdalla EK, Vauthey JN.** Blood neutrophil-to-lymphocyte ratio predicts survival in patients with colorectal liver metastases treated with systemic chemotherapy. Ann Surg Oncol 2009; 16: 614-622.

[10] **Buyukkaya E, Karakas MF, Karakas E, Akcay AB, Tanboga IH, Kurt M,** *et al.* Correlation of neutrophil to lymphocyte ratio with the presence and severity of metabolic syndrome. Clin Appl Thromb Hemost 2014; 20: 159-163.

[11] **Kaya A, Kurt M, Tanboga IH, Isik T, Gunaydin ZY, Kaya Y,** *et al.* Relation of Neutrophil to Lymphocyte Ratio With the Presence and Severity of Stable Coronary Artery Disease. Clin Appl Thromb Hemost 2013; 20: 473-477.

[12] **Balta S, Demirkol S, Celik T, Kucuk U, Unlu M, Arslan Z,** *et al.* Association between coronary artery ectasia and neutrophil-lymphocyte ratio. Angiology 2013; 64: 627-632.

[13] **Kurtul S, Sarli B, Baktir AO, Demirbas M, Saglam H, Dogan Y,** *et al.* Neutrophil to lymphocyte ratio predicts SYNTAX score in patients with non-ST segment elevation myocardial infarction. Int Heart J 2015; 56: 18-21.

[14] **Nilsson L, Wieringa WG, Pundziute G, Gjerde M, Engvall J, Swahn E,** *et al.* Neutrophil/Lymphocyte ratio is associated with non-calcified plaque burden in patients with coronary artery disease. PLoS One 2014; 9: e108183.

[15] **Uthamalingam S, Patvardhan EA, Subramanian S, Ahmed W, Martin W, Daley M,** *et al.* Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol 2011; 107: 433-438.

[16] **Ergelen M, Uyarel H, Altay S, Kul S, Ayhan E, Isik T,** *et al.* Predictive value of elevated neutrophil to lymphocyte ratio in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. Clin Appl Thromb Hemost 2014; 20: 427-432.

[17] **Zakynthinos E, Pappa N.** Inflammatory biomarkers in coronary artery disease. J Cardiol 2009; 53: 317-333.

[18] **Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G,** *et al.* Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther 2013; 11: 55-59.

[19] **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: 653-657.

[20] **Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, Cocci F.** Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. Clin Chim Acta 2008; 395: 27-31.

[21] **Park BJ, Shim JY, Lee HR, Lee JH, Jung DH, Kim HB,** *et al.* Relationship of neutrophil-lymphocyte ratio with arterial stiffness and coronary calcium score. Clin Chim Acta 2011; 412: 925-929.

