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Original Article

The neutrophil to lymphocyte ratio improves the positive predictive value of dobutamine stress echocardiography

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Abstract: The neutrophil to lymphocyte ratio (NLR) predicts cardiovascular events. The aim of this study was to determine whether NLR improved the positive predictive value (PPV) of dobutamine stress echocardiography (DSE) in patients with stable coronary artery disease (CAD). We conducted a retrospective review of laboratory and DSE data from the medical records of 1,012 patients who were divided into two groups according to the presence of ischemia and further subdivided into three groups according to the extent of ischemia (nonischemic segments, 1-3 ischemic segments, or > 3 ischemic segments). NLRs were compared among these groups. NLRs increased in patients with ischemia and correlated with the number of ischemic segments ($P < 0.001$). The optimal cutoff value of NLR determined using receiver operating characteristic analysis was > 2.04, and the diagnostic value of NLR for discriminating patients with ≥ 50% coronary stenosis in at least one of the coronary arteries from those without significant CAD was high [area under the curve (AUC) = 0.671, standard error = 0.052, $P < 0.001$, 95% confidence interval (CI) = 0.569-0.773)]. An NLR cutoff value of > 2.04 predicted CAD presence with significant stenosis (62.10% sensitivity and 64.10% specificity). PPV of DSE for a significant coronary artery lesion identified using coronary angiography was 73.8% (95% CI = 75.1-88.5, $P < 0.001$, AUC = 0.818). On including a cut-off value of > 2.04 for NLR in this multivariable predictive model, the AUC value slightly increased to 0.905 (95% CI = 85.4-95.6) and PPV of DSE increased from 73.8% to 92.6%. NLR improved PPV of DSE for patients with stable CAD.

Keywords: Dobutamine stress echocardiography, myocardial ischemia, neutrophil to lymphocyte ratio, stable coronary artery disease

Introduction

Coronary artery disease (CAD) is a major cause of death and morbidity worldwide [1, 2]. Noninvasive tests for stratifying risk and identifying patients with a higher likelihood of CAD before elective coronary angiography are recommended in the current guidelines [3]. However, these tests have limited prognostic discrimination and are unable to detect CAD severity. To increase cost-effectiveness, it is critical to correctly decide whether to perform elective coronary angiography [4, 5].

Dobutamine stress echocardiography (DSE) serves as a reference method for the diagnostic and prognostic evaluation of CAD, particularly in patients with a capacity for limited exercise or those with uninterpretable electrocardiograms (ECGs), because DSE is a safe and relatively inexpensive noninvasive technique that exposes patients to ionizing radiation [6-8]. In daily practice, noninvasive tests applied before coronary angiography do not completely fulfill a "gatekeeper" role and require major improvements. Thus, the purpose for conducting this study was to investigate the additional contribution of DSE combined with hematological parameters to diagnostic power [9].

The neutrophil to lymphocyte ratio (NLR) is a simple ratio of the absolute neutrophil and lymphocyte counts obtained on the differential section of leukocyte count of a complete blood count (CBC) and is a marker of inflammation. NLR is a marker of inflammation [10], which is associated with increased mortality in clinically stable patients with CAD [11, 12].

The basic aim of our study was to investigate the diagnostic power of NLR combined with DSE because NLR is a more consistent mea-

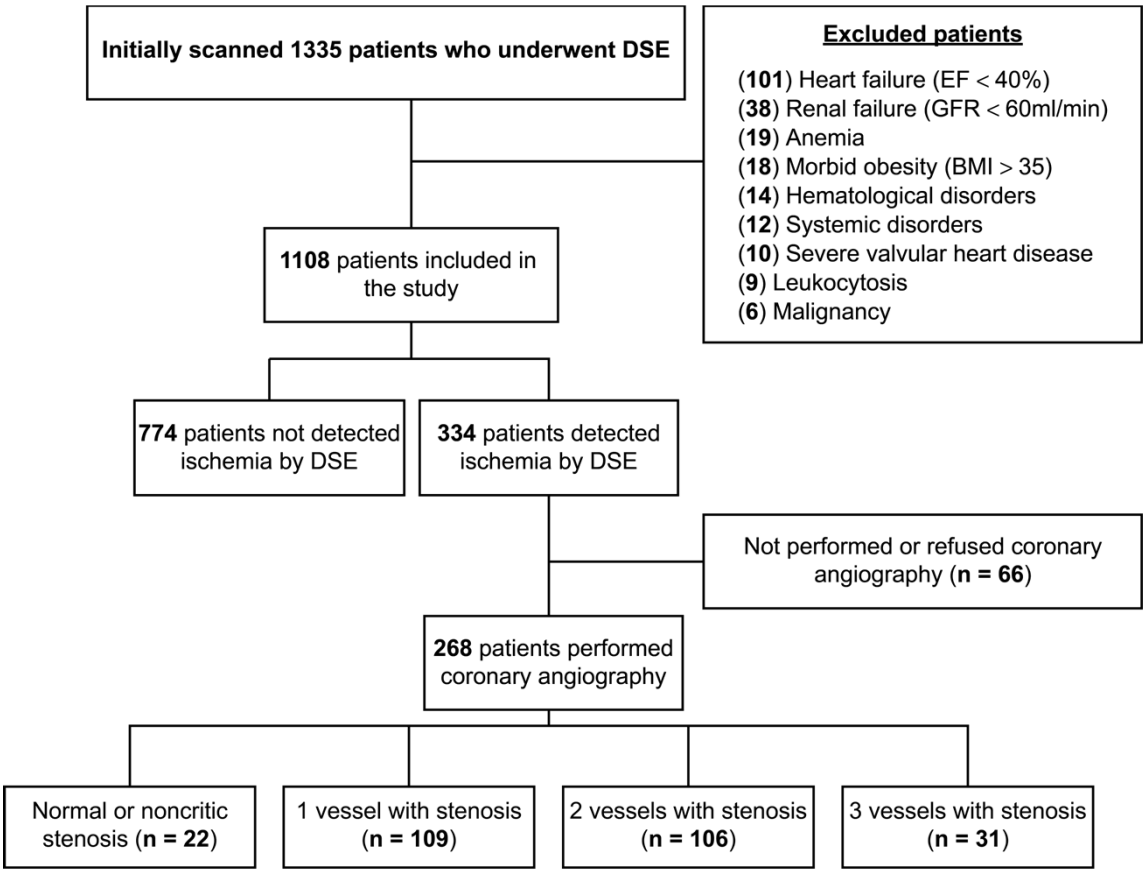


Figure 1. Flow chart of patients in study. *CAD*: Coronary artery disease, *DSE*: Dobutamine stress echocardiography, *EF*: Ejection fraction.

surement than individual hematological cell counts [13, 14].

Material and methods

Study population

We conducted a retrospective review of 1,334 DSE examinations of patients with stable CAD that were performed in our cardiology clinic between January 2010 and June 2014. The study included 1,012 patients and was approved by the local ethics committee (approval number B.30.2.KON.0.71.00.00/3397).

Exclusion criteria

Patients were excluded if they had heart failure [ejection fraction (EF) of < 40%)], severe valvular heart disease, anemia (hemoglobin of < 13 g/dl for males and < 12 g/dl for females), previous blood transfusion, acute infection and/or white blood cell count of > 11.0 × 10^9/l, chronic hemodialysis, creatinine clearance of < 60 ml/min, malignant hematological diseases; or chronic systemic diseases such as obstructive pulmonary disease, liver disease, inflammatory disease; or hormone replacement therapy for conditions such as thyroid disease or menopause. Furthermore, the estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault (CG) equation as follows: eGFRCG = [(140-age) × weight (kg)]/[plasma creatinine × 72]. This rate was 0.85 for a female patient. A flowchart of the study is shown in **Figure 1**.

Study protocol

The records of patients who underwent DSE were examined from the digital archive of the echocardiograph laboratory in our clinic and were matched with medical histories and laboratory records. The baseline values were the laboratory test results from admission or from the polyclinic the month before DSE was administered. The patients were divided into two groups according to the presence of ischemia

Table 1. Demographics and laboratory findings of DSE-negative and -positive patients

Parameters	DSE negative (n = 774)	DSE positive (n = 268)	*P*-value*
	Mean ± SD (median)	Mean ± SD (median)	
Age (years)	60.30 ± 10.82	61.56 ± 9.89	0.054
Female gender *n* (%)	370 (47.8%)	93 (34.3%)	**< 0.001**
BMI (kg/m^2)	28.44 ± 3.91	28.17 ± 4.0	0.484
Systolic BP (mmHg)	121.89 ± 13.70	122.62 ± 13.17	0.459
Diastolic BP (mmHg)	77.04 ± 8.96	76.32 ± 9.57	0.284
Hypertension n (%)	288 (37.2%)	98 (36.6%)	0.458
Diabetes mellitus n (%)	218 (28.1%)	90 (33.8%)	0.109
Smoking n (%)	105 (13.5%)	49 (18.2%)	0.106
Family history n (%)	93 (12.0%)	104 (38.8%)	0.807
Known CAD n (%)	225 (29.0%)	127 (47.6%)	**< 0.001**
Previous MI n (%)	96 (12.4%)	83 (31.0%)	**< 0.001**
Ejection fraction (%)	56.14 ± 8.37	54.47 ± 9.57	**0.009**
Glucose (mg/dl)	118.75 ± 41.78	120.70 ± 43.19	0.490
Creatinine (mg/dl)	1.02 ± 0.80	1.12 ± 0.95	0.063
Total cholesterol (mg/dl)	193.32 ± 44.28	181.73 ± 43.40	**< 0.001**
LDL-C (mg/dl)	121.49 ± 35.79	114.02 ± 36.39	**< 0.001**
HDL-C (mg/dl)	40.64 ± 18.93	39.00 ± 10.4	0.301
Triglyceride (mg/dl)	159 (131)	147 (127)	0.065
GGT	27.49 (26)	27.58 (72.5)	0.343
HbA1C	7.25 ± 1.53	7.63 ± 1.71	0.356

*Compared with the DSE without ischemia group; $P < 0.05$. Bold text: *P*-values indicating significant differences. DSE: dobutamine stress echocardiography, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, MI: myocardial infarction, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

Table 2. Hematologic findings of DSE-negative and -positive patients

Parameters	DSE negative (n = 774)	DSE positive (n = 268)	*P*-value*
	Mean ± SD (median)	Mean ± SD (median)	
Hemoglobin (g/dl)	13.74 ± 1.32	13.72 ± 1.36	0.848
Hematocrit (%)	41.38 ± 4.92	41.11 ± 4.52	0.371
WBC (× 10^9/L)	7.41 ± 1.98	7.81 ± 2.06	**< 0.001**
LYM (× 10^9/L)	2.41 (2.1)	2.74 (1.9)	0.205
NEU (× 10^9/L)	5.36 (4.2)	7.59 (4.9)	**< 0.001**
MONO	0.52 (0.5)	0.57 (0.5)	0.293
PLT	264.54 ± 70.8	246.01 ± 71.09	**< 0.001**
MPV	7.95 ± 1.35	8.31 ± 1.42	**< 0.001**
PCT	0.18 ± 0.06	0.51 ± 0.06	0.111
Hematologic Ratios			
NLR	2.53 (1.99)	3.03 (2.44)	**< 0.001**
PLR	141.96 (120.99)	143.33 (136.09)	0.334
PNR	64.05 (59.69)	55.24 (52.86)	**< 0.001**

*Compared with the DSE without ischemia group; $P < 0.05$. Bold text: *P*-values indicating significant differences. DSE: dobutamine stress echocardiography, WBC: white blood cell, NEU: neutrophil count, PLT: platelet count, MPV: mean platelet volume, NLR: neutrophil to lymphocyte ratio, PNR: platelet to neutrophil ratio, PLR: platelet to lymphocyte ratio, LYM: lymphocyte.

and were further subdivided into three groups according to the extent of ischemia (nonischemic segments, 1-3 ischemic segments, or > 3 ischemic segments). We identified patients with positive DSE results who underwent subsequent coronary angiography. These patients were divided into four groups according to the results of coronary angiography as follows: normal coronary arteries or no critical stenosis (≤ 50% lesion), single-vessel disease (> 50% lesion), two-vessel disease, or three-vessel disease. We compared NLRs of DSE and coronary angiography subgroups.

DSE assessment

DSE was performed by two senior cardiologists with 14 years of experience using a Philips HD 11 (Philips, Andover, MA, USA) echocardiography device with an S3-1 transducer. Dobutamine infusion and the DSE protocol were evaluated in accordance with the current guidelines [15]. The intra- and inter-observer variabilities of ischemia for DSE findings were 7.2% and 10.6%, respectively.

Blood sample analysis

CBC, including hemoglobin, hematocrit, and white blood cell (WBC) count, was analyzed using an automated CBC device (Abbott Cell Dyn; Abbott Laboratories, Effingham, Illinois, USA). Biochemical parameters were measured using an Olympus AU 600 auto-analyzer (Olympus Optical Co. Ltd., Schimatsu-Mishima, Japan). Total cholesterol, triglycerides, and high-density lipoprotein cholesterol levels were enzymatically determined using a Hitachi 747

Table 3. Comparison of hematological parameters according to the presence and number of ischemic segments identified by DSE

Parameters	Group 1	Group 2	Group 3	*P*-value between groups	*P*-value	*P*-value	*P*-value
	Non-ischemic segments (n = 744)	1-3 ischemic segments (n = 172)	> 3 ischemic segments (n = 96)		Group 1-2	Group 1-3	Group 2-3
PLT MASS	2.06 ± 0.56	2.01 ± 0.65	2.04 ± 0.62	0.557[a]	-	-	-
NLR	2.53 (2.06)	3.00 (2.33)	3.08 (2.32)	< 0.001[b]	0.029	0.030	0.571
PLR	141.96 (124.65)	146.41 (125.43)	137.06 (119.23)	0.594[b]	-	-	-
PNR	64.05 ± 24.90	56.48 ± 24.67	52.64 ± 21.73	< 0.001[a,c]	< 0.001[c]	< 0.001[c]	0.322

[a]One-way ANOVA. [b]Kruskal-Wallis test. [c]Post Hoc Test: Tukey HSD. PLT: platelet count, NLR: neutrophil to lymphocyte ratio, PNR: platelet to neutrophil ratio, PLR: platelet to lymphocyte ratio.

analyzer (Japan). Low-density lipoprotein cholesterol (LDL-C) level was calculated using the Friedewald formula [16].

Statistical analysis

All statistical analyses were performed using SPSS software version 15.0 (SPSS, Chicago, IL, USA). Categorical and nonparametric data are expressed as the median (interquartile range), and continuous data are expressed as the mean ± standard deviation. The Kolmogorov-Smirnov test was applied to determine the distribution of values. The differences between categorical variables were determined using the χ^2-test. The Student's *t* test was used to determine the differences between normally distributed data, and the Mann-Whitney test was used to compare the median values of the nonparametrically distributed variables. The differences in NLR between more than two groups were analyzed using one-way analysis of variance, and post-hoc analysis was performed using Tukey's test. A multiple stepwise logistic regression analysis was performed to identify the predictors of ischemia in DSE using the backward elimination method. Subsequently, multivariate logistic regression analysis was performed to identify the determinants of myocardial ischemia identified by DSE. Sex, CAD, previous myocardial infarction (MI), EF, total cholesterol and LDL-C levels, WBC count, neutrophil count (NEU), platelet count (PLT), mean platelet volume (MPV), NLR, and platelet to neutrophil ratio were entered into the regression model as independent determinants of ischemia. The criteria used for backward elimination were defined as $P > 0.10$ for each step. After the last step, independent determinants of ischemia were identified. The receiver operating characteristic (ROC) curve was calculated, and the specificity, sensitivity, negative predictive values (NPVs), and positive predictive values (PPVs) of NLR were analyzed for their ability to predict ischemia and CAD according to the DSE findings. A *P*-value of < 0.05 was considered statistically significant.

Results

We included 1,012 patients with stable CAD who underwent DSE (**Figure 1**). There were 744 patients (73.5%) who were not diagnosed with ischemia (DSE-negative group, mean age 60.30 ± 10.8 years, 49.8% females) and 268 patients (26.4%) who were diagnosed with ischemia (DSE-positive group, mean age 61.56 ± 9.8 years, 34.3% females). The demographic characteristics and laboratory findings of both groups are presented in **Table 1**, and the hematological findings of the DSE-negative and -positive patients are presented in **Table 2**. The following hematological parameters were significantly higher in the ischemic than in the non-ischemic group: WBC count = 7.4 ± 1.9 × 10^9/l vs. 7.8 ± 2.0 × 10^9/l, $P < 0.001$; NEU = 5.36 (4.2) vs. 7.59 (4.9) × 10^9/l, $P < 0.001$; MPV = 7.95 ± 1.35 vs. 8.31 ± 1.42, $P < 0.001$; and NLR = 2.53 (1.99) vs. 3.0 (2.44), $P < 0.001$ (**Table 2**).

NLR increased with an increase in the number of ischemic segments detected using DSE (**Table 3**) The patients were divided into three groups according to the number of ischemic segments: no ischemic segments, 1-3 ischemic segments, and > 3 ischemic segments. NLRs differed significantly among the nonischemic segment group ($n = 744$), the group with 1-3 ischemic segments (n = 172), and the group with > 3 ischemic segments ($n = 96$, $P < 0.001$) (**Figure 2A**).

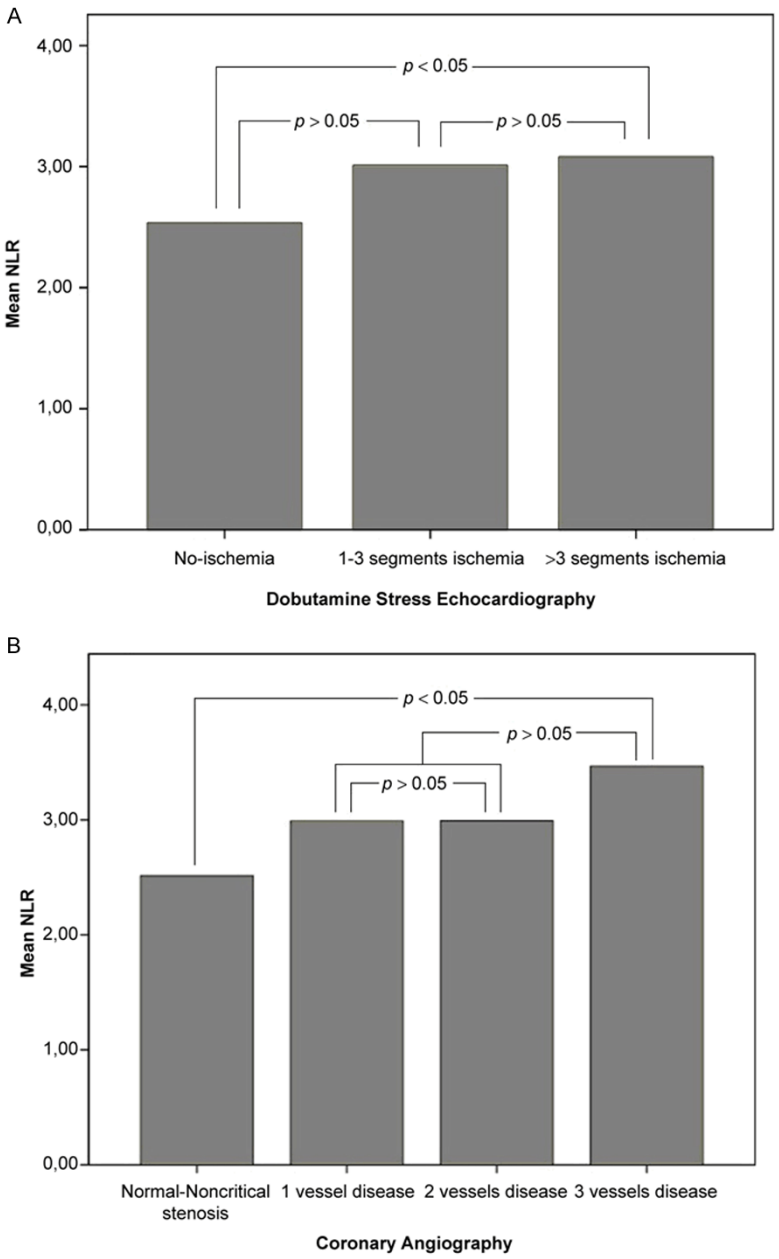


Figure 2. A. Comparison of NLR values according to the presence and number of ischemic segments identified by dobutamine stress echocardiography. B. Comparison of NLR values according to the presence and number of diseased coronary arteries identified by coronary angiography.

Multivariate logistic regression analysis was performed to estimate the independent predictors of MI in patients who underwent DSE. CAD [odds ratio (OR) = 6.984 (0.094-1.876), P = 0.001], previous MI [OR = 7.270 (1.113-2.382), P = 0.0001], EF [OR = 2.011 (1.006-3.016), P = 0.0001], and NLR [OR = 5.750 (1.214-2.087), P = 0.01] were independent predictors. When NLR variables were entered together, NLR and CAD remained as independent predictors, along with previous MI and EF (**Table 4**).

The severity and extent of CAD was evaluated using vessel calculations, and we divided the 268 patients into the following four groups after coronary angiography: normal coronary anatomy and noncritical disease (n = 22), one-vessel disease (n = 109), two-vessel disease (n = 106), and three-vessel disease (n = 31) (**Table 5**). NLRs differed significantly among patients with normal coronary arteries or noncritical stenosis with one-vessel disease, two-vessel disease, and three-vessel disease [2.53 (2.26), 2.98 (2.15), 2.99 (2.29), and 3.40 (2.63), P < 0.02, respectively]. There was a significant difference between NLRs of Group 3 and those of the other groups (P < 0.001) (**Figure 2B**).

The ROC curve was used to determine the sensitivity and specificity using the respective area under the curve (AUC) for optimal NLRs. Using an optimal cutoff value of > 2.04 for NLR, according to the ROC analysis, the diagnostic value of NLR to discriminate patients with ≥ 50% coronary stenosis in at least one of the coronary arteries from those without significant CAD was high [AUC = 0.671 (standard error (SE) = 0.052), P < 0.001, 95% CI = 0.569-0.773]. A cutoff value of NLR > 2.04 predicted the presence of CAD with significant stenosis with 62.1% sensitivity and 64.10% specificity. PPVs and NPVs were 60.10% and 74.10%, respectively.

Table 4. Independent predictors of myocardial ischemia detected using DSE revealed by the regression model

Variables	Beta	*Odds*	95% CI of Odds		*P*-value
			Lower	Upper	
First step					
Gender	-0.043	0.041	0.114	1.131	0.264
Known CAD	-0.004	6.984	0.094	1.876	**0.001**
Previous MI	0.244	7.270	1.113	2.382	**< 0.000**
Ejection fraction	0.206	2.011	1.006	3.016	**< 0.000**
Total cholesterol	-0.066	0.008	0.002	1.021	0.262
LDL-C	-0.021	0.005	0.002	1.341	0.724
WBC	0.062	0.015	0.026	1.057	0.465
NEU	-0.046	0.014	0.088	1.060	0.707
PLT	-0.055	0.006	0.001	1.561	0.476
MPV	0.042	0.015	0.013	1.042	0.292
NLR	0.250	4.270	1.213	2.382	**0.001**
PNR	0.015	0.001	0.002	1.002	0.796
Last step					
NLR	0.127	5.750	1.214	2.087	**0.017**
CAD	-0.113	7.018	1.015	2.001	**0.007**

Bold text: *P*-values indicating significant differences. CI*:* confidence interval, CAD*:* coronary artery disease, MI: myocardial infarction LDL-C*:* low-density lipoprotein cholesterol, WBC: white blood cell, NEU: neutrophil count, PLT: platelet count, MPV: mean platelet volume, NLR: neutrophil to lymphocyte ratio, PNR: platelet to neutrophil ratio, PLR: platelet to lymphocyte ratio. For a final multiple variable logistic regression, the adjusted factors are "Known CAD, previous MI, ejection fraction and NLR".

PPV of DSE for a significant coronary artery lesion identified using coronary angiography was 73.8% (95% CI = 75.1-88.5, $P < 0.001$, AUC = 0.818). In contrast, when an NLR cutoff value of > 2.04 was added to this multivariable predictive model, AUC increased slightly to 0.905 (95% CI = 85.4-95.6) (**Figure 3**), and PPV of DSE increased from 73.8% to 92.6%.

Discussion

The predictive value of NLR for cardiovascular events was defined by several prospective and retrospective studies [17-19]. Although these studies primarily focused on the relationship of NLR with adverse events, NLR was not sufficiently tested together with noninvasive diagnostic tests. The primary finding of the current study is that NLR, which can be easily obtained from routine CBCs, increased the diagnostic power of DSE.

Positive results were determined by others who analyzed hematological parameters such as WBC count, NEU, and MPV for the prediction and risk stratification of patients with acute or chronic CAD [20]. These findings are consistent with those of the present study, which reveal a significant relationship between angiographic vascular involvement and myocardial ischemic load with WBC count, NEU, and MPV. Moreover, we showed that WBC count and NEU were significantly higher in the group with ischemia than in the group without ischemia. However, when considered alone, the absolute NEU or absolute lymphocyte count was not predictive in multivariate logistic models.

A recent important study by Shah et al. revealed the contribution of NLR to risk stratification and showed that NLR significantly improves the prediction of CAD mortality of the Framingham Risk Score [21]. This relationship between NLR and the severity of MI is important because to the best of our knowledge, it was the first demonstration of a diagnostic approach using a noninvasive test combined with an analysis of biomarkers. Moreover, multivariable regression modeling revealed that NLR correlated with CAD as an independent risk factor.

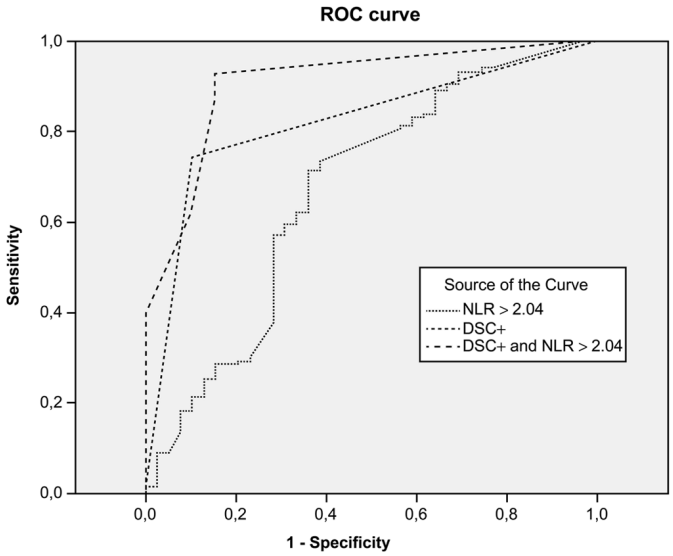
The development of a noninvasive approach before deciding on future invasive procedures is important for reducing costs and increasing efficacy. Recent studies focused attention on the use of parameters to increase the diagnostic performance of DSE, which has high prognostic and diagnostic values, and is frequently used in daily practice. To improve the diagnostic performance of DSE, several additional individual parameters were recently proposed. For example, according to a prospective study conducted by Akilli et al., the distribution of red cell width is related to the presence and extent of IM in DSE [22].

In the current study, when the ROC analysis was applied to determine PPV of NLR, AUC and optimal cutoff values were 0.671 and 2.04, respectively. NLR (3.4) of the multiple vessel patient group agrees with cutoff values determined in previous studies. Angela et al. found that NLR of > 2.42 indicates a gradually inc-

Table 5. Comparison of hematological parameters according to the presence and number of diseased coronary arteries identified by coronary angiography

Parameters	Group 1	Group 2	Group 3	Group 4	*P* value between groups
	1 VD (n = 109)	2 VD (n = 106)	3 VD (n = 31)	Normal or noncritical stenosis (n = 22)	
PLT MASS	2.06 ± 0.67	2.05 ± 0.55	2.08 ± 0.66	2.24 ± 0.78	0.641[a]
NLR	2.98 (2.15)	2.99 (2.29)	3.4 (2.63)	2.53 (2.26)	0.025[b,c]
PLR	147.66 (122.54)	139.29 (124.73)	137.18 (120.57)	200.02 (124.76)	0.089[b]
PNR	57.24 ± 22.82	54.95 ± 27.64	50.55 ± 20.28	59.42 ± 17.77	0.520[a]

[a]One-way ANOVA. [b]Kruskal-Wallis test. [c]*P* < 0.001 between Groups 3 and 4. VD: vessel disease, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PNR: platelet to neutrophil ratio.



	AUROC	*p* value	95% CI	Sensitivity	Specificity	PPV	NPV
NLR > 2.04	0.671	0.001	0.569–0.773	62.1%	64.1%	60.1%	72.4%
DSE+	0.818	< 0.001	0.751–0.885	76.9%	84.7%	73.8%	84.6%
NLR > 2.04 and DSE+	0.905	< 0.001	0.854–0.956	84.2%	89.6%	92.6%	89.74%

Figure 3. Receiver operating curve of NLR for significant coronary artery disease in coronary angiography. *AUC*: Area under the curve, *CI*: Confidence interval, *NPV*: Negative predictive value, *PPV*: Positive predictive value, *NLR*: The neutrophil to lymphocyte ratio.

reasing trend for the risk of cardiac mortality [12], and Horne et al. found that NLR of > 2.55 strongly predicts either death or MI [20].

The combination of NLR of > 2.04 with DSE ischemia-positivity in the ROC analysis was accompanied by a significant increase in the AUC value (0.818 to 0.905). In the DSE test applied in our clinic, AUC = 0.818, sensitivity = 76.9%, specificity = 84.7%, and PPV = 73.8% are consistent with literature. The primary result of this study shows that PPV of DSE increased from 73.8% to 92.6%, which supports the use of NLR, because it significantly contributes to improving PPV of DSE.

To conclude, LDL and C-reactive protein data are used as biomarkers for recommended peripheral blood series measurements of patients with coronary heart disease [3, 4]. The present results show that rather than discarding NLR from the hematological parameters used in routine practice, NLR should be combined with the DSE test to play a "gatekeeper" role, particularly to identify high-risk patients requiring invasive procedures. The question of whether a series of routine NLR measurements influences risk stratification and medication use (e.g., statins and anti-ischemic treatment) will continue to direct future studies.

This study was a retrospective and cross-sectional review of medical records. Two major limitations were the small patient population and the lack of data for inflammatory markers. Furthermore, the findings of this study were not adapted to individuals with inflammatory and autoimmune disorders, malignancies, or those who received corticosteroid therapy because they were excluded from our analysis. Moreover, the exclusion criteria prevented the extrapola-

tion of the findings to other populations with these comorbidities. Finally, there was no follow-up data for adverse events.

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Disclosure of conflict of interest

None.

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