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Could neutrophil/lymphocyte ratio be an indicator of coronary artery disease, coronary artery ectasia and coronary slow flow?

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Abstract

Objective: To determine whether neutrophil/lymphocyte ratio (NLR) differed between patients with isolated coronary artery disease (CAD), isolated coronary artery ectasia (CAE), coronary slow flow and normal coronary anatomy.

Methods: Patients who underwent coronary angiography were consecutively enrolled into one of four groups: CAD, coronary slow flow, CAE and normal coronary anatomy.

Results: The CAD ($n = 40$), coronary slow flow ($n = 40$), and CAE ($n = 40$) groups had similar NLRs (2.51 ± 0.7, 2.40 ± 0.8, 2.6 ± 0.6, respectively) that were significantly higher than patients with normal coronary anatomy ($n = 40$; NLR, 1.73 ± 0.7). Receiver operating characteristics demonstrated that with NLR > 2.12, specificity in predicting isolated CAD was 85% and sensitivity was 75%, with NLR > 2.22 specificity in predicting isolated CAE was 86% and sensitivity was 75%. With NLR > 1.92, specificity in predicting coronary slow flow was 89% and sensitivity was 75%. Multivariate logistic regression analyses identified NLR as an independent predictor of isolated CAE ($\beta = -0.499$, 95% CI -0.502, -0.178; $P < 0.001$), CAD ($\beta = -0.426$, 95% CI -1.321, -0.408; $P < 0.001$), and coronary slow flow ($\beta = -0.430$, 95% CI -0.811, -0.240; $P = 0.001$ Table 2).

Conclusions: NLR was higher in patients with CAD, coronary slow flow and CAE versus normal coronary anatomy. NLR may be an indicator of CAD, CAE and coronary slow flow.

Keywords

Coronary artery disease, coronary artery ectasia, coronary slow flow, neutrophil/lymphocyte ratio

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Introduction

Atherosclerosis develops as a result of inflammatory and fibro-proliferative events, and involves several factors that occur in response to localization of atherogenic lipoproteins on the intima layer of the blood vessel wall.[1] Affecting older adults in particular, atherosclerosis is a slowly progressing degenerative disease characterized by mechanical changes in the blood stream.[2] Several studies have reported that inflammation plays a key role in atherosclerosis pathogenesis, with inflammation being identified at every stage, from onset to progression, and until thrombotic complications develop.[3] White blood cells (WBCs) have been reported to play a significant role in atherosclerosis-related inflammatory process,[4] and identification of the relationship between atherosclerosis and inflammation has highlighted a role for inflammatory indicators in determining the risk of cardiovascular events.[5,6]

The main cell types involved in inflammation are WBCs, which are thought to be accountable for unwanted events in cardiovascular diseases, and levels of WBCs and their subtypes are used as indicators of inflammatory conditions.[7,8] Increased neutrophils, and stress-induced low lymphocyte levels (lymphopenia) both indicate changes in the immune system.[9,10] An index that reflects high neutrophil levels (indicating inflammation) and post-physiologic stress-induced lymphopenia, namely the neutrophil/lymphocyte ratio (NLR), has been used in studies along with other inflammatory indicators, and determined to be a good indicator of inflammatory conditions.[11] The NLR is shown to be a simple, reliable and inexpensive inflammatory indicator that can provide important information on many conditions, such as coronary artery disease (CAD) prevalence, and risk classification of acute coronary syndromes.[12,13]

In the absence of acute coronary syndrome, reasons for NLR variations in patients with isolated CAD, isolated coronary artery ectasia (CAE) and isolated coronary slow flow remain unclear. The aim of the present study was to investigate whether NLR values differ between patients with CAD, CAE and coronary slow flow, and patients with normal coronary anatomy in the absence of acute coronary syndrome.

Patients and methods

Study population

This prospective observational study recruited consecutive age, sex and atherosclerosis risk-factor matched patients who underwent coronary angiography while attending the cardiology clinic of Elazığ Education and Research Hospital, Elazığ, Turkey between January 2015 and December 2015. Patients aged between 45 and 75 years were consecutively recruited into one of four groups comprising: $\geq$50% lesions in at least one coronary artery (CAD group); coronary slow flow only; isolated CAE; or normal coronary anatomy. Recruitment of age, sex and atherosclerosis risk-factor matched patients continued during the study until each group count reached 40 patients.

Patients diagnosed with acute coronary syndrome, chronic kidney failure, chronic lung disease, malignant arrhythmia, systemic connective tissue diseases, heart failure, cardiomyopathy, cerebrovascular case history, any chronic or acute inflammatory disease, thyroid function disorder, malignancy, and/or chronic liver failure were excluded from the study.

The study was initiated following Presidential of T.C. Fırat University Ethics Committee approval, and was conducted under the regulations determined by the Helsinki Declaration. All participants provided written informed consent.

Laboratory measurements and coronary angiography

Blood samples (6 ml for full biochemistry and 5 ml for complete blood count) were obtained from the antecubital vein prior to coronary angiography and following a 12 h fast. Samples were drawn into vacuum tubes containing 15% K3 ethylenediamine-tetra-acetic acid (EDTA) and analysed within 30 min of being drawn. Haematocrit and haemoglobin, platelet, neutrophil, lymphocyte, monocyte and eosinophil levels were assessed using a Coulter® LH 780 automated haematology analyser via an electrical impedance method (Beckman Coulter Inc., Brea, CA, USA), according to the manufacturer's instructions. NLR was calculated by manually dividing the digital neutrophil and lymphocyte counts in $10^3/mm^3$ unit volume. Glucose, urea, creatinine, total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels were measured using a chemiluminescence method with a Cobas® e601 autoanalyser and associated reagents (Roche Diagnostics Ltd., Rotkreuz, Switzerland) according to the manufacturer's instructions.

Coronary angiography was performed after blood samples were obtained, using the Judkins technique[14] with a Siemens Axiom Artis FC diagnostic device (Siemens Healthcare GmbH, Forchheim, Germany). Following catheterisation, each patient was administered 350 mg/ml Iohexol (Amersham Health, Co. Cork, Ireland) as the contrast agent, and coronary angiography recordings were taken at the left anterior oblique, and cranial and right anterior oblique, and caudal and horizontal positions. All angiographic examinations were conducted by two experienced angiography specialists (MNB and OU).

Coronary slow flow measurement

The thrombolysis in myocardial infarction (TIMI) frame count method was used to identify patients with coronary slow flow.[15] To objectively assess coronary blood flow as a continuous numerical variable, the sine-frame count required for Iohexol contrast agent to reach the distal end of the left anterior descending (LAD) coronary artery was accepted as the TIMI frame count, and the mean of calculations for at least three positions was used. During the measurement period, the frame at which contrast agent entered the artery was accepted as the first frame, and the frame at which contrast agent reached the distal end of the LAD coronary artery was accepted as the last frame. The TIMI frame count was then calculated from the difference between the first and last frames.[16] Since the distance between proximal and distal bifurcation in the LAD coronary artery is longer than other coronary arteries, LAD TIMI frame count is significantly higher than right coronary artery (RCA) and circumflex (Cx) artery TIMI frame counts. A 1.7 constant coefficient is used to standardize the measurements and published mean reference values are 36 ± 1 for LAD, 22.2 ± 4 for Cx and 20.4 ± 3 for RCA.[15] In the present study, values that were two units above the published reference values were accepted as standard, and coronary slow flow was defined as values above 38 for LAD, above 30 for Cx and above 26 for RCA.

Coronary artery ectasia

Quantitative coronary measurements were obtained by same-day analyses of digital data obtained during coronary angiography for each participant, using Scientific Quantification Coronary Analysis software (Siemens Healthcare Gmbh, Forcheim,

Germany). To determine the actual width of the coronary artery lumen, a calibration was conducted using the catheter diameter. To identify the artery segment as ectatic, at least two measurements were taken at the proximal, mid and distal segments of the coronary arteries in patients with normal coronary angiography and normal coronary flow, and in patients who were considered to have an ectatic coronary segment. If the diameter of the artery segment was $\geq$1.5 times wider than the mean artery diameter of patients with normal coronary angiography and normal coronary flow, it was accepted as ectatic and the patient was included in the isolated CAE group.

Isolated coronary artery disease

Coronary lesion length and percent stenosis were assessed using a quantitative coronary angiography method with Scientific Quantification Coronary Analysis software, version 14432944 (Siemens Healthcare Gmbh), and $\geq$ 50% stenosis was accepted as the existence of CAD. Patients with $\geq$ 50% luminal stenosis based on angiography were included in the CAD group.

Statistical analyses

Continuous variables are presented as mean $\pm$ SD and categorical variables are presented as *n* (%) prevalence. Kolmogorov–Smirnov test was used to determine whether the variables were normally distributed. Between-group comparisons were conducted using one-way analysis of variance for continuous variables and χ^2-test for categorical variables. Multivariate regression analyses were performed to determine which clinical variables would independently predict CAE, CAD and coronary slow flow. CAE, CAD and coronary slow flow were entered into the regression model as dependent variables. NLR, age, platelet count, haematocrit, and triglyceride, glucose, urea, and creatinine levels were entered into the model as independent variables. Results are presented as β coefficients and 95% confidence intervals (CIs). Sensitivity and specificity of NLR and its optimal cut-off values were determined by receiver operating characteristic (ROC) curve analysis. Statistical analyses were performed using SPSS software, version 15.0 (SPSS Inc., Chicago, IL, USA). All *P* values were two-tailed, and values <0.05 were considered to indicate statistical significance.

Results

The study included 160 consecutive patients: 40 patients with $\geq$50% lesions in at least one coronary artery (CAD group); 40 patients with only coronary slow flow; 40 patients with isolated CAE; and 40 patients with normal coronary anatomy. There were no statistically significant differences between the CAD, coronary slow flow, CAE and normal coronary anatomy groups in terms of atherosclerosis risk factors such as age, sex, smoking, or diabetes mellitus, or in platelets, WBC, LDL, triglycerides, haematocrit, haemoglobin, glucose, Na, urea, creatinine and K values (Table 1).

The NLR values were significantly higher in the CAD, coronary slow flow and CAE groups compared with the normal coronary anatomy group (2.506 ± 0.65, 2.403 ± 0.75, and 2.604 ± 0.55 versus 1.725 ± 0.71, respectively; $P < 0.0001$). There was no statistically significant difference in NLR values between the CAD, coronary slow flow and CAE groups (Table 1; Figure 1).

The ROC curve analysis demonstrated that the specificity of an NLR value > 2.12 (measured prior to coronary angiography) in predicting isolated CAD was 85% and the sensitivity was 75% (area under the curve [AUC] 0.863, 95% CI 0.850, 0.876; $P < 0.0001$). The specificity of an NLR value > 2.22 in predicting isolated CAE

Table 1. Between-group comparison of demographic and clinical characteristics in 160 patients who underwent coronary angiography and were diagnosed with coronary artery disease (CAD), coronary slow flow (CSF), coronary artery ectasia (CAE), or normal coronary anatomy (NCA).

	Patient group				
Variable	CAD $n=40$	CSF $n=40$	CAE $n=40$	NCA $n=40$	Statistical significance
Sex, male female	21/19	22/18	22/18	19/21	NS
Hypertension, yes	9 (22.5)	9 (22.5)	10 (25)	8 (20)	NS
Diabetes mellitus, yes	6 (15)	5 (12.5)	7 (17.5)	5 (12.5)	NS
Smoking, yes	7 (17.5)	7 (17.5)	8 (20)	6 (15)	NS
Age, years	61.75 ± 10.36	58.15 ± 5.07	60.27 ± 8.71	58.01 ± 5.81	NS
Platelet, $\times 10^3/mm^3$	240.17 ± 60.43	254.60 ± 71.51	237.65 ± 62.16	265.50 ± 56.13	NS
WBC, $\times 10^3/mm^3$	7.97 ± 2.05	7.00 ± 1.85	7.58 ± 2.33	7.04 ± 0.96	NS
Haematocrit, %	41.87 ± 4.67	42.08 ± 5.04	42.77 ± 4.04	41.84 ± 3.38	NS
Haemoglobin, g/dl	14.04 ± 1.76	14.26 ± 1.82	14.38 ± 1.60	14.01 ± 1.31	NS
LDL, mg/dl	128.21 ± 37.64	107.20 ± 33.17	109.74 ± 37.19	111.30 ± 42.15	NS
Triglycerides, mg/dl	188.95 ± 99.93	171.86 ± 95.19	248.43 ± 490.58	156.11 ± 79.05	NS
Glucose, mg/dl	127.26 ± 73.88	99.48 ± 20.72	110.47 ± 32.63	109.64 ± 19.71	NS
Sodium, mmol/l	139.20 ± 3.03	139.09 ± 3.28	139.65 ± 3.66	139.11 ± 2.88	NS
Potassium, mEq/l	4.37 ± 0.58	4.32 ± 0.46	4.24 ± 0.51	4.31 ± 0.44	NS
Urea, mg/dl	34.09 ± 10.43	35.61 ± 11.53	33.63 ± 9.15	31.09 ± 8.85	NS
Creatinine, mg/dl	0.66 ± 0.15	0.74 ± 0.13	0.75 ± 0.17	0.65 ± 0.13	NS
Neutrophil, $\times 10^3/mm^3$	5.31 ± 1.45	4.29 ± 1.01	5.03 ± 1.44	3.59 ± 0.88	$P < 0.05$[a], NS[b]
Lymphocyte, $\times 10^3/mm^3$	2.17 ± 0.67	1.90 ± 0.62	1.98 ± 0.53	2.22 ± 0.57	NS
NLR	2.506 ± 0.65	2.403 ± 0.75	2.604 ± 0.55	1.725 ± 0.71	$P < 0.0001$[c], NS[d]

Data presented as mean ± SD or *n* (%) prevalence.
WBC, white blood cell; LDL, low-density lipoprotein; NLR, neutrophil/lymphocyte ratio.
[a]CAD versus CSF, CAD versus NCA, CSF versus NCA, and CAE versus NCA.
[b]CAD versus CAE, and CSF versus CAE.
[c]CAD versus NCA, CSF versus NCA, and CAE versus NCA.
[d]CAD versus CSF, CAD versus CAE, and CSF versus CAE.
NS, no statistically significant between-group difference ($P > 0.05$; one-way analysis of variance for continuous variables and χ^2-test for categorical variables).

was 86% and the sensitivity was 75% (AUC 0.901, 95% CI 0.820, 0.981; $P < 0.0001$), and the specificity of an NLR value > 1.92 in predicting coronary slow flow was 89% and the sensitivity was 75% (AUC 0.843, 95% CI 0.747, 0.940; $P < 0.0001$; Figure 2).

Multivariate logistic regression analysis identified NLR as an independent predictor for the existence of isolated CAE ($\beta = -0.499$, 95% CI −0.502, −0.178; $P < 0.001$). CAD ($\beta = -0.426$, 95% CI −1.321, −0.408; $P < 0.001$), and coronary slow flow ($\beta = -0.430$, 95% CI −0.811, −0.240; $P = 0.001$; Table 2). All other independent variables tested were not statistically significant for predicting CAE, CAD or coronary slow flow.

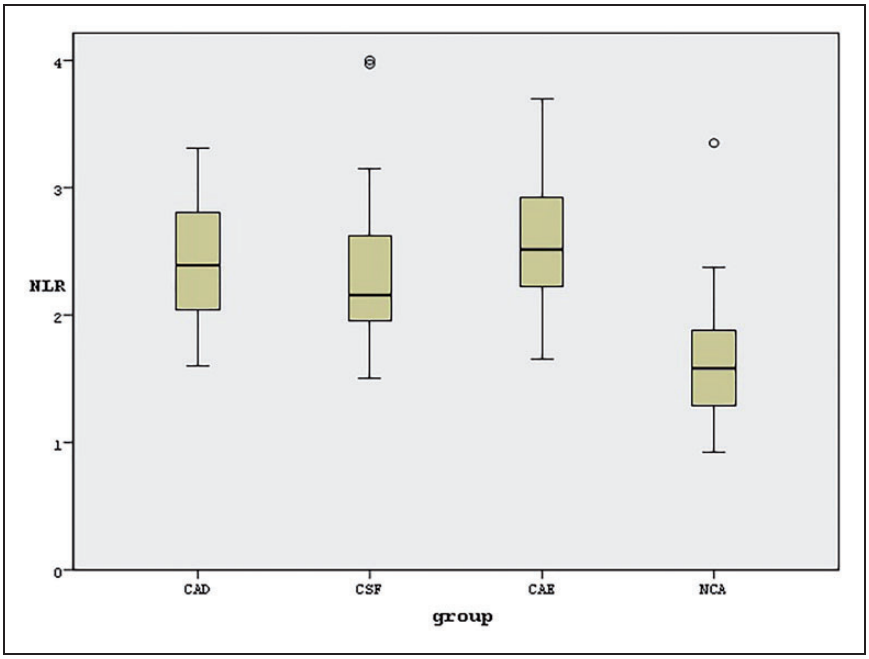

Figure 1. Box-whisker plots showing neutrophil/lymphocyte ratio (NLR) values for patients with isolated coronary artery disease (CAD; $n = 40$), coronary slow flow (CSF; $n = 40$), isolated coronary artery ectasia (CAE; $n = 40$), and normal coronary anatomy (NCA; $n = 40$). The heavy black horizontal lines for each group represent the means, the extremities of the box are the 25th and 75th percentiles, the error bars are the minimum and maximum outliers, and the circles above the CSF and NCA bars represent extreme outliers.

Discussion

The objective of the present study was to investigate whether NLR values differed between three different groups of patients with CAD, CAE or coronary slow flow, and patients with normal coronary anatomy in the absence of acute coronary syndrome. The present results demonstrated that NLR values were significantly higher in patients with CAD, coronary slow flow and CAE versus patients with normal coronary anatomy.

Atherosclerosis, which is the main cause of coronary artery disease, is a pathology characterized by endothelial dysfunction in the large and medium muscular arteries, vascular inflammation, and lipid and inflammatory cell accumulation on the intima layer.[17,18] Although it is known that inflammation plays a significant role in the onset and progression of atherosclerotic disease, biochemical and cellular events that initiate and cause the progression of atherosclerosis have not been completely explained.[19]

Several studies have investigated the role and relationship between inflammation and bio-indicators that reflect inflammatory conditions and unwanted events in coronary artery diseases.[20,21] The role of inflammation is under active investigation in terms of progression of atherosclerosis and acute and chronic forms of artery disease, and also in CAE and coronary slow flow.[11]

Coronary artery ectasia is one of the congenital or acquired coronary anomalies.[22] Although CAE demonstrates a

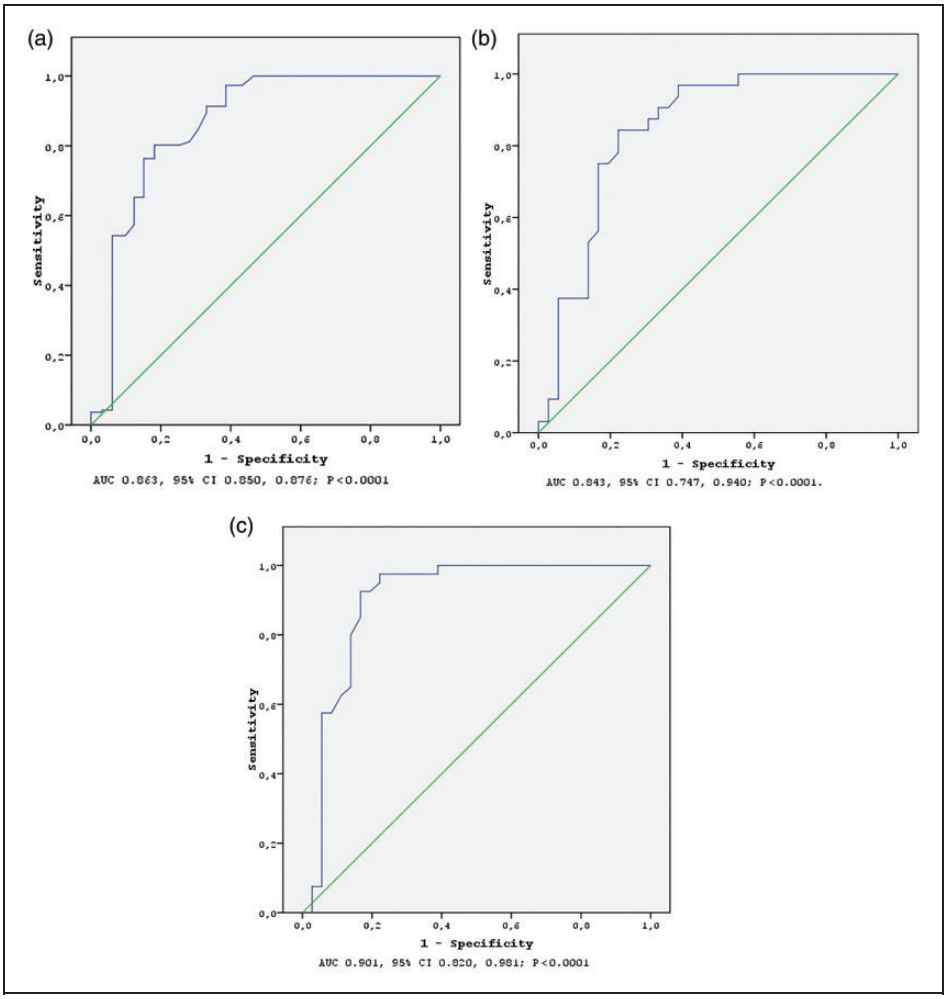

Figure 2. Receiver operator characteristic curve analysis against normal coronary anatomy showing specificity and sensitivity of neutrophil/lymphocyte ratio in predicting (a) isolated coronary artery disease; (b) isolated coronary slow flow; and (c) isolated coronary artery ectasia. AUC, area under the curve; CI, confidence interval.

Table 2. Multivariate logistic regression analysis of neutrophil/lymphocyte ratio for predicting coronary artery disease, coronary slow flow and coronary artery ectasia in the absence of acute coronary syndrome in patients who underwent coronary angiography.

Patient group	β	Statistical significance	95% confidence interval
Coronary artery disease, $n = 40$	−0.426	$P < 0.001$	−1.321, −0.408
Coronary slow flow, $n = 40$	−0.430	$P = 0.001$	−0.811, −0.240
Coronary artery ectasia, $n = 40$	−0.499	$P < 0.001$	−0.502, −0.178

heterogeneous etiologic character, its most common etiologic cause among adults is atherosclerosis.[23,24] Regional or generalized angiographic extension of 1.5 times the normal artery diameter in epicardial coronary arteries is defined as CAE, and a further extension is defined as coronary artery aneurism.[24,25] Underlying histologic changes in CAE have been demonstrated as equivalent to the changes observed in atherosclerotic lesions (generalized hyalinization, intimal and medial deterioration).[26] CAE might accompany occlusive coronary artery disease, however, it may also be observed as isolated CAE, and several studies have reported findings that indicate a more intense inflammation than occlusive coronary artery disease.[27,28] Investigations into the relationship between inflammation and CAE showed a relationship with well-known inflammatory indicators such as matrix metalloproteinase, interleukin-6, tumour necrosis factor-α, WBC count, neutrophil count, monocyte count, and C-reactive protein (CRP).[28,29] Similar studies assessed CRP levels in patients with isolated CAE, CAD without coronary ectasia, and angiographic normal coronary arteries. CRP levels were found to be higher in patients with CAE than the other two groups and it was claimed that a more intense inflammatory process could be active in patients with CAE versus patients with CAD.[20,27]

Coronary slow flow is a condition characterized by the slowing down of coronary artery flow rate, and is defined as delay in the filling of epicardial coronary arteries with contrast agent without the existence of stenosis.[30] The underlying mechanisms and aetiology remain unknown, however, studies have shown that endothelial dysfunction, vasomotor dysfunction, microvascular disease and generalized atherosclerosis may play a role in aetiopathogenesis.[31–34] In patients with coronary slow flow, studies have identified lengthwise extensive calcification without narrowing the lumen, diffuse intimal thickening, and atheroma plaques in the vessel wall.[33–35] Significant differences have also been observed between proximal-distal coronary artery pressure (reflecting the increase in microcirculation resistance) and fractional flow reserve values compared with healthy controls.[36] As a result of these findings, it was concluded that coronary slow flow is an atherosclerotic process in the capillaries and large vessels that results in an increase in microvascular resistance. Endothelial activation and inflammation may play a significant role in coronary slow flow pathogenesis.[37,38]

Two studies have shown that NLR could be used as a parameter that indicates both neutrophil elevation, which reflects acute inflammation, and low lymphocyte levels, which reflects physiologic stress.[39,40] Furthermore, high NLR in patients with both stable CAD and acute coronary syndrome may be an independent predictor of coronary atherosclerosis progression.[41] WBC count and WBC sub-type ratios could be used as indicators of inflammation in cardiovascular diseases,[42] and WBC count and sub-types have been demonstrated as important inflammatory indicators in predicting cardiovascular outcomes.[43]

In the current study, NLR was found to be significantly higher in patients with at least 50% or more lesions in at least one coronary artery, in patients with coronary slow flow, and in patients with CAE, versus patients with normal coronary anatomy. These findings are consistent with published results that considered NLR as an independent predictive parameter in coronary artery disease onset and progression.[40,44]

The results of the present study are limited by the relatively low number of patients included in the research, the exclusion of patients with acute coronary syndrome, and the lack of comparison between NLR and other inflammatory indicators.

Another limitation is the fact that, as demonstrated by intravascular ultrasound and autopsy studies conducted in cases of atherosclerotic heart disease, the vessel lumen could be observed as normal even though there is an atherosclerotic plaque over a wide area.[45,46] Finally, the study lacked intravascular ultrasound in the diagnosis of normal coronary anatomy, isolated CAE and coronary slow flow.

In conclusion, NLR is an inexpensive, routinely used inflammatory indicator that can be obtained during complete blood counts. The present study attempted to measure the inflammatory process by calculating NLR, and demonstrated that NLR was higher in patients diagnosed with CAD, isolated CAE and coronary slow flow using angiography versus patients with normal coronary anatomy, and may be an indicator of CAD, CAE and coronary slow flow in the absence of acute coronary syndrome. There was no statistically significant difference, however, between NLRs in these three cardiovascular groups that represented different variants of coronary artery disease.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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